ID: T-OP-01

Modeling and experimental validation of hypothermal-induced mechanisms in cardiac tissue

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Hypothermia, a condition of abnormally low body temperature, has a relevant impact on physiological regulatory mechanisms in the cardiovascular system. Electrophysiological changes in hypothermia can be observed through morphological variances in the ECG caused by alterations in ion channel dynamics. These changes lead to modulations of the action potential morphology and a decreased intercellular conduction of atrial and ventricular cells, and subsequently to changes in the ECG. These changes comprise e.g. an alteration of the T-wave, a prolongation of electrocardiographic time intervals and the formation of an additional wave (J-wave). This work provides an overview on mathematical modeling and experimental validation of hypothermal-induced mechanisms in the heart. A temperature-dependent cardiac cell model was developed, allowing for simulation and investigation of the action potential of single cells and the modulation of the electrical excitation and wavefront propagation in ventricular tissue. Using this model, a pseudo ECG can be computed, demonstrating alterations in ECG formation during cooling. To investigate transmural temperature profiles in the ventricular wall in strong hypothermia, a finite element model (FEM) using the Pennes' bioheat equation was developed. In cardiac cryoablation, a minimal invasive clinical procedure to treat cardiac arrhythmias, different ablation scenarios such as multiple freeze-thaw cycles can be applied. This FEM-Model was now used to simulate and evaluate different ablation scenarios to optimize the clinical intervention. In-vivo and in-vitro experiments were carried out to prove and validate the computer models. Changes in electrical excitation and ECG formation could be confirmed via ECG and field potential measurements in the house swine and chicken cardiomyocyte cell layers, respectively using multi electrode array technology. Our work contributes towards a better understanding of electrophysiological and biophysical mechanisms in cardiac tissue in hypothermia which is urgently needed for the development of new diagnostic and therapeutic applications in clinical cardiology.

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Virtual electrode polarization under myocardial acute ischemia: dependence on ischemic area and border zone sizes of the exciting electric field

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Myocardial ischemia arises due to a mismatch between the tissue's metabolic demand and the blood supply of substrates. It can degenerate in acute ischemia and infarction (irreversible cell death). Ischemia is also followed by profound metabolic changes: hyperkalemia (increment of extracellular potassium), hypoxia (deprivation of adequate oxygen supply) and acidosis (increment of blood acidity).
In this study we present a modified version of the Luo Rudy I model under acute ischemic conditions, in which the mentioned metabolic changes have been introduced. Simulations are run in 2D anisotropic and heterogeneous sheets of myocardial tissue according to the bidomain formulation, taking into account the effects that acute ischemia exerts on tissue's conduction properties. In this perspective, ischemic heterogeneities are treated as less conductive areas subdivided into three different regions: a central ischemic zone (IZ), a border zone (BZ, linear transition between physiological and ischemic values) and healthy tissue.
This study also relies on the theory of virtual electrode polarization (VEP) in response to far field pacing. As widely investigated, heterogeneities can serve as cores for functional and anatomical reentries. In response to an applied electric field and under certain conditions, areas near the cores experience greater (positive and negative) polarization compared to the homogeneous surrounding tissue. As consequence, cores might behave like virtual electrodes able to excite and de-excite the tissue: we discuss the possibility to consider VEP as a basic mechanism of defibrillation against lethal cardiac arrhythmias, including reentrant ventricular tachycardia and fibrillation. Moreover, we investigate the relation between the heterogeneity size and the electric field that has to be applied to get VEP. We shall demonstrate that the excitation threshold of VEP may be decreased or increased by the size of IZ depending on the width of BZ.

ID: T-OP-06

Comparison of Two Spatio-Temporal Approaches for Solving the Inverse Problem of ECG

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Noninvasive electrocardiographic imaging has a great potential for facilitating improved diagnosis and treatment planning in cardiology. In clinical applications, the best results have been reported for approaches incorporating spatio-temporal solution dynamics into the regularization. In the present simulation study, performance of two spatio-temporal methods is evaluated for localization of ventricular ectopic beats.
In the forward calculations, monodomain model was used for generation of the transmembrane potentials (TMP) and associated activation sequences in the heart; the body surface potential maps (BSPM) were computed for a realistic FEM-based body volume conductor with anisotropic heart model. For the inverse reconstructions, the surface TMP source model in combination with two spatio-temporal regularization techniques was employed. The first approach is based on the fastest route algorithm (FRA): realistic activation sequences starting from each cardiac node are generated with FRA and afterwards converted into the ECG, which is compared to the reference signal based on the correlation criterion. The best solution estimate is obtained by the activation sequence delivering the highest correlation. Another approach is data-driven and solves a Tikhonov-like minimization problem for all time steps at once imposing a nondecreasing time course of the solution.
Both methods performed well in identifying the areas of earliest activation. The localization accuracy was higher for the constraint optimization approach, whereas the FRA-based full-search was better in classifying the ectopic beats with respect to their endo- or epicardial origin. Furthermore, the FRA method has an advantage of much lower computational time.
The obtained results encourage further investigations on combining both regularization techniques in order to achieve an optimal performance in terms of computational load and localization accuracy.

