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Scientific Program - Timetable

Sunday 22	Time	Monday 23	Tuesday 24	Wednesday 25	Thursday 26	Friday 27
	9:15		Contributed sessions (15 in parallel)	Plenary Lecture Moritz Diehl	Contributed sessions (15 in parallel)	Contributed sessions (14 in parallel)
	9:30					
	9:45					
	10:15	Registration		von Mises prize lecture		
	10:30					
	10:45					
	11:15		Coffee Break	Coffee Break	Coffee Break	Coffee Break
	11:30					
	11:45					
	12:15		Plenary Lecture Thomas Böhlke	General Assembly	Plenary Lecture Ferdinando Auricchio	Contributed sessions (11 in parallel)
	12:30					
	12:45					
	13:15	Opening	Lunch	Lunch	Lunch	
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	13:45	Univ. Chorus Performance				Closing
	14:15	Prandtl Lecture Keith Moffatt	Plenary Lecture Enrique Zuazua	Contributed sessions (15 in parallel)	Plenary Lecture Daniel Kressner	
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	15:15	Plenary Lecture Giovanni Galdi	Plenary Lecture Nikolaus Adams		Plenary Lecture Stanislaw Stupkiewicz	
	15:30					
	15:45					
Registration pre-opening	16:15	Coffee Break	Coffee Break Poster session	Coffee Break	Coffee Break Poster session	
	16:30					
	16:45	Minisymposia & Young Reseachers' Minisymposia (10 in parallel)	Contributed sessions (14 in parallel)	Contributed sessions (15 in parallel)	Contributed sessions (15 in parallel)	
	17:15					
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	18:15		Public lecture Francesco D'Andria			
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S02: Biomechanics

The section will be focused on numerical and experimental models for the study of structure, function and evolution of biological systems at a broad spectrum of scales: from cells to tissues and from organs to the entire body and its interaction with the environment. The discussed topics will be: gait analysis and foot biomechanics, musculoskeletal and orthopedic biomechanics, remodeling, cardiovascular biomechanics, multiphase modeling of biological tissues, tumor growth modeling, transport oncophysics, nanomechanics of biological materials, nanomedicine, modeling of drugs delivery.

A new fully explicit algorithmic strategy for the simulation of bone healing directly on computed tomography data

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Starting with a routinely acquired tomographic data set of a real patient with a fractured tibia, a segmentation procedure is used to generate a mesh and to assign the material properties. This mesh is the initial point for a diffusion–based algorithm that generates a realistic callus shape for the individual fracture of the patient by a finite element simulation taking the influence of the mechanobiological stimulus on the early callus formation into account [4].

In the next step, the computed callus shape is the basis for the definition of the bone healing area. After an appropriate meshing of this area, the bone healing is simulated with a fully explicit finite difference scheme of an elastic material model combined with a mechanoregulation algorithm to describe the cellular processes involved in the healing process, e.g. proliferation, migration, apoptosis, and differentiation of cells [3].

The main part of the algorithmic healing strategy is based on the ideas presented in [1, 2] namely an iterative procedure working directly on the mesh cells initialized from the resolution of the computed tomogram. The healing process itself is realized with a dynamic and competitive model describing the influence of mechanical parameters and criteria.

The boundary conditions of the simulations are assumed from an OpenSim simulation of a gait cycle with respect to the size and the weight of the considered patient. This allows the implementation of realistic muscle loading forces into this patient–specific simulations.

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Evolution of Mechanical Properties in Tissues Undergoing Deformation-Related Fiber Remodeling Processes

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This research deals with biological soft tissues containing collagen fibers embedded in an isotropic matrix. The mechanical properties of the material is described by the additive strain energy density function

$$W = W_m + W_f. \tag{1}$$

The mechanical properties of the matrix are considered to be time independent, and represented by the strain energy density W_m. The fibers undergo a remodeling process which depends on the deformation of the fibers. The strain energy density of the fibers W_f is modeled in terms of the strain energy density function ψ of the protofibers, and a factor denoted as the *survival kernel*

$$\zeta = \chi_c \exp\left(-\int_\tau^t \eta \, \mathrm{d}s\right), \tag{2}$$

with a constant fiber creation rate χ_c and a deformation dependent fiber dissolution rate η. This dissolution rate is a function of the fiber stretch and is modeled to approximate experimental results such as [1]. The survival kernel describes the changes of the mechanical properties of fibers created at time τ, $\tau \leq t$, so that the mechanical properties of the material not only depend on the current deformation but also on the entire deformation history. While the matrix deforms from a reference configuration κ_0 into a deformed configuration κ, fibers created at time τ might have a different natural configuration κ_f. Topol et al. [2] investigate the development of the fiber density for different uniaxial deformation histories when the fiber network is considered to be unstructured and the fibers undergo the deformation-related remodeling process. Based on these results, Topol et al. [3] describe the uniaxial load-deformation relation for such a material model. This research seeks to generalize the results obtained in [2, 3] by investigating multiaxial deformation processes.

