Computer aided Modelling of Nasoalveolar Molding Devices for Cleft Lip and Palate Treatment

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Introduction

Nasoalveolar Molding is an effective but time-consuming presurgical therapy of Cleft Lip and Palate. The devices needed for the Nasoalveolar Molding therapy require a weekly manual adaption by the maxillofacial surgeon or orthodontist. Therefore, improvements of manufacturing and frequent adaption of the molding devices would be appreciated. To improve the extensive process of manual manufacturing and manual frequent adaption of the molding devices, a new technique of automated modelling and manufacturing of the molding devices by CAD/CAM technology is under research.

Methods

The initial cast of the infant’s maxilla is digitalized with a triangulation laser scanner. The digital model of the maxilla is registered within the coordinate system by characterizing specific features. The initial alveolar model is formed with a parametric growth-model and manually by the practitioner. Based upon the newly generated model the geometry of the molding devices are virtually designed. Out of these STL data the final molding devices are manufactured by stereolithographic 3D-SLT-printing with a biocompatible Polymethylmethacrylate (PMMA).

Results

With a 3D-Scan processing software the results were verified upon the plaster casts of patients who have already undergone Nasoalveolar Molding. The maximum deviation between the target model and the deformed start model were under 1 mm in the relevant regions of the maxilla, regardless to the remodeling method.

Conclusion

The first results are very encouraging. Necessary steps are to improve the parametric growth-model and to get all computational sections combined into one tool.
Patient-specific computational modelling of the mitral valve

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Introduction

Current approaches to valve repair/replacement are based to one-size-fits-all. As such there is a big drive towards more personalised surgical interventions. The aim of this project is to develop a novel prognostic/forecasting computational simulation tool that will provide patient-specific pre-operative optimisation of mitral valve (MV) replacement/repair.

Methods

MicroCT images of porcine MV were segmented in Simpleware and the whole MV apparatus was reconstructed. In preliminary computational models, the leaflets were simplified as membranes and the chordae as tension strings. Anterior and posterior leaflet samples, together with samples from the two main chordae tendineae types (strut & commissural) were tested under uniaxial tension to obtain the regional biomechanics of the MV. The stress-strain data obtained was imported in the computational model to specify the regional material properties of the MV. The model was imported into LS-DYNA, where a pressure driven (max 120mmHg) MV closure was simulated for one cardiac cycle.

Results

The MV apparatus demonstrated significant regional and directional mechanical anisotropy. The anterior leaflet demonstrated significant directional anisotropy, whereas the posterior showed a rather isotropic behaviour. Significant differences in the mechanical properties were also found between the different types of chordae tested. The computational simulations predicted regions of both leaflets with elevated stress concentration during the cardiac cycle, in accord with failure regions observed clinically. Moreover, the simulations indicated variable loading of the different chordae during the cardiac cycle.

Conclusion

This study has indicated that different components of the MV experience different levels of stress and strain, which has an implication in the selection of appropriate repair materials for MV reconstruction. Future work will focus on developing blood-structure interaction models and incorporating the left ventricle, aortic valve and aortic arch anatomy from clinical scans.
Sensitivity Study: Efficiency of Ventricles of the Human Heart Depending on Fiber Orientations

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Abstract

Introduction
Shortening of myocyte fibers is responsible for the contraction of the human heart and is the main driving mechanism for blood circulation in the cardio-vascular system. Currently, two methods exist for initialization of the fiber orientation in a computational heart model. Setting of fiber orientation using diffusion tensor MRI is preferable, but can introduce possibly large inaccuracies and is nearly impossible for alive patients. As alternative approach, rule-based algorithms are used, being able to generate a fiber orientation based on a few physiological parameters only. The drawback is, that model-based errors are introduced and a wrong choice of the parameter set might turn the whole simulation useless. In this study, the influence of different fiber angles in the ventricles on the pumping function of the heart was determined.

Methods
Different set of fiber angles were compared using computer simulation of an elastomachanical model of the whole heart. The heart geometry was based on segmented MRI data from a healthy volunteer. Fibers in the ventricles were set using a semi-automatic Laplace-Dirichlet Rule-Based algorithm presented by J. D. Bayer et al. 2012. The algorithm took four angles as input parameters, describing absolute and relative orientation of fibers on the endo- and epicard.

Results
From the simulation results, PV-diagrams were created for the left ventricle for all fiber orientation settings. Results showed, that the pump function of the heart depended significantly on the fiber orientation angles. Furthermore, the atrioventricular plane displacement was analyzed for all fiber orientation settings. Also here, a strong dependency on the fiber orientation was found.

Conclusion
Since the pumping function of the heart depends significantly on the fiber orientation, it is essential to know in which way errors introduced to the model due to uncertainties in the fiber orientation affect the mechanical behavior. Here, a sensitivity analysis can help to gain insight.
Quantification of loads on the lumbar spine of children with different body weight – a comparative study with the help of computer modelling

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Abstract

In highly developed industrial and affluent societies obesity is increasingly becoming a widespread disease. While the effects of obesity on the cardiovascular system are in focus of many studies, the effects of obesity especially on spinal structures are still nearly unknown. In this study the effects of normal weight, overweight and obesity with the help of multi-body simulation (MBS) on the child’s spine is investigated. The in the model implemented vertebral bodies, intervertebral discs, facet joints and ligaments are adapted in such a way that they correspond to the anthropometric data and biomechanical properties of a child. To quantify the loads on the lumbar spine of children of different weight classes, the first lumbar vertebra is respectively loaded with of the weight of a normal weight, an overweight and adipose child. In particular, the structural changes of the intervertebral discs, the facet and the ligaments are investigated.

The different load varies within the intervertebral discs, resulting from the different weight forces. In all three simulations, the lower functional spinal units are more loaded than the upper. In comparison to the loads of the spinal structures of a normal-weight child with an adipose child, these are generally loaded more. For example, the intervertebral discs of the adipose child compared with those of normal weight children are twice as heavily loaded.

Due to the general higher load of all spinal structures of adipose children, may be the risk of degenerative damage in the spine increased. The MBS modeling is validated by comparing the results of selected load cases with data from literature.

1 Introduction

The World Health Organization (WHO) called overweight and obesity as the biggest chronic health problems. Overweight and obesity are contributing cause for many ailments and can favor the development of chronic diseases. More than 40 million children under the age of five were overweight in 2011. [1] While there are a large number of studies of the effects on the cardiovascular system and the psyche of the concerned person, the potential consequence of orthopedic injuries, particularly of the spine, associated with obesity are yet hardly known.

Three multi-body simulation (MBS) models of the child’s lumbar spine were created to quantify the effects of normal weight, overweight and obese children to the kinematics and transmitted forces and torques of the different spinal structures. With the help of these three-dimensional models dynamic movements and static situations can be simulated. In this research project the effects on intervertebral discs, facet joints and ligamentous structures during most natural load case, the upright standing, were analyzed.

2 Method

The MBS models of the lumbar spine consist of os ilium, os sacrum, and vertebrae L1-L5. The vertebrae are connected by joints with appropriate degrees of freedom and about 160 ligament structures, which are attached to characteristic points of the skeletal parts. The facet joints are realized as 3D- contact areas, so that the acting contact forces avoid the penetration of two corresponding joint surfaces. All the individual structures are modeled with different material properties in order to simulate their realistic mechanical behavior. The general model properties like the mechanical behavior of the spinal elements, the generation of the vertebral surface and it’s alignment is described in detail in [2].
from X-ray images of a 10 year old child and the individual vertebrae surfaces were scaled accordingly.

![Image of vertebrae surfaces scaled according to child's spine dimensions](image)

**Fig. 2** Schematic representation of the Scaling of the vertebral body surfaces L3 a) based on dimensions of a child's spine with radiographs b).

### 2.2 Realization of different weight classes in the simulation

To simulate the effects of overweight or obesity, the data of the weight classes was detected using the BMI course of BzgA [3], [4] as average values.

![Image of BMI course](image)

**Fig. 3** Determination of the average body weights of the various weight classes of 10-year-old children

It is assumed as a representative value for the body mass of a normal-weight child 38kg, 46kg for an overweight child and an obese child 54kg. For these weight classes, the percentage mass distributions are calculated, which are used as the basis for the mass fractions of the segments head, upper body, lower body, upper arm, forearm and hand. To ensure a realistic modeling, the anthropometric measurements such as shoulder width, chest circumference, waist circumference, hip circumference and upper and lower arm length / width and hand width / length of the childlike body segments were considered in the model. Based on the human bodies the individual bodies segments were represented by corresponding geometries, which take the anthropometric data, like length of the extremities and circumference the center of rotation and inertia tensors in to account. [5]

The different body segments are connected by joints with 0 degrees of freedom with each other. The force application point of the total weight force of all segments is the lumbar vertebrae L1. On the top surface of this vertebra, the weight force of all body segments is directed.

### 3 Results

For simulation and load calculation of the effects of different weight classes, the masses of the body segments are adapted to these weight classes. Therefore the first lumbar vertebra L1 is loaded with the weight of the upper body segments of a normal weight, an obese and an adipose child in different simulations. The total mass fractions of the segment parts is $m_{\text{normal}} = 22.91 \, \text{kg}$ for normal weight child, $m_{\text{overweight}} = 27.73 \, \text{kg}$ for overweight child and $m_{\text{obese}} = 32.56 \, \text{kg}$ for obese child. In following, the effects of the three weight forces on the intervertebral discs, the facet joints and ligaments are investigated. In all models the weight forces causes small movements in the spinal structures and they get unbalance, until a new state of equilibrium is reached. The following results refer to this new state of equilibrium and do not represent the time course of kinematic and kinetic values.

#### 3.1 Effects of different weight classes on intervertebral discs

The in vertical direction on top of the surface of the vertebra L1 acting force of gravity leads to a deformation of the intervertebral discs. In all three cases, the load deformation increases. The largest deformation is reached in the intervertebral discs of the lowest functional unit L5-Sac. Comparing the deformations of the three load cases, it can be seen that the deformations is 1.5-fold higher in overweight and twice as large in obesity. (see Fig. 5)

![Image of intervertebral disc deformation](image)

**Fig. 5** Comparison of deformation of the intervertebral discs

During the process of deformation the intervertebral discs produce reaction forces. In general, the intervertebral discs develop an even greater reaction force, the more they are deformed.
The loading of the intervertebral discs of an overweight child are, compared with a normal-weight child, about 1.5 times higher. The load on an obese child is twice as high in the same functional units. (see Fig. 6)

The intervertebral rotation describes the rotational movement about the body width axis. A forward movement of the upper body is called flexion and a backward movement extension. In these simulations, only flexion movements are caused, which will be shown by positive values. (see Fig. 7) For all vertebrae, a nearly identical percentage increase in intervertebral rotation is observed. The intervertebral rotations of an obese child are twice as high as a normal-weight child and of an obese children about three times higher than a normal weight child.

### 3.2 Load situation of ligamentous structures

To investigate the effects of the ligaments, the acting forces of all posterior ligaments were added and comparatively shown the effects of the three weight classes of the different functional units. It is obvious that the ligament force of normal weight to overweight is doubled and tripled compared to the obesity. (Fig. 8)

The results in Fig. 8 can be explained in connection with the intersegmental rotation. Through the forward rotation of the vertebral bodies, the posterior ligaments are strongly stretched. With respect to the double large flexion in overweight or triplicate large flexion in obesity, the posterior ligaments in overweight are stretched twice more and in obesity triple. The stretching of the ligaments has the consequence that they develop a correspondingly large counterforce. The higher the stretching of the ligaments, the higher their forces. The ligaments are most loaded of all functional units in case "obesity". (see Tab. 1)

### 3.3 Loading of facet joints

The increased weight acting on the body, which is caused by overweight or obesity, affects a correspondingly higher weight force on the whole lumbar spine. The previously considered higher loading conditions of the structures by an increased weight are also observed in the facet joints. Is difference from normal weight to overweight and obesity in L1-L2 and L3-L4 also increased by the double and triple, the values approximated at the functional spine units L4-L5 and L5-Sac.

It is striking out, that at level L2-L3 no force arises in the facet joints, neither in the model with normal weight, even in models with overweight or obesity. One possible explanation for this could be the strong flexion of the upper body. Through the "forward bending", the contact surfaces of the corresponding joint surfaces do not touch, so that no contact forces occur in the facet joints of L2-L3. (see Fig. 9)
While there are a number of studies concerning the relationship between bone mineral density and obesity of children [6][7][8][9], no study that contains a biomechanical model of the child's lumbar spine to determine the effect of overweight or obesity on the internal structures is known. Therefore the established method of validation by comparing the calculated kinematic values with other modeling data and in vivo studies from literature is not possible. Because the general accuracy of the modeling ought to be checked and there are a variety of studies [10], [11], [12], [13], that deal with the effects of upright standing on “adult” lumbar structures, a model of the lumbar spine was created that takes the anthropometric data of adults into account. In all the studies the research focus was to investigate the effects of the upright stand at the lumbar structures. The results of these studies were compared and are shown in Figure 10.

![Fig. 9 Contact forces in the facet joints](image)

**Fig. 9** Contact forces in the facet joints

The pressure in the discs of the different functional spine units is shown. It is seen that results of the disc pressure of the MBS-model is in the range of the results of the FE-Model and in vivo experiments. For more validation details see [2]. Furthermore, the finding of further verification mechanisms for validation of this modeling is sought.

### 4 Conclusion

Computer modeling is an appropriate method for calculating the distribution of load in the internal structures during different load situations. With the simulation it is possible to determine the impact of obesity on spinal structures. It is clearly seen that the weight gain has strong effects on all spinal structures and this can lead to long-term damage. In order to make patient-specific statements, in a future project a routine will be developed that makes an automatic segmentation of individual vertebrae from CT data and automatic determination of the mass distribution on the basis of MRI data possible. These data are included in the MBS models to provide the modeling to a higher level.

### 5 References


Using CFD for a Sensitivity Analysis of Stent Design Parameters

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Abstract

The implantation of a stent is one option of treatment for cardiovascular diseases, which are the most common causes of death in the western industrial countries. The stent provides a mechanical force to the vessel wall, thereby restoring the required blood flow. It is commonly known that the stent alters the blood flow and therefore the wall shear stress distribution. It is also well established, that the occurrence of regions with low wall shear stress correlates with the prevalence of atherosclerosis. Thus, the hemodynamic influence of the stent should be regarded in the design process.

In this paper we present a sensitivity analysis of different design parameters of a coronary stent model. CFD simulations were used to investigate the influence of the crown number, the strut thickness, the strut width, the strut length, the crown radius and the strut distance over a wide range. We are able to show that the strut thickness is the most important design parameter. Furthermore, the parameters describing the strut pattern can be reduced to one which indicates the angle of incident flow on the strut.

Keywords: non-Newtonian, CFD, sensitivity analysis

1 Introduction

The stent struts extending into the vessel lumen cause unphysiological flow situations such as recirculation and stagnation zones. As a result, the wall shear stress (WSS) in these regions significantly decreases. It is well known that the alteration of the WSS distribution and especially low WSS values (< 0.5 Pa) increase the risk of in-stent restenosis and thrombosis [1, 2]. One option of treatment is the implantation of a drug eluting stent (DES). These stents are coated with an anti-inflammatory drug which suppresses the proliferation of smooth muscle cells [3]. However, the healing of the endothelial cell and therefore the engraftment of the strut is also delayed by the drug resulting in a higher late thrombosis risk [4]. The clinical results concerning the improvement of DES towards bare-metal stents are inconsistent [5, 6].

To avoid post-operative complications such as thrombosis and in-stent restenosis, the hemodynamic performance of the stent has to be taken into account. This leads to a need for fluid mechanical investigations to analyse the influence of the stent design on the blood flow. Several clinical studies, as well as experimental and numerical investigations have been performed to analyse the effects of the stent design on the blood flow in stented coronary vessels. Garasic et al. found that stents with a crown number of six show less post-operative complications than stents with only four crowns. They proposed that an increasing strut number provides a more circular vascular lumen, resulting in proper physiological blood flow [7]. The strut thickness seems to be one of the most significant design parameters [8]. Nevertheless, comprehensive parameter studies of different stent models which consider the non-Newtonian behaviour of blood are hardly available. Hsiao et al. varied the strut thickness, the strut width and the crown radius over a range of 30 % compared to a basic stent model and analysed the stent performance according to the critical WSS value of 0.5 Pa. They announced that the strut thickness is the most sensitive design parameter [9]. Stiehm et al. conducts a sensitivity analysis for a mirrored pattern stent. In addition to [9], a combination of parameter variations was investigated. The influence of the strut thickness was confirmed [10]. In the present study six independent design parameters of a coronary stent with struts aligned in a row are varied and compared to a basic stent model. According to [11, 12], the vessel wall surface with a WSS value below 0.5 Pa is used for the comparison.

2 Methods

The open source software package OpenFOAM was used for the numerical flow simulations. To obtain
physiologically correct WSS values the Car reau-Yasuda rheology model was implemented.

\[ V = V_n + \left( V_0 - V_n \right) \left( 1 + \left( \frac{\lambda}{\nu} \right)^{\alpha} \right)^{-1/a} \]

This model is needed to consider the non-Newtonian flow behaviour of blood. As mentioned in [13], the rheological properties play an important role, especially in regions with a low shear rate, such as up and down stream of the stent strut. The model parameters used here (\( v_0 = 1.6 \cdot 10^{-6} \text{m}^2/\text{s} \), \( v_n = 1.8 \cdot 10^{-6} \text{m}^2/\text{s} \), \( \lambda = 0.606 \text{s} \), \( a = 0.874 \) and \( n = 0.486 \)) are adopted from [14]. The inlet condition was defined by a fully developed steady state velocity profile with a representative Reynolds number of \( \text{Re} = 160 \). Previous simulations [15] showed that flow under steady state conditions approximate the results of pulsatile simulation. Therefore, for the first step in the design process, this assumption is valid and also serves to save calculation time. The velocity on the vessel wall and on the struts is defined by the no-slip condition and a zero-gradient condition is used for the outlet.

The computational domain consists of a rigid, cylindrical tube with a diameter of 3.5 mm, which approximates the coronary vessel, and the generic stent model. The stent is composed of six meander formed strut rings, which are arranged in the fashion of a row pattern. Thus, the distance between the strut rings is constant along the perimeter. Fig. 1 illustrates the strut pattern as well as the varied design parameters in detail.

### Table 1: Variety and range of the investigated design parameters

<table>
<thead>
<tr>
<th>Design parameter</th>
<th>Range/parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>strut thickness [( \mu )m]</td>
<td>60, 100*, 140, 180</td>
</tr>
<tr>
<td>strut width [( \mu )m]</td>
<td>60, 100*, 140, 180</td>
</tr>
<tr>
<td>strut distance [( \mu )m]</td>
<td>300*, 600, 900</td>
</tr>
<tr>
<td>strut length [( \mu )m]</td>
<td>500, 1000*, 1500</td>
</tr>
<tr>
<td>crown radius [( \mu )m]</td>
<td>130*,180,230,280</td>
</tr>
<tr>
<td>crown number</td>
<td>3, 4, 5, 6*, 7, 8</td>
</tr>
<tr>
<td>crown + length [( \mu )m]</td>
<td>8 + 500</td>
</tr>
</tbody>
</table>

*basic stent model

### 3 Results

Fig. 2 illustrates the dependence of the size of the normalised risk surface on each design parameter. The sensitivity corresponds to the gradient of the individual graphs.

It can be clearly seen, that a variation of the strut width and distance has nearly no effect on the size of the risk surface. The sensitivity is about -0.1 and 0.01 for the strut width and distance, respectively. The sensitivity of the strut length reaches high negative values of -2.26 for small strut lengths and decreases to -0.38 for longer struts. Therefore, a small strut length should be avoided in this configuration. The crown radius and the strut thickness exhibit an oppositional behavior. Here, small values are preferable. The sensitivity is about 0.1 and 1.05 for the crown radius and strut thickness, respectively. The crown number shows a parabolic behaviour with an optimum for a crown number of five. Additionally, the crown angle (see...
Fig. 1) of the different strut lengths, strut distances, crown numbers and crown radii were calculated and used as a characteristic design parameter. Afterwards, the resulting risk surfaces of the vessel wall were analysed with respect to the strut angle for each strut thickness. The data was fitted to a quadratic equation of the form $f(x) = ax^2 + bx + c$ by using the least square method, see Fig 3.

![Fig. 3: Dependence of the surface risk on the strut angle and strut thickness](image)

It can be seen that the quadratic equation fits the results very well. The lowest restenosis risk is reached for a strut angle between $67^\circ$ and $75^\circ$ for a strut thickness of $60 \, \mu m$ and $180 \, \mu m$, respectively. It seems that the design parameters influencing the blood flow can be reduced to two parameters only: One being the strut angle, which describes the stent pattern, and the other being the strut thickness, which describes the strut cross section.

4 Conclusion

In this study, a number of numerical flow simulations were performed to evaluate the influence of six design parameters of coronary stents on the blood flow. These parameters can be categorised into two groups. On the one hand, there are the parameters defining the strut cross section, namely the strut width and the strut thickness. On the other hand, those describing the strut pattern such as the crown number, the crown radius, the strut length and the strut distance. From the first group the strut thickness displays the highest sensitivity. From a fluid mechanical point of view, the strut width can be neglected over a wide range. These results could have a major impact on the stent design process due to the requirements of the structural mechanical dimensioning, because the strut width mainly determines the radial stiffness [9].

The spectrum of the design parameters which defines the strut pattern can be reduced to the strut angle alone. Hence, it is irrelevant if the angle is adjusted either by the crown number, the crown radius, the strut length or the strut distance. The ideal strut angle is between $67^\circ$ and $75^\circ$ depending on the strut thickness.

It should be noted that the hemodynamic performance of a stent is just one aspect for an improved stent design. Other fields of research such as structural mechanics and clinical studies must also be taken into account. For instance [6] found that an increasing crown number leads to better clinical results.

Further investigations should consider the pulsatile inflow condition to confirm the results obtained here from steady state simulations. Additionally rounded cross sectional strut areas could lead to even better hemodynamically improved stent designs [16] and should therefore be considered in future work. Furthermore, the results revealed here should be applied to other strut patterns to implement a set of general fluid mechanical design rules for stents.

Acknowledgement

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5 References


Towards the CFD-based simulation of rigid body movement and shear stress of human cells in fluid flow

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Abstract

To support the development of a new WAL device for autologous adipose tissue transplantation, CFD simulations of the fat cell movement are to perform. The fan-shaped water jet that loosens the human fat cells for the aspiration and the aspiration itself are to simulate using Computational Fluid Dynamics (CFD). The individual movement of the adipocytes is simulated using the ANSYS FLUENT Six-Degree-of-Freedom (6DOF) model. To investigate the capabilities of the 6DOF model, two rigid body ellipsoids moving in the shear flow of a channel are simulated.

1 Introduction

Autologous adipose tissue transplantation opens new possibilities for tissue regeneration. In reconstructive plastic surgery adipose tissue is used for breast reconstruction after a mastectomy, correction of soft tissue defects, treatment of burn and radiation scars and treatment of chronic non-healing wounds and ulcers. Also adipose tissue is used to extract adipose-derived stem cells for regenerative medicine. Furthermore, adipose tissue is more and more used in dermatology as natural filler for face and hands.

Using water-assisted liposuction (WAL), adipose cells can be separated from subcutaneous fat tissue more gently than using traditional methods [1]. Therefore a jet of water (saline with adrenalin and lidocaine) is injected into the body through a cannula with a special nozzle. The fan-shaped jet loosens the adipocytes from the fat tissue in the body so they can be aspirated via the cannula openings without getting destroyed (see Fig. 1). The aspirate consisting of fat cells, stem cells and water is extracted from the body via vacuum pump.

Fig. 1 WAL-dissector with illustration of basic principle of water-assisted liposuction [2]

Water-assisted liposuction and lipotransfer is mainly used for reconstructive surgery. For autologous adipose tissue transplantation it is important that as many fat and stem cells as possible are vital after the aspiration.

To develop a new device for autologous adipose tissue transplantation using the WAL method, CFD simulations of WAL injection and aspiration are to perform. Therefore the shear stress during aspiration is to investigate and the individual movement of the adipose cells during injection and aspiration is to simulate.

2 Methods

2.1 Investigation of Shear stress

We assume that the vitality of human cells that are moving within a fluid is dependent on the shear stress occurring in the flow. The shear rate

$$\gamma = \frac{du}{dy}$$

is defined as the gradient of flow velocity u of the mean flow perpendicular to the direction of the mean flow x. Big changes of velocity u over direction y therefore lead to high shear rates γ (see Fig. 2).

Fig. 2 Human cell in shear flow

The shear stress can be investigated simulating single phase flow. The governing equations for mass

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho u) = 0$$

and momentum

$$\frac{\partial (\rho u)}{\partial t} + \nabla \cdot (\rho u u) = -\nabla p + \rho g + \nabla \cdot \tau,$$

the Navier-Stokes equations, have to be solved numerically for every grid cell of a computational grid to gain the scalar field for pressure p and the vector field for velocity u. The derivation of u leads directly to the shear rate γ.
these investigations the CFD solver ANSYS FLUENT 14 is used.

As soon as the geometry is not completely filled with cell suspension and air is also present, a multiphase model is required. The Volume-of-Fluid (VOF) multiphase model can describe two or more phases that do not interpenetrate but form an interface - the so called free surface. This free surface between liquid and gaseous phase has to be tracked by calculating the continuity equation

$$\frac{1}{\rho_q} \frac{\partial}{\partial t} (\alpha_q \rho_q v) + \nabla \cdot (\alpha_q \rho_q v v) = S_{\alpha_q} + \sum_{p=1}^{n} (m_{pq} - m_{up})$$

for the volume fraction of one or more phases [3]. Because the phases do not interpenetrate, they all share one velocity field. This velocity field is gained from solving the momentum equation

$$\frac{\partial}{\partial t} (\rho \vec{v}) + \nabla \cdot (\rho \vec{v} \vec{v}) = -\nabla p + \nabla \cdot \left[ \mu (\nabla \vec{v} + \nabla \vec{v}^T) \right] + \rho \vec{g} + \vec{F}$$

for every grid cell [3].

### 2.2 Rigid body simulation of the cell movement using the FLUENT Six-Degree-of-Freedom model

Previous investigations of the cell movement in a cell-mixing device [4] have been performed using the FLUENT Discrete Phase Model (DPM) with its Euler-Lagrange approach. The DPM tracks the trajectories of particles individually using the force balance

$$\vec{F}_{\text{drag}} + \vec{F}_{\text{pressure}} + \vec{F}_{\text{gravity}} + \vec{F}_{\text{other}} = m_p \frac{d\vec{u}_p}{dt}$$

at the particle [3]. The DPM particles have a volume and a mass for the force balance, but do not displace the surrounding fluid. In contrast to the FLUENT Discrete Phase Model with its particles, the FLUENT Six-Degree-of-Freedom (6DOF) model uses the method of dynamic meshing to simulate the movement of bodies with arbitrary shape. The fat and stem cells are then represented by domain walls that are set as rigid bodies. Since the rigid bodies are represented by walls and do not belong to the fluid domain, they displace the surrounding fluid. The movement of the rigid bodies is calculated by the FLUENT Six-Degree-of-Freedom model based on the forces and moments of the surrounding fluid. The translational motion

$$\ddot{\vec{u}} = \frac{1}{m} \sum \vec{f}_d$$

of the rigid body in the center of gravity is calculated with the fluid forces \( \vec{f}_d \) acting on the rigid body with mass \( m \) [3]. The angular motion

$$\ddot{\omega}_B = L^{-1} \left( \sum \vec{M}_B - \vec{\omega}_B \times \vec{L} \vec{\omega}_B \right)$$

doesthe rigid body is computed based on the inertia tensor \( L \), the moment vector \( \vec{M}_B \) and the angular velocity vector \( \omega_B \) of the rigid body [3].

The rigid body mass and the moments of inertia of the rigid body are set manually in a UDF by using the function DEFINE_SDOF_PROPERTIES [5].

Since the rigid bodies move through the fluid domain, the grid has to be remeshed to conserve the mesh quality and therefore ensure a proper calculation of the conservation equations for mass and momentum. This can be executed after every single time step.

While the FLUENT DPM is designed to work with a large number of particles due to the simplicity of the model, the 6DOF model has been developed for rigid bodies with arbitrary shape. The initial mesh for the simulation has to be set up by hand using e.g. ANSYS DesignModeler and ANSYS Meshing. Since every rigid body has to be set up manually, the FLUENT 6DOF model is not intended to simulate large numbers of bodies.

In CFD investigations of Choi and Kim [6-8] the individual movement of red blood cells (RBC) has been simulated using an FSI method based on the Arbitrary-Lagrangian-Eulerian (ALE) approach. The individual movement of a single RBC, which is represented by a body with biconcave shape, is compared to the individual movement of a disk, a sphere and an ellipsoid. The simulations performed in [6-8] show the principal ability of rigid body models for the simulation of movement of human cells in a fluid. In this investigation the ellipsoidal shape is taken to also prove the ability of the FLUENT Six-Degree-of-Freedom model to be used in simulations of the movement of human cells in a fluid.

### 3 Results

#### 3.1 Simulation of the movement of two rigid body ellipsoids moving within the shear flow of a channel

To investigate rigid body movement using the FLUENT Six-Degree-Of-Freedom model, a test simulation of two ellipsoids moving within the shear flow of a channel has been performed (see Fig. 3). These two ellipsoids with a major axis of 9.74mm and a minor axis of 2.43mm are much bigger than the actual human cells to simplify the observation of rigid body movement and remeshing. The velocity at the inlet is defined as 1m/s while atmospheric pressure is set at the outlet. In this CFD simulation the Reynolds-averaged Navier-Stokes equations (RANS) are solved using the k-\( \omega \) SST turbulence model.
Since both ellipsoids are actually walls, the no-slip condition applies. To account for the large gradients of velocity near these walls, the mesh at the ellipsoids has to be refined (see Fig. 4). To preserve the static mesh refinement, a cell zone that surrounds the ellipsoid and contains the mesh refinement of prism layers has been created for each of the ellipsoids. These two cell zones have to be set as passive rigid bodies so that they do not move on their own and follow the actual rigid body ellipsoids.

The grid cells of the outer mesh grow with increasing distance from the ellipsoid to keep the number of grid cells relatively low. The entire mesh consists of 7.2 million tetraeders and prism grid cells. For each of them the governing equations are solved.

The ellipsoids translate and rotate independently from each other through the channel - with respect to the forces and moments due to the surrounding fluid (see Fig. 5).

To account for cell-cell or cell-wall interactions and prevent the simulation from stopping due to the mesh deformation when an ellipsoid approaches another ellipsoid or a domain wall, a contact detection is included into the simulation. As soon as the distance between two ellipsoids or an ellipsoid and a wall falls below a pre-defined threshold of 5mm, a User-Defined Function (UDF) will be executed. This UDF reflects the ellipsoid over the wall by calculating a new direction and a new velocity based on arriving angle and velocity of the ellipsoid.

3.2 Simulation of a WAL-dissector spraying water in a rigid body 8x8x8 fat cell package causing individual fat cell movement

The next step is to simulate an actual application like the movement of a package of 512 fat cells that are pushed apart by the fan-shaped jet of a WAL-dissector to leave the subcutaneous fat tissue less traumatized and allow an easier aspiration of the fat cells. FLUENT’s Six-Degree-of-Freedom (6DOF) model is supposed to compute the individual movement of every single fat cell. Each adipocyte has a diameter of 100µm. At the start of the simulation the adipocytes are ordered in a cube-shaped pattern of 8x8x8 fat cells with a distance of 10µm to each other (see Fig. 6). The distance between the fat cells is set to 10µm to prevent the grid cell zones with the grid refinement that surround the fat cells to interpenetrate and deform the mesh. The distance between the cell package and the WAL-dissector is roughly 2mm.

Because the simulation setup with individual movement and contact detection of 512 cells is very complex, at first a simulation of the WAL-dissector spraying water into air without any cells present has been performed (see Fig. 7). The VOF model is used to describe the interface between the liquid spray and air. As seen in Fig. 7, the water is deflected at the baffle of the WAL-dissector to open up to a fan-shaped spray. In subsequent simulations this spray has to push the fat cells apart to leave the subcutaneous fat tissue less traumatized.
The simulation of the WAL-dissector that sprays water in a rigid body 8x8x8 fat cell package to cause individual movement of the fat cells did not finish to date due to problems with mesh deformation.

4 Conclusion

A CFD simulation with rigid body movement of two ellipsoids has been performed showing the capability of the FLUENT Six-Degree-of-Freedom (6DOF) model to simulate the movement of human cells in a fluid. Several sophistications like mesh refinement in a separate cell zone and reflection after collision of the rigid bodies with walls and other rigid bodies via contact detection have been used to perform the simulation.

The simulation of a WAL-dissector spraying water in a rigid body 8x8x8 cell package to move the cells individually and push them apart hasn’t been finished so far. After this simulation has been finished the aspiration of the loosened fat cells is to simulate to investigate the shear rates in the aspirate.

5 References

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Finite element modelling of the distal radioulnar joint

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Abstract

Distal radius fractures cause mechanical instability in the distal radioulnar joint (DRUJ) which can lead to altered biomechanical load transfer from the hand to the forearm. The soft tissue around the joints plays an important factor in the load transfer mechanism through the joint. In the presented study, a finite element model was created of both a healthy wrist and a pathological wrist recovering from a distal radius fracture. From the results it could be seen that the strain of the ligaments surrounding the DRUJ was greater for the pathological model in addition to it being more susceptible to bone fracture.