ID: T-OP-07

Deformation and Contraction Energy in a Simulated Human Heart

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Human heart is a muscle that beats constantly during the whole life cycle of a human being. Myocyte fibers are responsible for applying active forces to the heart tissue in defined directions. These evoke the contraction of the heart, a decrease of intra-ventricular volume, and finally ejection and circulation of blood. An efficient energy usage is expected to be responsible for a long and faultless lifetime of the heart muscle.
The heart model contains both ventricles, atria and the pericardium. Heart tissue is characterized by a Guccione-type material law for the ventricles and Mooney-Rivlin material in the atria. Interior of the ventricles is connected to a Windkessel model to represent blood pressure. Outer surface is coupled to the interior of the pericardium to allow frictionless sliding. The emerging equations are solved on a tetrahedral mesh using a finite element method of second order. The results were evaluated for different energies: deformation energy and kinetic energy.
Simulations were performed on six different sets of heart fibers with orientations generated with a rule-based Laplace-Dirichlet algorithm to avoid negative influences of "bad" orientations. The algorithm expects as input endo- and epicardial fiber angles similar to the ones measured in reality in human subjects. Results show that all tested configurations of heart fibers lead to similar kinetic energy during the different parts of the heart cycle. However, deformation energies that arise mainly from active myocyte forces are about three magnitudes larger than kinetic energies. They show also more deviation in relation to each other. One reason is a large stiffness of heart tissue during the contraction due to the active tension. Another reason is the forced contact between epicardium and pericardium that restricts the movement of the epicardial surface without any real compression effect. Other reasons might be of physiological nature, to create a more durable muscle by avoiding large displacements.

ID: T-OP-08

Virtual angiography of complex vascular networks to assist arteriovenous malformation therapy

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Arteriovenous malformations (AVM) are congenital abnormalities in the connectivity and morphology of blood vessels. Such lesions are characterized by the presence of anomalous connections between arteries and veins, which exhibit a decreased vascular resistance compared to the largely bypassed capillary bed. This may result in insufficient tissue perfusion, increased venous pressure and cardiac volume overload. AVMs are primarily treated with reiterative endovascular embolization and sclerotherapy sessions. Reliable lesion localization and treatment is often difficult and requires repeated X-ray angiography recordings, exposing the patient to high radiation and contrast agent (CA) doses.

We aim at reducing treatment duration and inherent risks by introducing a novel augmented-reality angiography system for AVM treatment.

The virtual angiography tool is based on a patient-specific lumped-parameter description of the vascular network to compute blood pressure and flow rates within the region of interest. Boundary conditions were provided by a coupled human circulation model, tuned towards meeting duplex-sonography findings of the patient. CA transport was determined by coupling the hemodynamic model to the 1D advection-diffusion equation, which was discretized with second-order finite differences in space and a low-storage Runge-Kutta time integration scheme. A geometrical description of the vascular network was obtained by semi-automatic segmentation and skeletonization of time-resolved subtraction gradient echo magnetic resonance imaging instances.

Virtual angiography was performed retrospectively for patients treated at the University Hospital Bern. The simulated CA spread was visualized within a 3D representation of the affected vasculature. This allowed to correctly identify the cluster of vessels representing the pathological arteriovenous shunt, without the need for extensive radiation and CA exposure. Additionally, computed pressure and flow velocities were mapped onto the 3D geometrical model to virtually assist the clinical practitioner in the choice and planning of specific interventional techniques, such as coiling and ethanol sclerotherapy.

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System Identification of a Left Ventricular Assist Device for Sensorless Estimation of the Pump Flowrate.

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Left ventricular assist devices (LVAD) are increasingly implanted in end-stage heart failure patients. Due to the lack of long term stable pressure sensors for monitoring hemodynamics and the interaction between pump and circulation, the pump flowrate needs to be estimated. This estimation from available pump parameters necessitates the identification of the LVAD system, which was the aim of the current study. Based on hydraulic testing in a mock circulation, which included a powerful linear motor for load variation, a mathematical model was designed comprising both static and dynamic components. The static component was a third degree polynomial relating pump flow (Q), pump speed (ω), current uptake (I) and fluid viscosity. The dynamic component was designed as a second order linear model of Q, ω and I. To identify the model parameters, five static- and 23 dynamic datasets with working points covering the clinical operation range (0-12 L/min flowrate, 2400 and 3600 rpm pump speed and 0-12Hz sinusoidal pressure head sweeps) were used in 2, 3 and 4cP water/glycerol mixtures. Additionally, 22 datasets were used for validation. During the identification, 4 of the 5 coefficients varied less than ±10% between different datasets. The fifth coefficient showed a variability of ±26%. Nevertheless, with the mean values of these sets of coefficients the identified model allowed flow estimation with a root mean square error of 0.35±0.06 L/min, of which the static component introduced a bias of 0.17±0.08 L/min. In conclusion, the developed model is able to reproduce the dynamic behaviour of this complex nonlinear system by using a nonlinear static and a linear dynamic system. This enabled robust estimation of flow.