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Numerical Calculation of Fiber Orientation in Three-Dimensional Arterial Walls

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In the field of biomechanics soft biological tissues are usually described by quasi-incompressible nonlinear anisotropic material models. In the case of arterial walls multilayered fiber reinforced materials, characterized by two fiber families which are embedded in a soft matrix material and which are arranged crosswise helically around the artery in axial direction, are a suitable choice for a proper material description. Due to their living nature biological tissues continuously change and adapt according to their mechanobiological environment. Hence, the consideration of a biomechanically motivated fiber orientation approach will yield a more realistic description of arterial tissues that goes beyond the assumption of a constant fiber orientation in each layer of the tissue. Such an approach is motivated by the fact that the embedded collagen fibers have a major impact on the overall mechanical behavior inside arterial walls, i.e. their orientation strongly influences the passive response and transmural stress distribution of arterial tissues. Especially with respect to atherosclerotic arteries a biomechanically motivated fiber orientation is advantageous since the experimental determination of fiber orientations in the individual components is difficult. Suitable approaches for the calculation of the fiber directions are given in [1] and [2], based on the assumption that the fiber orientation is mainly governed by the principal stress directions, in order to maximize the load-bearing capacities of the tissue. Based on this assumption, in this contribution an approach is presented, which focusses on volume-averaged principal stresses. Then, an effective iterative fiber reorientation algorithm is proposed and applied to the polyconvex nonlinear anisotropic material model presented in [3]. Furthermore, the presented fiber reorientation approach is investigated for patient-specific arterial geometries and the resulting fiber distributions are studied. For this purpose, the so-called virtual histology is taken into account, which provides information regarding a stack of axially distributed two-dimensional cross-section images from which the individual components of the arterial wall such as the media, adventitia and plaque can be segmented, cf. [4].

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Towards an accurate mechanical characterisation of human's aortic leaflets during the heart cycle

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While the available, conventional prosthetic valves satisfy most of the needs of the valvular replacement market, they do not represent a satisfactory solution for a specific part of the population. This specific group of the population is composed by the pedriatic population, women of child-bearing age, patients with infective endocarditis, small aortic roots and patients intolerant to anticoagulants [1],[2]. The specific cases mentioned above can be treated by the use of human allografts or tissue-engineered valves. Since the tissue-engineered valves are considered to be in an experimental stage, the use of human allografts is more widespread but restricted by availability. An important source of human allograft valves is the explanted hearts from patients receiving a transplant as treatment for ischaemic (ICM) or dilated cardiomyopathy (DCM) [1].

The construction of a mechanically oriented 3-D Finite Element Model of an aortic leaflet is presented in detail. In order to investigate the stress distribution in the tissue and have a better insight of the mechanical response of the leaflet under physiological conditions, we aim to build an accurate, reliable model which incorporates a more realistic geometry of the leaflet and also the fibrous tissue network, composed mainly by collagen and elastin. Being collagen the principal load-bearing element in such soft tissues. The main challenge relies on finding the correct mathematical model able to account for the nonlinear, anisotropic behaviour of the leaflets. We describe the process of fitting existing strain-energy functions to available data and analyse their applicability in the model. The latter includes the results of implementing each adapted mathematical model and the direct consequences of them on the modelling assumptions, and features, like geometry, fibre distribution and boundary conditions used, for example.

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Towards effective properties of active muscle tissue via homogenisation

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The constitutive modelling of skeletal muscle tissue in a continuum-mechanical framework demands the consideration of many complex material characteristics. This complexity stems from the microscopic arrangement of different structural elements, such as, for example, sarcomeres and connective tissue. The former are responsible for the active contractile behaviour while the latter are mainly responsible for the passive stiffness of the muscle tissue. Thus, it is highly challenging to construct appropriate macroscopic models based on phenomenological descriptions in order to take into account most of the complex material behaviour. As a result, strain energy functions are adapted for every significant material phenomena coming from experimental testing of muscle tissue.

Another way to treat the modelling of active muscle tissue is to describe important parts of the heterogeneous microstructure and use homogenisation techniques to derive effective overall properties. From a continuum-mechanical point of view, the primary goal is to obtain a homogenised strain energy function. To do so, various techniques exist in this field. This contribution will present the initial steps towards the homogenisation of skeletal muscle tissue including the active behaviour.

Modeling of skin anisotropy directions for realistic finite element simulations of the female breast

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Biomechanical simulations of the female breast are important for surgical applications such as implants augmentation, tumorectomy and reconstruction after the tumor removal. One of the main challenges for such breast simulations is to define its reference configuration which can be considered as a stress free state. Indeed, MRI scans of the breast can be obtained only under gravitational load which introduces a considerable stress and strains level for any position of the patient. Moreover, realistic material properties especially anisotropy of skin should be taken into account. This anisotropy can play an important role but have not so far been considered in biomechanical simulations of the breast.

In the current contribution, we implement an iterative method to define the reference configuration of the breast model according to MRI data of certain individuals in the prone position. In order to automatically generate principal material directions of skin, a numerical procedure based on the Laplacian smoothing method of user-drawn strokes [1] is proposed. A polyconvex model [2] and a new type mixed element [3] are exploited to simulate large deformations of breast tissues. Finally, the accuracy of the proposed method is validated by comparing FE breast simulations to 3-D surface imaging data in the standing position.