1 Introduction

The dislocation of the distal radio-ulnar joint is one of the most frequent causes of painful joint limitations. As a result of a fall on the palm of the hand, the twist of forearm creates a disjunction of distal radio-ulnar joint (DRUJ); subsequently the traumatic impulse could be transmitted to the radius leading to fractures. The diagnosis of this injury is often missed, due to unclear clinical signs and occasional difficulties to obtain appropriate images. Depending on the severity of the fracture and surgical procedures to stabilise the fracture, a proximal shift on the radiocarpal joint can be seen due to shortening of the radius bone. The distal radioulnar joint will become incongruent causing loss of motion in pronation and supination of the wrist. That can have detrimental effect on the overall biomechanical response of the wrist and the forearm bones. The DRUJ plays an important role of the wrist function both in terms of kinetic and kinematic aspect of the joint1. During activities of daily living such as gripping, force generated in the fingers is transmitted as joint reaction forces down the phalanges, metacarpals and the carpal bones before reaching the forearm bones. The triangular fibrocartilage complex (TFCC) is a structure located distally to the ulna which transmits some of the load on the ulnar head from the proximal carpal row. In 1984, Palmer and Werner2 measured the load through the radius and the ulna of a cadaveric wrist, reporting that under normal scenario, 60% of the load was transmitted through the radius and 40% through the ulna. After excising the TFCC, they reported that 95% of the load was distributed through the radius and 5% through the ulna, indicating that the distal head of the ulna plays some role in the overall load transfer mechanism. This was further demonstrated by excising the distal ulnar head and reporting that 100% of the load was transmitted through the radius. Distal radius fractures and DRUJ instability can therefore reduce the overall loading on the ulna, thus possibly leading to reduced bone quality which would have a long term detrimental effects on the biomechanical stability of the wrist. Little is known about the biomechanics of the DURJ and how the load is transmitted through the joint. The joint is very dependent on the soft tissue structure around it such as the TFCC and the interosseous ligaments (IOL). Manson et al3 demonstrated the importance of the IOL with regards to forearm rotation and demonstrated that the location of the highest strained portion of the ligament depends on forearm rotation. The presented study looks at the load transfer between the radius and the ulna during gripping in both a healthy subject and a patient recovering from a distal radius fracture. The finite element method was used to calculate the stresses in the bone tissue under loading.

2 Methods

A finite element model was created of the distal radius and the ulna using CT scans obtained from a healthy wrist and a pathologic wrist suffering from traumatic dislocation of the ulna. The in-plane resolution of the scans were 0.5 mm and the slice thickness was 1 mm. The scans were imported into Mimics (Materialise) where the segmentation of the bones was carried out as can be seen in Figure 1. Once the bones were segmented, three dimensional models of the radius and ulna were created and meshed using tetrahedral elements.
Since the soft tissue configuration was not possible to be determined from the CT scans, geometrical model of the TCFF was superimposed onto the bone model by creating a new mask intersecting both the radius and the ulna over the DRU joint. By using Boolean operators, the mask was subtracted from the bones thus creating a cartilage entity that connects both bones and borders perfectly the external surfaces of both the radius and the ulna. Figure 2 shows the geometrical model of the distal ulna, radius and the TFCC for the healthy subject. The 3D model of the TFCC was imported to the pathological model where the misarticulation of the DRU joint could be identified.

The ultimate tensile strength of the bone was assumed to be

\[
\sigma_{UTS} = \begin{cases} 
137 \rho^{1.81} & \rho < 0.317 \\
114 \rho^{1.72} & \rho \geq 0.317 
\end{cases}
\]

according to Keyak et al\(^5\).

The material properties of the TFCC were estimated to be same as for articular cartilage and were modelled using a hyperelastic material model. The ligaments were given linear elastic material properties with an elastic modulus of \(E=515 \text{ MPa}\). Although the ligaments were modelled as linear elastic, they were not allowed to transmit compressive stresses.

Loading conditions were determined from the findings of Gisason et al\(^7\), where the joint reaction forces on the distal aspect of the radius were calculated. The location of both the radioscaphoid joint contact force and the radiolunate joint contact force was determined manually from the finite element model. The force values used for the analysis were given as follows:

<table>
<thead>
<tr>
<th>Joint</th>
<th>Force [N]</th>
<th>Angle in coronal plane [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radioscaphoid</td>
<td>537</td>
<td>15</td>
</tr>
<tr>
<td>Radiolunate</td>
<td>529</td>
<td>7</td>
</tr>
</tbody>
</table>

where the angle in the coronal plane represents the direction of the resultant force in that plane. The proximal ends of the radius and ulna were kept fixed and not allowing any displacement or rotation.

The contact between the ulna and the TFCC was modelled as surface-to-surface contact whereas the TFCC was tied to the radius. The insertion and attachment points of the three ligaments modelled were fully tied to the bone surfaces of the radius and ulna.
3 Results

The two models were solved using Ansys Workbench (v.12.1). Von Mises stress plots were generated and from them it could be seen that the maximum stress in the healthy model was around 81 MPa but 134 MPa in the pathological model. The highest stresses were seen near the proximal part of the radius. Figure 4 shows the stress distribution in the healthy model.

![Figure 4: Stress distribution in the healthy model.](image)

Strain plots were created of the model which showed greater strain on the IOL for the pathological model. Figure 5 shows the strain distribution in the two models.

![Figure 5: Strain distribution in both models.](image)

Looking at the risk of fracture, it could be seen that the pathological wrist was more susceptible to fracture. The risk of fracture was calculated by dividing the calculated von Mises stress in each element with its estimated tensile strength. Should the ratio exceed unity, the element was assumed to have fractured. Figure 6 shows the stress distribution in the two forearm bones as a function of bone mineral density. The red dots in the figure represent fractured elements and the green dots elements which don’t fracture under the given load case. From the figure it can be seen how the lower density elements in both the radius and the ulna are more susceptible to fracture. From the calculations it was found that 2% of the radius elements were found to be at risk of failing, but 1.3% of the ulna elements.

![Figure 6: Risk of fracture in the two forearm bones.](image)

The location of the fractured elements can be seen in Figure 7.

![Figure 7: Location of the fractured elements](image)

From the figure it can be seen that the fractured elements can primarily be seen in the distal radius and ulna.

4 Discussion and conclusions

The results showed that by applying the same loading conditions in a healthy and a pathological model there is a greater risk of fracture in the pathological model. Additionally the models showed greater strain on the soft tissue structures in the pathological model, thus supporting that the overall load transfer of the DRUJ is highly dependent on the soft tissue configuration. The interosseous ligament plays an important role in the biomechanical stabilization of the distal forearm and load transfer mechanism between the wrist and the arm.

Although the findings of the study is in agreement with other published studies on the biomechanics of the forearm, there still are various limitations on the modelling...
aspect. The greatest limitation is the material properties of the ligaments which were modelled as linear elastic which can be a large source of errors. Additionally the geometrical representation of the TFCC was not possible to identify from the CT scans.

The presented paper is one of the first attempts to create a finite element model of the DRUJ incorporating soft tissue and physiologically relevant loading conditions.

5 References


**Influence of chronic atrial fibrillation induced remodeling in a computational electrophysiological model**

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**Abstract**

Atrial fibrillation (AF) is a common arrhythmia with progressive nature. This progression is partly caused by AF itself by modifying — amongst others — the electrophysiological properties of the myocytes. These changes are referred to as electrical remodeling and were integrated in a computational model of human atrial myocytes in this work.

In particular, the maximum conductivities of \( I_{Na} \), \( I_{K1} \), \( I_{Kur} \), \( I_{Ca,L} \), \( I_{Ca,Ca} \), and the \( Ca^{2+} \) leak current from the sarcoplasmic reticulum, as well as the cell capacitance were altered. In an additional setup, the influence of potential gap junction remodeling was investigated.

Wavelength was reduced from 225 mm to 110 mm, respectively 92 mm when considering gap junction remodeling at a basic cycle length of 400 ms. Action potential morphology was changed from spike-and-dome to a more triangular repolarization phase. However, our results show that including \( I_{Kur} \) remodeling prevents the plateau phase from disappearing completely.

1 **Introduction**

Atrial fibrillation (AF) is the most common sustained arrhythmia in industrialized countries. Already today, about 1% of the total population is affected with the number of patients being likely to double within the next 20 to 30 years [1]. AF is associated with severe complications, such as cerebral stroke and increased mortality. Hence, it is a major burden both to patients and healthcare systems.

AF is characterized by chaotic, high frequency excitation of the atria with rates above 300 bpm. A substantial portion of AF episodes is asymptomatic and self-terminating. If the episodes last longer than a few weeks, the term long-standing persistent or chronic AF (cAF) is used [2]. The rapid atrial rate drives various long-term transformations including changes in different ionic currents known as “electrical remodeling”. The result of these changes is a shortening of the effective refractory period (ERP) yielding a reduction of the wavelength (WL). Thus, remodeling promotes functional re-entry and enhances the formation of a substrate for AF (“AF begets AF”) [3]. On the other hand, the adaptation of ionic currents prevents cell death due to intracellular \( Ca^{2+} \) overload and allows to maintain rapid atrial firing with minimal metabolic cost [4].

In this study, cAF induced electrical remodeling was introduced in the Courtemanche et al. model of human atrial myocytes [5]. The complex, non-linear effect of the remodeling on the action potential (AP) and electrophysiological markers, such as action potential duration (APD), ERP, conduction velocity (CV), and WL was investigated to gain insight into the progressive nature of AF.

2 **Methods**

2.1 **Introducing cAF induced remodeling**

We performed a comprehensive literature research on cAF induced changes of the currents that are included in the Courtemanche et al. model. We focused on data measured in human tissue and neglected data obtained in patients with reported comorbidities, such as valvular heart disease. The change of the maximum conductivities is summarized in Table 1. The change of the maximum conductivity of \( I_{Na} \) ranged from \(-84\% \) to \(-44\% \) [6, 7, 8, 9, 10, 11, 12], that of \( I_{K1} \) from \(+0\% \) to \(+137\% \) [6, 8, 10, 13, 14, 15, 16], that of \( I_{Ks} \) from \(+0\% \) to \(+150\% \) [9], that of \( I_{Kur} \) from \(-60\% \) to \(-25\% \) [6, 7, 8, 9, 10, 11, 12], that of \( I_{Ca,L} \) from \(-73\% \) to \(-42\% \) [6, 10, 17, 18, 19, 20, 21], that of \( I_{Na,Ca} \) from \(+60\% \) to \(+85\% \) [17, 20], that of the \( Ca^{2+} \) leak current from the nonjunctional sarcoplasmic reticulum (SR) from \(+50\% \) to \(+280\% \) [17, 22], and that of \( INaK \) [23] and \( I_{Na} \) [6] showed no significant change. No data from humans were available for \( I_{Ks} \). However, measurements in dogs revealed no change in maximum conductivity [24, 25].

The reported increase of cell capacitance ranged from \(+5\% \) to \(+71\% \) [6, 7, 8, 9, 12, 13, 14, 15, 18, 19, 26]. In the model, \( I_{Na} \) was reduced by 65%, \( I_{K1} \) was increased by 100%, \( I_{Ks} \) was increased by 100%, \( I_{Kur} \) was reduced by 50%, \( I_{Ca,L} \) was reduced by 55%, \( I_{Na,Ca} \) was increased by 60%, and the SR leak current was increased by 50%. The cell capacitance was increased by 20%.

Because the data on connexin expression is equivocal as reviewed in [27], the initial conductance \( \sigma = 0.076 S/m \) of the monodomain equation was reduced by 30% for the setup “RemodCV” and left unchanged for the setup “Remod”.

2.2 **Single cell investigations**

The models were paced 50 times with a basic cycle length (BCL) of 1000 ms in a single cell environment. A stimulating current of 1.3 mA was applied for 3 ms. The resting membrane voltage \((V_{m,rest})\), AP amplitude, and APD at 90% and 50% repolarization were analyzed for the last AP.
2.3 Restitution in one-dimensional tissue strand

Excitation propagation was simulated in a homogeneous one-dimensional (1D) tissue strand of size 20 × 0.1 × 0.1 mm³ using the monodomain model. After an initialization phase of 50 beats in the single cell environment, stimuli of 7 nA were applied at the first 3 voxels for 3 ms to elicit a train of 6 APs as described before [28]. Restitution curves for APD₉₀ and its slope, CV, ERP, and WL were obtained by analyzing the 5th and the 6th AP at 25 different BCLs distributed linearly in the frequency domain ranging from 150 to 1300 ms.

2.4 Numerical methods

To solve the ordinary differential equations of the electrophysiological model, the Rush-Larsen scheme was used for the gating variables and a forward Euler scheme for the remaining variables. The time step was set to 10 μs. The monodomain equation was discretized using the finite difference method and solved by acCELLerate [29]. The side-length of the cubic voxels was 0.1 mm. The monodomain conductivity σ was set to an isotropic value of 0.076 S/m to obtain a CV of 750 mm/s at a BCL of 1000 ms in the control model and reduced by 30% to a value of 0.0532 S/m for the “RemodCV” setup.

3 Results

3.1 Single-cell simulations

Fig. 1 shows the APs elicited by a short stimulus for the proposed remodeling setup (“Remod”) in comparison with physiologic conditions (“Control”) and an older setup not considering more recent experimental data (“cAF2010” [30]). Compared to “Control”, Vₘ,rest was hyperpolarized by 3.2 mV for “Remod” as compared to 3.7 mV for “cAF2010”. AP amplitudes were increased by 1.5 mV and 2.4 mV, respectively. APD₉₀ was reduced by 55% for “Remod” as compared to 69% for “cAF2010”. Values for APD₇₀ were 66% and 64%, respectively. The “Remod” setup showed a less pronounced triangulation of the AP compared to “cAF2010”. However, the initial notch was missing and the plateau phase was significantly shorter compared to the spike-and-dome shape of the “Control” setup.

On the single-cell level, “RemodCV” did not show any differences compared to “Remod” because the conductivity is not considered on this level.

3.2 Tissue restitution properties

On the tissue level, the 3 remodeling setups were compared to the physiological setup for BCLs between 180 and 1300 ms. For “Remod”, the ERP was shortened compared to “Control” by between 142 ms (BCL = 341 ms) and 160 ms (BCL = 504 ms) for “Remod” and by between 80.5 mm/s (BCL = 313 ms) and 164.5 mm/s (BCL = 504 ms) for “cAF2010”. The CV difference between “Remod” and “RemodCV” was smaller than 2 ms for all BCLs (compare Fig. 2C). The APD₉₀ curves showed a qualitatively similar course as the ERP curves (compare Fig. 2A). APD slope with respect to the diastolic interval (DI = BCL - APD₉₀) did not show significant differences for the 3 remodeling setups. However, the slope was reduced by up to 0.2 for BCLs lower than 700 ms compared to “Control”. “cAF2010” showed marked oscillations for low BCLs (compare Fig. 2B).

CV was slowed by between 43.9 mm/s (BCL = 504 ms) and 80.5 mm/s (BCL = 313 ms) for “Remod” and by between 46.9 mm/s (BCL = 313 ms) and 164.5 mm/s (BCL = 504 ms) for “cAF2010”, respectively. The CV difference between “cAF2010” and “RemodCV” was smaller than 8 mm/s for
Future work may extend the analysis to two or three dimensions also including regional heterogeneity of remodeling.
5 References


Specific antiarrhythmic therapy for familial atrial fibrillation in a numerical model of human atrial electrophysiology

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Abstract

Atrial fibrillation (AF) is still a major health problem in the western society. Especially for familial AF, the pharmacological therapy is still not sufficiently successful. In this work, channel blocker properties were in-silico adapted to optimize drug therapy for patients suffering from familial AF. The Courtemanche-Ramirez-Nattel (CRN) cell model was the basis for the simulations. Adaptations in the model due to familial AF were implemented using an existing description of the L532P mutation. A fitting algorithm was designed which adapted all conductivities of the ion channels described in the CRN model to restore the healthy action potential (AP). To find the minimal deviation of the healthy AP and the AP of the L532P mutation, the trust-region-reflective algorithm was used. The best matched APs were achieved by a significant blockade of the I\textsubscript{Kr} and the I\textsubscript{Kur} current. 1D tissue strand simulations were performed using different basic cycle lengths (BCL) to evaluate the results of the optimization. It was shown that for the found adaptation of the conductivities, the AP duration, and the progressions of the conduction velocity, effective refractory period, and wavelength (WL) could be restored. The WL was increased by 53.37% compared to the mutation and had a value of 233.48 mm (BCL = 1 s).

1 Introduction

Cardiovascular diseases and especially atrial fibrillation (AF) are still a major health problem in the western society. Despite the medical progress in this area, pharmacological therapy is still not sufficiently successful. Some drugs showed even deleterious effects [1]. It has been observed that mutations of specific genes, encoding cardiac ion channels, render patients vulnerable to AF. This context is known as “familial AF” [2]. In this work, the idea is to restore the action potential (AP) to the non-mutated cell with a designed drug. Though AF is one of the most common cardiac diseases, the possible molecular reasons are hardly identified. In this work, the L532P mutation of the hERG channel (as an example of familial AF) is closer investigated. L532P causes changes in the I\textsubscript{Kr} \(-\alpha\)-subunit, the so called hERG channel. Residue L532 is located within the S4 domain of the hERG channel in the area of the voltage sensor segment. The mutation is peculiarly associated with AF due to changes in the repolarisation phase being reflected in shorter AP duration (APD) and shorter reentrant wavelength (WL) [3].

2 Methods

2.1 Modelling the L532P mutation

In a previous study [3], the mutations were generated in hERG cRNA. Wild-type (WT) as well as mutated cRNA were transferred into Xenopus oocytes, in which voltage clamp measurements were conducted three to four days after the injection. The effects of the L532P mutation and its changes on cellular electrophysiology were incorporated in the cell model by adjusting several model parameters of I\textsubscript{Kr} [4]. For this purpose, a combination of a particle swarm optimization (PSO) and trust-region-reflective (TRR) algorithm was used to tackle the optimization problem, which was formulated to fit the model to the measured current data. The mutation was modeled heterogeneously. Therefore, an additional I\textsubscript{Kr} current with unaltered parameters compared to the Courtemanche-Ramirez-Nattel (CRN) model was included in the altered model. Both formulations of I\textsubscript{Kr} were weighted by 50%. A more detailed description of modeling the L532P mutation is given in [4].

2.2 Tuning pharmacological effects

The aim of this work was to find a certain adaptation of the ion channel conductivities in the mutated cell which leads to a restored healthy electrophysiology. For the adaptation, a vector \( \vec{g} \) was created with the same size as the number of the different ion channels in the CRN model [5]. The vector elements are restricted to values between 0 and 1, depending on the level of block ranging from 0 (completely blocked) to 1 (completely uninfluenced). With this definition, the assumption was made that a drug cannot enhance channel conductivities:

\[
\vec{g} = \begin{pmatrix} \tilde{g}_{Na} \\ \tilde{g}_{K1} \\ \tilde{g}_{lo} \\ \tilde{g}_{Kr} \\ \tilde{g}_{Ks} \\ \tilde{g}_{CaL} \\ \tilde{g}_{bCa} \\ \tilde{g}_{bNa} \end{pmatrix}, \text{with } \tilde{g}_i \in [0, 1] \tag{1}
\]

In the CRN model, an ion current I\textsubscript{i} is expressed by the conductivity of the respective channel \( g_i \), the transmembrane voltage \( V_m \) and the equilibrium potential \( E_i \) of the ion [5]:
\[ I_x = g_x \cdot (V_{m} - E_x). \]  
(2)

With the matching vector element of \( \tilde{g} \), the ion current was adapted by the drug:

\[ I_{x, adapted} = g_x \cdot \tilde{g}_x \cdot (V_{m} - E_x) \]  
(3)

### 2.2.1 AP simulation

The original CRN model (control) as well as the adaptation to the L532P mutation were implemented in MATLAB (R2013b, The MathWorks, Natick, MA, USA). Since the beat-to-beat transient response of the model should not influence the results of the algorithm, the original model was simulated for a time span of 5 s and the adapted model for a time span of 15 s (BCL = 500 ms).

The differential equations of the CRN model were solved using variable time steps for each stimulation. To consider the initial conditions of the differential equations, the results of the previous simulation were taken as initial conditions.

### 2.2.2 Calculating the discrepancy function

The idea was to implement an algorithm that evaluates the present AP curve (\( V_m \) values over time). The difference between healthy AP and mutated-plus-drug-AP was defined as the quality measure of a particular adaptation.

The adapted AP curve was compared to the control curve for the last 500 ms of the simulation. Both AP curves were sampled equidistantly (500 points) and compared in a nearest neighbor manner (compare Fig. 1). The sum of squares of the differences was taken as the discrepancy function:

\[ \Delta AP(\tilde{g}) := \sum_{i=1}^{500} f(x_i, \tilde{g})^2 \]  
(4)

\[ f(x_i, \tilde{g}) := [V_{m, normal}(x_i) - V_{m, adapted}(x_i, \tilde{g})] \]  
(5)

Figure 1 The discrepancy function evaluates the AP shapes and is defined as:

\[ f(x_i, \tilde{g}) := [V_{m, normal}(x_i) - V_{m, adapted}(x_i, \tilde{g})]. \]

The aim of the optimization was to find the vector \( \tilde{g}_{min} \) that results in a minimum of the discrepancy function:

\[ \tilde{g}_{min} = \text{argmin}_g \| \Delta AP(\tilde{g}) \| = \text{argmin}_g \left( \sum_{i=1}^{500} f(x_i, \tilde{g})^2 \right) \]  
(6)

To find the vector \( \tilde{g}_{min} \), 22 minimizations were performed using uniformly distributed random initial guesses of \( \tilde{g} \). The minimum was derived using the TRR algorithm, which uses a quadratic approximation of the function \( f(x) \) in the optimization [6]. For the optimization, the gradient \( g(x) := \nabla f(x) \) and the Hessian matrix \( H(x) := \nabla^2 f(x) \) are considered. In this work, the TRR algorithm provided by MATLAB (lsqnonlin) was used for the optimization. The algorithm calculates the Hessian matrix and the gradient numerically.

### 2.3 1D tissue simulation

To further evaluate the results of the minimization gained on the single cell level, tissue simulations were performed. For the simulation, a tissue strand consisting of 200 voxels was used. The voxels were arranged in a row and had a resolution of 0.1 mm. For the measurement of the arriving APs, effective refractory period (ERP), conduction velocity (CV), and WL, two \( V_m \) sensors were used as described before in [7]. Since the markers are rate dependent, the simulations were performed at thirty different basic cycle lengths (BCL) from 300 ms to 1300 ms distributed linearly in the frequency domain.

Furthermore, the APs were investigated. The shapes of the last three in a train of five APs were classified into five different categories: Category I included all “normal” AP shapes (\( V_{m, max} \geq -40 \text{ mV} \) and upstroke velocity \( \geq 10 \text{ V/s} \)). If the amplitude of the arriving APs decreased, they were classified in category II. Category III included APs with a 2-to-1 block. This means that the second AP could not be initiated since the tissue was still refractory from the first arriving AP. Category IV included all APs, which were not classified as physiological (\( V_{m, max} \leq -40 \text{ mV} \) or upstroke velocity \( \leq 10 \text{ V/s} \)). Finally, category V included all other AP shapes.

### 3 Results

#### 3.1 Restoration of AP

TRR minimization yielded varying results for \( \tilde{g}_{min} \). The minimization often ended in very high squared errors (> 10000 mV²). For all 22 minimizations, the algorithm stopped because the minimal step size of the algorithm was reached. Since the TRR algorithm is known to be susceptible to local minima, the minimization problem of the drug tuning might be a non convex one.

Nevertheless, the results showed that six vectors \( \tilde{g}_{min} \) could achieve a small squared error (≤ 90 mV²). Regarding the resulting vectors with the lowest squared error, a significant blockade of the \( I_{Kr} \) and the \( I_{Kur} \) channel led to the best results. Furthermore, the \( I_{Kr} \), \( I_{CaL} \), and the \( I_{BCa} \) channel were...
also blocked in a range of 15% to 35%. The resulting blockage rates of $g_{\text{min}}$ is shown in Table 1. An overview of the results of the optimization is shown in Table 2.

Table 1 Resulting blockages for the computed vector $g_{\text{min}}$ which achieved the lowest squared error.

<table>
<thead>
<tr>
<th>Ion current</th>
<th>Blockage [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>0.20</td>
</tr>
<tr>
<td>K1</td>
<td>6.61</td>
</tr>
<tr>
<td>to</td>
<td>0.28</td>
</tr>
<tr>
<td>Kr</td>
<td>70.00</td>
</tr>
<tr>
<td>Ks</td>
<td>33.84</td>
</tr>
<tr>
<td>CaL</td>
<td>14.80</td>
</tr>
<tr>
<td>bCa</td>
<td>27.06</td>
</tr>
<tr>
<td>bNa</td>
<td>0.00</td>
</tr>
<tr>
<td>Kur</td>
<td>93.70</td>
</tr>
</tbody>
</table>

Table 2 Overview of the results of the TRR optimization. The result with the lowest, the highest and the average squared error is given. For each result, the error itself, the average difference per time step, and the maximal AP difference is shown.

<table>
<thead>
<tr>
<th></th>
<th>Best</th>
<th>Worst</th>
<th>$\phi$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norm [mV²]</td>
<td>66</td>
<td>23410</td>
<td>5259</td>
</tr>
<tr>
<td>Average difference [mV]</td>
<td>0.29</td>
<td>5.73</td>
<td>1.80</td>
</tr>
<tr>
<td>Highest difference [mV]</td>
<td>2.65</td>
<td>23.26</td>
<td>21.25</td>
</tr>
</tbody>
</table>

With $g_{\text{min}}$, the AP of the healthy cell could be restored (see Fig. 2). The squared error was 66.04 mV². Furthermore, the average difference per time step was 0.29 mV and the highest occurring difference was 2.65 mV.

Figure 3 Resulting APs of the optimization (red), the mutation (green) and the normal cell (blue) in the 1D strand (BCL = 1 s).

The AP curve of the tuned model was not restored to the AP curve of the normal cell. The plateau phase of the AP was significantly increased compared to the mutated cell but also compared to the normal cell. In the classification of the arriving AP shapes, only three different categories of APs could be observed. At BCLs $< 326$ ms, 2-to-1 block occurred (category III). At $326$ ms $\leq$ BCL $\leq 574$ ms, alternations (category V) within the APs could be observed. At longer BCLs, only normal APs (category I) were observed.

3.2 Resulting restitution properties

In Fig. 3 the resulting AP of $g_{\text{min}}$ in a tissue strand can be seen. The depicted AP curves were measured at a BCL of 1 s and only the last of five arriving APs was evaluated.

Figure 4 ERP restitution courses for the result of the tuning (red), the mutation L532P (green) and the normal cell (blue).

The average WL was increased by 53.37% compared to the mutation and had a value of 233.48 mm. The average WL of the normal cell was 227.19 mm, which was 2.77% less than the average WL of the tuned model.
In addition, the action potential duration (APD$_{90}$) could be also restored to that of the normal cell for a BCL of 1 s. For the L532P mutation, an average APD$_{90}$ (over BCL) of 197.9 ms was measured. The tuning increased the APD$_{90}$ by 34.12%, which led to a value of 265.4 ms. For the normal cell, an average APD$_{90}$ of 299 ms was measured. At a BCL of 1 s, the APD$_{90}$ of the tuning was 327 ms, which was slightly higher than the APD$_{90}$ of the normal cell (318 ms).

### 4 Conclusion

In this work, the CRN model was used to find an ideal drug for the treatment and the prevention of familial atrial fibrillation due to the L532P mutation. For the drug tuning, a fast and accurate implementation of the model was established in Matlab. Using the TRR algorithm, a vector $g_{min}$ was found which resulted in an accurate restoration of the AP in the single cell. The resulting vector $g_{min}$ showed that both the $I_{Kr}$ and the $I_{Kur}$ channel were significantly blocked. The finding appears reasonable since the L532P mutation affects the $I_{Kr}$ channel.

The result was further evaluated in a 1D simulation. Here, the AP curve of the tuned model was not restored to the AP curve of the normal cell. This can be explained by the highly pronounced inhibition of $I_{Kur}$. Nevertheless, the WL, the ERP, and the APD$_{90}$ could be increased. Summarizing, the drug tuning could mostly restore the major characteristics of the normal cell.

Although the drug tuning achieved satisfying results for the markers, it could be further advanced for a more reliable result. An improvement could be to consider a different cell model: In the CRN model, there is no distinction between hERG and $I_{Kr}$. This could be problematic because the examined mutation causes specific changes in the hERG channel, which is the $\alpha$-subunit of $I_{Kr}$. In addition, an AP, which might be close to the one seen in the Crista Terminalis, is present in the CRN model [5, 8]. Generally, the AP shapes differ depending on their position in the atria. Therefore, future research might focus on electrophysiological heterogeneities as well, as e.g. shown in [9].

Generally, the drug tuning could be advanced by considering more than just the ion channels included in the CRN model. An integration of exchangers and pumps could lead to different results. Furthermore, the tuning only affected the conductivities of the ion channels. An additional adaptation of the channel kinetics could be a goal for an advanced tuning.

The different AP shapes of the tuning in the single cell and the tissue could be also avoided by directly using the AP in tissue or the restitution properties for the drug tuning. However, this would be computationally far more extensive.

In any case, the found results can be useful to design a specific drug for treatment of familial AF due to the L532P mutation and lead to a better anti-arrhythmic therapy.

### 5 References


Geometrical model and corresponding conductivities for solving the inverse problem of ECG

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Abstract

Solving the inverse problem of electrocardiography could help to diagnose and to plan the treatment of heart diseases. The conductivity distribution within the body is important to solve the inverse problem. In this work the influence of neglecting an organ as an inhomogeneity on the forward and inverse problem was investigated. For different simplified body models optimal conductivities were determined by minimizing the error between the BSPMs produced by this model and reference BSPMs calculated with a complex model containing eight segmented organs. The BSPMs from simulated catheter stimulations were used for the optimization. With the obtained optimal conductivities lead-field matrices were calculated and compared to the lead-field matrix of the complex model. Besides the heart, the lungs and the intracardial blood, we found that the liver also plays an important role to describe the relationship between the activation in the heart and the body surface potential map correctly.

1 Introduction

The goal of ECG imaging is the reconstruction of cardiac electrical sources from the body surface potential map (BSPM). The method could have a great clinical potential by providing cardiologists quantitative information about the heart condition, thereby enabling pre-interventional planning and facilitating the intervention procedures themselves. In order to describe the relationship between the cardiac electrical sources and the BSPM, the model geometry and the corresponding conductivities are important. This model can be obtained from the segmentation of different organs from MRI data, but two problems arise: with state-of-the-art technology the segmentation cannot be done completely automatically. Hence it is labour-intensive to create the geometrical model from the MRI scans and every segmented organ leads to additional expenditure. Finding the corresponding conductivities for the organs is another emerging problem. The experimentally determined tissue conductivities found in literature are inconclusive and vary to a great extent. Besides that, the conductivities vary between different patients and some diseases can cause a pathological change in the conductivity [1]. Weber et al. [2] tested whether the conductivities of the most important organs could be found by minimizing the error between given reference BSPMs and BSPMs whose dependence on the conductivities was approximated using principal component analysis (PCA). In this work this approach was further pursued using signals produced by catheter stimulations. For catheter stimulations the electrical activation within the heart can be estimated precisely for a short time after the stimulation. For different body models only containing the most relevant organs the optimal conductivities were determined from BSPMs after catheter stimulations. The reference ECG signal was calculated using a body model containing eight segmented organs, each assigned conductivities according to Gabriel et al. [3]. With this method it will be possible to determine the optimal conductivities at the beginning of a procedure in the catheter laboratory and with these conductivities the electrical activation within the heart can be reconstructed, after and during the procedure.

2 Methods

2.1 Modelling catheter stimulations

The electrical activity within the heart after a catheter stimulation was modelled as an extrasystole initiated by the stimulation point. For 10 different stimulation points the transmembrane voltages (TMVs) were calculated for 100 ms after the stimulation using a cellular automaton. Information on the anisotropic and inhomogeneous conduction velocity and the different action potential courses were incorporated in the cellular automaton.

2.2 Forward calculation

For the catheter stimulations the BSPMs were calculated for a electrode configuration consisting of 120 electrodes. With the TMVs, calculated with the cellular automaton, the forward problem was solved using finite element method for the bidomain equation with Neumann boundary conditions on the torso surface

\[ \nabla \cdot (\sigma_e \nabla \phi_e) = -\nabla \cdot (\sigma_m \nabla V_m), \]

with extracellular potential \( \phi_e \), intra- and extracellular conductivity tensors \( \sigma_e \), \( \sigma_m \) and the transmembrane voltage \( V_m \).

The reference BSPMs were calculated with a complex reference body model obtained from MRI scans. The segmented organs include ventricles, lungs, skeletal muscle, intestine, liver, spleen, kidneys and the blood within the heart. Except for the ventricles all tissues were assumed to be isotropic. For the ventricles the anisotropy ratio was set to 3:1. The conductivity values for these tissues were those reported...
by Gabriel and Gabriel [3] at 10 Hz. These values will be referred to as the GG values. In order to test which organs are essential for solving the forward and inverse problem of ECG, different body models were considered which contained different numbers of initial organs as inhomogeneities. The rest of the organs was assigned the conductivity value of the skeletal muscle. As Keller et al. [1] found out that the conductivities of blood, lung, heart and skeletal muscle have the greatest influence on the ECG, models were analyzed only containing subsets of these organs as heterogeneities. Four body models were investigated: model A contained the ventricles, the lungs, blood and the skeletal muscle as different tissues, model B contained the ventricles, lungs and blood, model C contained the ventricles and skeletal muscle. Based on the first results, another model D, which contained the liver additionally to ventricles, lungs, blood and skeletal muscle, was tested.