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Differences in tension development due to electrophysiological apico-basal heterogeneity gradients in a computational rabbit ventricle model

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Heterogeneities within the ion channel density throughout the ventricle have a major influence on the electrophysiological properties of the respective cells, affecting not only the repolarization sequence but also regional tension development.
Aim of this work was to compare the impact of different heterogeneities on the tension development within a rabbit ventricular model of single cell tension development. In order to investigate the impact on a whole heart level, a finite element model approach was used, including the interaction with the surrounding tissue, and the influence of the circulatory system. Tension development and the electrophysiological properties of cells were based on computational models, with stretch (preload) influencing the cross bridge cycle and hence the respective tension development. Electrophysiological and mechanical models were coupled during the simulation via stretch, tension and deformation. Three different apico-basal heterogeneity gradients, based on measured data, and a full homogeneous ion channel density distribution were implemented in the model. Different outcomes were compared in terms of ejection volume, pressure development, contraction velocity and tension development within different segments of the left ventricle.
Even though introduction of certain heterogeneities led to a significant change in overall tension development at single cell level, this did not subsequently give rise to a change in myocardial deformation at tissue level. Rather than an alteration in ejection fraction, the time to maximal tension development shifted. This can be explained by the correlation between developed tension and the stretch of the cell. During shortening of the cell due to contraction, stretch decreases, which subsequently leads to a decrease in developed tension.
Our results suggest that heterogeneities that influence the amplitude of tension development at single cell level manifest themselves via changes in contraction velocity and sequential activation at whole heart level, while only marginally influencing total deformation and ejected volume.

ID: T-OP-12

Computational model of a fractal lung to simulate and visualize gas transport for diagnostic purposes and patient education

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The airways of the human lung form a dichotomous tree comprising about 23 generations. Local airway obstructions can significantly change ventilation dynamics and efficiency of gas exchange. In patients with e.g. Cystic fibrosis airway obstruction occurs already during childhood. Multiple breath washout with nitrogen (N_2MBW) is used for the follow-up of CF lung disease by measuring the N2 concentration in the expired airstream. However, it is not possible to infer local gas transport and ventilation dynamics from the measured N_2 concentration. Therefore, a numerical model of a fractal lung was developed for the simulation of the washout test and to visualize local ventilation inhomogeneities in the whole airway tree.
The conducting airways of the lungs are modelled as a fractal tree. A non-linear lumped-parameter model is attached to every terminal branch to represent the acinar gas transport. Gas transport during the washout test is modelled by a one-dimensional advection-diffusion equation. The lung model is adapted specifically to a patient by using the patient's functional residual capacity and respiration profile as input parameters. Locally changing the morphology or biomechanical parameters allows to simulate ventilation inhomogeneities.
The respiration profile from a healthy person was taken to simulate a baseline N_2MBW with unobstructed ventilation. Local changes in the morphology were then implemented to model pathological obstructions. The simulation of the N_2MBW with these morphological changes showed typical inhomogeneous ventilation patterns and longer washout times of N_2.
Comparing the ventilation and gas transport for a healthy and an obstructed lung model enhances our understanding of lung disease and can support a targeted therapy. Furthermore, the visualization of the gas transport in the whole airway tree can help patients and parents of patients to better understand the pathology and the severity of their lung disease.

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Cascaded Control Environment for a CPAP-Device

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Breathing-dependent sleep disorders are a big and increasing issue in our prosperous society, which leads to high costs in the treatment of their complications. Due to breathing interrupts at night the blood oxygen concentration decreases and causes repeated sleep disruptions (as an automatic alarm function of the human body). Symptoms of sleep apnoea like fatigue, lack of concentration and high blood pressure are related to a higher risk of coronary thrombosis and apoplexy. The most important and most comprehensive method to treat the obstructive sleep apnoea syndrome (OSAS) is the positive pressure ventilation. The continuous pressure in the upper airways (continuous positive airway pressure - CPAP) prevent the collapse of the upper respiratory tracts and the pharynx. In this work a possibility to model and control the real system in a four-stage cascaded control environment is provided.
In a first step the dc-motor with the impeller was modeled. The relationship between the motor voltage and the motor speed can be modeled as a linear second order state space system. The second model for the pneumatic part, simplified as a gas tank with system mass flow, leakage mass flow and patient mass flow, can be derived from the thermal equation of state. With respect to four main states of the system (motor current, motor speed, system mass flow and mask pressure) a four-stage cascaded control environment was developed. Due to the physical equations describing the electro-mechanic and pneumatic part, model-based feedforward control and model-based closed-loop controls could be developed to improve the control quality.
The developed cascaded control environment shows good results at the real process in case of breathing compared to the existing (two-cascaded) control environment. The breathing interaction of the patient was simulated by the ASL 5000 lung simulator to mirror the specification of the DIN EN ISO 17510-1 (tidal volume of 500 ml, sinusoidal patient flow). The pressure deviation at a therapy pressure of 4 hPa is reduced from 54 Pa to 28 Pa - at a therapy pressure of 12 hPa it is reduced from 44 Pa to 38 Pa. Some other tests with the ASL 5000 have been performed to show the quality of the closed-loop pressure control. During artificial ventilation with a pressure controlled ventilation mode (PCV - pressure controlled ventilation) the closed-loop control shows good reference tracking between the pressure levels of the inspiration and expiration phase. Furthermore, a voluntary test person with a tidal volume of 1100 ml was treated. Due to a stronger breathing effort the pressure deviation is larger.