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Experimental testing of transversely isotropic biological tissues - interaction between fibre and matrix material

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Fibre-reinforced materials are used in many fields of engineering. They combine favourable characteristics of the fibres and a matrix material in which the fibres are embedded. The basic idea of fibre-reinforced materials also applies to a large variety of soft biological tissues, where fibres are surrounded by an extracellular matrix. On the one side, this includes skeletal muscle tissue, the striking feature of which is the ability of force generation based on a large number of contractile muscle fibres embedded in a composition of connective tissues forming the extracellular matrix, blood vessels and nerves. On the other side, also tendon tissue, to be a specialised tissue that usually connects muscles and bones, consists of collagen fibres embedded into a non-collagenous matrix. Aforementioned types of soft biological tissues are often tested using various experimental protocols. However, the load transfer between fibre and matrix materials is far from well-understood. Therefore, this paper deals with the role of the fibres and matrix material in muscle as well as tendon tissue when it is subjected to compressive loads [1, 2]. To this end, dissected tissue samples were tested in compression modes which induced states of fibres in compression (I), in tension (II) or at constant length (III), respectively. A comparison of the stress responses indicated that the tissue behaviour is significantly different for these modes, including differences between the modes (I) and (III). This contradicts the paradigm of many constitutive models that the stress response can be decomposed into an isotropic part relating to the extracellular matrix and an anisotropic fibre part the contribution of which can be neglected under compression. Conversely, the results provide experimental evidence that there is an anisotropic contribution of the fibre direction to the compressive stress. Interpreting these results in terms of recent microscopical studies, potential connections between the observed behaviour and the structure of muscle extracellular matrix are established.

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A porous media approach for plantar tissue during gait

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Recently a new computational model, based on the thermodynamically constrained averaging theory [1], has been proposed to predict tumor initiation and proliferation [2-4] and afterwards to study plantar tissue mechanics [5]. The foot tissue is modeled as an elastic porous medium, in large strain regime and completely filled by a fluid phase. In detail, the tissue cells and their extracellular matrix form the solid skeleton with pores saturated by the interstitial fluid. The primary variables of the model are: the interstitial fluid pressure p^f, the displacement vector of the solid phase $\mathbf{u}^s$, and the mass fraction of oxygen dissolved in the interstitial fluid, $\omega^{\overline{of}}$. With respect to these primary variables, the governing equations are discretized in space by the finite element method, in time by using the ϑ-Wilson method and then solved numerically. By considering the interstitial fluid, it is possible to mimic the viscoelastic behavior of the plantar tissue observed experimentally by Gefen [6]. This is shown in the simulated cases, where a foot during stance and some gait cycles are modeled. The presented examples integrate experimental data at different scales (patient specific foot geometry, tissue elasticity and permeability, possible tissue vasculopathy, global forces measured during gait, etc.) and allow validating the developed modeling procedure by comparisons between numerical and measured plantar pressures. Being the global response of the bi-phase system viscoelastic, it is shown that the duration of stance as well as of each of gait cycle has an influence on tissue strain and stress fields.

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A multi-scale time-dependent constitutive model of soft collagenous tissue

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This contribution presents a micro-mechanically motivated, time-dependent constitutive model of soft biological tissues. It considers seperate contributions of the matrix material, collagen fibrils, proteoglycans (PGs) as well as their interactions. PG bridges facilitate sliding between fibrils (Rigozzi et al. [1]), described in the proposed model by the Coulomb law in zones where the fibrils are not separated by PGs.

The initial overlapping lengths of the PG bridges are statistically distributed and decrease due to slippage.. A linear-elastic force response of a PG bridge is assumed, where the stiffness depends on the overlapping length. Damage in PG bridges is reversible and decays over time (cf. Gupta et al. [2]). This behaviour is taken into account by a healing model based on the evolution of the overlapping length.

The damage in the PG bridges decreases the PG density and in turn increases the contact area of the fibril contact, leading to fibril stretch. The strain energy function of fibrils is based on the response of a single tropocollagen and takes both, an entropic and an energetic regime into account. At higher strains, fibrils can additionally undergo damage, which in contrast to the PG damage is irreversible.

The so obtained constitutive model is capable to predict several mechanical phenomena of soft tissues, such as non-linearity, Mullins effect, hysteresis and permanent set. Finally the model is compared against experimental data available in the literature.

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Extremal loading of soft fibrous tissues: multi-scale mechanics and constitutive modeling

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In the current contribution, we present a multi-scale constitutive model capturing macroscopic inelastic effects (like stress softening and permanent set) in soft tissues under cyclic loading. To this end, the mechanics of single soft tissue components and their mutual interactions are described and taken into account.

Soft biological tissues can be described as a biological composite material. The extracellular matrix is hereby reinforced by collagen fibers which themself are an assembly of collagen fibrils embedded in a proteoglycan (PG) rich matrix. Micro-damage induced by cyclic loading is treated by an interaction scenario between the fibrils and the PGs. At the low strain regime PGs promote sliding between fibrils [1, 2] until yielding of statistically distributed overlapping segments starts. The breakage of the PG-bridges is defined by a decreasing PG-density. The damage accumulated in PG-connections increases strains in the collagen fibrils. This finally drives the overstretching of the fibrils, associated with a permanent rupture of the hydrogen bonds inside of the tropocollagen molecules [3]. The so obtained model is in line with recent experimental findings available in literature [3, 2].

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A Numerical Study of Fluid Flow in Articular Cartilage Based on the Darcy-Forchheimer Law

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The study of the flow of a fluid in a binary system, comprising the fluid itself and a deformable porous medium, is usually performed by relating, through the permeability tensor $\boldsymbol{k}$ of the porous matrix, the average (or macroscopic) velocity of the fluid with the pressure drop inside the system.