2.3 Optimization of conductivities

In order to optimize the conductivities for the simplified body models, the RMSE between the signal calculated with the complex body model and a conductivity dependent signal with the simplified body models was minimized. The influence of a changing conductivity was treated independently for each organ and approximated using principal component analysis (PCA). For each tissue class a forward calculation was performed for a range of conductivity values, while the conductivity of the other tissues was set to the default GG value. The conductivities were varied by ±25%, ±50% and ±75% from the GG value. For each conductivity the BSPMs were calculated for each time step and the results were ordered in a spatiotemporal signal vector

\[ x_i = (s_{q_1}^{(1)}(l_0) \ldots s_{q_1}^{(1)}(l_{\text{max}}) \ldots s_{q_7}^{(120)}(l_0) \ldots s_{q_7}^{(120)}(l_{\text{max}})), \]

where \( s_{q_k}^{(r)}(l_k) \) describes the potential at electrode \( r \) at the moment \( k \) for the conductivity \( q_k \). These vectors were combined in a matrix \( X \), such that each row corresponds to an observation and each column to a variable. For each variable the mean was calculated and subtracted from the corresponding column of the matrix leading to the mean-free matrix \( X_{\text{mf}} \), whose covariance matrix \( S \) was calculated by

\[ S = \frac{1}{6} X_{\text{mf}}^T X_{\text{mf}} \]  

(1)

The principal components \( p_1, \ldots, p_7 \) with variances \( \lambda_1 \geq \ldots \geq \lambda_7 \) were then calculated by finding the orthonormal eigenvectors of \( S \) with non-zero eigenvalue. The signal vectors could be expressed in the new basis as

\[ x_i = \bar{x} + \sum_{k=1}^{7} s_{i,k} p_k, \]

(2)

where \( \bar{x} \) is the mean signal and \( s_{i,k} \) are the coordinates, called scores, of \( x_i \) with respect to the basis \( p_1, \ldots, p_7 \). When the first eigenvalue \( \lambda_1 \) is large in comparison to other eigenvalues, other principal components \( p_2, \ldots, p_7 \) could be neglected producing only a small error and the signal could be approximated as

\[ x_i \approx \bar{x} + s_{i,1} p_1, \]

(3)

which will be assumed in the following.

2.3.1 Interpolation of scores

For each organ the scores for the sampled conductivities depended monotonically on the conductivity and were interpolated with a monotone polynomial. Since the dependence of the score from the conductivity was monotone, it was also bijective and the optimal conductivities could be determined by finding the optimal scores. The signal could be approximated for every conductivity within the interval as

\[ x(\sigma) = \bar{x} + s(\sigma)p_1, \]

(4)

where \( s(\sigma) \) is the interpolation function of the scores of the first principal component with respect to the conductivity. The influence of different organs were combined using the common signal with all conductivities set to the GG value as a starting point and shifting the scores respectively.

\[ x(\sigma_1, \ldots, \sigma_k) = x_{\text{GG}} + \sum_{n=1}^{k} \delta_n(\sigma_n)p_{1,n}, \]

(5)

The RMSE between \( x(\sigma_1, \ldots, \sigma_k) \) and the reference signal calculated with the complex body model was minimized using the downhill simplex method. The first principal components were tested on linear independence to guarantee a unique solution. The angle between the principal components should not be too small, otherwise the influence of the different organs could be indistinguishable int the present of some noise.

2.4 Evaluation of conductivities

Since the geometrical models should be used to solve the inverse problem of ECG, the conductivities were evaluated by comparing the lead-field matrix calculated with the simplified model to the lead-field matrix of the complex model. Therefore the relative error between the matrices concerning the 2-norm was calculated. Furthermore the correlation between the columns of the matrices were calculated in order to test whether the error is just an error of amplitude or whether the morphology of the BSPMs is changed.

Figure 1 Polynomial interpolation of the relation between the score of the first principal component for blood as varying organ and the conductivity of the blood.
3 Results

3.1 Validation of methods

For all executed simulations the ratio between the first and the second eigenvalue exceeded 50. The absolute value of the first eigenvalue depended strongly on the stimulation point. Therefore neglecting all but the first principal component caused only a small error. The principal components were always linear independent and the smallest encountered angle between principal components was 28°.

3.2 Conductivities for model A

In table 1 the optimized conductivities for model A for different stimulation points are shown. The values are shown in relation to the GG conductivity of the respective organ, so the value 1 corresponds to the GG conductivity. The conductivities vary to a great extend depending on the stimulation point. In some cases the optimal conductivity lied outside the considered range. In these cases the boundary value was returned, since the relation between conductivity and score is unknown. These cases coincided with a low first eigenvalue of the corresponding tissue. A small dependence of the signal from the conductivity might lead to unreliable conductivity values. For the lungs the first eigenvalue varied the most between 130 and 1.5. High values were obtained for stimulation points near the lungs. The relative error between the reference BSPMs and the reconstructed BSPMs lied between 6.6% and 24.5%. The ECG signal according to Einthoven II lead didn’t occur. The conductivity might lead to unreliable conductivity values. For the lungs the first eigenvalue varied the most between 130 and 1.5. High values were obtained for stimulation points near the lungs. The relative error between the reference and reconstructed ECG are given for different stimulation points. The relative error between optimized and reference signal to Einthoven II lead didn’t occur. The conductivity values for the other tissues became more stable (var($\sigma_{B,r}$) = 0.011, var($\sigma_{L,r}$) = 0.035, var($\sigma_{S,r}$) = 0.004, var($\sigma_{V,r}$) = 0.069 for the optimization over one stimulation point. In some cases the optimal conductivity lied outside the considered range. In these cases the boundary value was returned, since the relation between conductivity and score is unknown. These cases coincided with a low first eigenvalue of the corresponding tissue. A small dependence of the signal from the conductivity might lead to unreliable conductivity values. For the lungs the first eigenvalue varied the most between 130 and 1.5. High values were obtained for stimulation points near the lungs. The relative error between the reference and reconstructed ECG are given for different stimulation points. The relative error between optimized and reference signal to Einthoven II lead didn’t occur. The conductivity values for the other tissues became more stable (var($\sigma_{B,r}$) = 0.011, var($\sigma_{L,r}$) = 0.035, var($\sigma_{S,r}$) = 0.004, var($\sigma_{V,r}$) = 0.069 for the optimization over one stimulation point.

![Figure 2](image_url) Reference and optimized signal according to Einthoven II lead (stimulation 4 and stimulation 9)

Table 2 Variation between the different optimized conductivities for optimization over 1, 3 or 5 catheter stimulations.

<table>
<thead>
<tr>
<th># Stim.</th>
<th>var($\sigma_{B,r}$)</th>
<th>var($\sigma_{L,r}$)</th>
<th>var($\sigma_{S,r}$)</th>
<th>var($\sigma_{V,r}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1554</td>
<td>0.4702</td>
<td>0.03062</td>
<td>0.3172</td>
</tr>
<tr>
<td>3</td>
<td>0.0756</td>
<td>0.06391</td>
<td>0.002694</td>
<td>0.1079</td>
</tr>
<tr>
<td>5</td>
<td>0.0232</td>
<td>0.00336</td>
<td>0.000977</td>
<td>0.0793</td>
</tr>
</tbody>
</table>

3.3 Model B and C

Model B and C led to higher errors between optimized and reference signal. The highest error for both models was 39%, with an average relative error of 24.6% for model C and 18.5% for model B. The optimized conductivities were less stable, even after combining the BSPMs from different stimulation points.

3.4 Model D

Adding the liver as an inhomogeneity led to a reduction of the relative error between optimized and reference signal to an average of 6.9%. Changes in the morphology of the ECG signal according to Einthoven II lead didn’t occur. The conductivity values for the other tissues became more stable (var($\sigma_{B,r}$) = 0.011, var($\sigma_{L,r}$) = 0.035, var($\sigma_{S,r}$) = 0.004, var($\sigma_{V,r}$) = 0.069 for the optimization over one stimulation point.)
tion). The largest eigenvalue from the PCA for the liver conductivity was smaller than other organs.

### 3.5 Comparing lead-field matrices

The relative error in the lead-field matrices calculated with the optimized conductivities can be seen in table 3. Optimizing the conductivities instead of using the GG values reduced the error in the lead-field matrix (Model A: From 38.99% to 25.40%). Model D leads to the smallest error, with 14.25%. The spatial distribution of the relative error between the single columns of the lead-field matrix can be seen in fig. 4. Model A, B and C have a high relative error in an area in the right ventricle. In the complex model the points in this area are adjacent to the liver, which has a considerably lower conductivity than the skeletal muscle ($\sigma_{GG, Liver} = 0.0277 \, \text{S/m}$ and $\sigma_{GG, S} = 0.202 \, \text{S/m}$). The average correlation between the columns of the lead-field matrices is high for all models (see table 3), though there were some points with negative correlation. A low correlation was often found for points on the boundary between three different organs.

<table>
<thead>
<tr>
<th>Model</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>$</td>
<td>A_k - A_k^F</td>
<td>/</td>
<td>A_k^F</td>
<td></td>
</tr>
<tr>
<td>$\phi$ Corr</td>
<td>0.9728</td>
<td>0.9583</td>
<td>0.9346</td>
<td>0.9941</td>
</tr>
</tbody>
</table>

#### Table 3 Relative errors in the lead-field matrices calculated with different body models and conductivity distributions obtained from the optimization.

Figure 3 The spatial distribution of the correlation between the columns of the lead-field matrix calculated with model A, B, C and D

Figure 4 Spatial distribution of the relative errors of the single columns of the lead-field matrices calculated with model A, B, C and D

### 4 Conclusion

In this work different geometrical models of the human torso were analyzed with regard to their influence on the lead-field matrices. For these models, which contain less segmented organs than the model considered as the ground truth, optimal conductivities were determined. Conductivities were considered optimal, if they reproduce the right relation between activation in the heart and the BSPM. Therefore the conductivities were determined by minimizing the RMSE between conductivity dependent BSPMs and reference BSPMs for simulated catheter stimulations within the ventricles. The dependency of the conductivities was approximated using the PCA. For the optimal conductivities the lead-field matrices were calculated. The resulting lead-field matrices showed a surprisingly high error. This error is mainly an error of amplitude and the correlation between the columns is high. Neglecting the liver as an inhomogeneity led to a great error in the lead-field matrices and changed the morphology of the ECG signals. Even though the conductivity of the liver has a smaller influence on the BSPM than the ventricles, lungs, blood and skeletal muscle, the liver has a very low conductivity compared to the skeletal muscle and thereby homogenizing skeletal muscle and liver to one tissue class causes a large error.

### 5 References


Synthesis and analysis models for sparse signal reconstruction in the inverse problem of ECG

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Abstract

Electrocardiographic imaging (ECGI) is a non-invasive diagnostic tool solving the inverse problem of ECG, which means the reconstruction of electrical potentials in the heart from the ECG data. The ill-posedness of this problem makes necessary addition of a-priori information. A typical approach is the Tikhonov regularization looking for the best balance between minimizing the data misfit and the regularization term which characterizes desired properties of the solution. However, the quality of an obtained solution, and as a result its clinical relevance, could be significantly improved by application of methods for non-smooth regularization. In this work we introduced a possible dictionary definition for the electrical sources in the heart: we subdivided the heart into 100 pieces and considered them to constitute the columns of our dictionary. We also provided a short discussion on differences between synthesis and analysis models, tested the analysis algorithm with a penalty matrix which is not related to the defined dictionary (discrete gradient operator for all heart points) and compared the performance of these three algorithms for two simulated ventricular ectopic foci. The analysis method with the gradient operator showed a slightly superior performance although all methods correctly identified the regions of interest.

1 Introduction

The equations describing electromagnetic phenomena that arise in human body can be derived from Maxwell equations using quasiclasticity assumptions. Furthermore, Miller and Geselowitz [1] introduced the concept of homogenized intracellular and extracellular spaces occupying the heart volume and possessing averaged properties over the whole heart domain (bidomain model). The main differential equations governing in the heart and passive volume conductor are Poisson and Laplace equations respectively:

\[ \nabla \cdot (\sigma_e + \sigma_i) \nabla \phi_e = \nabla \cdot (\sigma_i \nabla \phi_i) = 0 \] (1)

\[ \nabla \cdot (\sigma_e \nabla \phi_e) = 0 \] (2)

with the corresponding boundary conditions on the heart and body surfaces. In Eq. (1)-(2) \( \phi_e \) are the transmembrane potentials (TMV, the actual electrical generator), \( \phi_i \) are the electrical potentials (extracellular potentials for the heart in Eq. (1)), \( \sigma_e, \sigma_i \) denote the extra- and intracellular conductivities.

As we see, Eq. (1)-(2) are linear, therefore a principle of superposition on TMV and the potentials \( y \) at electrode positions can be established [2].

\[ Ax = y \] (3)

The problem of finding the voltages \( x \) (TMV) from measured body surface potential maps (BSPM) \( y \) is ill-posed. Mathematically, it means that the solution of Eq. (3) is not unique and becomes unstable in the presence of noise. A most common approach to deal with the ill-posedness is to stabilize Eq. (3) by introducing a regularization term. This method is called the Tikhonov regularization [3]. From the numerical point of view it improves the condition number of the original system of equations [4]:

\[ x = \arg \min_x \left\{ \|Ax - y\|^2 + \lambda \|Lx\|^2 \right\}, \] (4)

where \( L \) is the regularization matrix enforcing desired properties to the solution, \( \lambda \) is the regularization parameter. Depending on the matrix \( L \) being an identity matrix, discrete approximations of the gradient or Laplace operator one distinguishes between the Tikhonov 0., 1st or 2nd order. According to that, a minimum norm-solution or a solution with minimal spatial derivatives is sought. Although serving a good approximation of real potentials, a solution regularized in \( L_2 \) sense lacks high frequency components and sometimes is over-smoothed. To overcome these drawbacks non-smooth regularization can be applied, when the regularization term is treated in \( L_1 \) space or in a space of bounded total variation (TV) [5, 6, 7, 8, 9].

In this work we propose to use synthesis and analysis models for achieving sparse reconstructions. In Methods section we will introduce the basic principles of the methods and in Simulation Setup section we will adapt these concepts to the transmembrane potential based inverse problem of ECG.

2 Methods

Synthesis Model

In the sparse synthesis model [10] the solution \( x \in \mathbb{R}^n \) is assumed to be a linear combination of few columns of the matrix \( D \in \mathbb{R}^{n \times d} \) called dictionary, i.e.

\[ x = D\alpha = \sum_{i=1}^{d} D_i \alpha_i \] (5)
with \( \alpha \in \mathbb{R}^d \) being a representation vector, \( D \) corresponding to the columns of \( D \). This model is used when it is known that the signal \( x \) lies in a lower dimensional space in a transformed domain (e.g. \( D \) is a wavelet transformation or spatial derivative matrix). It implies that the number of non-zero components in \( \alpha (\|\alpha\|_0 - l_0 \text{ norm}) \) should be small. Instead of minimizing \( l_0 \text{ norm}, \) which is known to be a NP hard problem [11], we will promote sparsity of \( \alpha \) by minimizing its \( l_1 \text{ norm}. \) The resulting minimization functional reads

\[
\min_{\alpha \in \mathbb{R}^d} \|AD\alpha - y\|_2^2 + \lambda \|\alpha\|_1 \tag{6}
\]

or alternatively

\[
\min_{\alpha \in \mathbb{R}^d} \|\alpha\|_1 \text{ s. t. } \|AD\alpha - y\|_2 \leq \epsilon \tag{7}
\]

where \( \epsilon \) is the noise estimate when known.

**Analysis Model**

In the analysis model the sparsity in a transformed signal space is promoted. Let us define

\[
\alpha = Gx
\tag{8}
\]

and require the sparsity of \( \alpha \). As shown in [12], in case of an overdetermined dictionary \( D \) (i.e. when \( d \leq n \)) both models would yield the same results with \( G^T = D \). After we have defined \( \alpha \) as in Eq. (8) with a bit of algebra we can show that \( G\alpha = x \) and therefore we should require that \( \alpha = G G^T \alpha \) which is not always the case. Thus the functional to optimize can be written as

\[
\min_{\alpha \in \mathbb{R}^d} \|AD\alpha - y\|_2^2 + \lambda \|\alpha\|_1
\tag{9}
\]

subject to \( GG^T \alpha = \alpha \)

which could lead to quite different results compared to the synthesis model [10] when the matrix \( D \) does not have full column rank. As we will see our choice of the dictionary \( D \) supports the usage of both synthesis and analysis models separately. In case when the matrix \( G \) is not related to the dictionary matrix \( D \) (e.g. \( G \) is a discrete derivative approximation) the problem can be formulated as

\[
\min_{\alpha \in \mathbb{R}^n} \|Ax - y\|_2^2 + \lambda \|Gx\|_1 \tag{10}
\]

In our experiments we used \( l_1 \text{ norm} \) relaxation of the problems for both penalty terms in synthesis and analysis models. The optimization in this case becomes convex and robust compared to \( l_0 \text{ norm} \).

**Simulation Setup**

For testing performance of the proposed algorithms we simulated two ventricular extrasystoles in a realistic human geometry (see Fig. 1). For the wavefront propagation in the heart we took a cellular automaton model. It requires an initial point where the excitation starts and the information about conduction system in the heart in order to reproduce desired action potentials (TMV). In our automaton implementation each next state (in time) of a cell depends on the states of its immediate neighbors and history of the cell itself.

For the reconstruction we concentrated ourselves on the initial time instances in order to locate the origin of extrasystoles. In clinical environment it would help a physician during an ablation procedure. According to this we divided the heart into pieces and assigned each subregion to be an entry in our dictionary in the following way: each subregion corresponds to a column in the matrix \( D \). The values of the points in this column vector which lie in the subregion obtain the value of +20 mV while others are set to -80 mV. After performing several tests we recognized that 100 subregions in the heart provide a good compromise between the accuracy and computational time. Thus our dictionary covers the whole heart and represents 100 extrasystoles originating from different places. It is worth noting that the simulations and dictionary building were done independently from each other, i.e. no subregion in the heart dictionary coincides with the simulated extrasystoles origin. Exemplary visualizations of the dictionary columns are shown in Fig. 2. From the way we built the matrix \( D \) it becomes clear that \( A \ast D \) has column deficient rank.

For solving the inverse problem we used three formulations: the synthesis model given by Eq. (6) with the defined above dictionary matrix \( D \), the analysis model from Eq. (9) with the matrix \( G = D^T \) and the optimization problem (10) with \( G \) being a discrete approximation of the gradient operator (we will call this problem \( l_1 \text{ norm} \) gradient minimization).

For our implementation of \( l_1 \text{ norm} \) gradient minimization we also added physiological boundary conditions on the so-
In the current work we considered three approaches for sparse sources reconstruction in the inverse problem of ECG. The two first correspond to the synthesis and analysis models. It is assumed that the signal of interest could be expressed as a linear combination of some signals which constitute a dictionary. The original regularization problem becomes a minimization problem of finding sparse representation of the sought vector in the dictionary. To build the dictionary we divided the heart into 100 parts and assigned to each part a signal corresponding to an extrasystole originating from there. As a result the constructed matrix $D$ covers the whole heart and can be used to approximate any ectopic focus at an initial time point very well. The analysis model is closely related to the synthesis one and in some cases both models are identical. But due to the structure of our matrix $D$ these two approaches are not the same which is also clearly seen from the reconstruction results in Fig. 3. The idea of the method is to require sparsity of the solution in some transformed domain. In a classical case this transformation matrix is taken to be the pseudo-inverse of the dictionary matrix $D$. Although prominent differences in the solution of two optimization problems can arise, for our application both methods provide very similar results.

Alternatively to the described above techniques, a spatial derivative of the unknown signal can be used as the regularization term for the ill-posed problems. $l_2$-norm minimization provides a smooth approximation of the solution, and thus the $l_1$ penalty norm problem (Eq. (10)) with the matrix $G$ being a discrete gradient operator is a good candidate for sparse reconstruction of TMV in the heart. In our experiments this method performed at the best although all approaches delivered very good qualitative results. Even though we considered only the initial time point from the activation sequence for our reconstructions, all methods can be naturally used for solving the problem for the whole depolarization cycle. It could be expected that the synthesis and analysis models would produce a good estimation despite usage of the dictionary with a limited number of entries.

For other heart abnormalities, such as ischemia or infarction, the dictionary can be generated in a different way, still containing physiological information about the solution and hence can be always used. However adaptation of these values to the specificity of the problem (e.g. in case of ischemia or infarction) could lead to further improvements.
Figure 3 Simulations and reconstruction results, obtained with (see from left to right) synthesis model formulation (Eq. (6)), analysis model formulation (Eq. (9)), analysis model with $G$ being a discrete approximation of the gradient operator (Eq. (10)).

Acknowledgement

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3 References

Effect of mesh resolution on forward calculations of the electrocardiogram in a simplified thorax model

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Abstract

Electrocardiographic imaging (ECGI) facilitates the non-invasive reconstruction of electrical activity in the entire heart at once. ECGI requires both recordings of multi-channel ECG signals as well as an MRI-based model of the thorax. The model is used to solve the underlying Poisson’s problem, which relates the gradient of transmembrane voltages in the heart to the ECG and is a spatial differential equation. In ECGI, this relationship has to be established before starting inverse calculations, i.e. the forward problem has to be solved. It solution depends strongly on the spatial discretization of the model, as its resolution affects the representation of the source gradients. To study the convergence of resolution-related effects in the forward problem, we use a simplified thorax model which allows for very high resolutions. An ECG is produced for the excitation origin of a premature ventricular contraction in the apex. The study reveals that the greatest resolution-related effects vanish below a resolution of 5 mm of the cardiac tissue. At below 1 mm, resolution effects stabilize and only marginal effects from the spatial structure of the mesh persist down to a resolution of 0.25 mm.

1 Introduction

In electrocardiographic imaging (ECGI) electrical activity in the myocardium can be reconstructed for the entire muscle at once and without catheterization. ECG signals are recorded on the thorax surface using body surface potential mapping (BSPM), and an MRI-based model of the thorax is produced, including organs and the heart. Works in the field have mostly focused on the imaging of epicardial potentials [1] or surface activation times [2, 3]. This resolution study relates to the imaging of transmembrane voltages in the myocardium [4, 5, 6, 7, 8, 9], which requires solving the Poisson’s problem of the underlying source-to-ECG relationship with the finite element method. To this end, the resolution of the underlying heart mesh is tested in two scenarios: First, the resolution is adjusted for the entire heart. Second, to achieve even higher resolutions, the resolution is only adjusted in a region-of-interest around the actual source.

2 Setup

MRI scans were acquired from a patient (male, age 56) with premature ventricular contractions (PVCs). A whole heart MRI scan (volumetric interpolated breath-hold examination, VIBE) with resolution of 0.72 mm × 0.72 mm × 1.40 mm and a thorax scan (VIBE) of 1.95 mm × 1.95 mm × 2.00 mm were acquired during expiration. The study was approved by the local ethics committee and written informed consent was obtained from the patient. The imaging data was used to produce a manual heart segmentation and a segmentation of the thorax surface, which was generated using otsu-based foreground masking with 3D Slicer (http://www.slicer.org) [10]. Besides skeletal muscle, tissue-specific conductivities were assigned to the left and right ventricular blood and muscle.

Simplified thorax model

To facilitate a study of high resolution, a simplified model of the thorax was used, see Fig. 3: the thorax was cropped to the region that covers the entire heart and still includes the closest body surface, where 28 virtual electrodes were placed to sample the computed extracellular potentials, see Fig. 1. Although the cropped thorax model leaves out volumes that would influence the produced electric fields, i.e. the computed ECG signals are not completely realistic, the extracellular potentials can well be assumed to reflect the quality of spatial sampling at the cardiac source. Electrodes in close proximity to the source also suffer least from the spatial smoothing of signals by the volume conductor, i.e. they are expected to show the strongest effects from poorly represented gradients in the source.

Heart model, simulation and forward calculation

For the same reason the cardiac activity was simulated close to the apex, where a PVC was simulated at 5.5 ms after initiation using a cellular automaton [11]. To this end and to start from a source with precise representation, a structured grid of the cardiac tissue with 0.2 mm resolution was produced for solely the volume around the excitation origin. A tetrahedral mesh was then generated from another 0.2 mm-resolution voxel-grid of the segmentation of the en-
Figure 1 Left: heart model (blue: right ventricle, red: left ventricle) with fiber orientations in grey. Right: virtual electrodes that sample extracellular potentials on the body surface of the simplified thorax model.

tire simplified thorax model. A 30-voxel-thick sub-surface layer was meshed with 2mm cell size to reduce effects of spatial sampling by the mesh on the representation of the electrode positions. The transmembrane voltages in the volume around the excitation origin were interpolated on the tetrahedral mesh. To work with high resolution in this volume, TMVs in other parts of the heart were assigned the default value of the simulation, i.e. these areas needed not to be represented in the simulation’s voxel-grid. Fiber orientation was introduced in the heart according to [12] at 0.4mm resolution. The forward calculation was then performed using the bidomain model [13].

2.1 Tetrahedral mesh generation

To produce 3-D tetrahedral meshes for the forward calculations with different meshing parameter the computational geometry algorithms library (CGAL) [14] was used. Meshes are generated in CGAL using Delaunay refinement, i.e., for a given geometrical pattern, a tetrahedralization is produced that satisfies the Delaunay criterion [15]. Starting from an initial mesh, additional points are iteratively introduced according to quality criteria (see Table 1), while maintaining the Delaunay criterion. The criterion requires that no point is inside the circumsphere of any tetrahedron. This yields a maximization of the minimum angle of all angles in the tetrahedralization [16], see also [7, Fig. 3.2]. CGAL may bypass the Delaunay criterion locally though to protect small angles in the surfaces of subdivisions and boundaries of the given geometrical pattern [17].

2.2 Choice of resolution parameters for the heart

This study intends to find proper resolution parameters for the representation of the cardiac tissue and its electric sources. The resolution of the underlying heart mesh is tested in two scenarios:

- The resolution of the cardiac tissue is refined throughout the entire heart, see Fig. 2.
- The resolution is only refined in a region-of-interest around the actual cardiac source. This scenario allows for higher resolutions to be tested, see Fig. 3.

Mesh resolution parameter refine_cell_size (cell size in the refined area) is tuned according to Table 2. It is reduced in an incremental manner, starting from 8mm and going down to 0.5mm for refinement of the entire heart and down to 0.25mm when only the region-of-interest is refined. The meshing parameters without immediate influence on the resolution remain fixed (facet_angle, facet_distance, cell_radius_edge_ratio), along with the facet_size and refine_facet_size, both of which are set to a value that is expected not to interfere with the resolution study.

Figure 2 First setup: The resolution of the cardiac tissue is adjusted for the entire heart. The blue color in the region of interest represents the wireframe lines, not TMV. Only TMV of high voltage is represented and superimposed over the image.

Table 1 Quality criteria for Delaunay refinement.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>facet_angle</td>
<td>Lower bound for the angles of facets that belong to the surface of the volumetric mesh (algorithm converges for $f_a \leq 30^\circ$ for smooth surfaces). The four 2-dimensional faces of a tetrahedron are called facets [18].</td>
</tr>
<tr>
<td>facet_size</td>
<td>Upper bound for the radii of surface Delaunay balls that describe the size of surface facets.</td>
</tr>
<tr>
<td>facet_distance</td>
<td>Upper bound for the approximation error of boundary and subdivision surfaces of the geometrical pattern.</td>
</tr>
<tr>
<td>cell_radius</td>
<td>Upper bound for the circumradius-to-shortest-edge ratio (algorithm converges for $c_r,e &gt; 2$)</td>
</tr>
<tr>
<td>edge_ratio</td>
<td></td>
</tr>
<tr>
<td>cell_size</td>
<td>Upper bound for the circumradius</td>
</tr>
</tbody>
</table>

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**3 Results**

Fig. 4 and Fig. 5 demonstrate the effects of the resolution of the cardiac tissue in the tetrahedral mesh on the forward-calculated ECG. Fig. 6 demonstrates how the computed ECGs differ from one another. The root mean squared error is computed for the ECGs with respect to the ECG obtained for the highest tested resolution (0.5 mm for the first setup and 0.25 mm for the second).

**4 Discussion and conclusions**

Both the ECGs in Fig. 4 and Fig. 5 and the decay of the root-mean-squared error in Fig. 6 demonstrate that the greatest resolution-related effects vanish below a resolution of the cardiac tissue of approximately 5 mm. The found effects stabilize in both representations at below 1 mm and only marginal effects from the spatial structure of the mesh persist down to a resolution of 0.25 mm. This behaviour is expected due to the better representation of the source gradients with the meshes of higher resolution. Even with the highest resolution a re-meshing with almost exactly the same resolution parameters still has small but noticeable influence on the ECG. For most purposes, especially in ECGI, where smoothing occurs in the reconstructed cardiac sources, a cell size of 1 mm may well lead to a precise enough representation.

**Acknowledgements**

We thank the CGAL developers community for sharing the software libraries. This project was funded by the German Research Foundation under grants DO637/10-1 and DO637/13-1.
Figure 6 Root mean squared error of the computed ECG with respect to the ECG obtained for the highest tested resolution. Left: first setup, the resolution of the cardiac tissue is adjusted for the entire heart. Right: second setup, the resolution is only adjusted in a region-of-interest around the actual cardiac source.

References


[12] Computational geometry algorithms library (www.cgal.org)


Real-Time Single-Trial Source Localization using RAP-MUSIC and Region of Interest Clustering

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Introduction

Up to date scanning approaches for the localization of neuronal sources, such as RAP-MUSIC, are hardly able to deliver results in real-time due to their computational effort. RAP-MUSIC source localizations provide not only feedback about a location of a neuronal active area, but also an insight in correlated processes. This real-time estimation of active functional networks can help to identify cognitive processes with a higher reliability and can therefor help to pivot experimental parameters to subject’s reactions during acquisition.

In this work we present a high performance RAP-MUSIC source localization algorithm delivering localizations based on single-trial data in real-time.

Methods

We adapted the forward as well as the inverse solution. For the forward solution, we calculate region-wise clusters based on Destrieux’s cortical brain atlas, which results in a downsized gain matrix. For the inverse solution, we reduce the computational costs of RAP-MUSIC by modifying and precalculating components of the subspace correlation. Moreover, we apply a modified Powells Conjugate Gradient method, which accelerates the search process. Since the subspace correlations of the RAP-MUSIC are independent, we provide an CPU OpenMP and GPU CUDA implementation to further accelerate the computation.

Results

Our algorithm is able to handle Elekta Neuromag® VectorView™ 306 channel MEG measurements with a sampling rate of 1250 sps. Studies using human MEG evoked data show that the proposed real-time technique is able to handle single-trial raw data using a sliding window approach. We tested the proposed method with data recorded during auditory and somatosensory stimulation. The response to auditory stimuli are localized in the gyrus temporalis superior on both hemispheres, while somatosensory stimuli lead to activation in the contralateral gyrus postcentralis.

Conclusion

We conclude that our modified RAP-MUSIC algorithm is fast and can localize on single-trial raw data which is a usefull addition to common acquisition methods.
Development of a hybrid surgical training simulator for the replacement of the aortic valve facilitating porcine hearts

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Abstract

We present a basic example of how to develop a hybrid surgical simulator for the replacement of the aortic valve. The simulator combines the use of porcine hearts as a destructible element and synthetic materials for the human parts that remain intact during surgery. The simulator is easy to use in terms of set up as well as preparation and cleaning of the heart carrier module. This approach takes advantage of the use of porcine hearts already being common practise for this kind of surgery. They are a cheap and easily available resource. Our project is promising in leading to a simple and affordable system for improving the training of surgeons considerably. The final goal is to evaluate the merit of different aspects in simulator design.

1 Introduction

Heart disease is the first-leading cause of death [1]. Usually, a large number of people suffering from heart disease are treated through surgery. For example, Germany has more than 30,000 surgeries per year for heart valves only. A portion of 60% of those operations target the aortic valve [2]. These numbers are expected to rise due to demographic change. In turn, surgeries will get more complicated as the average age of the population increases. Patients of higher age tend to have more comorbidities [3].

In aortic valve replacement (AVR) [4], the patient’s diseased valve is removed and replaced by a new artificial valve. The operation is usually performed via chest-side access (median sternotomy). Before accessing the heart, the patient is connected to the heart-lung machine in order to temporarily immobilise the operational area. After that, a cut in the aorta enables the surgeons to access the aortic valve. The procedure is often perfomed as conventional surgery. However, many clinics tend to substitute this procedure with the minimally invasive cardiac surgery (MICS) where the incision is considerably reduced in size due to partial upper sternotomy.

As the risk of death for this procedure is quoted between 1-3% [5], the operation can be regarded a commonplace procedure. However, the different steps of the operation must be trained well as they are completely executed by hand. Especially the transition to the MICS approach poses a risk. The surgeon is forced to use different, specialised surgical instruments in a more constrained environment. Hence, the haptic sensation is different from the open-surgery approach. Young and experienced surgeons alike transitioning from open surgery to MICS need to be trained. At this moment, training outside of the operating room is done either using laboratory pigs or porcine hearts from agriculture. The use of laboratory pigs is not suitable for training on a daily basis as it is high in cost and low in social acceptance. Thus, ethical tenability has become a big issue for clinics. However, the use of cheap porcine hearts is devoid of these drawbacks. Nonetheless, it makes little sense to conduct the overall operation on a loose, inanimate heart. Another problem, among others, is the lack of constraint in the handling of surgical instruments (Image 1). The joint research project PASCAL aims to find new ways for the training of the aortic valve replacement as an important introductory operation in heart surgery. It is a project with both, technical as well as medical staff and has been running for one year. The next section will explain how we intend to develop a hybrid simulator mixing the approaches of using animal organs as well as synthetic structures in combination. Furthermore, we will show the current status of the project with preliminary results. A final conclusion will summarise and point out future work.

2 Methods

There are different ways to provide surgeons with the means to operate outside the operation room and without actual human patients. For the last years, our institute has been building several training simulators based on fully operational models of the human body. Those physiologi-
called models are based on patient data and build using modern rapid prototyping techniques. They are especially expensive if they represent a complex structure like the heart. Hence, such an approach is not convincing if a more cost-effective item, such as a porcine heart, is available. Therefore, we decided to build a hybrid simulator with the idea of improving rather than reinventing the existing solution. Our concept is to use the porcine heart as an efficient, replaceable model placed inside the developed simulator.