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Dynamic Model of an Upper Limb Exoskeleton with User Interaction

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This work presents a dynamic model to determine the connection between internal and external applied forces and torques to the resulting movement of a 7 DoF upper limb exoskeleton. The dynamic properties are computed with Euler-Lagrange differential equations of the serial kineamatic chain. The identification of the internal model parameters is based on general physical properties, such as masses, inertia and coriolis constants, and estimated correlations of nonlinear frictional torque in the motor and serial joint. The function of the frictional torque is dependent on the position, velocity and acceleration of the joint and each further joint in the kinematic chain. For the identification of the external model parameters, additional sensors are included to the structure of the exoskeleton.
In order to measure applied forces and torques of the exoskeleton, a six-axis force sensor is integrated at the endeffector. Furthermore, interaction forces with the user are estimated with integrated torque sensors at each joint and implemented into the dynamic model. This approach shows an alternative solution compared to torque sensing via motor current, which leads to instable results due to noisy PWM signals. For the detection of changes in the rotation of the gravity vector to the base of the exoskeleton an inertia measurement unit is installed.
The basic function of the dynamic model is examined with a zero-torque control mode, where the estimated torques in the joints are fed back to the current controller of the DC-motors. The algorithm computation is implemented on a real-time target with a sampling time of 2 kHz. As a result, the exoskeleton feels weightless to the arm while moving. Furthermore, applied static loads to the endeffector up to 5 kg can be compensated. Future work includes a dynamic model based controller for positioning tasks of the endeffector under consideration of user movement intention.

ID: T-OP-24

Interdisciplinary modeling of nanotherapy targeting the tumor microenvironment

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The development of nanotherapeutics targeting cancerous lesions has garnered increasing effort and resources in recent times. However, few formulations have reached clinical application, in large part due to the challenge presented by the complex and highly variable interactions between tumor, nanoparticle, and drug parameters. Insufficient blood and lymphatic vascularization can limit access to and from flow in the tumor microenvironment, and a denser-than-normal extracellular matrix may hinder interstitial transport. Accordingly, solid tumors are typically characterized by metabolic waste buildup leading to an extracellular acidic pH and high interstitial fluid pressure, as well as hypoxic tissue which may be insensitive to the effects of cell-cycle specific drugs. The multi-faceted interactions between these parameters characteristic of such a highly heterogeneous system preclude tuning nanotherapy characteristics solely through experimental evaluation. Engineering and physical science approaches have therefore been applied to complement empirical work in order to gain further insight into these interactions and optimize the nanotechnology design. We present recent mathematical modeling and computational simulations analyzing nanoparticle transport and efficacy in the heterogeneous tumor microenvironment, with the model parameters constrained by experimental data. The results provide insight into the design of cancer nanotherapy targeting tumor tissue and its vasculature, and, further, highlight the need for an even closer interdsciplinary effort between engineering, physical and basic scientists to overcome the challenges presented by the complex interactions between tumor, nanoparticle, and drug parameters.

ID: T-OP-26

Investigating the constitutive activity of Ghrelin Receptor by Molecular Modelling

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Ghrelin (GHR) system is involved in a large number of physiological and pathological problems, making this system an appealing pharmacological target. In particular, it has a pivotal role in the regulation of food intake, energy homeostasis, and alcohol/drug reward. The related pleiotropic peptide, the GHR, carry out its role through the interaction with the growth hormone secretagogue receptor isoform 1a (GHS-R1a). The GHS-R1a is a seven trans-membrane G-Protein Coupled receptors member of Class A subfamily, characterized by a unique constitutive activity (up to 50% of the total activity is ligand-independent). Despite the importance of this system in terms of pharmaceutical R&D and medical benefit, the molecular mechanism driving the GHS-R1a basal activity is not fully clarified yet. In this work, after the creation of a novel, accurately refined homology model, Classical Molecular Dynamics in combination with Metadynamics were employed to get insight into GHS-R1a receptor structural dynamics. Specifically, several conformational changes have been highlighted and fully characterized from the energetic point of view, therefore elucidating the molecular events governing the ligand-independent activity. In agreement with the speculation based on experimental data, peculiar residues located in the GHS-R1a binding pocket (Trp276, His280 and Arg283) have been identified as fundamental elements affecting the process. In detail, it has been proposed that the Arg283 is able to stabilize the basal activation, affecting the Trp276 position through its interaction with His280. This is of great importance considering that an improvement in the knowledge of molecular processes regulating the GHS-R1a function may help the rational design of new drugs for the treatment of a large number of pathologies.