In most of the cases, Darcy's law, which states a linear relationship between the pressure gradient ∇p and the fluid filtration velocity $\boldsymbol{q}$, is employed to model such physical systems. However, in some cases, the Darcy-Forchheimer law provides a more accurate description for the microscopic interactions between the solid and the fluid. This is particularly true for those cases in which a strongly heterogeneous solid structure, high flow rates, or critical pressures for low permeabilities have to be considered. For instance, such an improved model of the relation between pressure gradient and fluid filtration velocity should be adopted when dealing with multifaceted materials, which form the porous matrix, or fluids that have to be described by means of non-standard rheological laws [1]. This is the case of human cartilage.

Human cartilage can be viewed as a mixture, which comprises a porous matrix with a depth dependent permeability, collagen fibres, which strongly contribute to the fluid behaviour, and the synovial fluid, which has non-Newtonian properties [2].

In this work, we present some numerical results regarding both confined and unconfined compression tests on a sample of human cartilage. In the numerical solution of the coupled and non-linear equations governing the system, the permeability tensor has been expressed as a function of the deformation of the solid matrix, and the distribution of collagen fibres as done in [3, 4]. Moreover, also the role played by the fibres in the elastic properties of the solid has been taken into account. For what concerns the Darcy-Forchheimer law, the following relation is assumed to hold in the spatial framework [5, 6]

$$-\boldsymbol{k}\nabla p = (1 + \rho\beta k_{\mathrm{eq}}||\boldsymbol{q}||)\,\boldsymbol{q},$$

with ρ, β and k_{eq} being the fluid density, the factor accounting for the inertial effects related to the fluid motion at the pore scale, and an equivalent permeability, respectively. Many authors have supplied semi-empirical correlations for β as a function of porosity, permeability and, in some cases, of the tortuosity of the porous matrix [7]. Some of these correlations have been considered in our simulations and adapted to the anisotropic case in order to show the main variations induced by the Forchheimer correction to the pure Darcian case.

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Forchheimer's Correction in Modelling Flow in Poroelastic Materials with Statistical Fibre-Reinforcement

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Soft biological tissues are often macroscopically described as biphasic media, comprising a fluid and a solid phase. In the case of articular cartilage, the fluid phase is in osmotic equilibrium with the synovial fluid, and hosts ions, hyaluronic acid, nutrients for the tissue's cells, and byproducts of the cellular metabolism, while the solid phase is identified with a porous medium whose main constituents are cells, collagen fibres and extracellular matrix. Due to the arrangement of the collagen fibres, the solid phase is modelled in many circumstances as a fibre-reinforced, poroelastic material with statistical distribution of reinforcing fibres [1]. The saturation condition is usually assumed to hold, which means that the volumetric fractions of the solid and fluid phase, denoted by ϕ_f and ϕ_s, respectively, are required to respect the constraint $\phi_\mathrm{f} + \phi_\mathrm{s} = 1$ at all times and at all points of the tissue.

A widely accepted hypothesis in the biomechanics of articular cartilage is that the motion of the fluid phase follows Darcy's Law [2, 3]. Accordingly, the specific discharge $\boldsymbol{q} = \phi_\mathrm{f}\boldsymbol{v}_\mathrm{fs}$ ($\boldsymbol{v}_\mathrm{fs}$ is the velocity of the fluid relative to that of the solid) is prescribed to be driven by the pressure gradient in the tissue, $\mathrm{grad}(p)$, through the expression $\boldsymbol{q} = -(\boldsymbol{k}/\mu)\,\mathrm{grad}(p) \equiv \boldsymbol{q}_\mathrm{D}$ [4]. Here, $\boldsymbol{k}$, which is referred to as the permeability the of the porous medium, is a second-order tensor function depending on the deformation of the solid phase and, in the case of anisotropic materials, on the orientation and volumetric fraction of the fibres [1, 3], while μ is interpreted as the dynamic viscosity of the interstitial fluid.

When Darcy's Law is used, the following hypotheses are accepted: (i) negligibility of the inertial forces acting on the fluid phase at the macroscale (these inertial forces involve only the volume-average of the fluid mass density and the mass-average of the fluid velocity); (ii) no body forces act on the fluid phase other than the momentum exchange with the solid phase; (iii) the dissipative part of the momentum exchange rate between the fluid and the solid phase is linear in the specific discharge; (iv) the fluid phase is macroscopically inviscid (i.e., the only stress bearable by the fluid is hydrostatic and given by $-\phi_\mathrm{f} p \boldsymbol{g}^{-1}$, where $\boldsymbol{g}$ is the metric tensor). While the first two hypotheses are *a priori* statements on the dynamic regime of the fluid phase and on its interactions with the environment external to the tissue, the third and the fourth hypotheses are constitutive prescriptions that relegate the information about the pore scale behaviour of the fluid to $\boldsymbol{k}$ and μ. Although, on the one hand, these approximations reduce considerably the computational effort required to perform realistic simulations of articular cartilage, on the other hand, they do not require any knowledge about the pore scale dynamics and constitutive behaviour of the fluid. In particular, if μ is given from the outset as a model parameter, or as a function of the composition of the fluid phase, but is left uncorrelated with the fluid velocity, there is no way to model the non-Newtonian behaviour of the fluid phase, which can be inferred from the non-Newtonian behaviour of the synovial fluid that has been observed by some authors. Indeed, Barnett [5] (cf. also references therein) pointed out that the synovial fluid shows non-Newtonian behaviour, except when it is quite dilute, while Tirtaatmadja *et al.* [6] found out that the synovial fluid can be modelled by means of a rheological model of Carreau type.