In order to generate results and conduct research on how to effectively develop such a simulator, we decided to build several prototypes with every generation adding a feature to the simulator. Those features are validated by experienced surgeons regarding their merit. To do this, we are providing an in-house training operation room as well as the usual operating room used by Leipzigs hospital for heart surgery. The first generation simulator comprises of a fully adjustable framework positioning a thorax model above the heart. It also includes a heart carrier module to position and fix the porcine heart. Beside proofing our concept, the framework also includes a sternotomy in order to restrain the surgeons access to the heart. During validations, practising surgeons adjust the framework. Hence, positioning the thorax and heart together as suggested is the most relevant configuration experienced during surgery.

![Image 2 First Generation Simulator](image2)

### 3 Results

At the current stage of the project, we have finished the first generation of the simulator as described above (Image 2). The thorax model is a fiberglass shell with silicone representing the patient’s body. It is possible to adjust it in height as well as its inclination. The sternotomy is mimicked by a pre-made cut into a layer of silicone. We position the porcine heart under that shell with a fully adjustable ball-bearing. It is necessary to remove the heart after each operation and place another into position. While being fixed in position, it was necessary to assure that the heart still has a limited amount of free space as the human heart is not a fixed structure. We produced a clay mold of the porcine heart which was the basis for producing a positive mold, i.e. a copy of the heart. We used special synthetic material with the prospect of being used for molding several times. As a final solution, we use washable silicon to produce a shell of one half of the positive. The heart is plugged into that resulting shell. The half shell is big enough to provide some level of footing without clamping the heart too much.

We conducted first validations with senior physicians of the Herzentrum Leipzig (JS) performing MIC on a daily basis. The next generation thorax will not be adjustable as the surgeons tilt the patient for gaining an ideal access anyway. However, there are big variations in the distance of thorax and heart (5-10cm), as well as in the positioning of the carrier underneath the sternotomy (0-5cm). Therefore, the second generation of the simulator will provide the surgeon with the possibility to change the arrangement within those regions. However, the half shell provides enough rotational flexibility. Thus, its orientation can be fixed.

### 4 Conclusion

Our team of interdisciplinary researchers presents how to improve surgical training with small effective developments. It is not always necessary to reinvent surgical training, particularly if model-based training is already established. Our approach exploits the fact that many clinics already use porcine hearts. Therefore, suppliers for the hearts, surgical instruments and a training room already exist. This simplifies the establishment of our simulator. The material costs are quite low, hence, the production cost for this reusable device will also be reasonable. Our approach is promising in a way that we are actually transporting our technology into the clinics.

The first validation included an aortic valve replacement from the point of opening and closing the aorta. It took more than one hour to perform the surgery (usually 45 minutes), however, the assistant physician was very committed and grateful for this opportunity. With promising preliminary results such as these, the next step in this project will focus on finishing the next generation of the simulator. As we plan to pursue several training units with it, we hope to come up with statistical data underlining the effectiveness of this kind of training. Our final goal is to give a tool to practice to trainees, provide a test environment for clinical trials for researchers and gather knowledge about aspects of importance in the design of surgical training simulators.

### 5 References

ANALYSIS OF BLOOD GLUCOSE DYNAMICS IN LIVER TRANSPLANTATION: A MODEL-BASED APPROACH

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Abstract: A safe, effective glycemic control would have beneficial effects on the outcomes of liver transplantation (LT) patients. The model-based validated glycemic control protocol, STAR, is proven for ICU patients. However, the ICING model used for STAR differs in the blood glucose dynamics compared to the LT patients who have no liver for part of the surgery. By localizing the places of extraordinary LT patient’s dynamics we can specify modifications for the ICU patient model. These dynamics mainly occur in the: 1) pre-anhepatic phase at the beginning of the surgery; 2) at the portal vein reperfusion; and 3) in the post-anhepatic phase before 500 minutes after the reperfusion.

Keywords: liver-transplantation, blood glucose dynamics, model-based analysis

1 Introduction

Validated models exist to describe blood glucose (BG) dynamics and variability for ICU patients [1, 2, 3]. Model-based glycemic control (GC) protocols can maintain the normoglycemic state in ICU patients [4]. Avoiding the severe variability of blood glucose, hypoglycemia and hyperglycemia, can reduce mortality [5, 6]. STAR (Stochastic TARget) is a validated GC protocol, based on model ICING (Intensive Control Insulin-Nutrition-Glucose). The method is already applied in clinical application in ICU in Christchurch, (New Zealand), Liege (Belgium) [7], Gyula (Hungary) [8, 9] for the MICU (medical intensive care unit), the CICU (cardiac intensive care unit) and for other specific patient cohorts as well [10]. Our aim is to improve the method for liver transplantation (LT), where patients may also benefit [11, 12]. The critical criteria for model-based control is an appropriate model, that can describe the metabolic changes over time. This paper describes a model based retrospective analysis, to define those BG behaviors, where the modifications are needed for the ICING, aiming the model to capture hepatic transplant dynamics. During Liver transplantation the metabolic system faces major alterations in (BG) dynamics, that don’t occur in any other patient, due to the removal and replacement of the liver, the most dominant metabolic organ. Preliminary studies report about the loss of endogenous glucose production (EGP) or the reduced non-insulin mediated glucose removal [13, 14, 15]. This article quantifies those phenomena, which occur generally during LT. Knowing the trends of deviations in BG and in time, that the model cannot capture, allows us to make adjustments to monitor the real metabolic process.

2 Methods

2.1 Data & Surgery

Budapest Transplantation Clinic provided measurement data from 23 patients, undergoing orthotopic liver transplantation (oLT); the blood glucose concentration, surgery events and times, feeding and insulin therapy. Most of the patients suffered from alcoholic cirrhosis. Surgery events, blood glucose concentration and administered exogenous insulin and nutrition were recorded. The nutrition was provided parenterally and the goal feed was 4 [g/hr] of carbohydrate according to the hospital protocol. The insulin was administered as a continuous infusion.

![Blood glucose trend during the surgery](image)

Figure 1: Trend of the BG concentration in certain surgery phases: A (pre-anhepatic phase), B (anhepatic phase), C (reperfusion between the unclamping of portal vein and hepatic artery), D (post-anhepatic phase I. [13, 15] ) and E (post-anhepatic phase II.)

The oLT can be divided into several phases (Figure 1). Specifically, the pre-anhepatic (pre-AH) phase (dissection of the porta hepatic), the anhepatic (AH) phase (clamping of the blood supplies) and the post-anhepatic phase (post-AH) which begins with the reperfusion through unclamping the portal vein, the hepatic artery and vena cava. The anhepatic (AH) states lasted $80 \pm 25$ [min], the time between the portal...
vein’s and hepatic artery’s unclamping was 54 ± 29 [min].
The administered nutrition was 0.33 ± 0.24 [mmol/l/min]
for the whole surgery, and 0.20 ± 0.21 [mmol/l/min], 0.21 ±
0.20 [mmol/l/min] for the AH states and the time between
the unclamping the portal vein and hepatic artery. Except
for the parenteral nutrition the patients did not receive any
other nutrition.

2.2 Model

The ICING model (Equation (1-4)) describes a three-
compartment system which contains the insulin changes in
the blood and in the interstitium and the glucose changes
in the blood [1]. Changes in BG arise from glucose release
as well uptake in terms of physiological constants, like
endogenous glucose production (EGP), non-insulin medi-
ated glucose uptake by the central nervous system (CNS),
and other organs (pG). The exogenous input is due to the
parenteral nutrition (Pn) in our case. Glucose uptake by
the cells is identified using an integral-based method. It is
characterized by the insulin sensitivity, SI, which indicates
the ability of the body to utilize insulin. The SI value has
been validated with independent clinical data [16, 17].
Setting up a stochastic model on the SI value changes,
can predict future patient-status and ability for insulin
utilization, enabling a designed intervention of exogenous
insulin and nutrition to maintain a normoglycemic state
with a certain probability. As the methods are validated,
the non-physiological range of SI (i.e. SI <0) shows
an extraordinary state, where this model’s population
constants for EGP and pG, are not able to capture LT
metabolic dynamics.

\[
\dot{G} = -p_G \cdot G(t) - S_I G(t) \frac{Q(t)}{1 + \alpha_G Q(t)}
+ P(t) + EGP - CNS + PN(t) \quad (1)
\]

\[
\dot{I} = -\frac{n_L I(t)}{1 + \alpha_I I(t)} - n_K I(t) - (I(t) - Q(t)) n_I
+ \frac{u_{ex}(t)}{V_I} + (1 - x_L) \frac{u_en}{V_I} \quad (2)
\]

\[
\dot{Q} = n_I (I(t) - Q(t)) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)} \quad (3)
\]

\[
u_{en} = k_1 G(t) + k_2 \quad (4)
\]

2.3 Model-based assessment of the clinical
data

The proper patient-specific values for the physiological pa-
rameter changes are not available. However the direct mea-
surement of EGP or Pg would be beneficial if possible.

Measurements in LT are limited and EGP is not able to be
clinically assessed in real-time [18, 19, 20]. In this case, SI
is identified without a lower positive limit to identify peri-
ods at extraordinary EGP-pG dynamics.

\[
BG_{SI} = \int SI \cdot G(t) \frac{Q(t)}{Q(t)(1 + \alpha_G)} dt \quad (5)
\]

Equation 5 assesses the BG removal by insulin. When it
is negative because SI<0, then it indicates a model failure.
The non-physiological range of the SI value (SI<0) lets us
know the features of the deviations through the SI-related
term’s integration over the related time span (Eq. 5)

3 Results

The fitting ability of the model to capture dynamics in LT is
analyzed on Figure 2. It indicates the times, where the BG
dynamics deviate from the MICU (medical intensive care
unit) or CICU (cardiac intensive care unit) assumptions in
the model. Each line represents a patient along the verti-
cal axis, the horizontal axis shows the time. The patients
data were shifted to t=0 portal vein reperfusion. Almost ev-
every patient episode shows some extraordinary BG glucose
dynamics. By integrating the SI related term (Equation 5),
also quantitative differences between LT patients and the
validated ICU patient model are quantified.

A threshold value was set to distinguish the dynamics. The
threshold value of 2 mmol/l BG input above the validated
ICU patients (Figure 2. A) shows the importance of the por-
tal vein reperfusion. It points out 11 patients, with higher
extra BG input above the threshold value 2 mmol/l, during
reperfusion period (Figure 2), with 5 patients in the pre-
hepatic phase and 6 patients in the post-anhepatic phase
with similar behavior. In some cases, due to the interpola-
tion between clinical blood glucose samples, the integration
intervals overlap two phases; (anhepatic and portal vein un-
clamping as in patients 1125, 1139, 1146, 1151). Figure 3
shows the tendencies for each phase separately, with an in-
creased case number for the portal vein reperfusion and 250
minutes after it.

4 Discussion

In the pre-anhepatic phase it is suggested that the general
deviations from the model are caused by stress response
for surgery interventions. The reperfusion by the release of
portal vein clamp causes generally a rapid rise of BG,
causing severe hyperglycemia. This phenomenon is well
known among clinicians [21, 22]. Based on the data in the
post-anhepatic phase, a critical time interval can be defined
up to 500 minutes after portal vein unclamping, where ex-
traordinary BG dynamics occur. For accurate models and
model-based glycemic control in hepatic transplant patients
we need to find accurate pG and EGP values, because from
these results they, or their balance are clearly not the same
as for general MICU and CICU patients. In this case, it is
clear that LT and that assumptions surrounding EGP, pG or both, are very different for LT patients.

5 Acknowledgements

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References


A prototype to generalize clinical cases of the glucose-insulin system

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Abstract

Simulating glucose–insulin system in normal life conditions can be very useful in medical research. The importance of simulation modeling in medical instrumentation is arriving to reduce medical errors, solve health problem and to improve patient safety. Without simulation, there was a delay in work progress and the cost was more expensive. There was a need for providing higher work productivity, minimum cost. This process enables to virtually investigate many prototypes and analyze all inputs and outputs, constraints and device behaviors. This work proposes a new prototype to generalize clinical cases of the glucose-insulin system, which help detecting performance of all system components. Mathematical representation of this model, and the implementation structure of it, that is composed from two main parts. The first part described as simulator components, contains patient, hardware interface components and scenarios. The second part concerning simulations representation, which can contains simulations of: a closed loop of glucose insulin system, framework for analyzing performance of the system, actuators, sensors and diabetic patient. The simulation of mathematical models used, sensors, actuators and a controller helps to diagnosis the implementation each components of this architecture. This architecture is implemented in case of glucose-insulin system and the simulation is for type 1 diabetes patient glucose metabolism. The implementation of work was using Keil development tools designed for ARM processors and simulated using cycle by cycle keil on microcontroller architecture.

1 Introduction

The glucose-insulin system within the human body acts normally as a regulator of the glucose concentration in the blood (BG), thus preventing hyperglycemia or hypoglycemia. The liver, muscle, adipose tissue and the pancreas have an effect on the glucose flow in the body; the brain and the kidneys also play a role in this equation. The blood glucose level should be maintained in a very narrow range [1]; insulin and glucagon, secreted from the pancreas, are the hormones that regulate this level. When the control of insulin levels fails, diabetes mellitus will result.

Diabetes can be associated with serious complications and premature death but it can be controlled by taking measures that lower the risk of complications. There are two main types of diabetes mellitus: insulin-dependent and non-insulin-dependent [2]. Diabetics persons have to be more or less constantly aware of the current concentration of blood glucose.

Simulating glucose–insulin system in normal life conditions can be very useful in medical research. Simulation models of the glucose-insulin control system during meals and normal daily life has been proposed for studying the pathophysiology of diabetes [3, 4]. Simulation experiments with the mathematical model of a system are valuable tools for student education and medical fields [5]. It can be used to create simulators to test different types of treatment.

However, Mathematical models of glucose regulation have been studied over years. It can be used to create simulators to test different types of treatment. Three compartment models of subcutaneous insulin absorption have been used for the bolus administration and the infusion of rapid-acting insulin [6, 7, 8]. Finally, four insulin action and glucose kinetics models are intended for different purposes: measurement of insulin sensitivity and control [9], simulation and control "Hovorka", simulation "Dalla Man", and control "Panunzi".

Nowadays, medical treatment uses more and more embedded devices such as sensors [10, 11], actuators [12] and controllers [13, 14]. Treatment depends on the availability of well-functioning of complex electronic systems, comprising thousands lines of codes.

The goal of this paper is to define a prototype of the mathematical model of a patient. This prototype must be more flexible and comprehensive so any mathematical models will be defined can be concluded from this prototype.

The outline of this paper is as follows: section II presents the prototype patient model presented in mathematical equations of glucose-insulin system, the implantation structure as well as the clinical cases generation and the results representation. Finally section III is dedicated for conclusions and perspectives.

2 Prototype patient model of glucose-insulin system

Let Mp be a mathematical model for a patient, Pf a set of personal information about the patient that may affect the system, Dm a set of daily meals, Ba a set of body actors, Ir a set of internal relations for the body actors and Er a set of external relations between the body actors, C a col-
lection of constants and Par a collection of parameters. Both C and Par are numerical values used by the relations (equations) in the model.

Let \( W \) is the weight, \( S \) to indicate stress, \( Sp \) to indicate if the person do sport, etc...

\[
Pf = \{W, S, Sp \ldots\} \tag{1}
\]

Let \( B \) is the set of breakfast food values such as calories fat protein etc., \( L \) the set of lunch food value, \( D \) the set of dinner food values and \( Af \) the set of additional portions values such as snacks.

\[
Dm = \{B, L, D, Af\} \tag{2}
\]

Let \( BName \) is the name of the body actor (such as Pancreas, liver), \( SC \) is a set of constants related the concerned \( Ba \), and \( SPar \) is a set of parameters related to concerned \( Ba \), \( SC \) is a subset of \( C \) and \( SPar \) a subset of \( Par \).

\[
Ba = \{Ba_1, Ba_2, Ba_3 \ldots Ba_n\} / \tag{3}
\\ Ba_i = \{BName, SC, SPar\}
\]

Let \( Ir_i \) are an internal relation (mathematical function) for a \( Ba_i \) that uses values from \( SC \) \& \( Ba \) and \( SPar \) \& \( Ba \).

\[
Ir = \{Ir_1, Ir_2, Ir_3 \ldots Ir_n\} \tag{4}
\]

Let \( Er_i \) are an external relation (mathematical function) between two or more \( Bai \) that uses values from \( C \) and \( Par \).

\[
Er = \{Er_1, Er_2, Er_3 \ldots Er_n\} \tag{5}
\]

Let \( C_i \) are predefined constants for the system / \( C = USC \), \( SC \in Ba \)

\[
C = \{C_1, C_2, C_3 \ldots C_n\} \tag{6}
\]

Let \( Par_i \) are input parameters for the system, \( Par = USCPar \), \( SPar \subseteq Ba \)

\[
Par = \{Par_1, Par_2, Par_3 \ldots Par_n\} \tag{7}
\]

Finally \( Mp \) would be a global and flexible model for a patient being able to contain required data for any specific or global medical case study.

\[
Mp = \{Pf, Dm, Ba, Ir, Er, C, Par\} \tag{8}
\]

This model can feed (input) the device model with its needed values via the results of the relations sets (\( Ir \) and \( Er \)) as well as the parameters set \( Par \).

### 2.1 Implementation structure

This part is described as “simulator components” (figure 1), contains a patient mathematical model; this model must be developed to better understand the mechanisms of the human organic system, hardware interface components described by input/output which represents hardware used like motherboard, sensor and actuators. Also, generating virtual patients in order to have multiple scenarios to analyze performance. There are many constants and parameters involved in the model. There are usually decided upon by collecting data or experimenting.

The part II named “Simulations representation” represents the simulations of: glucose-insulin system, patient, framework, actuator, sensors

![Simulator components & Simulations representation](image)

In the simulator components part I, the mathematical model “Hovorka” was implemented using Keil [15] development tools designed for ARM processor-based microcontroller devices that works with embedded C language. In the interface components, sensors and actuators were simulated using codes that simulate their functions.

Each components of part II has been simulated. Part II represents all the components that has been simulated (patient, sensor, actuator, controller, framework, glucose-insulin system closed loop). Also, a new tester model was created in order to analyze the performance of all the components of the glucose-insulin system [16]. All are simulated also using Keil development tools designed for ARM processor-based microcontroller devices and works with embedded C language.

The advantage of using Keil in our work is to define a model that works with embedded C language and can be implemented in a microcontroller.

The algorithm of the controller was programmed using embedded C program and simulated using cycle by cycle keil on architecture type 8051 [17]. His main role was to regulate the blood sugar level by insulin injection or by glucagon addition in order to maintain an existing trend in blood sugar levels between 70 mg/dl and 110 mg/dl.

### 2.2 Clinical cases generation

The Hovorka model used has been selected according to the need of the research. This is a complete model for the glucose-insulin system during a meal and it was developed using glucose tracers. This model which has two inputs meal disturbances and insulin infusions (d(t), u(t)) can simulate a diabetic person.

The parameters of the system are defined as follows: \( Q_1 \) and \( Q_2 \) represent the masses of glucose in the accessible and non-accessible compartments; \( x_1, x_2 \) and \( x_3 \) represents three actions of insulin on glucose kinetics; \( S_1 \) and \( S_2 \) are a two-compartment chain representing absorption of subcutaneously administered short-acting; \( I \) describes the plasma insulin concentration; \( D_1 \) and \( D_2 \) are a two-compartment chain representing the amount of carbohydrates digested (figure 2).
Eight variables were considered as the inputs data providing to each one of them different values in order to simulate the Hovorka model. The \((Q_1, Q_2, S_1, S_2, I, x_1, x_2, x_3, t)\) help to generate data while solving the Hovorka mathematical model. Indeed, solving mathematical equations inside each parameters helps to have “clinically accurate” results.

A simple modification in each parameters help to have different patient state. The severity of a patient can be modified by changing parameters values. The objective is to have multiple scenarios in order to use them in the implementation part. We have use the suitability of partially observable Markov decision processes [18] to formalizing the planning of clinical management (figure 3), Where \(\alpha_i\) the modification values when generation these virtual patients, taking into consideration the approximation range of each parameter [19].

A virtual population of subjects with type 1 diabetes comprises a simulation model of the glucose regulation accompanied by N parameter sets representing N virtual subjects.

The process flow in developing the methods used to generate and simulate glucose-insulin regulatory system is shown in Figure 4. Using Keil and a simple program help to test debug and simulate it, which can be very useful in testing fields.

There is also a need to improve the quality of the services provided, by ensuring biomedical are fit for purpose, which give an opportunity to develop new services or new diagnosis with an objective of upgrading and improvement.

2.3 Results graphic representation

In 1987, Clarke et al. designed the error grid analysis (EGA), taking into consideration not only the difference between the system-generated and reference blood glucose values but also the clinical significance of this difference [20]. There are 5 risk categories are defined as follows: A: no effect on clinical action; B: little or no effect on clinical outcome; C: likely to affect clinical outcome; D: could have significant medical risk; and E: could have dangerous consequences.

Later in 2008, to visualize the overall glycemic control, new tool has been introduced CVGA [21]. Use percentile, as measurement unit instead of the absolute minimum/maximum, reduces the vulnerability of the analysis to outliers.

Use this grid (figure 5) with the percentile function to represent virtual patients generated. We simulate 8 virtual patients for the glucose regulation, which are situated in Zone A and Zone B in the grid. The simulation period is 24 hours; in a day study each person would get a data point on the grid. This Grid help us to simulate virtual patients severity taking into consideration the modification values \(\alpha_i\).

3 Conclusion

The prototype was implemented using Keil development tools designed for ARM processor-based microcontroller devices with different parameters scenarios, which give the ability to co-simulate the glucose insulin model.

We have provided a model that represents a global view of the biomedical equipments, based on repeated simulation to minimize the error. The purpose of this architecture is to have a complete environment with the ability to co-simulate the glucose insulin model.

Further, future work will be carried out to define a prototype to generalize modeling of medical devices.
4 References


Estimating Relative Change in Ventricular Stroke Work from Aortic Pressure Alone: Proof of Concept Study

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Abstract

Continuous Ventricular Stroke Work (VSW) estimation requires accurate estimate of both stroke volume and aortic pressure. However, accurate beat-to-beat stroke volume measurement is highly invasive and typically unavailable in clinical practice. This study analyses the accuracy of a model-based method estimating relative change in VSW using only aortic pressure measurements. Using data from porcine experiment, the correlation coefficient was determined between the relative change of VSW from directly measured data and the model-based estimate of VSW. The result showed good agreement with, R=0.71. The model accurately captured the trend of VSW using only aortic pressure measurements and thus offers significant clinical value in early diagnosis and improving care for cardiovascular dysfunction.

1 INTRODUCTION

Ventricular Stroke Work (VSW) is an important physiological parameter for assessing cardiovascular function [1]. Decreased VSW is related to many cardiovascular dysfunctions and initial signs of heart failure [2]. Providing real-time continuous estimation of VSW could enable diagnosis of shock at an early stage improving patient outcomes [3].

VSW can be calculated using measured Stroke Volume (SV) and Mean Aortic Pressure (MAP) [4]. However, accurate, continuous SV measurement requires highly invasive instrumentation, such as admittance or conductance catheters directly inserted into the ventricles, and thus are not clinically feasible. Currently, intermittent estimates of SV are made by thermodilution or continuous estimates using continuous cardiac output monitors [5]. However, derived SV in the latter case are simply functions of MAP and the accuracy is low during haemodynamic instability due to fixing certain physiological parameters [6].

This paper presents an aortic model for estimating relative change in VSW from aortic pressure measurement. Pressure-velocity (PU) gradient in the aortic compartment is identified from aortic pressure contour and the relationship between VSW and the gradient is analyzed. The presented method updates physiological parameters every heart beat and thus, eliminates inaccuracy from constraining key metrics. To validate the model, the correlation was determined between measured VSW and estimated aortic PU gradient.

2 METHODS

The aortic model in this study incorporates two existing theories on flow in an elastic tube: 1) reservoir-excess pressure [7]; and 2) Pulse wave propagation [8]. The schematic of the process for estimating relative change in VSW from aortic pressure measurement is shown in Figure 1.

![Figure 1 - Schematic of estimation procedure](image)

2.1 Porcine Experiments

Experiments were performed on pure pietrain pig. During the experiment, several step-wise positive end expiratory pressure (PEEP) recruitment manoeuvres (RM) were performed, causing changes to SV and VSW [9]. This experiment were conducted to investigate respiratory failure, but extensive CVS measurements were recorded. Details of the experimental procedure are published elsewhere [10].

Left ventricular volumes and pressures were measured using 7F admittance catheters (Transonic Scisense Inc., Ontario, Canada) inserted directly into the ventricles through the cardiac wall. Proximal aortic pressure was measured with a 7F pressure catheter (Transonic Scisense Inc., Ontario, Canada) inserted into the aortic arch through the carotid artery. All data were sampled at 200
Hz and were subsequently analysed using Matlab (version 2013a, The Mathworks, Natick, Massachusetts, USA).

2.2 Aortic Model
Continuous aortic pressure waveforms were split into individual heart beat for analysis of beat-to-beat changes in the arterial energy. For each beat, model-based analysis of the pressure contour was performed to estimate aortic PU gradient.

2.2.1 Reservoir-Excess Separation
The pressure separation method used in the aortic model is based on the theory proposed by Wang et al. [11]. The theory states that aortic pressure (Pao) can be separated into two components, reservoir and excess pressure. Reservoir pressure (Pres), represents energy stored and released by the volumetric change in the aortic compartment. Excess pressure (Pex), defined as the difference between the measured aortic pressure and the reservoir pressure, which accounts for the propagation of waves through the aorta.

\[ P_{ao}(t) = P_{res}(t) + P_{ex}(t) \]  

(1)

The paper also describe the linear proportionality between each pressure component and flow dynamics in the aortic compartment

\[ P_{res}(t) - P_{msf} \propto Q_{out}(t), \quad P_{ex}(t) \propto Q_{in}(t) \]  

(2)

Where Qin, Qout are flow entering/leaving the aortic compartment and mean systemic filling pressure [12], respectively. In this case, proportionality constants are peripheral resistance (R), and characteristic impedance (R*) for Qin and Qout [13] respectively. By assuming that pressure decay in the diastolic region results from only volumetric change of the arterial compartment [14] and identifying the exponential decay time constant (τ) in diastole [15]. The diastolic reservoir pressure can be expressed:

\[ P_{res}(t) = (P_{ao}(t_d) - P_{msf})e^{-\frac{(t-t_d)}{\tau}} + P_{msf} \]  

(4)

Where \( t_d \) is the time of closure of the aortic valve. In this model, the identified exponential decay time constant \( \tau \) represents product of peripheral resistance and compliance of the aortic wall (\( \tau = RC \)) [16], and the start of diastole was defined by the time of the minimum rate of change of \( P_{ao} \) [17].

To identify reservoir pressure during the whole cycle, conservation of mass and proportionality described in Equation (2) was applied:

\[ \frac{dV(t)}{dt} = Q_{in}(t) - Q_{out}(t) \]  

(5)

\[ \frac{dP_{res}(t)}{dt} = a(P_{ao}(t) - P_{res}(t)) - b(P_{res}(t) - P_{msf}) \]  

(6)

Where \( a \) and \( b \) are \( 1/R_\circ C \) and \( 1/\tau \) respectively. The analytical solution to Equation (6) for \( P_{res} \) is defined:

\[ P_{res}(t) = e^{-\beta t} \left( \int_0^t e^{\beta t'} (aP_{ao}(t') + bP_{msf}) dt' + P_{res,0} \right) \]  

(7)

Where \( \beta = a + b \). The identification of \( b \) involves additional assumption that \( Q_{in} \) equals \( Q_{out} \) in the region between the point of maximum \( P_{ao} \) and \( t_d \) due to aortic valve closure. Using this additional information, Equations (5) and (6) can be rearranged:

\[ \frac{dV(T)}{dt} = 0 \]  

(8)

\[ P_{res}(T) = \frac{aP_{ao}(T) + bP_{msf}}{a + b} \]  

(9)

Where \( T \) is the time when \( Q_{in} \) equals \( Q_{out} \). The estimate of \( b \) is identified by nonlinear regression using Equations (7) and (9) with maximum value of aortic pressure as first guess of \( P_{ao} \) at time \( T \). To identify the correct value of \( b \), the value of \( P_{ao} \) is iterated until Equation (8) is satisfied.

Once the parameters \( a \) and \( b \) are identified from the aortic pressure contour, \( P_{ao} \) is separated into reservoir and excess pressure using Equations (7) and (1). Example of the separated pressures and flow dynamics in the aortic compartment for the whole heart beat is shown in Figure 2. In addition, volume stored and released by the aortic system (\( \Delta V_{ao} \)) is also shown as the difference between area under the curve of \( Q_{in} \) and \( Q_{out} \).

![Figure 2](https://example.com/figure2.png)

**Figure 2** - Top panel: example of aortic pressure separation showing estimated diastolic curve (red line), reservoir pressure \( P_{res} \) (blue line), excess pressure \( P_{ex} \) (shaded grey area), and measured aortic pressure \( P_{ao} \) (black line). Bottom panel: Estimated aortic inflow \( Q_{in} \) (black line), outflow \( Q_{out} \) (blue line), and zero net flow time \( T \) (vertical black line), and volume changes in aortic compartment (shaded grey area).
2.2.2 Pulse Wave Velocity
To determine the velocity of the pulse wave through aortic compartment, the Bramwell-Hill equation was applied [18]:

\[ c = (\rho D)^{-1/2} \] (10)

\[ D = \frac{\Delta V_{ao}}{V_{ao} \Delta P_{ex}} \] (11)

Where \( \rho \) and \( D \) are blood density and aortic distensibility, respectively, and \( c \) is PWV. The advantage of applying this theory is that knowledge on thickness, elasticity or radius of the arterial wall is not required to determine distensibility. In addition, only the value of aortic volume proportionality is necessary and the exact absolute value of volumetric change in the aortic compartment is not required.

To determine aortic distensibility, the integral of the separated pressure waveforms \( P_{res} \) was used with the assumption that aortic compartment volume at the start of systole equals the volume at the end of diastole [19].

\[ \Delta V_{ao} (systole) = \Delta V_{ao} (diastole) \] (12)

\[ \frac{\Delta V_{ao}}{V_{ao}} = \int_{t_0}^{t_f} P_{res}(t) - P_{msf} \, dt \] (13)

Where \( t_0 \) and \( t_f \) are time at start and end of the heart beat, respectively. Once the volume proportionality is identified, Equations (10) and (11) are used to calculate PWV in the aortic compartment. Finally, the pressure and velocity relationship \( \rho c \) defined by the Joukowsky equation [20] can be determined.

\[ \rho c = \frac{\Delta P}{\Delta V} \] (14)

2.2.3 Data Analysis
The original aortic waveform data was pre-processed by removing regions where obvious measurement error occurred due to equipment, catheter disturbance or failure. In this study, VSW were calculated from the area enclosed by the measured left ventricular pressure-volume \( (P_{lv} - V_{lv}) \) loop.

\[ VSW = \int P_{lv}(V_{lv}) \, dV_{lv} \] (15)

2.2.4 Limitations
Data from only one pig were analyzed in this study. However, more than 1500 heart beats across a range of SV values induced by changes in PEEP were analyzed. Thus, despite the analysis being subject specific, this study demonstrates the feasibility of accurately and continuously identifying the relative change in VSW using only aortic pressure measurements.

To fully examine the robustness in capturing the fluctuations in VSW using this aortic model, further study needs to be carried out with aortic pressure contours influenced by a range of cardiovascular dysfunction.

3 Results
Investigated ranges of SV, VSW, and MAP in this study are presented in Table 1. The estimated \( \rho c \) compared to the calculated VSW are presented in Figure 3. Correlation plots between estimated \( \rho c \) and measured VSW are presented in Figure 4.

Table 1: Investigated range of physiological parameters SV, VSW, and MAP. Data are presented as the median [5–95th percentiles]

<table>
<thead>
<tr>
<th>Investigated Physiological Range</th>
<th>SV (ml)</th>
<th>VSW (Joule)</th>
<th>MAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.1 [14.9–28.8]</td>
<td>0.27 [0.15–0.33]</td>
<td>80.7 [70.8–96.2]</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3 – Top Panel: showing VSW variation induced by recruitment maneuvers (blue line) and estimated PU gradient value \( \rho c \) from model based analysis of aortic pressure contour (green line). Bottom Panel: simultaneously measured airway pressure to show the PEEP changes.

Figure 4 – Estimated \( \rho c \) versus calculated VSW showing relationship between the two parameters. The plot indicates that there are high degree of agreement with correlation coefficient of \( R=0.71 \).
4 Conclusion

Physiological models are simplified representations of reality that can provide clinicians with information for decision making, without the need for additional invasive direct measurements. The model presented in this study show the potential for continuous, accurate VSW trend to be captured by estimating PU relationship in the aortic compartment and using the identified value as an index to evaluate relative change in VSW. Incorporating this model in clinical settings can lead to not only early diagnosis of deteriorating patients, it enables the response of clinical interventions such as inotropes, vasoactive, and fluid therapy to be evaluated. The aortic model shows the ability for improving cardiac and circulatory treatment in the critical care environment.

5 References


Enhanced Fluorescent Cell Simulation using Texture Mapping and Statistical Shape Model

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Abstract

Manual evaluation of fluorescent microscopy cell experiments is time-consuming and tedious work. Therefore, often automated segmentation algorithms are applied to ensure an efficient evaluation with constantly high quality for the whole dataset. Image segmentation quality is usually validated and rated with manually annotated data, being the “gold-standard”, but which is time-consuming, prone to errors and furthermore shows inter- and intra-labeler variances. As an alternative, cell simulation can be used for the generation of cell images and related real ground truth data. Within cell simulation frameworks, individual cells can be modeled with specific shape and texture. For the simulation of cell, we use statistical models computed from manually annotated real cell images. Different types of cell textures can be mapped from cells extracted from real micrographs into the simulated cell shapes. In this contribution we present resulting images for HeLa cells that show that our approach is suitable for the simulation of fluorescent micrographs.