ID: T-OP-27

Small myocyte enclaves may facilitate conduction of excitation through scar tissue: A one-dimensional simulation study

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Cardiac myocytes make up the majority of volume in the heart. More than half of its cells, however, are fibroblasts and other non-myocytes. Many experiments have shown electrical coupling between cardiomyocytes and fibroblasts. Previous computational studies at cell level have investigated the direct interactions between them numerically, often with regard to pathologies induced by electrical source-sink mismatch. This work aims to establish methods to study potential long-range interactions between the two cell types, and especially how electrical conduction may be maintained across heterogeneous scar tissue as reported by Walker et al.
A mathematical model of rat cardiomyocytes by Pandit et al. was used for nodes representing cardiomyocyte strands. Fibroblasts were modeled as purely passive cells, defined by a membrane capacitance C_m and membrane resistance R_m. Equidistant nodes in 50 µm intervals were used to simulate conduction of excitation through the cell-strand at a time step of 5 µs. Neighboring nodes representing myocytes were coupled with a resistance of R_{MM}, neighboring fibrotic nodes with R_{FF}, and myocyte-fibroblast connections with R_{MF}. The first node was paced at 2 Hz. Simulation results were evaluated after 20 beats.
Resistances and fibroblast parameters were adapted so that the 1D model approximately reproduces propagation delays measured experimentally by Gaudesius et al., resulting in $R_{MM} = R_{MF} = R_{FF} = 6$ MΩ, $R_m = 1$ GΩ, and $C_m = 100$ pF. It should be noted that the internodal resistances represent multiple parallel connections (i.e., 3 parallel myocytes and 10 parallel fibroblasts, as seen in cultured cell strands). In simulations, a fibroblast insert of 150 µm length caused a delay in propagation of 8.4 ms. Inserts of greater lengths caused blocked conduction. However, a 150 µm 'island' of myocytes between two fibroblast sections allowed recover of signal amplitude and sustained conduction through the simulated heterocellular scar, resulting in a delay of 17.6 ms across the 450 µm construct.

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Mathematical Modeling of Nanoparticle Transport and Cellular Uptake based on in Vitro Sedimentation Experiments

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Nanoparticles feature an extraordinary potential for various beneficial applications in human life thanks to their unique size-related properties. However, with increasing exposure, justifiable concerns about negative health effects have emerged, which necessitates fundamental understanding of interactions between nanoparticles and cells to efficiently assess nanoparticle toxicity. As sedimentation experiments investigating nanoparticle-cell interactions in vitro are time- and cost-consuming, mathematical modeling and in-silico studies of the physical processes have become of major importance in analysing nanoparticle-specific behaviour. Using ISDD+ (our enhanced version of ISDD - In Vitro Sedimentation, Diffusion, and Dosimetry Model), a simulation tool for fluid particokinetics, one can calculate the direct cellular dose depending on the particles' physicochemical properties and time. The program is based on the Mason-Weaver equation, a partial differential equation for the time-and space-dependent particle density, and describes diffusional and sediment transport. With cellular components typically featuring nanoscale sizes, nanoparticles can easily penetrate cells and provoke a variety of cellular response. Hence, cellular uptake is crucial for understanding the predominant biological interactions. ISDD+, however, merely implicitly incorporates particle-cell interactions by imposing an unphysical constraint at the lower system border, where cells reside, instead of the Mason-Weaver flux boundary condition. To alternatively describe the interdependency between transport and uptake in a systematic way, a novel multi-state model (Naptake) based on a system of differential equations for time-dependent cellular uptake of cell-associated particles has been developed. Having connected Naptake with the original Mason-Weaver equation by introducing it to the lower boundary condition, the resulting hybrid model can be solved using modified PDE and ODE solvers in MATLAB. Hereby, cellular uptake and its mutual interaction with particle transport can not only be considered within an effective theory, but originate from a consistent, consecutively constructed approach. Though exact parameters are not determined yet, the model yields promising and physically reasonable results.

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P-Wave Terminal Force Is Affected by the Site of Earliest Right Atrial Activation and its Proximity to Inter-Atrial Connections Independent from Atrial Size

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P-wave morphology correlates with the risk for AF. Left atrial (LA) enlargement could explain both the higher risk for AF and higher P-wave terminal force (PTF) in lead V_1. However, PTF-V_1 has been shown to correlate poorly with LA size. We hypothesize that PTF-V_1 is also affected by the earliest activated site (EAS) in the right atrium and its proximity to inter-atrial connections (IAC), which both show tremendous variability.
Atrial excitation was triggered from seven different EAS on the epicardial surface around the sinus node region in eight anatomically personalized computational models including rule-based myocyte orientation and spatial electrophysiological heterogeneity. EAS1 was located midway between the tip of the right atrial appendage (RAA) and its junction with the superior vena cava (SVC), EAS2 at the superior part of the anterior wall, and EAS3 at the junction of the RAA and the SVC. EAS4 to EAS7 were uniformly distributed along the crista terminalis between EAS3 and orifice of the inferior vena cava (EAS7). IACs connected the atria at Bachmann's bundle, coronary sinus and posteriorly. The posterior IACs were non-conductive in a second set of simulations. Body surface ECGs were computed using realistic, heterogeneous torso models.
Mid-septal EAS yielded the highest PTF-V_1 measured as the product of the duration and the maximal amplitude of the negative phase of the P-wave in V_1. More anterior/superior and more inferior EAS yielded lower absolute values deviating by a factor of up to 2.0 for adjacent EAS. Earliest right-to-left activation was conducted via BB for EAS1-3 and shifted towards posterior IACs for EAS 4-7. Non-conducting posterior IACs increased PTF-V_1 by up to 150%.
The electrical contributors EAS and intactness of posterior IACs affect PTF-V_1 significantly by changing LA breakthrough sites. This should be considered when assessing LA anatomy based on the ECG.