In this contribution, the Forchheimer's correction is incorporated into the equations describing the mechanical response of articular cartilage to the unconfined compression test. Following [7, 8], when the Forchheimer's correction is introduced, the specific discharge can be written as

$$\boldsymbol{q} = f\left(A, ||\boldsymbol{q}_\mathrm{D}||\right)\boldsymbol{q}_\mathrm{D}, \qquad f\left(A, ||\boldsymbol{q}_\mathrm{D}||\right) = \frac{2}{1+\sqrt{1+4A||\boldsymbol{q}_\mathrm{D}||}},$$

where $\boldsymbol{q}_\mathrm{D}$ is the specific discharge predicted by Darcy's Law, and A is referred to as Forchheimer's coefficient. The motivation for using the Forchheimer's correction is threefold: (a) there can be situations in which the fluid phase cannot be regarded as dilute; (b) the inertial forces acting on the fluid at the fibre scale may not be *a priori* negligible (for example, due to the combined effect of high pressure gradients and the anisotropy of the permeability, which is typically higher along the direction of local fibre alignment [9, 10, 11]), and (c) the

Forchheimer's correction permits to introduce an *effective viscosity*, $\mu_{\text{eff}} = \mu\,(1 + A||\boldsymbol{q}||)$, which, depending on the specific discharge, may be considered as a macroscopic representation of the non-Newtonian behaviour of the fluid.

The purpose of this contribution is to discuss the main differences between the standard model of fluid flow in articular cartilage, which is based on Darcy's Law, and the theoretical framework employing the Forchheimer's correction. Some of these differences shall be visualised with the aid of numerical results. A detailed explanation of the numerical simulations performed to achieve these tasks has been presented in [12].

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Relaxed incremental Variational Approach for Damage in Arteries

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A variety of damage models is proposed in the literature for arterial walls. This is because microscopic damage, mainly occurring in embedded collagen fibers, is believed to be the reason for macroscopic tissue softening as observed during balloon angioplasty. Thus, the modeling of this effect in predictive finite element simulations may help to better understand the tissue mechanics during the aforementioned clinical intervention and to improve the methods of treatment. Most of the available damage models so far are formulated in a (standard) continuum damage mechanics (CDM) framework, which in principle enables numerical damage calculations in arterial geometries by means of the finite element method. However, the drawback of CDM approaches is, that at certain deformations a loss of convexity of the underlying formulation occurs and mesh-dependent solutions may be obtained. A way to avoid this problem is the consideration of relaxed incremental incremental variational formulations for damage, see e.g. [2, 4] for small strains. In [1] an extension to large strains was derived for fiber-reinforced materials. Within this contribution we provide further extensions to the latter approach in order to appropriately account for the description of arterial tissues. In particular, hysteresis behavior is included by the construction of hyperelastic unloading and reloading paths and fiber dispersion is reflected by consideration of a microsphere-like model in the sense of [3]. Thereby, different amounts of dispersion are accounted for in tangential and in radial direction of the arterial wall. Moreover, a surrogate model is proposed, which enables the efficient adjustment of the above relaxed formulation to real experimental data of arterial tissue. The applicability of the newly introduced formulation to numerical simulations of overstretched arteries in a finite element framework is demonstrated.

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Computation of residual stress distributions and opening angles of 3D patient-specific arterial walls

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The stress distribution of a cylindrical segment over the radius is believed to have a sustainable influence on the arterial health. In order to improve simulations of all kind of mechano-biological processes, residual stresses should be taken into account. Classical computations, for example by [1], concerning the analytical opening angle method are based on the assumption of plane strain conditions. Theses models, based on only one parameter, are not able to incorporate axial residual stresses sufficiently.

Residual stresses are commonly accepted to be compressive on the innermost and tensile on the outermost layer. As a result the in vivo stresses are smoothed due to residual stresses and become more equally distributed, i.e. the radial stress gradient decreases. Based on the latter assumption, this contribution presents a model which is capable to predict the amount of residual stresses for 3D patient-specific arteries. The arterial model is generated based on VH IVUS images (Virtual Histology Intrvascular Ultrasound), for details see [2]. Because of the strong anisotropy displayed by soft tissues, suitable stress invariants have to be derived for this purpose. Building on those achievements the smoothing procedure is applied on the individual material layers independently. The algorithmic incrementation is explained in detail and numerical results of diseased arteries suffering from atherosclerosis under physiological conditions will be presented. The calculated residual stresses are applied on unloaded three-dimensional arterial segments and the so called opening angle is approximated by numerical simulations. This is motivated by several experimental studies, see e.g. [3] or [4]. The proposed numerical tool provides the possibility of adjustment to experimental data.

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Phase-field modeling of fracture in biological tissues

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This work presents the modeling of fracture phenomena in anisotropic soft biological tissues at finite deformations with the phase-field method. These tissues consist of an extra-cellular matrix which is composed of networks of elastin and collagen fibers surrounded by smooth muscle cells and fluids. Such a microstructure endows an incompressible, anisotropic and highly nonlinear macroscopic bulk response to these materials. To model fracture in these complex soft materials, recently developed phase-field methods [1, 2] are equipped with an anisotropic hyperelastic bulk energy and a Hill-type anisotropic failure criterion. The phase-field models present an innovative approach to thermodynamically consistent modeling of fracture, which is applicable to both rate-dependent or rate-independent, brittle and ductile failure modes. A regularized crack surface functional is introduced that Γ-converges to sharp crack topology for vanishing length scale parameter ℓ. A crack driving stress–based state function, derived from Hill-type failure criterion, governs the anisotropic crack phase-field evolution in a modular format. This allows flexibility to introduce alternative failure criteria, e.g. energetic or strain–based, whose maximum value from the deformation history drives the irreversible crack phase field. The resulting multi-field problem is solved numerically by a robust operator split scheme that successively updates the history field, the crack phase field and finally the displacement field in a typical incremental time step. The representative numerical simulations of fracture in human iliac arteries [3] are performed and a quantitative comparison with experimental data is provided for verification of the proposed methodology.