1 Introduction

Manual evaluation of microscopy cell experiments is a time-consuming, tedious and error-prone work. Therefore, most often automated or semi-automated image processing methods are applied to ensure an efficient and reproducible evaluation with a constant high quality for the complete dataset. Nevertheless, the most crucial processing step within the image processing pipeline is the segmentation step of individual cells and cell compartments (nuclei, plasma, skeleton). For rating and validation of various cell segmentation algorithms often manually annotated datasets are used as so-called “gold-standard”, but which are known to be erroneous and additionally show strong variations among different observers. E.g., a benchmark collection of cell micrographs including manually obtained ground truth data is offered by the Broad Institute and is available on the internet [1]. An alternative method to validate image segmentation algorithms is based on simulated image data. E.g. fully simulated cell micrographs are available from SimuCell [2] and generative models are used in [3]. In contrast, the generic simulation approaches integrated in our simulation framework as proposed in [4], utilizes shape and texture information obtained from real cell micrographs. The simulation is able to create a large variety of image sets based on a representative set of manually annotated ground truth data. New cell shapes are created with a statistical shape model which enables the generation of cell shapes for a wide variety of cells. Cell texture synthesis is obtained from available real images. In this contribution, we train the cell simulator with a HeLa micrograph dataset and test cell shape and cell texture generation for cells and nuclei.

2 Methods

A reference image dataset depicting HeLa cells and corresponding nuclei with manually annotated ground truth, presented in section 2.1, is used for the training of the statistical cell shape generator. The statistical cell shape generator and the cell texture generator will both be described in sections 2.2 and 2.3. Both generators have been integrated into our simulation framework recently described in [4].

2.1 Reference: HeLa micrograph dataset

The reference dataset, used to train a statistical cell shape model, contains 30 image sets (DiD-stained cells, DAPI-stained nuclei) depicting a total of 1,060 cell objects, which have all been manually annotated in the DiD channel. The corresponding DAPI channel contains 993 manually annotated nuclei. Image 1 shows exemplary micrographs from the reference dataset including their manually obtained annotations.

Image 1 fluorescent image of DiD stained HeLa cells (a); manually-acquired manual annotation of the cell plasmas (b); related DAPI stained cell nuclei (c); and corresponding manual annotation (d); scale bars corresponds to 100 µm, images a, c and e captured with 20x oil immersion objective with a spatial resolution of 1388x1040 pixels.
2.2 Cell shape generation

Within our framework, cell shapes can be generated based on statistical shape models [3, 5]. Each cell shape can be computed to describe and simulate a specific cell type with typical shapes. Image 2 shows the typical workflow to generate such model and to use it for cell simulation.

![Image 2 Workflow cell shape synthesis.](image2)

Starting point of the shape training is the manual annotation of N cells from real cell micrographs, to ensure that valid cell shapes are simulated with the calculated statistical model. Then each annotated cell’s contour is sampled with the same number C of points. These C points are then translated to have zero-gravity and rotated so that the first principle axis calculated with principle component analysis (PCA) of the C points is aligned to the x-axis in a Cartesian grid. Then all N shapes are transformed into a descriptive vector v. The pixel with the smallest distance from the x-axis in the right half of each cell shape yields the starting point v₀ in each vector. The N aligned cell shapes, respectively their representing vectors, are then analyzed statistically with the PCA. The number Nₑ of Eigenvectors incorporated into the model contain about 95 percent of the variability of the manual annotations. All other Eigenvectors are discarded. The Eigenvectors can be used to calculate a linear transformation between the model and the shape space.

Now, to simulate cell shapes, model parameters b (weighting factors for the Eigenvectors) are chosen within a valid range and transformed from the model to the shape space with:

\[ x = x_m + Pb \]

where \( x \) is the new shape vector and \( x_m \) is the mean shape vector. The matrix P contains the first \( N_e \) eigenvectors, which are weighted with the model parameters b [5].

2.3 Cell texture generation

The thus generated cell shapes need now to be texturized to represent a typical cell on a simulated fluorescent micrograph. We propose the texture mapping method, as illustrated in image 3. Central part of the method is the texture extraction algorithm which is used to obtain textures of real cells as reference and for mapping these extracted textures back to the simulated cell shapes. The algorithm is based on the cell shape and described in the following:

1. Search the center \((x_0, y_0)\) of gravity of the shape.
2. Select a border pixel \((x_b, y_b)\).
3. Ray trace between center of gravity \((x_0, y_0)\) and a selected border pixel \((x_b, y_b)\) and write the traversed intensity values into an array.

Image 3 Workflow for cell texture synthesis.

4. Calculate coordinates on texture patch for the \(i\)-th border pixel and the \(j\)-th pixel in the array with size \(s\) and texture patch height \(h\), with \(u\) and \(v\) being the coordinates in X and Y direction:

\[ u(i) = i \]
\[ v(j) = \frac{h}{s} * j \]

The coordinate system is illustrated in Image 4.

5. If further border pixels are available, go on to the next border pixel and repeat the steps beginning with step 3, else go to step 6.

6. Interpolate between the pixels on the patch to fill empty pixels.

In the first step of the proposed method the texture mapping is used to obtain texture patches from manually annotated cells from real micrographs. Therefore, the texture mapping algorithm is repeatedly applied for each selected cell. All resulting patches are added to the texture patch database and stored to in a disk repository. This texture database can now be used for repeated cell micrograph texture simulation with varying simulation parameters. The simulation allows the control of certain parameters such as number of cells or overlap of different cells which cannot be easily controlled within real cell experiments [4]. In the simulation step the texture patch is randomly selected from the database and mapped to the simulated cell shape with the above described texture mapping algorithm. In our simulation framework, these simulated cells are combined to cell micrographs according to the selected algorithms [4].

Image 4 Creating a texture database: original cell (a); manual annotation (b); resulting texture patch (c)
### 3 Results

The algorithms described in the previous section have been applied to simulate HeLa cell image sets with DiD and DAPI channels. The generators for cell plasma and cell nuclei shapes have been trained with the reference dataset presented in section 2.1. In this section the resulting statistical models and texture patch databases for DiD stained cells and DAPI stained nuclei are presented as well as an exemplarily simulated image set.

The model of the cytoplasm has been trained with \(N=200\) isolated (non-touching) cell shapes which have been manually annotated in the DiD channel of the reference dataset. Each cell boundary has equidistantly been sampled with \(C=40\) points. The model covers 95 percent of the cell variability with ten Eigenvectors. Mean shape and variability covered with the first Eigenvector of the model is illustrated in Image 5 (a-c).

The cell nucleus model has been calculated using \(N=801\) nuclei from the DAPI channel from the reference fluorescent image example dataset. The nucleus boundary was sampled with \(C=20\) points. 95 percent of the nucleus variability is covered by first five Eigenvectors (see image 5 d-f) for the variability of first eigenvector).

The texture patch database for the cytoplasm of the HeLa cells consists of \(N=200\) texture patches of isolated cells from the DiD channel of the example dataset. The nucleus database has been created from \(N=801\) nuclei from the DAPI channel.

Our cell simulation algorithms have been applied in our framework to simulate cell shape and texture for additional image pairs of DiD and DAPI channels. Also, the placement of the simulated cell compartments on the simulated micrographs can be controlled. Furthermore, the simulation provides additional information for the image background as well as noise generation for each channel. Both channels are simulated without any artifacts such as illumination errors. The DiD channel has been added with Gaussian noise with mean \(\mu=0\) and standard deviation \(\sigma=5\), while the DAPI channel shows Gaussian noise with mean \(\mu=5\) and standard deviation \(\sigma=5\). Image 6 shows a resulting image tuple of DiD stained cells and DAPI stained nuclei.

### 4 Conclusion

The resulting pictures in images 6 show that our approach is suitable for the simulation of fluorescent image sets. The critical point for the cell shape generation is the point correlation for the training of the statistical model. In particular, it is crucial for cell types with highly varying shapes to generate valid cell shapes. Furthermore, the quality of the simulated textures is dependent from the quality of the extracted texture patches. Therefore, datasets with a high signal to noise ratio are preferred for the texture patch extraction. In a next step, multiple texture patches could be combined to increase the number of possible cell textures. The evaluation and validation of the cell simulation is still an outstanding task and will be addressed in the next couple of months.

![Image 5](image5.png)  
**Image 5** Resulting model for the cytoplasm (a-c) and nucleus of HeLa cells (d-f): Mean shape of DiD channel (a); variation on first principle axis to \(-4\sigma\) (b); and variation on first principle axis to \(4\sigma\) (c) mean shape of cell nucleus (d); variation on first principle axis to \(-4\sigma\) (e); and variation on first principle axis to \(4\sigma\) (f) For illustration purpose all images have been resized.

![Image 6](image6.png)  
**Image 6** Image pair of simulated HeLa cells in DiD stain (top); DAPI stained nuclei (bottom).
Acknowledgement

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References

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Direct optical spectral modulation with a Digital Micromirror Device (DMD) – Raytracing simulations of two input slit variants

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Introduction
A novel approach for the testing and calibration of pulse oximeters based on the direct spectral and temporal modulation of the pulse oxymeter’s light signals has been proposed in the past. It uses a spectroscopic setup combined with a Digital Micromirror Device (DMD), to image the spectrum of the light signals on the DMD surface. The DMD reflection pattern then modulates the spectral components, which are finally guided back to the pulse oxymeter. A major problem is the overall light throughput, limited for example by the mechanical input slit. This work describes the possible replacement of the slit by a rectangular fiberbundle, which yields in an approximately 3-fold enhanced throughput.

Methods
Raytracing simulations were performed with FRED (64bit) Optimum 12.107 (Photon Engineering, Tucson, USA) to compare irradiance distributions in the spectrum plane for three different wavelengths (500 nm, 750 nm, 1,000 nm). Two different input slit variants were modelled: A circular thickcore fiber (core diameter 1 mm, NA = 0.22) with a mechanical slit (width 100 µm) placed in front, and a bundle of 45 linearly arranged fibers (core diameter 100 µm, NA = 0.22, total height of the bundle 6.35 mm) without a mechanical slit. Collimating and imaging optics were the same for both models. An iterative method was used to sum and average over multiple independent simulations to achieve statistically relevant data.

Results
The simulations showed an approximately 3-fold higher irradiance for the fiberbundle compared to the classical fiber-slit-combination. The greater height of the fiberbundle leads to a more efficient illumination of the DMD surface.

Conclusion
The results show a promising way to improve the overall optical throughput of the whole system, yet this has to be confirmed experimentally. There are additional bottlenecks which have to be assessed for a possible efficiency increase, e.g. spectral recombination of the decomposed light.
Using in-silico and real patient data to determine the influence of calibration on model prediction in a simple model of gas exchange

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Introduction

Applying mechanical ventilation has become a routine therapy in intensive care, but it poses the risk of inflicting further damage to the lung if ventilator settings are not set properly. Mathematical models are able to predict a patient’s reaction to changes in the therapy regime and might thus be exploited to determine optimal ventilator settings. Simple models provide the benefit of requiring only a small number of data for calibration, however measurement noise and the point of calibration have great influence on the predictive outcome. We have thus explored the influence of the calibration point on the predictive outcome of a simple gas exchange model.

Methods

A one-compartment gas exchange model was evaluated with both artificial and real patient data. All patients were ventilated at different levels of oxygen in the inspired air (FiO₂) and resulting PaO₂ was recorded. Artificial data was created using a two-compartment model and adding a random noise of 5%. The simple model was calibrated at different calibration points and results were compared to the clean artificial data and real patient data.

Results

Results show that the calibration point influences simulation error. The simple model is able to reproduce recorded data with a mean deviation of less than 10% if calibration is done at an FiO₂ of more than 50% in artificial patients and 70% in real patients. Calibration with noisy data resulted in a standard deviation of less than 5% in patients with a V/Q ration of less than 4.3 if calibration is done at an FiO₂ of 70%.

Conclusion

Calibrating in a noisy environment influence the predictive outcome of mathematical models. The study showed that in-silico data can be employed to define an optimal calibration point minimizing the influence of measurement noise on the simulation error. Results with artificial data were confirmed with real patient data.
The influence of measurement noise on parameter identification in a mathematical model of gas exchange

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Introduction
In acute lung failure, mechanical ventilation is a routine therapy to maintain a patients’ pulmonary function. Finding appropriate ventilator settings empirically is risky since inappropriate settings may lead to additional lung injuries. Mathematical models offer the advantage of providing predictions on a patient’s reactions to changes in therapy. Those predictions are based on physical principles rather than empirical observations. Thus they might serve as a tool to provide suggestions on optimal ventilator settings. Robust parameter identification is a cornerstone for providing reliable predictions being majorly influenced by measurement noise and the available number of data.

Methods
A two-parameter model of human pulmonary gas exchange with shunt (fs) and ventilation-perfusion mismatch (fA) was analysed using in-silico data sets, representing both mild and severe lung injury. To simulate measurement errors, uniformly distributed noise with a range of 10% was added to the previously computed PaO₂ and PaCO₂. Parameter identification was conducted at each of the computed measuring points and the identified parameters were compared to exact values used for generating the data.

Results
Using the mild lung injury data set, fA was identified with a standard deviation (std) of about 8.8%, while std of fs was 6.7%. In severe lung injury data, std for fA was 7.5% and 3.7% for fs. We also observed, that the calibration point, i.e. the applied FiO₂ at the time of calibration, has an additional influence on the correctness of the identified shunt fraction.

Conclusion
Results show that parameter fA is more sensitive to measurement errors in data used for model calibration than parameter fs. That influence increases with the severity of lung injury. Furthermore, reliability of parameter identification is depending on the calibration point. Thus, this work provides information about the reliability of identified parameter values and deviations when measurement accuracy of calibration data is known.
Evaluating selection criteria for physiological models of various complexities

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Abstract

The use of mathematical models of the human physiology is an established method for advanced clinical therapy of post-surgical or lung-injured patients. Such models may support the clinicians by predicting a patients’ reaction to changes in ventilator settings. This should aid in decreasing the risk of ventilator induced lung injuries and reduce the time a clinician needs to attend to a patient. Simulation results can be achieved with models of different complexities and simulation focus. Providing various models allows adoption of the simulation to different patient conditions. However, numerical measures that define how well a model fits the given situation need to be established. These selection criteria would allow an unbiased selection of appropriate models for the current patient status. Evaluating several gas exchange models on patient data and computing different selection criteria lead to the result that a combination of coefficient of determination with the corrected Akaike information criterion leads to a clear preference which model should be preferred in each case.

1 Introduction

Mechanical ventilation is a commonly used therapy in intensive care. Clinicians routinely choose ventilator settings for the treatment of lung-injured and operated patients, according to their symptoms and conditions. The goal is to ensure adequate gas exchange by providing sufficient oxygen transfer together with carbon dioxide removal. Using mathematical models allows prediction of patients’ behaviour to changes of ventilator settings. For instance, the expected change in arterial partial pressure based on different levels of inspired oxygen fraction can be predicted. Such models may be implemented in decision support systems to aid clinicians in selecting appropriate ventilator settings. This reduces the risk of ventilator induced lung injuries caused by mismatched settings and ensures sufficient oxygen supply. Physiological gas exchange models characterize oxygen and carbon dioxide distribution in lung, blood circuit and body tissue. Patient-individual parameterization is carried out by parameter identification, including suitable initial parameter values as initial guesses. With increasing model complexity the required detail of information for robust parameter identification inevitably increases. Thus, even though they may provide less detail, simpler models should be preferred as they require an accordingly smaller amount of data for robust parameter identification. Therefore, a compromise between the level of simulation detail and efficiency in terms of computing time and the actually needed information exists. Consequently, different model versions should be provided for various patient conditions and the amount of available data, respectively. In order to enable a decision support system to select the right model it needs to be provided with a numerical measure that describes how well a model fits the measured data with a minimal complexity. The relation between model parameters and the quality of simulation results can be classified by so called information criteria. Model selection should be performed by choosing the simplest model, that best describes the given data. In this work, three models with a different complexity, i.e. the number of free parameters are compared on the basis of different criteria using clinical patient data.

2 Methods

2.1 Gas exchange models

Model 1 is a one-parameter model including one ventilated compartment and a pulmonary shunt which is perfused but not ventilated [1-3]. Parameter $f_s$ defines the size of the shunt compartment, i.e. the amount of blood not taking part in gas exchange. Image 1 shows a schematic overview of model 1. Blood flow is depicted as solid line, air flow as broken line.

![Image 1 One-Parameter model with parameter $f_s$.](image1.png)

Model 2 includes two parameters. It is an extension of model 1 and includes an additional ventilated compartment [2, 4]. Both alveolar compartments in this model are ventilated and perfused with a different ratio. One com-
partment receives 10% of the non-shunted blood flow while the other one receives 90% [2]. Parameter $f_A$ characterizes the distribution of ventilation between the compartments. Image 2 gives a schematic overview of the model structure. Blood flow is depicted as solid line, air flow is shown as broken line.

Model 3 includes three parameters. It extends Model 2 by a third parameter ($f_Q$), which allows various settings for ventilation/perfusion in the two ventilated compartments [2, 5]. Thus, instead of a fixed distribution of blood among the compartments, the actual distribution is determined by $f_Q$. Image 3 shows a schematic overview of the model structure. Blood flow is depicted as solid line, air flow is shown as broken line.

In all models constraints are steady state assumptions, mass conservation and continuous ventilation [2].

2.2 Patient data and identification

Clinical data of five patients taken from a patient data management system was used for retrospective comparison of the models. Patient data included in the study had to contain at least three different levels of FiO2 in a period of less than 2 hours. Model parameters $f_S$, $f_A$ and $f_Q$ were tuned so that simulated PaO2 (arterial partial pressure of oxygen) and PaCO2 (arterial partial pressure of carbon dioxide) would fit the measured values. Table 1 shows all parameters that were included in simulation and parameter identification.

<table>
<thead>
<tr>
<th>Value</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Rate</td>
<td>RR</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>$Q$</td>
</tr>
<tr>
<td>Tidal Volume</td>
<td>$V_{td}$</td>
</tr>
<tr>
<td>Anatomic Dead Space</td>
<td>$V_d$</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>$H_k$</td>
</tr>
<tr>
<td>Temperature</td>
<td>$T$</td>
</tr>
<tr>
<td>pH-Value</td>
<td>$pH$</td>
</tr>
<tr>
<td>Base Excess</td>
<td>$BE$</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>$Hb$</td>
</tr>
<tr>
<td>End Tidal Oxygen Fraction</td>
<td>$FetO_2$</td>
</tr>
<tr>
<td>End Tidal Carbon Dioxide Fraction</td>
<td>$FetCO_2$</td>
</tr>
<tr>
<td>Arterial Partial Pressure of Oxygen</td>
<td>PaO2</td>
</tr>
<tr>
<td>Arterial Partial Pressure of Carbon Dioxide</td>
<td>PaCO2</td>
</tr>
<tr>
<td>Inspired Oxygen Fraction</td>
<td>FiO2</td>
</tr>
</tbody>
</table>

Parameter identification was realized with a weighted sum of squared errors approach (SSEW) minimizing the difference between measured and calculated values. Equation 1 shows the target function, where carbon dioxide measurements are weighted with a factor of 2 to account for the usually lower values compared to oxygen values. Here, $PmO_2$ and $PmCO_2$ are the simulated values, $PaO_2$ and $PaCO_2$ are measured values.

$$SSE_W = \sum_{i=1}^{n} (Pm_{O_2} - Pa_{O_2})^2 + 2 \sum_{i=1}^{n} (Pm_{CO_2} - Pa_{CO_2})^2$$  \(1\)

All Models were implemented in MATLAB (R2012a, The Mathworks, Natick, USA). Parameter identification was performed using the function fminsearchbnd, an extension of the fminsearch minimization-function allowing to provide boundary conditions. Both functions employ the Nelder-Mead Simplex method [6]. Each model was tested with all five patient data sets.

2.3 Information criteria

Objective selection of competing models can be achieved by applying information criteria or rather selection criteria. Both the sum of squared errors (SSE) and the mean squared residual (MSR) are measures to provide information on how well a model is able to represent the given data, i.e. how much the simulated results deviate from the recorded data. Equations (2) and (3) show the calculation of SSE and MSR. Here, $n$ is the number of measured values.

$$SSE = \sum_{i=1}^{n} (Pm_{O_2} - Pa_{O_2})^2 + \sum_{i=1}^{n} (Pm_{CO_2} - Pa_{CO_2})^2$$  \(2\)

$$MSR = \frac{SSE}{n}$$  \(3\)
The coefficient of determination (CD) provides information of the goodness of fit as well. However in contrast to SSE and MSR it provides a normalized measure, i.e. the calculated value for one data set can be compared with other data sets. A CD value of 1 denotes a perfect agreement between simulated and measured values, while a CD value of 0 means that the model has no relation to the data [7]. Equation 4 shows the calculation of CD, where \( \bar{PaO_2} \) and \( \bar{PaCO_2} \) are the mean of \( PaO_2 \) and \( PaCO_2 \), respectively.

\[
CD = 1 - \frac{SSE}{\sum_{i=1}^{n}(Pm_{O_2} - \bar{PaO_2})^2 + \sum_{i=1}^{n}(Pm_{CO_2} - \bar{PaCO_2})^2}
\] (4)

All of the above criteria favour models of higher complexity, i.e. with a higher number of free parameters. As described before, simple models should be preferred, if they are able to adequately represent the given data. The corrected Akaike Information Criterion (AICc) [8, 9] classifies the models by regarding MSR values, the amount of measured values \( n \) together with the amount of available parameters \( m \). Thus, it includes a penalty for models that use a higher number of parameters to fit the given data. Equation (5) shows the calculation of the AICc.

\[
AICc = 2 \cdot m + n \cdot [\ln (2\pi \cdot MSR) + 1] + \frac{2 \cdot m \cdot (m + 1)}{n - m - 1}
\] (5)

The model resulting in the lowest AICc-Value should thus be preferred. The calculated AICc value can however not be compared among different data sets as it is not normalized. It is only applicable as a tool for model selection in equal data sets and has to be recalculated for other data sets.

### 3 Results

Images 4 and 5 show the results of measured and simulated \( PaO_2 \) and \( PaCO_2 \) for patient 1 and patient 4. Table 3 shows the corresponding deviations of simulated results compared to measured data in patient 1. Here, model 1 results in a mean deviation of 4.1% with a maximum deviation of 7.4% for \( PaO_2 \). For \( PaCO_2 \) the mean deviation is 2.8% with a maximum deviation of 3.6%. For model 2, \( PaO_2 \)-deviations are equal to those of model 1, with a mean deviation of 0.3% and a maximum deviation of 0.5% for \( PaCO_2 \). The deviations of model 3 are 4.2% and 7.9% for mean and maximum deviation of \( PaO_2 \). The mean deviation of \( PaCO_2 \) for model 3 correlate with those of model 2.

In patient 4, model 3 leads to the smallest deviation between \( PmO_2 \) and \( PaO_2 \). For carbon dioxide model 2 provides the smallest values for mean and maximum deviation.

Table 2 shows the SSE, MSR, CD- and the AICc-Values for models 1 to 3. CD-Values increase with the number of free parameters in the model or remain at the same level.
Table 2 Selection criteria for Model 1 - 3

<table>
<thead>
<tr>
<th>Patient</th>
<th>Selection Criteria</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SSE</td>
<td>MSR</td>
<td>CD</td>
<td>AICc</td>
</tr>
<tr>
<td>1</td>
<td>347</td>
<td>35</td>
<td>0.95</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>621</td>
<td>52</td>
<td>0.89</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>835</td>
<td>83</td>
<td>0.97</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>1305</td>
<td>130</td>
<td>0.64</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>1672</td>
<td>209</td>
<td>0.91</td>
<td>68</td>
</tr>
</tbody>
</table>

Table 3 Mean and maximum deviations between measured and simulated values – Patient 1

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Deviation / %</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PmO2 – PaO2</td>
<td>Mean</td>
<td>4.1</td>
<td>4.1</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>Max.</td>
<td>7.4</td>
<td>7.4</td>
<td>7.9</td>
</tr>
<tr>
<td>PmCO2 – PaCO2</td>
<td>Mean</td>
<td>2.8</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Max.</td>
<td>3.6</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

4 Conclusion

Three physiological models of varying complexity have been used to reproduce PaO2 and PaCO2 measured in five patients on different FiO2 levels. All three models were able to reproduce the given data with reasonable deviation. Except for one patient results show that simulation error, observable in SSE and MSR values, decreases with increasing model complexity. At the same time, the coefficient of determination, identifying the ability of a model to reproduce a given data set increases with the number of free parameters. Models 2 and 3 showed a higher CD compared to model 1 in all patients indicating that a model needs at least two parameters to adequately represent the measured data. Table 3 shows that the second parameter allows reproducing the measured carbon dioxide levels, thus model 1 is not able to predict PaCO2 levels. Therefore, it can only be favoured for situations that only regard PaO2. Simulation error for PaO2 for patient 1 was higher in model 3 than in models 1 and 2 indicating a non-robust identification of the model parameters. Using SSE or MSR as measures to select models does therefore not allow an objective selection of models as complex models would always be preferred over simpler models. The corrected Akaike information criterion on the other hand includes a penalty for each additional model parameter, thus favouring simple models. Using CD in combination with AICc in the tested cases, model 2 should be preferred in 4 of the 5 cases, as model 3 does not provide any additional information. In patient 4, model 3 should be favoured as the major increase in CD is accompanied by only a slight increase in AICc. In patients 3 and 5 model 1 might be favoured, if only PaO2 is considered. In that case, CD would be equal in models 1 to 3 with the lowest AICc in model 1.

Summarizing, the combination of CD and AICc allows selection of appropriate models while considering their complexity.

References

Simulation of laminar-to-turbulent transitional flow with application to Obstructive Sleep Apnea

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Abstract

Computational fluid dynamic (CFD) simulations may help to understand the pathophysiology of the Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) by modelling the abnormal airflow in the human upper airway system. It is therefore necessary to accurately reproduce the transition from laminar to turbulent flow occurring in that area. It is examined whether this behaviour can be captured by a computation without turbulence modelling on a moderately fine computational grid. Simulation results are compared to experimental data of a similar biomedical task, a stenosis in an artery, and the simulation in usage of a low Reynolds Number $k - \epsilon$ turbulence model of previous open literature. It shows up that although the simulation using no turbulence modelling gives a well approximation to the experimental data, the low Reynolds Number $k - \epsilon$ turbulence model performs superior in predicting the transitional flow regime.

1 Introduction

2\% of the female and 4\% of the male middle-aged American population suffer from the Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) [21], which is a sleep related breathing disorder, characterized by repetitive partial or complete closures of the pharyngeal lumen due to soft tissue deformations leading to cessations in respiration, insufficient alveolar ventilation and arousals from sleep [2][3][5][16]. OSHAS may lead to or increase the risk of hypertension, depression, reduction in life quality, stroke and cardiopulmonary death [11][14][17][20].

For the purpose of a better comprehension of OSAHS computational fluid dynamics (CFD) are used to simulate the airflow in digital models of the human pharynx with the intention to extract pathophysiological parameters like the airflow velocity and its pressure. Several authors found a reduction in pressure drop by treatment of OSAHS patients using CFD simulations on digital patient-specific models [4][6][9][13][15][19].

CFD is based on a formulation of mass and momentum conservation suitable for flow applications called the Navier-Stokes Equations, which are discretized and solved numerically. A challenging task in CFD simulations is the discretization. Turbulent flow is characterized by statistical fluctuations of the velocity and the formation of eddies on a wide spread length scale. The spatial discretization has to be fine enough to resolve even the smallest eddies in order to simulate turbulent flow accurately. Instead of choosing a finer discretization it is possible to neglect the short time turbulent fluctuations by solving only for the mean velocity components. The contribution of turbulent effects on the mean flow is thereby modelled by introducing additional equations for turbulence parameters like the turbulent kinetic energy $k$ and the dissipation $\epsilon$.

Several authors showed that flow in the human pharynx is in the laminar-to-turbulent transitional regime by CFD simulations on models of the upper airways [12][15][18]. In a regime with small turbulent effects the turbulence modelling equations may overestimate the influence of turbulence. Within this context it is examined, whether the use of the original Navier-Stokes Equations without turbulence modelling may capture the transitional behaviour of airflow in the human upper airways sufficiently even on a moderately discretized computational grid.

The evaluation of numerical flow simulations shall be based on the comparison with experimental measurements. Due to the lack of experimental data of airflow in the human upper airways a comparable experimental setup is consulted: A model of blood flow in an artery with an axisymmetric stenosis by Ahmed and Giddens [1]. In the experiment the artery is modelled as a pipe with a sinusoidal constriction, which is comparable to the situation of the pipe shaped pharynx with a constriction due to soft tissue.

The simulation of the time dependent solution of the Navier-Stokes Equations without turbulence modelling is compared to the simulation results of a stationary simulation using a low Reynolds Number $k - \epsilon$ turbulence model by Jeong et al. [10].

2 Methods

Ahmed and Giddens [1] examined the flow characteristics of blood in a locally constricted artery with an experimental setup. An axisymmetric pipe with an unconstricted diameter of $d = 4$ inch and a sinusoidal constriction with a diameter of $d/2$ in the most constricted part is used as model for the arterial stenosis. Instead of blood a steady flow of a 63\% water glycerol dilution with a kinematic viscosity of $\nu = 0.12\,\text{stokes}$ was used for the measurements.

Numerical flow simulations are performed in usage of commercially available simulation software COMSOL.
Multiphysics® by COMSOL Inc. (www.comsol.com). The arterial stenosis model is therefore digitally rebuilt.

The flow of the blood within the arterial model can be described by a set of partial differential equations called the Navier-Stokes Equations, given by

$$\frac{\partial (\rho \mathbf{u})}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} = -\nabla p + \nabla \cdot \left[ \mu (\nabla \mathbf{u} + (\nabla \mathbf{u})^T) - \frac{2}{3} \mu \nabla \cdot \mathbf{u} \mathbf{I} \right]$$

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0,$$

where $\mathbf{u}$ is the fluid’s velocity vector, $p$ the pressure, $\rho$ the fluid’s density and $\mu$ its dynamic viscosity. $\mathbf{I}$ denotes the identity matrix. The density was estimated according to measurements by the Glycerine Producers’ Association [7] to be $\rho = 1.17 \times 10^3 \text{ kg/m}^3$, which gives a dynamic viscosity of $\mu = p \nu = 1.4 \times 10^{-3} \text{ kg/(m \cdot s)}$. An inlet boundary is defined with a distance of $d$ before the most constricted part of the pipe. A plane velocity profile in axial direction was chosen matching the Reynolds Number

$$Re = \frac{u_{in} d}{v} = 2000,$$

the velocity components orthogonal to the pipe axis are set to zero. An outlet boundary is defined $12d$ after the most constricted part with a pressure condition of 0 Pa. The walls of the pipe are assigned with a no-slip wall condition $\mathbf{u} = 0 \text{ m/s}$. The Navier-Stokes Equations are spatially discretized in the computational domain using a moderately fine mesh of 857,360 tetrahedral and prismatic elements and applying the Finite Element Method with linear element shape functions.

A discretization in time is performed by the IDA algorithm created at the Lawrence Livermore National Laboratory [8], which uses variable order and variable time step backward differentiation formulas.

The velocity and pressure of the flow is calculated from $t_0 = 0 \text{ s}$ to $t_{end} = 5 \text{ s}$.

### 3 Results

Image 1 shows the axial velocity component of the two different simulation methods and the measured data at the centerline along the tube.

It shows up that the calculations without usage of a turbulence model fit the measured data very well in most of the cases, except the axial velocity profile at the distance $\Delta z = 2.5d$ of the most constricted part, where the velocity of the flow in the center of the pipe is predicted about 22.5% to low. In comparison the simulations of the low Reynolds $k - \varepsilon$ turbulence model are superior in that plane as well as in the plane with a distance of $\Delta z = d$. The following two velocity profiles are slightly better approximated with the simulations that used no turbulence model. For the planes with distances $\Delta z = 0$ and $\Delta z = 6d$ the simulations match the measured profiles well, in that slices no results were published by Jeong et al.

In image 3 the axial velocity component of the two different simulation methods is shown.
The predictions of the centerline velocity by the low Reynolds $k - \varepsilon$ turbulence model are superior to the time dependent solution without turbulence model, especially in the area between $d$ and $3d$ distance to the most constricted part of the pipe. That matches again the different errors of the orthogonal profile at $\Delta z = 2.5d$. The measured velocity profile shows after the constriction an increase of the axial velocity, which stays constant at about $2.5d$. The simulations without usage of turbulence model fail to predict that plateau area.

The Navier-Stokes Equations are the exact formulation for the flow of fluids, the error in the simulations without turbulence model must therefore result of the numerical computation scheme, more precisely the simulations fail to exactly predict the measured flow profiles because of the insufficient resolution in the discretization process. An increase in spatial and time resolution probably reduces these errors, but with the drawback of increased computational costs. The computation on the used grid of 857,360 elements already demanded 7.55GB RAM and a computation time of 5d 11h 28min on a cluster with 48 cores and 4 2.1GHz processors.

In conclusion the comparison of flow simulations with experimentally measured data showed that although turbulence modeling uses equations that are not exact by nature, it can perform better to the moderately fine discretized solution of the time dependent Navier-Stokes Equations in a laminar-to-turbulent transitional area, which is the flow situation within the upper airways of OSAHS patients.

5 Acknowledgement

This work is supported by the SICAT GmbH & Co. KG, Bonn (www.sicat.de) and the Graduate School for Computing in Medicine and Life Science funded by Germany’s Excellence Initiative (DFG GSC 235/1).
6 References


ASL 5000 lung model fails to simulate preset mechanical parameters during HFJV and volume control ventilation with a decelerating flow waveform in some ventilators

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Abstract

ASL 5000 (IngMar Medical, Pittsburgh, PA, USA) is a widely used computer-controlled active lung model. The model precisely simulates preset mechanical parameters of the respiratory system for a wide range of conventional modes of mechanical ventilation. ASL 5000 lung model fails to simulate the preset mechanical parameters properly for High Frequency Jet Ventilation and for volume control ventilation with a decelerating flow pattern in some ventilators. The unexpected behavior is strongly dependent on the shape of the flow curve, i.e., on the ventilator setting and the ventilator used. The improper behavior occurs for low preset resistances and larger preset compliances of the respiratory system. Even in the case that the ASL 5000 does not simulate the preset mechanical parameters correctly, the delivered tidal volume measured by ASL 5000 is determined very precisely.