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Estimation of Dosimetric Parameters Based on the KNR and KNCSF Correction Factors for Small Field's Radiation Therapy at 6 and 18MVlinac Energies using Monte Carlo Simulation Methods

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Background and purpose: Small field sizes are increasingly used in radiotherapy to deliver higher dose gradient to patients. Estimating dosimetric parameters for such fields, lead to significant errors because of using conventional dosimeters at reference condition. To avoid this, two correction factors recommended by American Association of Medical Physicists (AAPM) were determined to investigate the variations caused by dosimeters' responses at the reference and non-reference conditions and increase dosimetric precision in small field radiotherapy.

Methods and Materials: The correction factors ($K_{NR,}$ K_{NCSF}) proposed by AAMP were determined for two common radiotherapy detectors, a Farmer and a Si-diode dosimeter, for 0.5×0.5, 1×1, 2×2, and 3×3 cm^2 small field sizes at 6 and 18 MV linear accelerator (linac) energies. An inhomogeneous phantom was also constructed to investigate the variations of dose profiles and percent dept doses (PDDs) after implementing the correction factors.

Results: At 6 and 18 MV energies, the maximum PDD was noted within the Polytetrafluoroethylene (PTFE) (2.2 $gr.cm^3$) slab of the phantom for the 3×3 cm^2 field size that can be attributed to the central axis dose changes due to the heterogeneity encountered in such field size. Extra attenuating of the beam in the areas with greater density than water was also observed due to the heterogeneity. Experimental and Monte Carlo dosimetry indicated a good agreement between the Farmer and Si-diode dosimeters regarding the PDDs in the PTFE. At 6 and 18 MV energies, the maximum PDDs was observed at the 3×3 cm^2 field size within the cork (0.2 $gr.cm^3$) slab. However, due to the presence of heterogeneous lower densities of the cork a decrease in the PDDs on the central axis was observed.

Conclusion: implementing the correction factors recommended by the AAPM in small field dosimetry could increase the accuracy and precision of radiotherapy practices in such field sizes.

Keywords: Small field dosimetry, Correction factors (K_{NR}, K_{NCSF}), Monte Carlo method

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Doppler optical coherence tomography for noise-reduced flow velocity measurements

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Recently, a new method called joint spectral and time domain optical coherence tomography (STdOCT) for flow velocity measurement in spectral domain OCT (SD OCT) was presented. This method analyzes the detected time-resolved interference fringe spectra by using a two-dimensional fast Fourier transformation (2D FFT) to determine directly the Doppler frequency shift instead of calculating the phase difference at each depth position of adjacent A-scans. In this study, we describe the link of joint spectral and time domain optical coherence tomography (jSTdOCT) and the commonly used phase-resolved Doppler OCT (DOCT). Moreover, we improve the classic jSTdOCT algorithm, detecting the maximum intensity signal of the broadened Doppler frequency spectrum for velocity estimation, by calculating the center of gravity. The resulting enhanced jSTdOCT (enhjSTdOCT) significantly reduces the noise of the velocity measurement by choosing an exponent depending on the transverse velocity component of the sample movement and the signal-to-noise ratio of the OCT data. To verify enhjSTdOCT, numerical simulations and a flow phantom model are used to find optimal parameters for maximal velocity noise reduction.

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Simulation a new mechanism of chaos in single ventricular cell

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Ventricular fibrillation (VF) is the most lethal arrhythmia in the heart. Many researchers have declared that the onset of VF in the heart is preceded by some kinds of bifurcations in the dynamics of the ventricular cells. With the bifurcation we mean a qualitative change in the dynamics of a system. Experimental evidences as well as computerized simulations support the idea that the bifurcations lead to VF is of chaotic one. So any research on the bifurcation mechanisms and control of ventricular cells, especially those that lead to the chaos are valuable and can save lives.

In this research we introduce a new route to chaos in a three state variables (3S) model of ventricular cell and show how we may control this lethal phenomenon. In this research we show for the first time that after generation of an early after depolarization (EAD) oscillation in the ventricular cell, some evidence of intermittency is observed when we change control parameter i.e. behavior of the system is predominantly periodic for some control parameter value but when we change the value, the time spent being chaotic increases and the time spent being periodic decreases. All of these mean that we have found some evidences of *intermittency and crises* in the ventricular cell that can be controlled by control parameter. We justify our findings using Lyapunov exponent as well as iterated maps i.e. models of Poincare map functions.