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Fluid structure interaction in hemodynamics

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We consider the fluid-structure-interaction problem in a blood vessel using a monolithic coupling approach, first using a Convective Explicit approach for the fluid. We believe that the prediction of transmural stresses requires the use of sophisticated nonlinear material models for the vessel wall. Fortunately, such models have been developed in the past and their parameters have been adapted to experimental data. Here, we use an anisotropic, polyconvex hyperelastic material model for the structure. The coupled simulations build on the LifeV software library and FEAP. Absorbing boundary conditions on the outflow are imposed to reduce reflections.

Linking structural dynamics to the nonlinear viscoelasticity and fatigue mechanics in fibrin biopolymers

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Fibrin is a fibrous biopolymer network that forms when our blood clots. Recent works have shown that fibrin can be stretched up to 5 times its original length and can stiffen more than 100 fold in the process. These extraordinary material properties are important in preserving clot mechanical integrity against shear-induced damage due to blood flow. Unraveling the physical mechanisms behind these phenomena not only can help us better understand how our body maintains haemostasis, but also can provide useful design principles for (bio)materials. In this study, we show that the viscoelastic properties of fibrin results in network weakening during cyclic shear loading. However, fibrin is observed to retain mechanical memory of the deformations that it has previously been subjected to, reminiscent of Mullins effect that is prevalent in elastomers and shape-memory alloys. Moreover, at large deformations, fibrin exhibits unexpected gradual yet reversible rupture weakening, suggesting a progressive crack propagation. We systematically examine the microstructural origins of these behaviors, and the results indicate a structural rearrangement that underlies the viscoelastic stiffening and viscoplastic response of fibrin network. Macroscopically, this rearrangement results in a material with large extensibility that remembers its deformation history, but forgets its shape history.

Mechanics of growing tumors: impact of modeling assumptions and boundary conditions on reliability of numerical results

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A new computational model based on porous media mechanics has been recently developed for prediction of tumor growth [1]. The tumor mass is modeled as a four-phase system consisting of a solid phase, the extracellular matrix (ECM), and three immiscible fluid phases: the interstitial fluid (IF); the tumor cells (TC) and the healthy cells (HC) (TC and HC are modeled as adhesive fluids). Being the tumor growth strongly influenced by nutrients availability, the diffusion of oxygen coming from the nearby existing vessels is also considered. The mathematical model – governed by mass balance equations of phases and species and by the linear momentum balance equation of the solid scaffold (ECM) – has been discretized in space by finite elements and in the time domain by finite differences, and implemented in Cast3M (FE code of the French Atomic Agency).

When in 2011 we started working on this model we introduced two simplifying assumptions: i) a unique pressure was considered for both cell populations ($p^{TC} = p^{HC}$) and ii) the ECM was assumed rigid. Then, the introduction of relevant constitutive relationships for the pressure difference among each pair of fluid phases (these are based on relative wettability of fluids and fluid–fluid interfacial tensions, see [2]) has allowed for relaxation of the first hypothesis and for a more realistic modeling of cell adhesion and invasion [3]. More recently also the second hypothesis has been relaxed and ECM deformability and its impact on tumor growth can be properly taken into account [4].

Our final aim is to develop a numerical tool which can be a complement for *in vivo* and *in vitro* experimental tests and help scientists in better understanding physical interaction between tumor and its surrounding. Hence, we will present our recent efforts to extensively validate the model, the impact of modeling assumptions and boundary conditions on reliability of numerical results, and some perspectives of enhancement of the model.

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Tumor growth in agarose and collagen-agarose co-gels

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The biomechanical environment of a solid tumor is in a transformed state in which tumor-associated cells stiffen the environment through increased deposition and rearrangements of matrix fibers. Additionally, the uncontrolled proliferation of tumor cells means that excessive stresses are built up due to tumor expansion [1]. The effects of such an altered mechanical environment are not completely understood, but it is becoming obvious that it plays a role in the progression of the disease. In order to extrapolate the significance of the mechanical interactions between a growing tumor and its environment, we use an *in vitro* tumor growth model whose mechanical and adhesive properties can be tuned.

The in vitro tumor growth model is based on hydrogels that vary in agarose and collagen I concentrations. Agarose provides a bioinert matrix whose stiffness can be varied over the range of healthy and diseased tissues (100s of Pa to 10s of kPa). Cell adhesion sites are introduced with the addition of collagen, whose stiffness is much lower than the most compliant agarose. Without collagen, tumors inside agarose gels grow to ellipsoidal shapes with very well defined boundaries [2]. This is remarkable because tumors with defined boundaries *in vivo* are described as ellipsoidal in shape [3]. Using the theory of elasticity we show how certain ellipsoidal shapes minimize the relevant free energy. Furthermore, tumor size distribution is dependent on many experimental factors including agarose mechanical properties, tumor seeding density, and time of growth. In the presence of collagen, however, invasive outgrowths and cell migration away from the tumor were observed.