1 Introduction

ASL 5000 (IngMar Medical, Pittsburgh, PA, USA) is a computer-controlled active lung simulator popular for many applications including design and testing of ventilators and ventilatory monitors, testing of ventilatory modes and interaction of a ventilator with the patient’s lungs, education, training of medical staff and other purposes [1, 2]. ASL 5000 is known as very reliable lung model with a very accurate measurement of delivered tidal volume over a wide range of tidal volumes [3].

Figure 1 Experimental setup when ASL 5000 did not performed well. High frequency jet ventilation of a patient simulator ESC (CAE Healthcare, Montreal, CA) with Paravent P ventilator equipped with a facial mask. ASL 5000 replaced the internal lung model of the ESC.

An unexpected behavior of ASL 5000 lung model was observed during our research of a possible combination of high frequency jet ventilation (HFJV) with a facial mask for non-invasive ventilation during cardiopulmonary resuscitation in the field. The experimental setup (Fig. 1) consisted of a Paravent P (Paravent P, Elmet, CZ) HFJV ventilator connected to a facial mask placed on a patient simulator ESC (CAE Healthcare, Montreal, CA). The original lungs of the ESC simulator were replaced with an ASL 5000 lung model so that various combinations of airway resistance and lung compliance could be used during the performed tests. We observed that the delivered tidal volume ($V_t$) into the ASL 5000 lung model decreased with increasing preset compliance of the model (Fig. 2).

![Figure 2](image-url) Unexpected decrease in the delivered tidal volume with increasing lung compliance in ASL 5000 lung model compared to other lung models (5600i and a set of rigid lung models RN) during non-invasive HFJV with $RR=2$ Hz. $R_{set}$—preset resistance, $C_{set}$—preset compliance, $V_t$—delivered tidal volume.
When the ASL 5000 was replaced with either 5600i (Michigan Instruments, Grand Rapids, MI, USA) purely mechanical lung model or a set of rigid (glass) lung models covering a range of lung compliances from 5 to 100 mL/cm H₂O, the delivered tidal volume increased with increasing lung compliance as was expected. The aim of the study is to investigate why ASL 5000 lung model does not deliver the expected tidal volumes during HFJV compared to other lung models.

2 Methods

First, the aim was to determine the ventilatory modes when the ASL 5000 lung model does not simulate preset mechanical parameters properly. Then, the cause of the improper simulation was searched. AVEA (CareFusion, San Diego, CA, USA) and EVITA XL (Dräger Medical, Lübeck, DE) ventilators in pressure and volume control modes with constant and decelerating flow waveforms were used. Paravent HFJV ventilator was also used but this ventilator is unable to evaluate mechanical parameters of the connected lung model. The delivered tidal volume was measured using VT Plus HF (Fluke Biomedical, Everett, WA, USA) flow analyzer. The experimental setup for a certain combination of a ventilator and a lung model is depicted in Fig. 3. In order to eliminate possible imprecision of mechanical parameters measurement by ventilators, we compared behavior of ASL 5000 with other lung models: solely mechanical model 5600i (Michigan Instruments, Grand Rapids, MI, USA) and a set of rigid lung models covering a range of compliances from 10 to 100 mL/cm H₂O. This range of compliances was also set on ASL 5000 and 5600i models. A linear resistor 5 or 20 cm H₂O·s/L (Hans Rudolph, Shawnee, KS, USA) was connected to 5600i and the rigid models during testing. The airflow resistance of 3.5, 5 and 20 cm H₂O·s/L was preset on ASL 5000. The following modes of ventilation were used in all the three lung models with various combinations of an airflow resistance and a lung compliance for comparison of the models’ performance: HFJV, pressure control ventilation and volume control ventilation both with a constant and a decelerating flow waveform. Respiratory rate was set from 5 to 180 min⁻¹. Mechanical parameters of the tested models evaluated by ventilators were recorded when the used ventilatory mode allowed their evaluation.

3 Results

Increased respiratory rate did not cased any difference in behavior of ASL 5000 from the other tested lung models during pressure control ventilation both with constant and decelerating flow patterns and during volume control ventilation with a constant flow in inspirium. The delivered tidal volume (Fig. 4) and the measured compliance of the models (Fig. 5) did not differ between the models.

Figure 3 The experimental setup for comparison of behavior of various lung models during mechanical ventilation. MTG—multiple jet generator is a part of the Paravent P ventilator.

Figure 4 Comparison of delivered tidal volume ($V_t$) into the models in dependence on respiratory rate (RR). In all models, a compliance of 42 mL/cm H₂O was set. Airway resistance of 5 cm H₂O·s/L was set on ASL 5000 or linear resistors of the same value were connected to 5600i and RN-42 lung models.

Figure 5 Comparison of compliance evaluated by AVEA ventilator in all three models. The preset parameters were identical as in Fig. 4.
The unexpected performance of ASL 5000 was recorded during volume control ventilation with a decelerating flow waveform and during HFJV only.

The observed minor error in simulation of compliance could not cause the wrong performance of ASL 5000 as there was only a small difference between simulated (measured by a ventilator) compliance and its preset value in ASL 5000. Furthermore, the simulated compliance was even slightly higher than the preset value and not lower which would be expected due to the decreased delivered tidal volumes.

The simulated airflow resistance, measured by ventilators, was significantly higher than its preset value in ASL 5000. The similar effect was not observed in other lung models tested (Fig. 6).

The error of airway resistance simulation in ASL 5000 depends on three conditions as it is apparent from Fig. 6:

1. Magnitude of the preset compliance of the model: The higher the preset lung compliance, the higher the difference between the measured airway resistance and its preset value.
2. Magnitude of the preset airway resistance of the model: The lower the preset resistance of the model, the higher the difference between the measured airway resistance and its preset value.
3. Ventilatory mode and airflow curve: The significant difference between measured and preset airway resistance in ASL 5000 was observed for volume control ventilation with a decelerating flow waveform, whereas the behavior described above were not observed when a constant flow waveform was selected. Furthermore, much stronger difference between preset and measured airway resistance in ASL 5000 was observed in AVEA ventilator, whereas this difference in Evita XL ventilator was weak but still noticeable.

During the ventilation modes, where ASL 5000 exhibited the error in simulation of airway resistance and therefore unexpected values of delivered tidal volume, there were not a significant difference between delivered tidal volumes measured by the VT Plus HF flow analyzer and the corresponding values of delivered tidal volumes evaluated by ASL 5000 lung model itself (Fig. 7).

No significant difference in performance between ASL 5000 lung model and other lung models tested was recorded during volume control ventilation with a constant flow waveform.
4 Discussion

ASL 5000 lung model performs well in a wide range of conventional modes of mechanical ventilation. The unexpected behavior of the model occurs only if sharp peaks of flow rate are present in the airflow signal as it is common for both HFJV and volume control ventilation with a decelerating flow pattern.

The inability to perform well during HFJV may be expected as unconventional HFJV was most likely not considered during the ASL 5000 design. Even though the simulated mechanical parameters of the respiratory system differ from their preset values in these cases, the delivered tidal volumes evaluated by ASL 5000 correspond with the externally measured values. The improper simulation of airway resistance and compliance at least partly compensates each other during their joint effect upon the delivered tidal volume. Therefore, the deviations between delivered and expected tidal volumes may not be disturbing. Nevertheless, when a certain or precise simulated value of airway resistance is required, a solely mechanical lung model will serve better than ASL 5000 when a low airway resistance together with a high lung compliance are required.

As a result of a closed-loop control utilized inside the active lung model ASL 5000, the response of the model to any change in airway pressure or airflow is oscillating. The oscillations are typically not apparent on ventilatory monitors as their upper cut-off frequency is often lower than the frequency of the oscillations. Nevertheless, these oscillations present in the airways may interact with the monitoring and control systems of the ventilator and therefore they may affect its close-loop control and contribute to an observed improper performance of the model.

5 Conclusion

Unlike in the majority of ventilatory modes where ASL 5000 performs very well, in some ventilatory modes (HFJV and volume control ventilation with a decelerating waveform) the ASL 5000 lung model does not simulate the preset mechanical parameters of the respiratory system precisely. The inaccurate functioning of ASL 5000 is caused by its inability to simulate a low preset airway resistance especially when a high compliance of the respiratory system is selected during HFJV and volume control ventilation with a decelerating waveform in some ventilators.

6 Acknowledgment

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7 References

Simulation and measurement of chromatic aberration reduction with diffractive-refractive hybrid lenses for medical applications

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Introduction

Several medical applications demand simple, cheap, and compact optics for imaging at two or more distances with reasonable low optical aberrations. While monochromatic aberrations can be reduced to a low limit with only one aspheric lens, chromatic aberration can only be reduced by using lens materials with high Abbe numbers, or by using lens systems containing different materials. The first option limits the selection to certain material types which often do not comply with requirements concerning for example fabrication, elasticity or biocompatibility. The second option increases the complexity of the optical system. As an alternative diffractive- refractive hybrid lenses can be applied, where the diffractive effects of the lens offset chromatic aberration of the refractive part. In this work, modelling and experimental characterisation of diffractive- refractive hybrid lenses are presented. It is shown that lens power, diffraction efficiency (light distribution along the optical axis) and chromatic aberration reduction for different focal positions can be adjusted independently within the presented simulation model. This provides the possibility to tailor diffractive-refractive hybrid lenses to specific applications, as e.g. multifocal intraocular lenses (IOLs) or multifocal lenses for flexible endoscopy.

Methods

Diffractive-refractive hybrid lenses were modelled with simulation software package VirtualLab™ (LightTrans GmbH), and fabricated lens prototypes were experimentally assessed with the test setup Optispheric IOL (Trioptics GmbH), which is able to characterize diffractive multifocal lenses.

Results

Dioptric power, diffraction efficiency, and chromatic aberration reduction for different focal planes of diffractive-refractive hybrid lenses can be adjusted independently. Chromatic aberration reduction for one resolution-critical focus has been established. Further, the simulation model was validated via prototype lens measurements of dioptric power, diffraction efficiency, and chromatic aberration reduction.

Conclusion

Using wave-optical simulation tools, various parameters of diffractive-refractive hybrid lenses can be tailored independently to fit the targeted application. The simulation model was validated successfully via measurements of prototype lenses.
Model based Prediction of Performance Change Introducing a Customised Barcode System in an Academic Laboratorial Workflow

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Introduction

Biomedical engineering at university laboratories aims at cutting edge research, however, the tools for quality management are often outdated. In the field of tissue engineering a complete, consistent and traceable documentation of all lab processes, materials and results with the focus on cell cultures is required. But in the academic laboratories an individual documentation with a low degree of standardisation/automation is common - in contrast to industry. The aim of this paper is to analyse whether the modelled integration of a barcode system within the workflow of an academic tissue engineering lab results in an improved performance.

Methods

The lab processes were identified and documented by creating a current state model with the process modelling software BONAPART. An agile approach was applied involving knowledge of domain experts and users through the use of interviews. On that base the target state was modelled, whereby the workflow was adjusted to the barcode integration. Finally, a requirement specification and data model were derived from the previous results.

Results

- Current and target state models with 198 processes and 1416 activities were created.
- A requirement specification with 95 specifications and entity relationship model for database design were defined.
- Regarding consumption of material, available space of material and information content 20,000 barcodes per year are needed.
- In the field of efficiency time saving up to 60% is predicted in example processes with simultaneous improvement in completeness and consistency.

Conclusion

Implying the process modelling provides the possibility to integrate a customised barcode system. It is predicted that this adjustment of the documentation system positively affects the workflow and the quality assurance including efficiency in the academical environment. The results are the basis for the implementation strategy and further research on the impact of digitalising academic workflow in biomedical engineering.
Comparison of interferometric measurement of a ballistic pressure pulse source with simulations using the spatial impulse response method and acoustic measurements

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Introduction
Since the end of the 90th radial Extracorporeal Shockwave Therapy devices (r-ESWT) are on the market and used for the treatment of soft-tissue pain situations, as for instance chronic enthesitis. The patients receive ca. 3 – 5 treatments with some 1000 pulses, which are directed at the pain spots by manual positioning and patient feedback. The technical principle of r-ESWT devices is based on the same techniques used in air guns. In a review of the publications available on the effectiveness of r-ESWT devices, some authors attest good results with ballistic pressure pulse sources, while others did not observe any effects or any advantages over traditional procedures. The varying results could be an indication for the influence of the hand-piece positioning and settings on the study-outcome. This is aggravated by the fact that the acoustic field of r-ESWT devices are neither well described nor are the acoustic measurements characterized by technical specifications. These uncertainties makes the need of acoustic field characterization essential.

Methods
Currently acoustic measurements are performed under the IEC standard 61846, which was originally intended for focused shockwave fields. Despite of not being applicable to all field variables of a radial fields, the requirements of the standard are difficult to obtain with r-ESWT devices. In order to characterize the acoustic field of a r-ESWT device, interferometric measurements of the applicator-surface velocity are used as an input for a spatial impulse response simulation.

Results
The simulations are compared with acoustic measurement using a polyvinylidene fluoride (PVDF) hydrophone and a fiber-optic hydrophone. Both comparisons show good agreement with the simulation, making the procedure an easy approach for field characterization without complicated acoustic measurements.
Orthotropic material parameters of short-fiber-filled epoxy cylinders as alternative test material for cortical bone

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Introduction

Artificial bones made out of short-fiber-filled epoxy are used as an alternative testing medium for human cortical bone. Correct material parameters are crucial especially when comparing mechanical testing and Finite Element Analysis (FEA). Our aim was to determine the material parameters necessary to describe orthotropic behaviour of a short-fiber epoxy cylinder (Sawbones #3403-31).

Methods

To determine the material behaviour compressive tests were performed in a material testing machine (Zwick 1456, Zwick, Ulm, Germany). In a first test, four samples were loaded up to 10 kN. For a second test, eight holes of 10 mm diameter were milled into three of the samples and also tested in compression. From the fourth sample 12 small cuboids were milled (four samples in longitudinal, transverse and radial direction). For each of the 12 samples one Young’s modulus and one Poisson’s ratio were determined using the material testing machine and a microscopy camera. Shear modulus was determined using a self-constructed torsional testing machine. The material parameters were evaluated using FEA (HyperMesh, OptiStruct & HyperView, Version 12.0, Altair Engineering, Böblingen, Germany).

Results

The Young’s modulus of the epoxy cylinders was 11.44±1.55 GPa. The orthotropic material parameters determined from the cuboids are given in table 1:

<table>
<thead>
<tr>
<th>Table 1: measured material parameters</th>
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<tr>
<td>$E_1$</td>
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The simulated longitudinal deformation of the milled cylinder with material properties from table 1 is 493.9 µm at 10 kN load. From the compression test a longitudinal deformation of 486 µm was calculated at the same load.

Conclusion

Mechanical testing and FEA using the measured material properties are in good agreement thus we consider the material parameters trustworthy. In comparison, the manufacturer only specifies the compressive Young’s modulus of 16.7 GPa, not only neglecting the non-isotropic material behaviour but also over-estimating the stiffness.

It is beneficial to use artificial bones as test medium but care should be taken to ensure correct material parameters.
Design of an Optical Transcutaneous Forward Data Telemetry for Brain Machine Interface

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Introduction
Transcutaneous data telemetry is a key part of the brain-machine-interface (BMI). By eliminating the percutaneous wires, the risks of the infection disappear and hence improving the patients’ safety and comfortableness. The flow of the information in BMIs is bidirectional. Neural signals are collected and be sent across the skin to external, known as back telemetry (uplink). The close-loop BMI, however, requires a forward telemetry (down link) to sent the information inside for neural stimulation and adjusting the parameters of the implants.

Methods
The wavelength-division multiplexing (WDM) is chosen to perform the bidirectional data transmission. Compared to other multiplexing technique, e.g., space-division multiplexing (SDM), time-division multiplexing (TDM), frequency-division multiplexing (FDM) and code-division multiplexing (CDM), WDM has the advantage of low power and easy implantation. Since the VCSEL(850nm)/silicon photodiode pair is widely used for back telemetry. We use the VCSEL(1310nm)/InGaAs photodiode to send data inside. This wavelength is located on the boundary of the tissue window. Therefore, the absorption ratio is still low. The wavelength of the transmitter in one channel and the frequency response of the photodiode in the other channel are not overlapped. Therefore, the two channels do not interfere with each other.

Results
The receiver contains a 1mm² InGaAs photodiode, a common gate transimpedance amplifier and a low power comparator to recovery the signal to digital domain for further processing. The integrated noise of the implant optical receiver is 14nA. Assuming an optical power of 20μW and the transmission efficiency of 1%, we achieve a SNR of 17dB.

Conclusion
We present a low power optical transcutaneous forward data telemetry for brain machine interface. With the WDM, the forward and back telemetry does not interfere with each other. The link achieves a 2MHz bandwidth and 17dB SNR, which is sufficient for neural stimulation and the power of the implants is only 87μW.
Real-Time Source Localization using Minimum Norm Estimation and Region of Interest Clustering

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Introduction

Whereas data analysis to date is mostly done subsequent to the acquisition process, we introduce an approach to monitor distributed brain activity at the source level in real-time. Brain monitoring provides a feedback which e.g. allows real-time adaption of experimental parameters to the subject’s reactions and increases time efficiency by shortening acquisition and subsequent offline analysis. In this work we present a clustering method for real-time distributed source localization which is able to handle low SNRs and reduces at the same time the high computational effort.

Methods

Our method is based on two assumptions: firstly it is assumed that the neural activity can be organized into functional cortical parcels. Secondly it is assumed that a low SNR reduces the number of distinguishable source localizations. Given these two assumptions, region-wise clusters are calculated based on Destrieux’s brain atlas which results in a downsized gain matrix.

A minimum norm estimation (dSPM) is used as real-time source localization algorithm which maps the MEG/EEG measurement to the clustered source space. The localization result is a distributed activity map of brain atlas regions.

Results

Our algorithm is able to handle Elekta Neuromag® VectorView™ 306 channel MEG measurements with a sampling rate of 1250 sps as well as ANT 128 channel EEG measurements with a sampling rate of 2048sps. Studies using human MEG/EEG evoked data show that the proposed real-time technique is accurate and fast using a moving average containing 10 averages. Responses to auditory and somatosensory stimuli are successfully localized.

Conclusion

The reduced number of dipoles and a preserved variance of the gain matrix improve the ability to distinguish active regions and speed up the localization. Online brain monitoring is a useful addition to common acquisition methods and allows to process more information during the measurement.
Reconstruction of Left Ventricular Active Tension Distribution from Wall Motion - Simulation Study of the Inverse Problem of Cardiac Mechanics

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Abstract

Introduction
Modern cardiac MRI techniques like Tagging, PCMRI and SENC provide quantitative measurements which help the cardiologist to assess the cardiac function. However, most measurable parameters, e.g. motion of tagging points are determined by underlying mechanisms, e.g. active tension development, which are not directly measurable. Imaging of these parameters could be of great diagnostic value. The estimation of these internal parameters from measurable values is referred to as an inverse problem. In this work, we present a new method to estimate the active tension distribution of the left ventricle from the motion of its surfaces. The method is applied on simulation data in order to be able to evaluate the outcome.

Methods
In this work we used an electromechanical simulation framework to simulate the ventricular contraction (forward simulation) in a whole heart model. The framework included an electrophysiological model in combination with an active tension development model of the human heart. This provided the input for a biomechanical model which was used to calculate the corresponding deformation of the heart. From the results, the motion of the endo- and epicardial surface of the left ventricle was extracted. This data was then used as input for a parameter estimation algorithm based on a Tikhonov regularization approach. This algorithm optimized the active tension development in the left ventricle for each time step in such a way, that the resulting deformation matched best to the input data.

Results
The reconstructed active tension matched well to the active tension of the forward simulation in terms of spatial distribution and magnitude over time during the contraction.

Conclusion
The presented algorithm allowed to reconstruct the active tension development distribution of the left ventricle from the motion of the heart surfaces. However, in this simulation study, other parameters like fiber orientation, passive mechanical properties and boundary conditions were identical. The next step will be a sensitivity analysis to evaluate how uncertainties of these parameters affect the reconstruction.
Modelling and Simulation of a Thermal-Time-of-Flight (TToF) Sensor for measuring the blood flow velocity

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Introduction

Within this publication, the modelling and simulation of a novel and nanoscale Thermal-Time-of-Flight Sensor will be shown. The sensor is developed for performing an intra-arterial and constant measuring of the blood flow velocity. The dimensions of the sensor will be within 10µm*10µm. It consists of four nanodiodes in a row and a heating filament between two pairs of diodes for creating heat packages by a current impulse. This heat package can be detected by one pair of the nanodiodes (in the downstream direction). The relative time between the detection of the heat package from these pair of nanodiodes and the given distance between it delivers the velocity of the blood.

Methods

For a decent simulation, the tool ANSYS has been used. It gives a mathematical solution by the use of the finite-element method (FEM) and the finite-volume method (FVM). The simulation delivers a first estimation of the general function of the sensor and it can be used for improving the dimensions of it. Hence, it will decrease the amount of prototypes needed.

Results

A two-dimensional simulation delivers a sufficient solution for the simulation of a blood flow within the velocity up to 1.5 m/s. It also shows that the blood can flow easily within the taken dimensions. A three-dimensional solution shows some challenges in creating a suitable channel.

Conclusion

A first prototype can be produced base on the results of the two-dimensional simulation. The next step regarding the simulation will be the creation of a sufficient three-dimensional simulation and an improvement of the dimensions based on this result. The experimental results also have to be considered then.
Influence of the electrode-electrolyte interface on the electric field in Deep Brain Stimulation

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Introduction

The treatment of movement disorders in patients with Parkinson’s disease can be performed with Deep Brain Stimulation (DBS). To understand the effects of the electric stimulation, a 3D field model has been created in Comsol Multiphysics, which allows the simulation of the electric field. Furthermore, a prototypic software suite has been developed that aims at covering the whole DBS process with a graphical user interface. The simulation results of the field model can be used in the suite for planning and navigation of the DBS electrode.

Methods

Stimulation pulses with a frequency of 130 Hz are often applied in DBS and previous studies indicated that capacitive effects exist between the electrode and tissue during low frequency stimulations. This influences the effects of the DBS. The interface between the boundaries is called “electrode-electrolyte interface” (EEI) and was investigated for the nonlinear case in a 2D field model, using two different setups. In the first setup, a thin layer was developed and a scale factor set due to the fact that the layer is only a few micrometers thick. The second setup of EEI was realized with contact impedances on the electrode.

Results

Comparisons between the modelling concepts were carried out. The simulation results of the electric field for both constellations of EEI showed that no significant differences between the thin layer and the contact impedance exists. The nonlinear EEI influences the electric field and results in a voltage drop between the boundaries at low frequency stimulations. For high frequency stimulation the effects on the EEI becomes less important.

Conclusion

The presented work on the EEI as a contact impedance can easily be integrated into the DBS suite, allowing an interactive adaptation of the model parameters. This results in enhanced visualization capabilities available to clinicians, opening new perspectives for clinical trials.
Distribution of the pressure and tidal volume in multicompartment model of the lung during mechanical ventilation

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Introduction
Regional changes of mechanical properties of lung tissue can be a cause of lung tissue injury by ventilator known as ventilator induced lung injury. The aim of this paper is to study the intrapulmonary parameters in the model of the respiratory system that was designed according to the morphometrical description of the lungs.

Methods
The model of respiratory system was designed for this study according to Horsfield morphological description. Central airways were modeled in the SolidWorks programme and printed on the 3D printer Objet 24 Pro (Stratasys, USA). Alveolar space of the model was divided into the five compartments according to the Horsfield model of the lungs. The alveolar space was modeled by glass demijohns. The model was prepared to allow measuring pressures and tidal volumes in each compartment. Model was ventilated by mechanical convention ventilator Avea (CareFusion, USA). The volume of the air was measured by respiratory monitory Florian (hot-wire anemometer). Measured data were processed by LabVIEW programme. Parabolic resistor was placed into the entry of alveolar space as simulation of airway obstruction and VT and pressure was measured.

Results
Conducted measurement on the model showed different effect of resistance and compliance upon the distribution of pressure and tidal volume into the compartments. The changed resistance has only small effect upon the delivery of tidal volume whereas the compliance of the compartment significantly affects the tidal volume. Time trend of the pressure is similar in all compartments with different compliance and also the effect of the changed resistance was only slight.

Conclusion
The multicompartment model of the respiratory system was designed according to the morphometry description of the lungs. The model allows measuring of pressure in each compartment and study the effect of the airway resistance and alveolar compliance on the regional distribution of the pressure and tidal volume.
Mutually decoupled self-resonant local coil array
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Abstract
Local coils are one of the major components in today’s MR imaging systems, leading to scan time reduction and improvements in image quality. Primarily they are used as receive antennas/antenna-arrays adapted to the particular body part, e.g. shoulder coils or spine array. Furthermore in some specific applications, local transmit coils can replace the conventional full body coil, for instance for knee and brain imaging. Nowadays, local coils are mainly realized as loop antennas, appearing in various geometric shapes, tuned and matched by additionally inserted discrete capacitors [1]. In order to create a homogeneous current distribution on the copper loop antenna, a minimum number of capacitors has to be integrated. Additionally, the increased number of capacitors has a beneficial effect on the electric field distribution and the SAR figures. However, it has to be taken into consideration that besides the cost for discrete high-quality elements, the capacitors have to be placed, soldered and tuned, altogether leading to higher expenses for local-coil manufacturing. Solder joints can also induce a non-negligible series resistance. Self-resonant loop antennas are used to overcome the previously mentioned disadvantages, [6]. This technique was improved by designing a mutually decoupled self-resonant antenna array on a single substrate without the need of a balanced-unbalanced feeding network.

1 Basic principle
The simplest form of a self-resonant antenna (or split ring resonator, SRR) consists of a pair of circular or rectangular copper loops placed on top of each other in a certain distance d, Fig. 1 and [5]. Each loop contains one or more discontinuities (gaps) which are oriented opposite to the other one. Considering the antenna as a LC-resonant structure, the inductance can approximately be calculated by $L_{SRR} = 2\pi \left( \ln \left( \frac{D}{d} \right) - 2 \right) \left[ nH \right]$ [3], where D is the diameter and d the conductor width of the coil in [cm]. The overlapping area forms a capacitance which is approximately $C_{\text{area}} = \varepsilon_0 \varepsilon_r \frac{d}{2} \left[ F \right]$, where A corresponds to the overlapping area, d is distance between both single loops and the dielectric constant of the substrate material [2]. The main capacitance of the split ring depends on the number of discontinuities (n), it then can be approximately calculated by $C_{\text{gap}} = \frac{C_{\text{area}}}{n}$.

Thus the resonance frequency of the split ring resonator depends on the radius of the coil, the conductor width, the substrate thickness and permittivity, the overlapping area and the number of discontinuities.

2 Methods
In an initial step, a material review was performed with special attention to the dielectric constant, available thicknesses and the flexibility of the material. With high-permittivity materials, one could achieve higher capacitances, but they are mostly associated to rigid substrates and therefore not suitable for application for flexible coil designs. Due to the characteristics of the antenna itself, only minimal further adjustments after fabrication are possible, calling for an extremely accurate simulation setup including specific convergence criteria. Regarding self-resonant antenna arrays, with a suitable number of well-positioned gaps it is possible to mutually decouple two loops using the same substrate, Fig 2, [4].

This is done by designing the SRR coil in a way that it is possible to use two gaps of one coil as pass-through for the second coil by changing bottom and top layer of the second coil, Fig. 2. In addition, the split ring also offers a special current and voltage distribution. The highest voltage occurs on the conductor end at the gap, whereas at the opposite side there is a current maximum with zero poten...
tial (virtual ground), where the coil can be fed without the need of a balanced-unbalanced network, Fig. 4. By appropriate choice of the gap positions, the nearest-neighbour decoupling by overlap can also be used in a longer row of coils (Fig. 5, 7).

Fig. 3 Calculated resonant frequency of each selfresonant coil

Fig. 4 Current density distribution of a split ring resonator at resonant frequency

3 Results

Fig. 2 shows the ANSYS HFSS simulation setup of two self-resonant coils, as well as a pair of small decoupled loop probes over each coil. Taconics TLY5 [2] was chosen as substrate material with a dielectric constant of 2.2 and a thickness of 0.127 mm. The coils were placed 40 mm above a flat conducting shield.

Calculation time was approximately six hours with 1 million tetrahedrons. For monitoring the resonance frequency, two decoupled loop probes in each of the split ring resonator were used, showing no frequency offset, Fig. 3.

Fig. 5 Manufactured split ring array (diameter of one loop is 30cm )

Fig. 6 Measured resonant frequency of decoupled mid coil

Fig. 7 Measured coupling between the two edge coils 1.3%

Fig. 5 shows three manufactured self-resonant antennas on the Taconics substrate with a diameter of 30 cm in a distance of 21 cm. Measurements with a decoupled twin probe showed consistency between the simulation results and the produced antenna array, Fig. 6 and Fig. 7. As expected, nearest neighbours are fully decoupled, whereas the outer coils exhibit a split resonance due to their uncancelled mutual inductance.

4 Conclusion

The calculation and manufactured of an array of self-resonant loops on a single substrate was successfully demonstrated. Further research will focus on SAR performance of a single loop and arrays of self-resonant coils.

5 References

Biomechanical Characterisation of Scaffold-free Cartilage Constructs with Dynamic Mechanical Analysis

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Abstract

For the therapy of damaged articular cartilage, three-dimensional scaffold-free cartilage constructs (SFCCs) were developed by fzmb GmbH. The biomechanical properties are an essential indicator for the functional characterisation of cartilaginous tissue. In this contribution, the viscoelastic material properties of native articular cartilage and SFCCs are measured under dynamic stress using dynamic mechanical analysis (DMA). The results were compared and evaluated.

1 Introduction

Articular cartilage and SFCCs are investigated and characterised by biomechanical, biochemical and histological analysis. The biomechanical properties contain a variety of relevant information for the functional characterisation of cartilaginous tissue. In this process, the modulus of elasticity $E$ is evaluated under single-phase consideration for a defined pressure applied to the cartilaginous tissue [1]. In order to characterise the viscoelastic effects two major types of experiments are performed: firstly transient experiments (creep or stress relaxation) and secondly dynamic experiments [2, 3, 4, 5]. Within the scope of this article DMA of native pork cartilage and scaffold-free cartilage constructs (SFCCs) were carried out and evaluated under dynamic stress in the range of 1 – 5 Hz.

2 Methods

In the following chapters the experimental approach and the dynamic viscoelasticity are explained.

2.1 Experimental approach

The experiments on native cartilage and SFCCs were executed at $25^\circ C$ using the material testing machine BOSE® ElectroForce® 3100 Test Instrument and the software WinTest® 7 DMA. In the process, the tissue sample was exposed to a sinusoidal stress (excitation signal) and the resulting displacement in the material was measured (response signal). In the DMA, distinction is made between force and way controlled measurement. In this experiment a force controlled measurement was carried out. A sinusoidal force was applied ($F = 0.5 \text{ N}$, $f = 1 – 5 \text{ Hz}$) resulting in cyclical yielding and deformation of the tissue sample. The experiments were carried out on five native cartilage specimens and three SFCCs. The native cartilaginous tissue was obtained from the pork knee joint (Tibia). The SFCCs were cultivated from equine cartilage cells (10 weeks and 24 weeks cultivation) and from pork aorta cells (16 weeks cultivation) according to the own patented technology [6]. The specimen geometries are listed in Table 1.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Height x Diameter [mm]</th>
<th>Cultivated</th>
</tr>
</thead>
<tbody>
<tr>
<td>native 1-5</td>
<td>2 x 6</td>
<td>native</td>
</tr>
<tr>
<td>SFCC 1</td>
<td>1.4 x 6</td>
<td>6 weeks</td>
</tr>
<tr>
<td>SFCC 2</td>
<td>2.27 x 6</td>
<td>24 weeks</td>
</tr>
<tr>
<td>SFCC 3</td>
<td>2 x 6</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

The measurement results of the five native cartilage specimens were averaged before used in further analysis.

2.2 Dynamic viscoelasticity

Viscoelasticity is marked by a partly elastic and partially viscous behaviour. The behaviour of perfect elastic materials follows Hooke’s law, where stress is proportional to strain and both are in phase. The perfect viscous materials are Newtonian fluids, in which the response of stress depends on the strain rate. In this case, stress and strain are $90^\circ$ out of phase under cyclic load. In a material, that combines characteristics of elastic solids and Newtonian fluids, a phase lag in between will occur and the modulus of elasticity $E$ may be defined. The $E$-modulus consists of both an elastic part (the storage modulus $E'$) and a viscous part (the loss modulus $E''$). $E'$ and $E''$ sum up to be the complex or dynamic elasticity modulus $E^*$. The complex $E$-modulus is calculated with equation (1), where $\sigma$ is stress, $\varepsilon$ is strain, and $\delta$ is the phase angle between stress and strain.

$$E^* = E' - i E''$$
The loss factor $\tan \delta$ is calculated with equation (2).

$$\tan(\delta) = \frac{E'}{E} \quad (2)$$

The storage modulus $E'$ represents the stiffness of the material and the fact that the energy of a mechanical load can be stored by elastic deformation and afterwards regained. The loss modulus $E''$ describes the dissipation of energy due to internal friction. The loss factor $\tan \delta$ gives the relation between elastic and viscous part [5, 7].

### 3 Results

In Images 2 and 3 the DMA results of native cartilage are depicted. Image 2 shows the E-modulus ($E^*$, $E'$ and $E''$).