ID: T-PP-06

Investigation of pharyngeal flow patterns using phase contrast-MRI

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Introduction

Obstructive sleep apnea (OSA) is a sleep disorder of disrupted breathing caused by partial or complete closure of the upper airway. Studies suggest the possibility of a relationship of flow characteristics with OSA. However, this hypothesis has not been tested. Phase contrast-MRI (PC-MRI) is an established technique to quantify fluid flow and has been previously used to study flow patterns in a stenotic phantom. Hence, it is used here to experimentally investigate pharyngeal flow patterns to extract pathophysiological parameters like fluid velocity in order to understand OSA.

Methods

Two 3D-printed phantoms were used for the experiments. First, to validate PC-MRI velocity measurements with published laser Doppler anemometry (LDA) and computational fluid dynamics (CFD) results, a stenotic phantom with 75% area reduction was used. Second, to study pharyngeal flow patterns, a computed tomography based human pharynx phantom (scaled 2:1) was used. Both experiments used glycerol (30% vol.) in water at 25°C. An MRI compatible flow pump (CardioFlow-5000MR, Shelley Medical Imaging Technologies) was used to achieve the required Reynold's number. The experiments were performed on a 3 T MR system (Ingenia, Philips) with 108 channel body coil using an RF-spoiled, gradient echo sequence (TR=20ms, TE=10ms, flip angle=10°, voxel-size=1x1x1mm^3).

Results

Comparison of flow pattern and magnitude of measured axial velocity in the stenotic phantom with LDA and CFD results shows good agreement, therefore validating the PC-MRI method. The 3D axial velocity distribution of the pharynx phantom determines the magnitude of the velocity, location of flow separation and recirculation region.

Conclusion

The validation experiments prove the reliability of the PC-MRI method for velocity measurements. Therefore, the method offers good perspective for pharyngeal flow studies. The preliminary results from the pharynx phantom give insight into the conditions leading to the collapse of the pharynx. Further work covers determining accurate velocity profiles of the pharynx and numerical simulation validation.

ID: T-PP-07

Sensitivity Analysis on Cochlear Implants with fluid Actuation

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The cochlear implant is a neuroprosthesis for the treatment of severe to profound hearing loss. An electrode carrier equipped with fluid actuation was newly developed. Hereby a directed steering of the implant during the implantation into the spiral-shaped cochlea to avoid insertion trauma within intracochlear membranous tissue, could be implemented. A finite element model of the previously introduced electrode carrier, comprising the silicone body, the pressurised inner hollow and the embedded fibre, which determines the direction of curavture, was used for sensitivity analysis. The adjustable input parameters were geometric parameters and pressure load. The input parameters were varied and the effects on the derived curvature under pressurisation was analysed. The numeral deviation of geometric parameters, like diameter and position of the inner hollow and the fibre and the resulting wall thickness of the silicone body, was based on the observed variation within manual fabrication process of laboratory samples and was additionally analysed.
The analysed output parameter was the curvature of the electrode carrier under pressurisation of 6 bar. The so derived curvature was described with a fitted circle sector and its radius and angle, in order to get a benchmark for comparison of the curvature results for different combinations of input parameters. The results show that the model is more sensitive to the variation of wall thickness than to such of fibre positioning.

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T-PP-09

A model for simulating Electrophysiological features of a Hypoglossal Motoneuron

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The hypoglossal motoneuron (HM) innervates the tongue and along with its roles in mastication and swallowing, the tongue plays an important role in breathing. Abnormal functionality of neurons in term of excitability causes different kinds of human nervous system diseases. This is why nowadays modeling of neurons is one of the important fields of research in neuroscience. Key electrophysiological features of a neuron action potential are rest state voltage (v_R), threshold voltage (v_T), peak voltage (v_P), and inflection point voltage of slope-voltage curve (v_I).
In this paper, a model for excitability of a hypoglossal motoneuron with two state variables is presented that has an electrophysiological formalism, i.e., good agreement with neurons realities and each parameter has an electrophysiological meaning. In fact, we look at HM as an excitable dynamical system and present a method for modeling it. The model efficiency is validated against the action potential morphology, slope-voltage curve and phase portrait.
The results show that the proposed model not only can properly reproduce features: slope-voltage curve and dynamical behavior in phase plan but also has low computationally cost due to the least number of state variables. One of the advantages of this model is that each parameter has an explicit electrophysiological meaning therefore it can be used for simulating different behaviors of neurons.