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The role of the microvascular tortuosity in tumor transport phenomena

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The role of the microvascular network geometry on transport phenomena in solid tumors and its interplay with the leakage and pressure drop across the vessels is qualitatively and quantitatively discussed. Our starting point are the asymptotic homogenization models developed in [1], [2], which are derived exploiting the sharp length scale separation that exists between the characteristic vessels and tumor tissue spatial scales, referred to as the *microscale* and the *macroscale*, respectively. The coupling between interstitial and capillary compartment is described by a double Darcy model on the macroscale, whereas the geometric information on the microvascular structure is encoded in the effective hydraulic conductivities, which are numerically computed solving classical differential problems on the microscale representative *cell*. Then, microscale information is injected into the macroscopic model, which is analytically solved in a prototypical geometry and compared with previous experimentally validated, phenomenological models, [3], [4]. In this way, we are able to capture the role of the standard blood flow determinants in the tumor, such as the tumor radius, tissue hydraulic conductivity and vessels permeability, as well as the influence of the vascular *tortuosity* on fluid convection. The results quantitatively confirm that transport of blood (and, as a consequence, of any advected anti-cancer drug) can be dramatically impaired by increasing the geometrical complexity of the microvasculature. Hence, our quantitative analysis supports the argument that geometric regularization of the capillary network improve blood transport and drug delivery in the tumor mass.

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Towards the continuum-mechanical modelling of metastatic tumour growth in the brain

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The spreading of malignant tumour cells to distant organs is a severe problem in cancer treatment. Extra hazardous are metastases in the brain. Unfortunately, lung cancer, one of the most common cancer types, often spreads to the brain and requires a therapy. The growth of the metastases increase the stress in the brain, create leaky blood vessels and disrupt regular brain cells. Malfunctions, respectively death, are the consequences. A promising treatment of the metastases in the brain can be applied via the direct infusion of a therapeutic solution into the extra-vascular space.

The liquid-saturated brain tissue is considered as a porous material. Therefore, the framework of the Theory of Porous Media (TPM) provides an excellent tool for its description. In particular, the TPM relates a homogenised macroscopic model to the processes occuring on the microscale. For this purpose, the microscopic structure of a representative elementary volume is volumetrically homogenised, resulting in superimposed and interacting continua for each constituent. The introduced model is composed of a solid skeleton and two immiscible pore liquids. The solid part is given by the brain cells and the metastases. The pore liquids are the interstitial fluid and the blood. These pore liquids consist of real mixtures of components including liquid solvents and several solutes. The specific components of the interstitial fluid are the solvent, nutrients, metastatic tumour cells and a therapeutic agent. The blood includes a solvent and metastatic tumour cells.

The mechanisms concerned in the model are migration of cells and substances, nutrient-induced growth, blood vessel growth (angiogenesis), cell death owing to a lack of nutrients (necrosis) and cell death due to the therapeutic agent (apoptosis). The mass exchanges and the transport of the involved components are realised within the concept of the TPM. Moreover, the proposed model represents a closed system, which only permits interactions between the constituents.

Additional information of the microscopic structure and tumour-specific data are incorporated through parameters into the model. Measurements of the apparent water diffusion tensor obtained by Diffusion-weighted Magnetic Resonance Imaging (DTI) are taken as a basis for the permeability and diffusion tensors of the respective constituents. Thus, the anisotropic structure of the brain is considered.

In conclusion, the goal of this study is to develop a multicomponent metastases-growth model to improve tumour-growth predictions and treatment options.

Theoretical and numerical aspects in the multiphasic modelling of human brain tissue

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A surgical intervention is often required if the functionality of the sensitive human brain tissue is seriously compromised, e. g., due to the occurrence of malignant brain tumours. A promising method for an effective tumour-treatment procedure is provided by the so-called convection-enhanced drug delivery. Therein, a direct extra-vascular infusion of a therapeutic solution is applied via catheters within the brain-tissue aggregate. By this means, the aim of this contribution is to simulate the expected effects as well as coupled impacts of a scheduled surgical procedure with numerical computations based on a sophisticated multicomponent and multiphysical theoretical modelling strategy for human brain tissue.

The enormous microscopical complexity of the multicomponent brain-tissue aggregate motivates the application of the well-known Theory of Porous Media (TPM). Certainly, this represents a well-suited way to model the brain tissue in a compact and elegant manner. Using the TPM, a volumetrical homogenisation procedure (smearing) of the underlying microscopical structure over a representative elementary volume (REV) leads to an idealised macroscopical model of superimposed and mutually interacting constituents. In this particular case, the modelling approach contains immiscible and miscible constituents, which are treated in the framework of the so-called extended TPM. More precisely, a quaternary model is proposed, which is strongly related to the drug-delivery problem within the brain's tissue. Therein, the model proceeds from an anisotropically deformable solid skeleton, provided by tissue cells and vascular walls. This solid skeleton is perfused by two mobile liquids, the blood and the interstitial fluid. Moreover, the latter is furthermore treated as a real mixture of two components, the liquid solvent and the dissolved therapeutic solute. Moreover, the anisotropic permeability properties of the brain tissue are considered by a spatial diversification of the permeability tensor coefficients obtained from diffusion-weighted Magnetic Resonance Imaging (DTI).