![Image 2 DMA of native cartilage (E-modulus)](image1)

With increasing frequency the complex E-modulus increases. Besides, the loss and storage moduli also increase. In Image 3 the phase angle $\delta$, the loss factor $\tan \delta$ and the attenuation of native cartilage as a function of frequency are shown. The phase angle $\delta$ and also the loss factor $\tan \delta$ increase with increasing frequency while the attenuation is decreasing.

Images 4 and 5 show the DMA results of the SFCCs. In Image 4 the E-moduli ($E^*$, $E'$ and $E''$) and in Image 5 the phase angle $\delta$, the loss factor $\tan \delta$ and the attenuation are plotted as a function of frequency.

![Image 4 DMA of SFCCs (E-modulus)](image2)

Analogous to the DMA results of native cartilage the E-moduli of the SFCCs ($E^*$, $E'$ and $E''$) increase with increasing frequency. The phase angle $\delta$ and the loss factor $\tan \delta$ increase also with increasing frequency while the attenuation decreases.

![Image 5 DMA of SFCCs (phase angle $\delta$, loss factor $\tan \delta$ and attenuation)](image3)

Comparing native cartilage and the SFCCs the E-modulus of the native cartilage is about doubled. The E-modulus ($E^*$, $E'$ and $E''$) increased with increasing frequency in both tissues. However, the values of native cartilage increased at a higher rate than those of the SFCCs. Considering the phase angle and the loss factor the native cartilage revealed the highest values, followed by SFCCs 1, 3 and 2. In all samples, the increase of the phase angle and loss factor
with increasing frequency is clearly visible while the attenuation decreases. In this case also, it is well recognisable, that native cartilage obtained the highest attenuation. Albeit the decrease of attenuation over the frequency is lower in the SFCCs in comparison to the native cartilage. The comparison of the SFCCs among each other revealed differences, which are due to the variations in cell types, cultivation time, and sample geometry. However, only minor differences occurred in the ascertained attenuation values.

4 Conclusion

In this contribution the viscoelastic behaviour of native pork cartilage (Tibia) and SFCCs from equine cartilage cells and pork aorta cells are examined under dynamic stress in the range of 1 – 5 Hz. The stiffness mismatch between native cartilage and SFCCs resulted from the incomplete maturing process of the SFCCs. This assumption was also evaluated and confirmed in static studies [8]. Hence, the complete (native) viscoelastic properties cannot be attained during manually stimulated in vitro cultivation [9], but only under physiological conditions and stress after implantation into the joint defect. Because of this fact the SFCCs may be used for the mathematical modelling of cartilaginous tissue as intermediate stages or for the development of a mathematical arthroisis model. The comparison of the SFCCs among each other showed differences in their viscoelastic properties (E*, E', E", phase angle and loss factor), which resulted from differences in cultivation time, cell types, and sample geometry. In addition, biochemical analysis may enhance the diagnostic conclusiveness. Future works will deal with the determination of the viscoelastic properties of uniformly prepared SFCCs under dynamic stress. Furthermore, investigations under dynamic shear stress in range of 1 – 5 Hz as well as experiments in higher frequency responses, e.g. 5 – 100 Hz, may broaden the comprehension of the dynamic behaviour of cartilage.

5 References


Acknowledgement

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Distribution of the ventilatory pressure in high-frequency oscillatory ventilation in the anatomically based model of the respiratory system

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Abstract
Amplitude of the pressure oscillations during high-frequency oscillatory ventilation is studied in the model of the respiratory system with five compartments based on the lung morphometry. The ventilatory circuit consists of high-frequency oscillatory ventilator 3100A with patient circuit and model of the lungs realized by a set of rigid demijohns. Transfer of the ventilatory pressure was measured in different compartments of the model for inspium to expirium ratio 1:1 and 1:2. Other ventilatory parameters were held constant during the experiment.

1 Introduction
Mechanical lung ventilation (MV) is used when the spontaneous breathing of the patient is insufficient or intentionally inhibited. MV is the most efficient method for treatment of acute respiratory failure however there are still strong adverse effects of ALV upon patient’s respiratory system [1]. These effects are known as ventilator induced lung injury (VILI) and they can develop as a result of high pressure or high volume applied during the ventilation. Protective ventilatory regimens with smaller tidal volumes are used to prevent the patient from VILI. High-frequency oscillatory ventilation (HFOV) meets the strategy of protective ventilatory regimen. HFOV is non-conventional ventilatory technique characterized mainly by decreased tidal volume and higher ventilatory frequency compared with MV. Ventilatory frequency 3–25 Hz and tidal volumes, which are comparable to anatomical dead space or even smaller, are used during HFOV. The continuous distending pressure (CDP) inflates the lungs during HFOV and pressure oscillations \( \Delta P \) that are superimposed to CDP deliver the tidal volume into the lung. Use of CDP and smaller tidal volumes during HFOV prevent the lungs from overdistension and barotrauma [2]. Differences in the ventilatory frequency, pressure and tidal volume represent the most significant difference between HFOV and MV.

It was shown that normocapnic HFOV affects differently pulmonary and extrapulmonary form of ARDS [3] and also that efficiency of HFOV depends on the mechanical mechanical properties of the respiratory system [4, 5]. The studies conducted on the mathematical model of the respiratory system show different effects of the changes in airway resistance and alveolar compliance upon the total impedance of the respiratory system and tidal volume [6, 7]. It is generally accepted that pressure oscillations are dumped in the alveolar space in HFOV. Animal experiments [8, 9], laboratory experiments [10] and mathematical studies [11] support attenuation of pressure oscillations in the ventilatory circuit.

2 Methods
The model of the respiratory system based on the morphological data was designed for this study. We have used geometrical dimensions of the central airways from Horsfield morphological description of the respiratory system [14]. The scheme of the central airways is depicted in Image 1 and dimensions of the central airways are summarized in Table 1. The model of the central airways was prepared in SolidWorks software (see Image 1) according to the dimension in Table 1 and the model was printed on 3D printer Objet 30 Pro (Stratasys for a 3D World, USA).

![Image 1 Scheme of the central airways with asymmetrical dividing with original numbering](image-url)
Table 1 Geometrical dimensions of the central airways of the laboratory model [14].

<table>
<thead>
<tr>
<th>Airway number</th>
<th>Diameter [mm]</th>
<th>Length [mm]</th>
<th>Angle [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>50</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>7,5</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>10</td>
<td>11,1</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>7,3</td>
<td>15,6</td>
<td>63</td>
</tr>
<tr>
<td>13</td>
<td>8,9</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>14</td>
<td>5,2</td>
<td>21</td>
<td>61</td>
</tr>
<tr>
<td>15</td>
<td>6,4</td>
<td>8</td>
<td>15</td>
</tr>
</tbody>
</table>

Image 2 Model of the central airways prepared in Solidworks software.

Table 2 Distribution of lung volume and lung compliance among the lung compartments [14].

<table>
<thead>
<tr>
<th>Lung lobe</th>
<th>Volume of Horsfield model [%]</th>
<th>Compliance of Horsfield model [L/kPa]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper</td>
<td>19</td>
<td>0,19</td>
</tr>
<tr>
<td>Right middle</td>
<td>10</td>
<td>0,10</td>
</tr>
<tr>
<td>Right lower</td>
<td>26</td>
<td>0,26</td>
</tr>
<tr>
<td>Left upper</td>
<td>19</td>
<td>0,19</td>
</tr>
<tr>
<td>Left lower</td>
<td>26</td>
<td>0,26</td>
</tr>
</tbody>
</table>

The ventilatory circuit consists of high-frequency oscillatory ventilator Sensormedics 3100A (Sensormedics, USA) and designed model of the respiratory system. Central airways printed on 3D printer, connecting silicon tubes and rigid demiijohns form the model of the lungs. Setting of the laboratory measurement is depicted in Image 3.

Image 3 Laboratory setting of the experiment with multi-compartment model of the respiratory system.

Pressure was measured at three compartments with different compliance. A special device developed to measure three pressures simultaneously in range 0–6.5 kPa was designed. The device consists of three sensors 26PC01 (Honeywell, USA) and multifunction data acquisition device Ni USB-6009 (Texas Instruments, USA). Each of the three canals was individually calibrated before experiment and offset of each canal was compensated. Sampling rate of the device is 1 kHz. Detail description of the system for measuring of the pressure is described in [3]. LabVIEW SignalExpress was used to gather data that were analyzed in Matlab software. The ventilatory frequency $f = 5$ Hz was used. Mean airway pressure (CDP) was maintained at 12 cmH2O with bias flow 30 L/min and ventilatory pressure $\Delta P$ was 20 cmH2O. These parameters were held constant during whole experiment. The measurement was made for different inspirium to expirium ratio 1:1 and 1:2.

3 Results

The pressure amplitudes were measured in the ventilatory circuit at compartments with different compliance; left lower, right middle and right upper compartment. The time trends of the pressure are depicted in Image 4 for inspirium to expirium ratio 1:1. The time trends of the pressure for inspirium to expirium ratio 1:2 are depicted in Image 5.
4 Conclusion

There are no significant differences in pressure distribution among the different compartments of the model of the respiratory system. The observed attenuation of the pressure amplitude is similar in all compartments of the model and confirms the results published earlier [10]. Change of inspirium to expirium ration cause a change in the time trend of the pressure wave however no other significant differences were seen.

We have observed the increase of CDP in the compartments of the model compared to 12 cmH2O set on the ventilator. The increase was caused by pressure oscillations ΔP and it should be further analyzed.

5 References


Acknowledgement

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Intracranial Pressure Declines During Cardiopulmonary Resuscitation in Animal Model

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Abstract

Intracranial hypertension represents a significant risk factor of poor neurological outcome in critically ill, specifically those with craniotrauma.

Methods: In a porcine model of cardiac arrest (CA) the dynamics of intracranial pressure (ICP) was studied. Three-minutes of untreated CA were followed by 5-minutes of cardiopulmonary resuscitation (CPR) with chest compressions and mechanical ventilation. No other interventions were allowed since out-of-hospital resuscitation was simulated. Throughout the protocol the ICP, arterial and venous pressures and carotid blood flow were continuously recorded.

Results: During cardiac arrest ICP increased to 27 +/- 4.8 mmHg, i.e. hypertensive values. Mechanical chest compressions resulted in a transient ICP increase followed by a steady decline at approximately 2.25 mmHg/min. By five minutes of CPR intracranial pressure reached prearrest values despite significant elevation of central venous pressure (39 mmHg) and gradual decrease of arterial pressure and flow. We hypothesize that cerebral autoregulation is capable of maintaining ICP even during failing circulation.

1 Introduction

Intracranial hypertension represents a rather common neurological complication in critically ill. Pathophysiology of increased intracranial pressure has been extensively studied both in clinical and basic research. Based on etiology we recognize primary and secondary intracranial hypertension. The primary causes include direct craniocerebral conditions such as trauma including hematomas, tumor, infection, intracerebral bleeding, ischemic stroke, hydrocephalus, etc. Secondary causes originate in other organ systems than brain, the most typical being airway obstruction, hypoxia, hypercapnia, malignant hypertension, hypotension, hypovolemia, sedation, hyperpyrexia, metabolic reasons and intoxication including select medications. Rather common reasons represent high altitude hypoxia and hepatorenal failure [1]. Effective therapy of intracranial hypertension should always avoid pathophysiological mechanisms that would lead to secondary elevation of already increased ICP.

Surprisingly few therapeutic procedures for ICP reduction have been subject of randomized clinical trials and thus most of clinical recommendations are based on clinical experience.

Probably largest published, randomized trial recruited 155 patients in Australia, New Zealand and Saudi Arabia between 2008-2011[2]. This trial compared conservative and surgical treatment of intracranial hypertension to decompress brain. While surgical approach (craniotomy to temporarily elevate calva) required less medication, shorter period of mechanical ventilation and shorter stay in intensive care unit, the six-month mortality was worse.

Other trials were focused at the strategy of oxygenotherapy, i.e. fraction of inspired oxygen (FiO2) in craniotrauma and ischemic stroke patients. Though oxygen is essential for cerebral metabolism it has been demonstrated that high oxygen concentration increases risk of oxidative stress and reperfusion injury. Thus it is presently recommended not to expose resuscitated patients to 100% oxygen unless necessary. Instead, FiO2 should always be titrated to reach target saturation of peripheral arterial blood (SpO2) in the range of 94-96 % [3,4]. It has been demonstrated that brain is particularly sensitive to ischemic reperfusion injury that is accelerated by hypoxia, hyperoxia, hyperventilation with secondary hypocapnia and alkalosis, or central hyperthermia and hyperglycemia. This strategy has been confirmed by several studies including animal research. The results demonstrated, that after prolonged CA the administration of 100% oxygen for 10 minutes post resuscitation results in hyperoxic reperfusion affecting the most sensitive cerebral regions such as hippocampus, striatum and periaqueudal gray matter. The mortality of animals where arterial partial pressure of oxygen (paO2) reached 300 mmHg increased three-fold [5].

Current evidence regarding ICP and intracranial hypertension is rather heterogeneous and the results often largely different lacking physiopathological details. It is expected that more compact recommendations for cerebral resuscitation will be published with the new resuscitation guidelines scheduled for 2015.
2 Methods

2.1 Monitoring

ICP and hemodynamic data were obtained in experimental animal study performed in accredited university lab. The study was approved by institutional animal care and use committee at Charles University, Prague. The data from seven swine (49±3 kg) are presented.

Following anesthesia induction (ketamine, midazolam) animals were intubated and mechanical ventilation was initiated at 8-10 ml/kg/min, target etCO2 38-42 mmHg (G5 ventilator, Hamilton Medical, Switzerland). Surgical level of total intravenous anesthesia was maintained throughout the study with propofol, midazolam and morphine (10, 0.2 and 0.2 mg/kg.hod respectively) and i.v. fluids (unlactated ringer solution) were continuously administered to maintain target central venous pressure (CVP) at 5-7 mmHg. Subsequently, the monitoring systems were introduced: intracranial pressure sensor (Neurovent, Raumedic, Germany) inserted via a 4 mm burr-hole and a bolt 5 mm deep into parietal parenchyma 2 cm laterally from the sagittal line. Direct blood pressure catheters providing continuous traces of arterial and venous blood pressures were inserted into anterior vena cava, femoral artery and descending thoracic aorta. Fluid-filled pressure transducers (Truwave, Edwards Lifesciences, USA) were used to obtain pressure signal. Transit time ultrasound probe was surgically placed over the right carotid artery to monitor blood flow (4PSB, Transonic, USA) were monitored and recorded at 125 Hz by patient monitor (Lifescope TR, Nihon Kohden, Japan). All parameters were continuously recorded and analyzed offline.

2.2 Protocol

After the monitoring systems insertion, a baseline period followed with no interventions until all the data expressed stable values for minimum of 15 minutes. Cardiac arrest was then induced by rapid pacing (4-10 Hz, 4V) via electrophysiological mapping catheter placed in the right ventricular apex. Once pulseless activity appeared (confirmed by characteristic ECG pattern of VF/VT and arterial blood pressure cessation) mechanical ventilator was disengaged and time referred as T=0 min. Three minutes of untreated cardiac arrest followed. At T=3 min mechanical cardiopulmonary resuscitation (CPR) was initiated. Chest compressions were provided by means of automated device (LUCAS 2, Physio-Control, Sweden) at 100 cycles/minute. The correct position of the piston was confirmed by X-ray. The mechanical ventilation was resumed and set to 10 ml/kg.min, 18 breaths/min, FiO2 80% and adjusted to keep target SpO2 at 94-96%. After 5 minutes of CPR, i.e. T=8min up to three defibrillation attempts were performed to restore spontaneous circulation (200J biphasic, TEC-5500, Nihon Kohden, Japan). At this time ICP sensor was disconnected as per recommendations by the manufacturer and reconnected after defibrillation once resuscitation effort allowed.

2.3 Statistics

Non-parametric Friedman test and Wilcoxon test was used to compare two sets of values. P values < 0.05 were considered statistically significant. All the results are expressed as averages +/- SD. Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA)

3 Results

A typical time-course of pressure parameters is presented in Image 1. During the baseline all the values attained physiological limits. Once cardiac arrest was induced, arterial pressure dropped rapidly, while intracranial and central venous pressures gradually increased over the whole arrest period. All the pressures nearly equilibrated within the first minute of CA. Towards the end of 3-minutes arrest period, the ICP increased to 27.1 (+/- 4.8) mmHg thus reaching intracranial hypertension levels. Once the chest compressions were initiated, ICP transiently further increased but started to decline after 10-20 seconds at 2.26 (+/-0.72) mmHg per minute. At the end of 5-minutes CPR period ICP returned to baseline values (16.1 +/- 6.0 mmHg). The averaged ICP data at baseline, at the end of CA period (T=3) and before defibrillation, i.e. after 5 minutes of resuscitation (T=8) are presented in Image 2.

Image 1 Sample waveform of intracranial pressure (ICP), venous pressure (CVP) and Arterial pressure (ART) during cardiac arrest and cardiopulmonary resuscitation (CPR).
Averaged intracranial pressure (ICP) just before cardiac arrest (T=0), after 3 minutes of arrest (T=3) and after 5 minutes of CPR (T=8). * p=0.01

4 Conclusion

During CPR ICP tends to return to normal values, however, both arterial pressure (ART) and central venous pressure (CVP) remain abnormal: mean arterial pressure (MAP) stays low (~50 mmHg vs. 80 mmHg at baseline) despite ongoing chest compressions and keeps falling. Simultaneously CVP attains very high values (~40 mmHg vs. 7 at baseline), possibly due to the backflow of blood in major veins. Thus, based on pressure values, the perfusion pressure (MAP-CVP) is extremely low also is the cerebral perfusion pressure (CPP; CPP=MAP-ICP).

These findings draw some controversy. On one hand it is known that adequate CPR can result in a good neurological recovery even after ten of minutes of CA. This argues against the cessation of perfusion. On the other hand, the decrease of blood pressure and carotid blood flow significantly below 50% of baseline already after three minutes of ventilated CPR cannot support cerebral metabolism. This decline could only be avoided by procedures other than chest compressions, such as administration of vasopressors, fluid replacement or use of mechanical adjuncts. However, at such early stages of CPR these procedures are unavailable and thus were excluded from our protocol. Nevertheless, despite rapidly deteriorating hemodynamics during CPR, cerebral autoregulation manages to maintain ICP within normal values for at least 10 minutes post arrest.

4.2. Study limitations.

The study was performed on healthy pigs. Though this represents a standard CPR model, due to anatomical differences to humans, especially large antero-posterior chest dimension, the early CPR efficacy may differ noticeably from human medicine. A correct compression site and depth are more crucial here and may be responsible for large variation seen in CVP.

Acknowledgement

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5 References

Modeling endogenous glucose production for model-based tight glycaemic control in the neonatal intensive care unit

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Abstract

Hyperglycaemia is common in very low birthweight (VLBW) preterm infants in the neonatal intensive care unit (NICU) as a result of stress and prematurity, and is associated with increased morbidity and mortality. One cause of hyperglycaemia is failure to suppress endogenous glucose production (EGP) with increased blood glucose (BG) levels. STAR glycaemic control is a model based insulin therapy system to treat hyperglycaemia in very low birthweight preterm infants. One aspect of the model is concerned with EGP. A literature review collected information on EGP, plasma insulin, plasma glucose, and plasma glucagon. The data was analysed for trends between these species, and models were developed and tested to observe their effect on glycaemic control using virtual trials based on clinical patient data. It was found that plasma glucagon decreased with increasing blood glucose, but no clear relationship between plasma glucagon and EGP was observed. EGP was suppressed in the presence of increased glucose infusion (GI), and in some studies, decreased with increasing blood glucose. Models were developed for the suppression of EGP with BG and GI, and tested using virtual trials, along with a simple population constant model derived from the literature data. A population constant resulted in the best model fit to clinical data, and performed the best with respect to glycaemic control. Results suggest that due to prematurity and stress EGP is highly individual between neonates, and is best modelled across the population using a population constant.

1 Introduction

Hyperglycaemia (elevated blood glucose (BG)) is commonly seen in very or extremely premature infants in the neonatal intensive care unit (NICU) as a result of stress and prematurity. It is associated with increased morbidity and mortality [1]. Treatment varies, and can involve glucose restriction, which may deprive the neonate of necessary substrate for growth, or insulin therapy, which incurs the risk of hypoglycaemia.

Neonatal hyperglycaemia is thought to result from defective beta-cell processing of insulin [2], relative insulin resistance [2], no suppression of endogenous glucose production (EGP) with increasing glucose infusion [3, 4], drug therapy [5], or stress [6]. Stress can cause increased levels of cortisol, glucagon and catecholamines, which increase endogenous glucose production [7]. Increased levels are associated with surgery and anaesthesia [8], respiratory distress, cardiac failure, sepsis, and necrotising enterocolitis [5].

Glucose can be produced from fats, from proteins via gluconeogenesis, and from glycogen via glycogenolysis. Glucagon helps regulate gluconeogenesis. Elevated plasma insulin levels, such as after a meal, stimulate glucagon secretion by the pancreas and mobilise glucogenetic precursors. Elevated glucagon concentrations in the portal vein stimulate both gluconeogenesis (persistently) and glycogenolysis (transiently) in the liver. In turn, increased hepatic glucose production raises blood glucose levels, which suppresses glucagon secretion [7].

STAR (Stochastic TARgeted) glycaemic control is a model based framework that utilises a patient specific time-varying insulin sensitivity (SI) parameter to describe the varying response to insulin over time. Statistical population models of changes in SI for a given current SI are used to forecast likely changes in SI, and thus blood glucose for a given insulin-nutrition intervention. STAR selects insulin doses such that the band of likely outcomes for a given intervention overlaps a target clinical band. STAR has been used in the NICU, where it has proven effective [9] and did not increase the incidence of hypoglycaemia [9] seen in other NICU insulin therapy studies [10, 11].

STAR relies on accuracy of underlying physiological model based dynamics. This study aims to more accurately model endogenous glucose production to improve glycaemic control in the very preterm neonatal NICU cohort.

2.0 Methods

2.1 Literature Review

A literature review was examined trends in EGP in very premature infants, focusing on the contribution of blood glucose and glucagon concentrations to EGP. Key terms in literature search were: “glucose”, “production”, “preterm”, and “neonate” in PubMed. Excluded studies included those with non-human subjects, term or older infant, BW>2kg or GA>32 weeks, insufficient data, and subjects with with maternal or foetal diabetes. A total of 177 data points were collected from 21 studies, the process of which is documented elsewhere [9]. Of these 7...
also reported plasma glucagon and 8 reported plasma insulin.

2.2 Data Analysis
Literature data was analysed with respect to EGP and plasma glucagon, BG, plasma insulin, glucose infusion rate (GI), and potential development markers such as gestational age (GA) and weight. The relationship between plasma glucagon and BG and plasma insulin was also examined. Where models were fitted, two main types of model were used: linear and power-law models. Power-law models were used where an inverse relationship was apparent that either displayed or would be expected to approach an asymptote due to physiological saturation or suppression of substrate.

2.3 Validation using clinical data
The clinical patient cohort (Table 1), consists of data from 25 retrospective patient episodes and 53 patient episodes from prospective BG control studies using STAR [12]. The clinically validated NICING (Neonatal Intensive Care Insulin-Nutrition-Glucose) model describes glucose-insulin dynamics in the extremely preterm neonate, and is presented elsewhere [12]. Virtual patients are created using this model by fitting a patient-specific, time-varying SI profile from clinical data using integral based fitting methods [13]. SI is fit on a retrospective hour-to-hour basis and assumed constant over an hour. SI=0 is the lower physiological bound, where no glucose leaves the blood plasma via insulin-mediated uptake.

2.4 Effect on Control
Modelling EGP as a function of BG, glucose infusion, or as a population constant was examined. Population constants of EGP were determined from a range of EGP values based on percentiles of the literature data (Table 2). For each EGP value SI was identified for the whole cohort and a new statistical forecasting model generated. Control was tested using clinically validated virtual trial methods [14] and the control protocol selected insulin dynamics in the extremely preterm neonate, and is presented elsewhere [12]. Virtual patients are created using this model by fitting a patient-specific, time-varying SI profile from clinical data using integral based fitting methods [13]. SI is fit on a retrospective hour-to-hour basis and assumed constant over an hour. SI=0 is the lower physiological bound, where no glucose leaves the blood plasma via insulin-mediated uptake.

2.5 Performance metrics
Accuracy of model fit to clinical data was one metric to evaluate the effect of the new EGP models, defined as the average percentage difference between real and modelled blood glucose levels at BG measurements. Percentage time in band (BG between 72–144 mg/dL) evaluated control performance, while the number of hypoglycaemic patients (BG < 47 mg/dL) evaluated safety.

3.0 Results

3.1 EGP and glucagon
Results show large variation in EGP for any given glucagon concentration (Figure 1). At low glucagon concentrations EGP is higher in neonates born at GA>=29 weeks, and seems to decrease with increasing glucagon concentration. For neonates born at GA>=29 weeks, EGP is approximately constant across the entire plasma glucagon range. For any given plasma insulin concentration, plasma glucagon shows large variation, particularly with lower plasma insulin levels (Figure 1). There is no distinguishable and consistent trend in plasma glucagon levels with age, birth weight (not shown), or plasma insulin (Figure 2). Plasma glucagon levels drop with increasing blood glucose concentration (Figure 2). In addition, plasma glucagon levels are seen to be higher with higher gestational age, with the same trend of decreasing plasma glucagon with increasing BG.

Across all literature studies, suppression of EGP with increasing GI can be seen, but with significant variation in EGP for any given GI (Figure 4). A piecewise linear trend of GI and EGP from Figure 4, with EGP and GI in units of mg/kg/min, is defined:

\[ EGP(GI) = \begin{cases} 
-0.55 \times GI + 4.96, & 0 < GI \leq 7 \\
1.11, & GI > 7 
\end{cases} \]  

A sub-cohort of studies show some degree of increase in EGP with BG. These studies are plotted in Figure 5a, with each study showing a different trend in the magnitude of EGP with respect to BG. All studies show high variation, as reflected in the R² values from 0.2-0.5. If all the remaining studies are considered, EGP suppression with increasing BG is seen (Figure 5b).

3.2 Endogenous glucose production and BG and plasma insulin.
There was little or no correlation of EGP with BW and GA (not shown). High inter-patient variability between similar patients is seen in the variation of EGP across all metrics. There is no distinct correlation between BG and EGP (Figure 3), or plasma insulin and EGP (not shown)

Table1: Clinical vs Literature data. Data is Median [IQR]

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Gestational Ages [weeks]</th>
<th>Birth Weight [g]</th>
<th>Blood Glucose [mg/dL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literature data</td>
<td>27.5 [26-29]</td>
<td>1080 [921-1315]</td>
<td>73.8 [68.4-97.2]</td>
</tr>
</tbody>
</table>

Figure 1: EGP and glucagon
From Figure 6b a suppressed EGP with BG can be modelled. The EGP variation with BG is modelled:

\[
EGP(BG) = \begin{cases} 
4, & BG < 36 \\ 
5.75 - 0.049 \times BG, & 36 \leq BG \leq 108 \\ 
0.5, & BG > 108 
\end{cases} \quad (9)
\]

EGP has units of mg/kg/min and BG mg/dL. With the suppression of EGP with BG, there was a fitting error of 3.77% over the whole cohort. However, many patients had one or more instances where SI was constrained to a lower limit of SI = 0 L/mU/min without fitting the data, indicating insufficient EGP production in the model.

3.3 Effect on control

Fitting and virtual trial control performance metric results for different EGP models are shown in Table 5. EGP as a function of GI and EGP as a function of BG both performed worse than the currently used constant of EGP = 5.11 mg/kg/min[15]. In the first case, fitting error increased, and in both cases, percentage time in band and number of patients with hypoglycaemic events increased. Due to high variation in EGP in Figures 1 and 6, a range of constant EGP values were investigated. Table 5 shows that EGP < 2 mg/kg/min had high fitting error due to insufficient EGP to reach clinically measured BG levels, and during simulation EGP was insufficient to maintain a positive BG. Increasing EGP decreased fitting error and increased the performance and safety of STAR model-based glycaemic control. However, fitting errors for EGP > 2 mg/kg/min are within measurement error. Thus, compared to BG values in Figure 1, the current value of EGP = 5.11 mg/kg/min appears reasonable. From a control standpoint, EGP = 6.0 mg/kg/min provides the best compromised across all key metrics in Table 5. However, this improvement is unlikely to be clinically significant.

4.0 Discussion and conclusions

While glucagon was seen to decrease with increasing BG, as would be expected physiologically, EGP decreased with increasing glucagon, which is counter physiological. As a result, further models were not created or tested in control. This perhaps suggests that while the pancreas is able to suppress glucagon production with elevated BG to some degree, the liver is not yet able to respond fully to the EGP stimulus.

The piecewise linear models of suppressed EGP with increasing BG, and EGP with GI resulted in poor fitting and control performance because EGP values in the literature were too low during hyperglycaemia to sustain the BG values measured clinically. These results suggest that hyperglycaemic very preterm infants often fail to suppress or otherwise regulate EGP with BG or GI, compared to normal infants. No strong relationship was found with EGP and BW, plasma insulin, or GA over the entire literature data. This result implies that EGP may be higher in these preterm hyperglycaemic infants, which is physiologically intuitive as BG is likely high, at least in part, due to elevated or unsuppressed EGP due to stress of their
Table 2: Comparison of EGP models in control

<table>
<thead>
<tr>
<th>Case</th>
<th>Fitting</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGP</td>
<td>2.77</td>
<td>EGP too low to sustain modelled BG levels, indicating inability of the EGP model to replicate clinical results.</td>
</tr>
<tr>
<td>1.40 (25%)</td>
<td>3.07</td>
<td></td>
</tr>
<tr>
<td>2.1 (50%)</td>
<td>2.58</td>
<td>74.8</td>
</tr>
<tr>
<td>4.6 (75%)</td>
<td>2.11</td>
<td>78.0</td>
</tr>
<tr>
<td>5.11**</td>
<td>2.11</td>
<td>78.4</td>
</tr>
<tr>
<td>6.00*</td>
<td>2.09</td>
<td>79.2</td>
</tr>
<tr>
<td>7.00</td>
<td>2.08</td>
<td>79.8</td>
</tr>
<tr>
<td>7.7 (95%)</td>
<td>2.08</td>
<td>80.7</td>
</tr>
<tr>
<td>EGP(GI(t))</td>
<td>2.28</td>
<td>73.7</td>
</tr>
</tbody>
</table>

Optimum, **Currently in use with EGP = 5.11 mg/kg/min [19]

condition. The literature BG data was in the normal range, so it is likely that the majority of these infants were healthy, and therefore representative of normal EGP dynamics. In contrast, the clinical data is based on hyperglycaemic infants, with higher average BG levels, suggesting this cohort is less healthy. In support of these outcomes, the clinical data patients typically have a lower GA and weight, and generally start hyperglycaemic, unlike literature data. This reflects a limitation in the use of literature data to describe EGP in hyperglycaemic preterm infants. However, no other data for EGP in this cohort exists. Due to the practical difficulty of measuring EGP in this cohort, literature data provides a valid basis for extrapolation.

Figure 6a suggests some neonates are at higher BG levels because of a physiological in ability to regulate EGP. Thus, it is extremely difficult to define a direct cause and effect relationship between BG and EGP.

As the overall result of this study, we conclude that a population constant of EGP = 5.11 mg/kg/min is adequate and safe for use in control. The population constant model best accounts for and reflects uncertainty due to variability between patients [16]. Increases in controller performance at higher assumed EGP values are unlikely to be clinically significant.

Finally, this analysis is only relevant in the context of this model. The model itself has been validated by very successful, safe and prolonged use in neonates [12, 17]. The same model framework and in-silico control modelling approach has been validated in adult cases where more independent data is available [14]. Thus it is felt that the overall results showing enhanced EGP with elevated BG is realistic.

5.0 References


Measuring and evaluating system designed for high frequency oscillatory ventilation monitoring

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Abstract
The study deals with design and testing of a measuring and evaluating system suitable for high frequency oscillatory ventilation (HFOV). The main features of the system are the real time monitoring of HFOV including precise evaluation of ventilatory parameters including tidal volume and minute ventilation, real time modeling of the respiratory system and its mechanical parameters and a model-based computing of alveolar pressure. The study also deals with a calibration and testing of the designed monitoring system.

1 Introduction
High frequency oscillatory ventilation (HFOV) used as an alternative ventilatory strategy for treatment of acute respiratory distress syndrome (ARDS) patients offers potential advantages of lower tidal volumes and lower pressure changes in the alveolar space conducted on such a value of continuous distending pressure on which the oxygenation reaches its maximum value [1]. HFOV uses very high ventilatory frequencies between 2 to 15 Hz, what is up to 100 times higher than the physiological breathing frequencies or ventilatory frequencies used during conventional mechanical ventilation (CV). Therefore, the respiratory monitors designed for CV cannot be used during HFOV. There are no commercially available respiratory monitors suitable for HFOV monitoring.

Commercially available HFOV ventilators for clinical use measure only pressure $P_{aw}$ in the airways. The ventilator calculates other pressure parameters as positive end-expiratory pressure, mean airway pressure (referred to as continuous distending pressure during HFOV), peak inspiratory pressure and pressure amplitude $\Delta P_{aw}$. These parameters are determined mostly to assure maximum safety of HFOV for patients. Measurement of airflow $Q_{aw}$ in the airways, that can be used for calculation of tidal volume ($V_t$), does not exist in any commercially available HFOV ventilator.

The inability of proper monitoring during HFOV affects the initiation and control of HFOV, which is mostly empirical based on table values, observation of patient’s chest wall movement magnitude and a frequent analysis of arterial blood gases. A long-time stability of the HFOV ventilatory mode cannot be achieved easily as any change in the mechanical parameters of the patient’s respiratory system causes a change in delivered tidal volume, minute alveolar ventilation and gas exchange.