ID: T-PP-10

Development of a simulation model to assess time in stroke treatment

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Every year, about 24,000 people in Austria suffer a stroke, with more than two thirds being above the age of 69 years. The risk factors range from medical preloads such as diabetes and hypertension to physical inactivity or smoking. Stroke is considered a medical emergency, because affected brain areas are eventually destroyed. Hence timely treatment is crucial for the patient. Annual expenses for the treatment of ischemic stroke in Austria are estimated to be approximately 117 million euros according to DRG points, without even accounting for rehabilitation or follow-up costs due to early disability and home care services.
The aim of this thesis was to simulate the factor time in stroke care based on a model combining the discrete event and agend based methodologies. The built model allows to analyse and compare different ways of transport and types of treatment for each patient to assess key parameters such as time, lysis rate and inpatient expenses. The treatment was divided into three time ranges: from suffering the stroke to the admission to hospital, to first imaging and finally to the administration of thrombolysis. With the underlying data probability distributions for the simulated course of treatment as well as methods of transport and potential delays could be derived.
The results show that the time between suffering the stroke and admission to hospital or a stroke unit is critical. Therefore direct transport and admission to a stroke unit distinctly increase the lysis rate. Measures such as prenubral selection, point of care tests or data transfer during transport can positively affect the success of thrombolytic therapies. Through an appropriate choice of transport and treatment types significant improvements of the lysis rate and the time to thrombolysis could be achieved.

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Deducing spectral information in a µ-CT scanner for use in verified drug transport simulations

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Complex biological tissues like bone pose considerable difficulties in modelling due to the variety of structures on all scales and bone being opaque towards most imaging modalities. Even though tracer studies take their part in analysing transport processes, non-destructive techniques for measurements are needed. Micro-CT-Scanning with its high magnification and high spatial resolution is a primary candidate for 3D inspection of bone. Given contrast enhancing chemicals, transport processes can be mimicked inside the scanner. However, challenges arise from artefacts such as beam hardening due to use of polychromatic radiation. Overcoming such difficulties involves knowledge of the scanning system's spectrum. In this work, spectral information for a micro-CT scanner (GE nanotom M, GE Phoenix Xray, Wunstorf, Germany) was obtained using a sensor (X-123CdTe X-ray Spectrometer, Amptek Inc., Bedford, MA, USA) and transmission measurements on a copper wedge. This information is used in x-ray transmission simulations of modelled tracer/bone systems, using an accelerated raytracing algorithm and optionally more precise Monte-Carlo simulations. The simulated projection images are related to the experimental ones: in the long run, quantitative information about the tracer concentration shall be obtained in an iterative procedure combining the forward simulations and experimental projections with cone beam reconstruction. Finite-element simulations of the diffusion processes in the material shall complete the combination of transport experiments, x-ray transmission and tomographic reconstruction on one hand and simulation and modelling on the other hand. Hence, the method shall be used to establish a relationship between experimental data and computer simulation models of drug eluting in porous tissues like bone.

ID: T-PP-14

Finite-Element and Network-Model Based Performance Studies of a Fully Implantable Hearing Aid in the Incudostapedial Joint Gap

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In recent work it could be demonstrated that fully implantable hearing aids which are combined sensor-actuator-transducers designed for insertion into the incudostapedial joint gap (ISJ) achieve a functional gain of 30 dB and more in the frequency range above 2 kHz. The introduction of an additional transducer unit in the case or of appropriate signal processing, stabilizes the transducer. An assembly of the transducer with 1 mm thickness considerably increases the stiffness of the annular ligament, which leads to a loss in functional gain for the transducer.
The present study is aimed to determine the influence of different geometries, e.g. the total thickness smaller than 1mm, and involved part masses, respectively, as well as different piezoelectric materials on the sensitivity and performance of the implantable transducer. The investigations were carried out by help of a combined finite element (FE) model of the implantable transducer and the human middle ear, and a lumped parameter (network) model. All simulations are done as harmonic analyses from 50 Hz to 6100 Hz and all FE-simulations with three different types of piezoelectric materials: Single crystal PMN-PT- (lead magnesium niobate lead titanate) piezo elements, ceramic composite PZT (lead circonate titanate) piezo elements and thin film PZT piezo elements. Therefore an assessment, which kind of piezoelectric material if any is principally appropriate for the intended purpose, can be made.
As a result, the network parameter studies show the effect of lower involved masses on the poorer mechanical stabilization at lower frequencies as well as on the larger transducer vibration towards the malleus. The FE-simulations showed, that the transducer with single crystal PMN-PT piezo elements for sensor and actuators element offers promising results for the use as a prospective hearing device. The other examined piezo materials are not suited for this particular application.

ID: T-PP-15

Mechanobiological simulation of forg gastrocnemius muscle using advanced activation model

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Modelling of soft tissues remains to be one of the driving issues in the implementation of large-deformation large-strain incompressible hyperelasticity in non-linear finite element analysis. Studies related with the computational models of soft tissues provide a basis for a deeper understanding of underlying continuum mechanics theories, as well as shedding light onto the role of certain parameters found in various strain energy functionals employed in hyperelasticity. On the other hand, availability of open-source finite element analysis softwares greatly enhances the implementation of user defined subroutines for testing combinations of material behavior versus types of analysis. In this study, the Sfepy (Simple finite elements in Python) platform will be employed in the characterization of frog gastocnemios muscle. Results of in vitro experiments will be reported in an accompanying paper in this conference, which will provide data on muscle twitch and tetanic response. The advanced activation muscular model proposed by Kockova and Cimrman (2009) will be used to fit model parameters to the experimental data. The neo-hookean as well as mooney-rivlin hyperelastic models will be compared against actual data.