As the airway flow rate and volume parameters are not measured during HFOV, other important variables as mechanical parameters of the respiratory system (airway resistance and lung compliance) cannot be evaluated. The amplitude of alveolar pressure $\Delta P_{alv}$ is very important as it is the pressure acting directly inside the lungs. Contrary to conventional ventilation, $\Delta P_{alv}$ is very different from the proximal airway pressure amplitude $\Delta P_{aw}$ during HFOV, and its magnitude depends strongly on mechanical parameters of the respiratory system. Unfortunately, none of the HFOV ventilators is able to evaluate alveolar pressure.

The aim of the study is to design and test a monitoring system suitable for HFOV that allows measurement of all common ventilatory parameters including parameters of the lung mechanics and alveolar pressure.

2 Methods

The designed monitoring system consists of electronic pressure and airflow transducers, analogue-to-digital converter and a computer (notebook) with original software for evaluation and monitoring of HFOV. The overall scheme of the system is depicted in fig. 1.

Figure 1 Scheme of the monitoring and evaluating system for HFOV.

2.1 Airflow and airway pressure measurement
Airway airflow $Q_{aw}$ measurement is assured by a differential pressure transducer that measures a pressure drop developed on a fixed orifice as a consequence of an existing airflow. There are two different types of a coupling con-
taining the orifice designed for use in adult or in neonatal or pediatric patients.

The adult version of the coupling, depicted in Fig. 2, is equipped with standard medical male and female 15 mm cones so that the coupling might be inserted between the Y-piece of a ventilator circuit and an adaptor of the patient’s endotracheal tube. The orifice is 0.5 mm long and has three possible diameters of 4, 6 or 8 mm so that the airflow measurement covers a wide range of the patients’ weights.

Figure 2 An adult version of the coupling for airflow and pressure measurement during HFOV.

The neonatal/pediatric version of the coupling is depicted in Fig. 3. It ends with a standard medical 15 mm male cone that fits the Y-piece of a ventilator circuit on one side and a cone for a direct attachment of the patient’s endotracheal tube (ETC) on the other side. Such a solution allows minimizing the apparatus dead space that is important especially for neonatal use. The orifice is 0.5 mm long and 2 mm (for ETC 2.5 – 3) or 3 mm (for ETC 3.5 – 5) in diameter.

Figure 3 A neonatal/pediatric version of the coupling for airflow and pressure measurement during HFOV.

A significant nonlinearity of the fixed orifice is corrected in the computer using the following equations:

\[ Q_{aw} = a \cdot |U_{measured}|^b \cdot \text{sign}(U_{measured}), \]

where \( Q_{aw} \) is the airflow, \( U_{measured} \) is the output voltage from the pressure transducer followed by an amplifier, \( a \) is a constant dependent mainly on the diameter of the orifice and a gain of the used voltage amplifiers, and \( b \) is a constant characterizing the non-linearity. The value of the \( b \) constant is very close to 0.5 as the structure of the coupling is a parabolic resistor used very often in equipment for respiratory care. The orifice has a symmetric response in inspirium and expirium. A minor difference between its inspiratory and expiratory pressure-volume characteristics are corrected in the computer based on its precise calibration.

The airway pressure is measured 10 mm behind the airflow measurement orifice proximally to the patient. The diameter of the measuring port is 1.2 mm. Because of a very high velocity of the gas along the pressure measurement port in the coupling an error in measured pressure develops according to the Bernoulli effect. The error is corrected in the computer using the following equation:

\[ P_{aw} = P_{measured} + c \cdot |Q_{aw}|, \]

where: \( P_{aw} \) is the corrected airway pressure, \( P_{measured} \) is the pressure measured by the transducer, \( Q_{aw} \) is the airflow and \( c \) is a constant characterizing the Bernoulli effect. A differential pressure transducer for airflow measurement and a pressure transducer for airway pressure measurement are connected to the coupling by three pieces of PVC hose 120 mm long and 2 mm in diameter. Signals from the transducers are amplified and sampled by a 12-bit analog-to-digital converter with a sampling rate of 2 500 Hz. The obtained data are sent to a computer using a serial line or USB port.

The constants \( a \), \( b \) and \( c \) in the above stated equations were obtained during calibration of the system by interpolation of a measured static pressure-flow curve using the least square technique. Calibration gas mixture comprised 60% of oxygen and 40% of air at 37 °C and 100% humidity.

2.2 Modeling of the respiratory system, alveolar pressure evaluation

A special algorithm has been developed for the real-time evaluation of the lung mechanics and alveolar pressure. The only way how to determine these parameters and variables noninvasively is their computing from the courses of proximal airway pressure \( P_{aw} \) and airflow \( Q_{aw} \) using a model of the respiratory system. A special model (Fig. 4) of the respiratory system has been derived suitable both for conventional ventilation and HFOV [2].

Figure 4 Model of the respiratory system.

The first part of the model represents the endotracheal tube and the bronchial tree. The second part of the model represents the lungs in the chest with a compliance as their main component.

The parameters of the model are evaluated from the courses of \( P_{aw} \) and \( Q_{aw} \). The iterative method uses the Fast Fou-
rier Transform (FFT). An auxiliary proximal pressure is computed from the proximal airflow and the model input impedance. Parameters of the model are periodically changed until the measured and the computed auxiliary proximal pressures are the same or very similar. Some of the model parameters represent important characteristics such as compliance of the lungs ($C_L$), airway resistance ($R_{aw}$) and inertance of the airways ($L_1$). They describe a state of the respiratory system. The input impedance of the model in frequency domain can be expressed by equation:

$$Z(\omega) = \frac{P_{aw}(\omega)}{q_{aw}(\omega)} = \frac{R_{aw} + j \omega L_1 + R_1 + \frac{1}{j \omega C_L}}{R_{aw} + j \omega L_1 + R_1 + \frac{1}{j \omega C_L} + \frac{1}{j \omega C_1}}$$

where $C_1$ and $R_1$ are additional parameters representing connection of the respiratory system to the ventilator circuit, $P_{aw}(\omega)$ and $q_{aw}(\omega)$ are the Fourier spectra of the proximal pressure and airflow. Constant $j$ represents the imaginary unit.

The error of approximation of measured proximal airway pressure and the computed auxiliary pressure is evaluated in time domain as a sum of absolute deviations by equation:

$$\xi = \sum_{i=1}^{N} |P_{aw}(i) - P_{aux}(i)|$$

where $N$ is number of samples of the signals and $P_{aux}$ is the computed auxiliary pressure. During the iterative optimisation process the model parameters are being changed with the aim to reduce this error of approximation. When the error is minimal the mathematical model represents the respiratory system best and the parameters of the model are equal to the mechanical parameters of the respiratory system.

After identification of the model, the course of the alveolar pressure $P_{alv}$ is computed using the transfer function $T_{p_{alv}}(\omega)$ of the model:

$$T_{p_{alv}}(\omega) = \frac{P_{alv}(\omega)}{q_{aw}(\omega)} = \frac{1}{\omega^2 C_L C_1 \left( \frac{1}{j \omega C_L} + R_1 + \frac{1}{j \omega L_1 + R_1} \right)}$$

The transfer function describes relation between airflow $Q_{aw}(\omega)$ and alveolar pressure $P_{alv}(\omega)$ in the frequency domain.

### 2.3 Testing of the monitoring system

For verification of the accuracy of airflow and volume measurement, a special apparatus generated precisely known volumes has been constructed. The apparatus consists of a calibrated 10 or 20 mL glass syringe and a crank mechanism providing cyclical linear shifts of the syringe piston. The piston mechanism is driven by a DC motor. Scheme of the apparatus is presented in Fig. 5.

![Scheme of the airflow and volume calibrator.](image)

**Figure 5** Scheme of the airflow and volume calibrator.

The calibrating volumes are adjustable to 3, 6 and 9 mL with the 20 mL syringe and to 1.7, 3.4 and 5.1 mL with the 10 mL syringe. Frequency of the generated waves is adjustable by the CD motor speed. Airflow signals generated by this apparatus are very close to the sinusoidal waves. The output port of the syringe is connected to the orifice coupling being calibrated. The connected orifice represents a pneumatic resistance for the moving gas (approx. 30 kPa.s/L measured at 0.2 L/s) and the actual inner space in the syringe represents a compressible compliance. These parameters cause that the volume generated by the apparatus is slightly lower then the volume corresponding to the volume displacement of the piston. This phenomenon may be described by a differential equation which can be easily solved numerically using an iterative solving of real-gas transport process and its consequent pressure and volume changes.

### 3 Results

The designed monitoring and evaluating system has been constructed for use during HFOV in neonates, pediatric and adult patients. The system has been thoroughly tested by HFOV ventilation of physical models and also animal objects.

With the aim to increase clinical applicability of the system, an increased attention was paid to the presentation of the measured variables. The software can display all the measured and computed curves and computed values. A copy of the basic monitoring screen is presented in Fig. 6, captured during HFOV in a neonate at 10 Hz on a ventilator SensorMedics 3100A (CareFusion, Yorba Linda, CA, USA).
Figure 6: Basic screen of the designed respiratory monitor. Curves displayed: measured airway pressure (cyan), computed auxiliary pressure (red), alveolar pressure (purple) and airflow (green).

In the first graph field the measured proximal pressure $P_{aw}$ is displayed. A curve of the computed auxiliary pressure $P_{aux}$ is displayed behind the measured proximal pressure $P_{aw}$ so that a functioning and precision of the respiratory system modeling may be visually verified. The course of the computed alveolar pressure $P_{alv}$ is displayed in the same field. The curve of the measured airflow $Q_{aw}$ is displayed in the second graph field. Computed values characterizing ventilatory parameters are displayed in the tables on the right-hand side.

The system can be used not only for HFOV, but for conventional ventilation as well. For this case additional display modes are available, for example pressure-volume loop, airflow-volume loop etc. Other capabilities of the program are possibility of visualization of history of ventilation and data archiving and export.

Accuracy of the airflow and volume measurement has been tested using the apparatus described in section 2.3. Results of the test are presented in Table 1 for tidal volumes 1.7, 3, 6, and 9 mL (this values cover all range of tidal volumes used in neonatal patients) and ventilatory frequencies 5 and 10 Hz. These adjusted tidal volumes corresponding to the working space of the piston and oscillatory frequencies are displayed in the first and the second columns. The third column shows a relative deviation of the delivered volumes computed by the numerical simulations described above caused by the resistance of the orifice and the internal compliance of the syringe. These values show that the volume generator error is very low and its maximum error was 1.26%. The next column of the table shows the volumes measured by the tested monitoring system. The values are calculated as mean values from 10 consecutive measurements. Standard deviations are less then 0.06 mL in all the cases. The last column displays a relative deviation of the monitoring system for each setting, calculated as a difference between the measured and the generated volumes divided by the generated volume and expressed in percents. The results of the test prove the precision of the volume measurement as the maximum error of volume determination is 3.75% over the whole range of possible neonatal tidal volumes.

<table>
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<th>Measured Vt (ml)</th>
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4 Discussion
The monitoring system, particularly the software, is not able to record and evaluate every ventilation cycle because the mathematical algorithm is quite complicated and evaluation takes some time. Consequently, the monitor records only some ventilation cycles. A typical refresh rate is between 2 and 5 s. The response time of the pressure sensors is 1 ms ($f_m = 1000$ Hz) and represents the biggest time constant in the system. This constant is enough low in comparison with the maximum spectral components of the measured signals (about 400 Hz) to reproduce the signals without any frequency distortion.

5 Conclusion
The designed monitoring system is suitable for HFOV monitoring in neonates, pediatric and adult patients with a very good accuracy of the delivered tidal volume measurement. Continuous monitoring of HFOV parameters, evaluation of lung mechanics and computation of the alveolar pressure may help optimization and control of the HFOV ventilatory strategy.

6 Acknowledgment
The research was supported by the grant of the Ministry of the Interior of the Czech Republic no. VG 20102015062 and the grant of the Czech Technical University in Prague no. SGS14/216/OHK4/3T/17.

7 References
Wear simulation and wear testing of simplified ceramic knee implant components


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Introduction
Wear limits decisively the lifetime of orthopaedic joint implants and determines the date of implant revision. Since all-ceramic implant components exhibit show less attrition, implantat revisions can be minimized. Moreover, the risk of osteolysis is reduced due to less wear particles. Within the Collaborative Research Center 599 “Sustainable bioresorbable and permanent metallic and ceramic implants” novel all-ceramic knee implant components were manufactured and their wear behaviour was measured on a rolling-gliding-test of the human knee kinematics over 3 million motion cycles. The simplified specimens represent the tibial surfaces and the condyles of the knee. The wear was gravimetrically measured and verified by optical analysis of the wear areas and depths.

Methods
By means of non-linear Finite Element Methods (FEM) and with help of the software MARC Mentat® a finite element model simulating the wear behaviour of simplified all-ceramic knee components under knee-similar physiological conditions was established. The simulation was based on the Archard’s wear model. The friction coefficient μ were parametrized by experimental measurements in the rolling-gliding test. Thus, the simulation was done for experimental wear pairings, the wear coefficient K for Archard’s Model and the wear loss was determined.

Results
A maximum difference of wear loss between simulation and experiment of 4 % was achieved. The experimental wear depth profile of the femoral component equals the simulated profile. Differences were found between the wear depth profiles of the tibial component. However, the maximal wear depth values are similar.

Conclusion
With a maximum deviation beween measured and simulated wear loss of 0.89 mm a simulation model has been developed, which is representative for the conducted rolling-gliding-implant wear tests. Further investigation will focus on the influence of different implant radius congruencies and the resulting wear contact areas. By this, simulative predictions of the wear volume for variable implant curvatures in frontal and sagittal plane can be done. This will be used to design a ceramic specific and patient sufficient knee implant endoprosthesis.
Finite element simulations for development of cardiovascular implants to support biological grafts

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Introduction
Lesioned myocardial tissue due to ischemic incidents and several pathologies of the thoracic aorta require surgical treatment. One therapeutic option is the surgical substitution with biological grafts. Tissue transplants often have a low initial strength that is not sufficient for application in high pressure zones such as the left ventricle or the aorta. Our objective is to develop degradable magnesium alloy scaffolds that temporarily support these biological grafts until physiological remodelling leads to sufficient strength. Since in vitro and in vivo testing is very costly and time consuming, we use the finite element method to enhance the developing process.

Methods
A finite element (FE) model was developed that mimics myocardial movement between systolic and diastolic state. This allows for simulating scaffolds during cardiac motion, evaluating resultant stresses and strains, and performing shape improvements. Also, the swelling of a vessel due to high blood pressure was modelled with finite elements. With help of these models, several newly designed myocardial as well as aortic scaffolds were assessed.

Results
It was shown that myocardial scaffolds adjusted to the targeted myocardial region are preferable to flat ones. Different scaffold designs were compared and it revealed that complex shapes not necessarily lead to better results. Often simple structures were lower stressed. Similar results were obtained for aortic scaffolds.

Conclusion
The finite element method is a useful tool for the development of stabilizing magnesium alloy scaffolds. Even though experimental testing still remains inevitable, the number of needed costly and time consuming in vitro or in vivo tests can be reduced significantly. This new knowledge of correlation between the scaffold’s design and its resilience can accelerate development of highly specific implants.
Early public relations of research groups to facilitate industrial partnering for future translation activities

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Introduction

The transfer of innovative biomedical implants or devices from basic research into clinical applications often requires substantial support from industrial companies. Hence, professional public relations activities (PR) can be recommend even to basic research groups to early establish links to industrial development partners. However, successful PR requires full support of the scientists. To this end, we asked scientists from collaborative research centres (CRC) for their preferred goals and target groups of PR.

Methods

Researchers of 61 CRC in the life sciences area were surveyed for goals and target groups of their CRC for a period of 6 months. Speaker and members of the board of the CRCs were interviewed in person via phone conferences, whereas projectleaders and other scientists answered to an online questionnaire (www.surveymonkey.com).

Results

The evaluation of 71 interviews and 351 completed questionnaires showed differences between both surveyed groups: The interview group named third-party funders, industry, and other scientists as their primary focus of PR, whilst the questionnaire group preferred students, young academics, and the public as addressees of PR. The future acquisition of industry partners was not subject of any PR concept or measurement.

Conclusion

PR of research groups is without doubt of high importance. Nevertheless, the reported targets and target groups of research PR are congruent, but not significantly directed towards future partnering processes with companies that would support translation of research into clinical applications. However, the latter often is the ultimate motivation of research. Thus, early research PR and communication platforms should be employed to facilitate approximation of scientists and industry. Finally, protection of intellectual property should be safeguarded for the scientists by all means.
Intramedullary nails out of magnesium alloy: a finite element study

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Introduction
The use of intramedullary nails for fracture stabilization of long bones is a common treatment. Normally the implant need to be explanted after the healing process. The biocompatible and slow degrading magnesium alloy LAE442 seems to be an alternative. Before implanting an intramedullary nail out of LAE442 in a fractured bone, finite element simulations are performed to test the primary stability.

Methods
A finite element model of an ovine tibia was generated on the basis of micro computed tomography data using Mimics and geomagic. An intramedullary nail (Ø 9 mm, 130 mm length, 4 locking screws) was implemented into the model. Different fracture scenarios were simulated. The gap size and the direction of the fracture were varied. The material properties of the ovine tibia were assumed to be similar to human bone material parameters. The Young’s modulus for the screws and the nail was 43GPa. Within a next step the Young’s modulus of the nail and the screws was changed to 210 GPa, the Young’s modulus of steel. The loading was taken from the literature. This study is followed by simulations of intramedullary nails within human tibiae.

Results
All simulations of a fractured ovine tibiae with the used intramedullary nail geometry showed that the principal von Mises stresses exceeded the yield stresses of LAE442 as well as the yield stresses of steel.

Conclusion
In the case of an ovine tibia the primary stability of the chosen intramedullary nail geometry was insufficient independent from the used material (LAE442 or steel). This might be caused by high bending moments in an ovine tibia. Further simulations have to be carried out to see, whether the different loading scenario of a human tibia leads to lower stresses.

Acknowledgement
Thanks to the DFG for funding the sub-project R6 within the SFB 599.
Model-based Monitoring of Hip Prosthesis Vibrations for Loosening Detection

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Introduction

The application of vibration techniques to aseptic prosthesis loosening detection has been investigated as more sensitive alternative to X-ray and other diagnostic methods. Theoretical studies and laboratory experiments of the linear properties show that changes of the femur-prosthesis system can be noticed in the frequency spectrum. These changes are related not only to changes of the length of the loosening zone, but also to changes of the bone mass, the thickness of the coupling tissue, the damping, and other parameters, which is problematic. A new approach is presented, where the vibration measurements are processed based on a parametric mechanical model of the femur-prosthesis system.

Methods

Fig. 1 shows the parameter estimation loop of the model-based signal processing approach. A sinusoidal input force of a specific frequency $f_1$ excites model and the lateral epicondyle of the femur. Femur and prosthesis are modeled 1D as coupled bending wave guides using Finite Network Elements. This way, a physically-based model is given. Equal parameters, like finite masses or bending compliances, can be combined to one influence parameter. The dynamic behaviour was simulated with a circuit simulator.

Vibration measurements, taken at the prosthesis, and model output (see Fig. 2) are compared by their vector difference, which is the residual. The scalar product of the residual is minimized by parameter estimation. At the figure of merit minimum the parameters express in an ideal situation the system state.

Fig. 1: Estimation of femur-prosthesis parameters to determine loosening and other changes
Fig. 2: Model output for 2 different loosening states without damping

**Results**

At first preliminary simulation results were obtained in the frequency domain and displayed in a topographical style with chosen network parameters as arguments and the colors expressing the vibrational magnitudes to investigate the system dependency. Based on a laboratory experiment, system parameters were estimated.

**Conclusion**

The invoked lumped parameter or network model requires a significantly lower computational effort than Finite-Element models and no other special software than a circuit simulator like Spice combined with a mathematical optimization tool. This is a prerequisite for an efficient parameter estimation. Further processing of experimental data is obligatory to determine the limits of the approach.
Canine Hip-Joint Forces: Model Development and Calculation by means of Multi-Body Simulation

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Introduction

Dogs are often clinical models for the validation of human prostheses [1,2]. In order to reduce animal testing, the use of simulation methods has been established. In the framework of this study a Multibody simulation (MBS) model of the canine hindlimb is created to determine the hip-joint forces. These forces can be used for example as boundary conditions for Finite Element simulation as is already the case for numerical investigations concerning human prostheses [3].

Methods

The MBS model is created on the basis of a healthy laboratory dog (Beagle; BW: 17.9 kg). Gait analysis as well as bone data originated from the laboratory dog. The bone data are taken by gathering CT-data and segmenting them with the Open Source Software YaDiV. For the modelling and simulation, the software Anybody Modelling System™ is used. Knee and ankle joint are modelled as joints with only one rotational degree of freedom (DOF), whereas the hip joint has three rotational DOF. The created hindlimb model comprises a set of muscles based on the literature [4, 5]. For muscle modelling the so-called AnyMuscleModel is used. Using the created MBS model, the hip resultants normalized to body weight (BW) for four consecutive strides are determined.

Results

The force pattern of the four strides shows an undulating course. The local maxima of the hip joint resultant lie in the range of 165\% BW and 230\% BW. The mean peak force of all four strides is about 201\%.

Figure 1: Normalized hip resultant of four consecutive strides
Conclusion

The calculated peak forces show a good accordance with published values measured in dogs [6,7]. In the future it is planned to optimize the model concerning muscle paths and used muscle models.

References

An integrated multi-scale computational approach for the biomechanics of bones

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Abstract

Based on a phenomenological model on stress adaptive bone remodelling a sophisticated computational technique for patient individual studies on hip-joint endoprosthetics will be presented. A central topic will be on the geometrical modelling approach based on CT-data and a more sophisticated approach based on radiographs. Another subject is on the description of the loading conditions for different time scales. Model refinement strategies will be discussed, for example the computation of the primal osseointegration of implants. For a deeper insight into the biological mechanism of osseointegration a bio-regulatory model of fracture healing will be suggested, including the communication of different involved types of cells. Going down in length-scale to a cellular level, the mechanical behaviour of individual osteocytes will be described by a tensegrity like structural model. Embedded in a multi-scale computational environment the mechanical response of osteocytes embedded in between the lamellas of cortical bone will be computed in order to study the signalling process for bone remodelling initiation.

The integration of these so far isolated modelling steps into an integrated simulation environment will be task for future research. At this time strategies for coupling the simulation with clinical database informations are forced.
Simulation-assisted prosthetic design

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Introduction
The market-worthiness of prosthetic components and systems are tested extensively in time-consuming experiments (ISO standard tests). However, if any component fails, more time must be invested for redesigning and testing. Simulations can verify the conformity of these components before experimental testing, and, hence, reduce the time-to-market. As an example, we consider the development of lower limb prostheses.

Methods
The gait of an amputee is recorded using a Qualisys motion capture system. A minimum of three markers on each body segment defines a rigid body, whose translation and orientation are captured at each instant of time. For the purpose of computer simulations, a virtual environment of the experiment is created. The subject is virtualized using a dummy from LSTC (crash-test dummy). The prosthesis to be tested is semi-automatically fitted to the dummy. The dummy is scaled to match the subject anthropometry and the rigid-body trajectories are imparted on it.

Results
A simple and effective workflow technique that pre-and post-processes the simulation data has been developed. This includes the modified LSTC dummy wearing a prosthesis. Furthermore, an intuitive visualization technique that overlays the simulation results on a video has been realized. The developed virtual environment can also be used for performing virtual ISO tests.

Conclusion
This study demonstrates the potential of using a virtual dummy for Finite Element analysis (FE) of a prosthesis during gait. The possibility of analyzing several gait patterns and prostheses in different patients is made relatively easy by the developed workflow methodology. The main advantage of the workflow is the ease of creating and using FE input files for individual cases.
A large-scale patient-specific multi-physical finite element model of the heart

Abstract

The adequate predictive modeling of cardiac mechanics, that is capable of indicating the heart’s functionality and response to external disturbances, remains a challenging task. Especially the different physical domains involved, i.e. structural and fluid mechanics as well as electrophysiology, pose high demands on the numerical solution strategies. We present a high-resolution 3D nonlinear finite element model of patient-specific heart geometries, which includes a one-way electro-mechanical coupling to an active material law prescribing the ventricular contraction. In addition, a passive material model captures the highly anisotropic nonlinear behavior of the myocardium. Furthermore, the structural model is strongly coupled with the ventricular blood compartments, addressed by so-called windkessel models serving as 0D fluid representations of the cardiovascular system. This leads to a monolithic windkessel-structural system of equations being solved within an iterative Newton-Raphson scheme with adequate block preconditioners at hand and allows for the physiologically meaningful solution of the heart contraction mechanics without considering a full fluid-structure interaction problem. We show that the model allows for reproducing a healthy state of ventricular contraction and present cases of heart insufficiency and other indicators for reduced heart functionality. Fields of applications for the model’s predictive abilities are outlined and potentials of improvement for future-generation heart modeling are addressed.
Modeling Supra-Physiological Loading of Human Arterial Walls – Damage, Anisotropy and Component-Specific Behavior

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Abstract

In this contribution an approach for the modeling of the mechanical behavior of arterial walls under supra-physiological loading conditions is investigated. One example of an overstretched atherosclerotic artery is provided using a finite element simulation. Therefor, the constitutive model from [1] is utilized, which reflects the anisotropic material behavior as well as damage-induced softening. This model is adjusted to the uniaxial stress response of the media and adventitia of an atherosclerotic artery is circumferentially overstretched by a supra-physiological internal pressure, as it may, for example, occur during balloon angioplasty.

1 Introduction

The role of the main structural components of arterial tissues, namely elastin and collagen, in terms of their contributions to the overall mechanical response was first investigated in [5]. Therein, it was found that elastin is mainly load bearing at low loadings, whereas at higher loadings the contribution of the collagen becomes more relevant due to the successive recruitment of collagen fibers. These findings are widely accepted and considered accordingly in material modeling of arterial tissues. In the well-known model by [4], a decoupled strain-energy function was introduced, accounting for the separate contributions of the ground substance (mainly composed of elastin), and the embedded collagen fibers. However, little is known about the specific contributions of elastin and collagen under supra-physiological loading conditions. First results to determine the uniaxial mechanical response of elastin- and collagen-digested human abdominal aortic specimens in the supra-physiological loading domain are summarized here, see also [7] for a more complete picture. A material model from [1] is adjusted to this component-specific response as well as to the response of an untreated control specimen (containing elastin and collagen). The material parameters obtained from the adjustment are then used within a finite element simulation, wherein a simplified atherosclerotic artery is circumferentially overstretched by a supra-physiological internal pressure, as it may, for example, occur during balloon angioplasty.

For the media and adventitia subsequent testing was carried out. Thereby, one strip of each specimen served as a control sample, for another strip elastin digestion was performed by elastase treatment, and the third strip was subjected to collagenase yielding a collagen-free tissue.

2 Methods

Within the experimental study [7] seventeen non-atherosclerotic human abdominal aortic specimens were extracted within 24 h after death (≥67). From each specimen three dog bone shaped circumferential strips were cut out and dissected into intima, media and adventitia.

For the media and adventitia subsequent testing was carried out. Thereby, one strip of each specimen served as a control sample, for another strip elastin digestion was performed by elastase treatment, and the third strip was subjected to collagenase yielding a collagen-free tissue.

All strips were subjected to cyclic uniaxial loading (10 cycles per load level). Thereby, increasing load levels of 50, 100, 300 and 500 kPa were applied to the control and elastase-treated samples, and 20, 50, 100 and 300 kPa were applied to the more fragile collagenase-treated samples.

For the modeling of the experimentally observed material behavior, the constitutive model from [1] was adjusted to the stress-stretch response of the control and enzyme-treated strips, respectively. Within the above-mentioned model, the material is described by a decoupled strain-energy function

\[ \Psi = \Psi_{\text{elas}} + \Psi_{\text{coll}} \]

wherein

\[ \Psi_{\text{elas}} = c(I_1 - 3) \]

accounts for the isotropic contribution of the ground substance, which is mainly composed of elastin, and

\[ \Psi_{\text{coll}} = \sum_{a=1}^{2} \frac{k_1}{2k_2} \left\{ \exp[k_2(1 - D_a)P_a - 1] - 1 \right\} \]

with

\[ P_a = \kappa I_1 + (1 - 3\kappa)J_2 \]

contains the transversely-isotrop contribution from two (a = 1, 2) families of embedded collagen fibers, while c, k_1 and k_2 represent material parameters, whereas c and k_1 have the dimension of stress and k_2 is dimensionless. The invariants I_1 = tr(C) and J_2 = a_4 \cdot C a_4 are formulated in terms of the right Cauchy-Green tensor C, and of the preferred fiber direction a_4. In P_a the parameter \kappa, cf. [2], is included to account for dispersed fibers. A damage variable D_a is associated to each fiber family a and defined to increase in loading and reloading paths. All parameters occurring in \Psi_{\text{elas}} and \Psi_{\text{coll}}
were adjusted to the stress response of a collagenase- and an elastase-treated strip of the media and adventitia, respectively, by means of least-square fitting of the experimentally determined stresses and the constitutive stresses. Additionally, the stress response resulting from the total energy $\Psi$ was adjusted to the experimental data of the associated untreated control strips.

The parameters for the media and the adventitia obtained from the adjustment to the control strips were used within a finite element simulation of a simplified atherosclerotic artery [6] containing five different layers. The parameters for the other layers (fibrotic media, fibrous cap and lipid pool) were adopted from [1]. A circumferential overstretch of the arterial wall was simulated by applying a supra-physiological internal pressure of 150 kPa. Furthermore, an axial prestretch of 4% was applied to include eigenstresses in that direction.

### Figure 2: Distribution of normalized damage $D_{\text{norm,1}} = D_1/\text{max}D_1$ in the first main fiber family ($\lambda_1$) after the circumferential overstretch ($\text{max}D_1 = 0.0184$).

### Figure 3: Distribution of fiber stretch in the first main fiber family ($\lambda_f$) at a physiological internal pressure of 24 kPa before (a) and after (b) the circumferential overstretch.

![Figure 2](image2.png)

![Figure 3](image3.png)

## 3 Results

The collagenase-treated strips showed a linear response without softening. For the elastase-treated and control strips remanent strains and a continuous softening was observed, which was much less pronounced in the control strips (see [7]). The material model from [1] turned out to be well-suited to reproduce the response of the control strips as well as the component-specific behavior of elastin and collagen when only considering the associated contribution within the strain-energy, cf. Fig. 1. However, it was found that the stress response of the control cannot be simply represented by the sum of the stresses of elastin and collagen, and the interaction of both constituents requires further studies.

The numerical example shows high damage values within the healthy media due to the circumferential overstretch (Fig. 2). Furthermore, the induction of damage led to remanent strains under physiological pressure after the overstretch, cf. Fig. 3.

## 4 Conclusion

With respect to the modeling of arterial tissues in the supra-physiological domain, we have demonstrated that a damage approach with continuous characteristics should be included into the corresponding part of the strain-energy, which represents the contribution of the collagen, while not affecting the elastin. Furthermore, remanent strains after unloading should be considered [7]. The numerically computed over-inflation of the arterial model showed, that due to the damage approach [1] remanent strains are obtained under physiological pressure after a supra-physiological overstretching of the tissue. Furthermore, high damage values were observed in the healthy media, which is in line with other observations from the literature [3].

## 5 References

Mechanical Stimulated Biochemical Fracture Healing within a Finite Element Framework

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Introduction

Stem cells play a major role during the early stages of bone fracture healing. They are recruited by the expression of growth factors in the region of the injury and differentiate to e.g. chondrocytes and osteoblasts, depending on the biochemical and mechanical milieu. The subsequent tissue development gradually stabilises the fracture site. Computational models of this process have been developed in recent years. In this contribution a biochemical model of fracture healing is adopted from literature and combined with a mechanical simulation of the fractured bone. A mechanical stimulus is defined, which controls the stem cell differentiation.

Methods

The bioregulated fracture healing model developed in [1, 2] describes the healing process by a set of instationary advection-diffusion-reaction equations

\[
\frac{\partial c_i}{\partial t} = \nabla (D(c_j) \nabla c_i) - (C(c_j) \nabla c_i) + R(c_j)c_i,
\]

where \(c_i\) is the concentration of interest and \(D, C\) and \(R\) represent the diffusion, advection and reaction coefficients, respectively, which may depend on concentrations of other concentrations \(c_j\), e.g. growth factor concentrations or extracellular matrix densities.

The necessary stabilisation for a Finite Element approach is provided by the Finite Calculus method proposed in [3, 4] combined with a Time Discontinuous Galerkin scheme [5].

The mechanical simulation provides insight on the local mechanical demand inside the callus region. From this a mechanical stimulus is calculated, e.g. by evaluation of the equivalent deviatoric strain

\[
\eta := \varepsilon'_{\nu} = \frac{2}{\sqrt{3}} \sqrt{\frac{1}{6} ((\varepsilon'_1 - \varepsilon'_2)^2 + (\varepsilon'_2 - \varepsilon'_3)^2 + (\varepsilon'_3 - \varepsilon'_1)^2)}.
\]

and defining stimulation factors \(\psi = [0, 1]\) according to the value of \(\eta\), see figure 1. Three stimulation factors \(\psi_b, \psi_c\) and \(\psi_f\) are considered for stem cell differentiation. These factors scale the likelihood of the stem cell population to differentiate along the according pathways.
Results

Figure 2 shows the tissue development during the healing period. After ten days cartilage formation has taken place in the callus, initial bone formation is seen only in the vicinity of the periost. Secondary ossification has replaced the cartilage in wide regions of the periosteal and endosteal callus after twenty days and the bridging of the fracture gap was successful. Finally, the callus mainly consists of immature woven bone.

Conclusion

The presented model simulates fracture healing on the basis of biochemical process controlling cell activities during the healing period. Computation of the mechanical demand in the callus region enables to define stimulation parameters, which provide the means to include the need for mechanical stability of the fracture site into the model.
References