The computational setting of the proposed model is based on four primary variables. These are the solid deformation, the effective pore pressures of the interstitial fluid and the blood as well as the molar concentration of the therapeutic agent (uppc formulation). For the numerical solution of the arising coupled partial differential equations, the system is discretised in space by the Finite-Element (FE) Method and in time by an implicit (Euler) time-integration scheme. Finally, the system is solved monolithically via an implementation within the in-house FE tool PANDAS. Numerical examples demonstrate the applicability of the presented model for selected problems. In particular, the anisotropic therapeutic spreading of the infused drug, using a single catheter or multiple infusion catheters, and accompanying coupled effects (such as local deformation or pressure states) are shown.

On a Multi Scale and Multi Phase Model for the Description of Drug Uptake by the Human Liver

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Metabolism in the liver is a complex time depending and non-linear coupled function-perfusion-mechanism. The function of the liver, e.g. nutrient storage and uptake of drugs, is directly coupled to its blood perfusion. In this talk we present a computational model that describes both mechanisms in a coupled manner influenced by a change of perfusion due to lipid inclusions.

The metabolism happens in the liver cells, the hepatocytes, which are arranged in hexagonal functional segments, the liver lobules. Nutrients, oxygen, and other substances are transported to the hepatocytes via a delicate system of capillaries, so called sinusoids. The inhomogeneous distribution of the sinusoidal network leads to an anisotropic blood flow in the liver lobules. Due to this highly complex inner structure of the lobules it is impracticable to give an accurate geometrical description in a continuum mechanical manner. Therefore, a multiphase mixture theory based on the theory of porous media (TPM) is used; see [1].

In case of the presented liver model is considering a porous solid body φ^{S} and a fluid φ^{L}. Both phases are considered as immiscible, heterogeneously composed materials. Each phase contains one carrier phase and $\nu - 1$ miscible concentrations $\varphi^{\alpha\beta}$, whereas the solid carrier phase φ^{S} contains a set of internal concentrations $\varphi^{\mathrm{S}\beta}$, such as glycogen and triglyceride, and the fluid carrier phase φ^{L} a set of external concentrations $\varphi^{\mathrm{L}\beta}$, such as glucose and lactate. For the microscopic cell level use of an embedded set of ordinary differential equations (ODE) is used. The ODE model mimics a simplified metabolism that takes place in the hepatocytes converting nutrients into vital products, such as glucose. Knowledge of glucose production, utilization, and storage is a necessity for the description of fat accumulations within the liver; see [2].

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Mechanics of cell-division: A new continuum model for growth inhomogeneities

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The self-reproduction ability of mitotic cells results in an increase of the number of cells with the same characteristics in living bodies. While cells grow in volume and divide themselves, the living body consequently increases in volume and changes its mechanical properties depending on the internal distribution. When the factors which regulate the growth process are inhomogeneously distributed, growth takes place at different rates and directions.

If loads are applied to the living tissue, cell-division is reorientated following the main direction of the stresses [1]. The new cells will be created in the direction of the stresses while relaxing the elastic deformations in the body at the same time. However, the amount of cells which change their cell-division orientation will increase depending on several factors and the orientation in the body is usually not complete [2, 3]. Further, the material relaxation can be seen as a viscoelastic flow of the new material contribution although the material behaviour is typical of a solid [3]. Considering extreme volume expansion of the body, cells become quiescent when volume restrictions appear.

In this work, we present a modelling approach for bodies which grow in volume and are able to change their growth direction. We use the multiplicative split of the total deformation gradient into growth and elastic contributions. The growth part is computed by considering the orientation of cell-division which depends on the stresses. The elastic part is responsible for the stresses and for the compatibility between the particles of the body. If the hydrostatic pressure increases critically due to volume restrictions, the growth process is expected to stop. The growth rate will change depending on this volume availability by decreasing its value in a smooth way [4]. Three-dimensional examples for different growth cases are shown and discussed in order to illustrate the behaviour of the new modelling approach.

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A geometric approach to characterize rigidity in proteins

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Proteins operate and interact with partners by changing between conformational substates on a wide range of spatiotemporal scales. Structurally characterizing these changes is challenging, both experimentally and computationally. Experimental methods such as X-ray crystallography yield highly detailed structural data, but are mostly limited to a low-energy ground state of the molecule. While molecular dynamics (MD) simulations can provide atomically detailed insight to dynamics, computational demands to adequately sample conformational ensembles of large biomolecules and their complexes often require tremendous resources. By contrast, time-independent or non-deterministic sampling-based algorithms together with simplified biomolecular representations can efficiently explore the conformational landscape, which have lead to new biological insights [1]. Here, we model a protein as a kinematic linkage, with groups of atoms as rigid bodies and covalent, rotatable bonds as links with a torsional degree of freedom. Hydrogen bonds are encoded as additional constraints, which lead to nested, interdependent cycles that require coordinated changes of the torsional angles [2]. Admissible velocities of the torsional angles that maintain cycle closure lie in the tangent space T_qQ to the constraint manifold Q at the current configuration q which coincides with the nullspace of the constraint Jacobian matrix [3]. We characterize biomolecular rigidity directly from detailed analysis of the nullspace. The velocity equation

$$\dot{\mathbf{q}}_\mathrm{N} = \mathbf{N}\dot{\mathbf{u}},$$

relates generalized velocities of the internal degrees of freedom $\mathbf{u}$ to admissible angular velocities $\dot{\mathbf{q}}_\mathrm{N}$ of the torsional angles through the nullspace matrix $\mathbf{N}$. We identify the set of rigid clusters in the biomolecule and validate our method on a small set of proteins. In contrast to methods based on explicit, combinatorial constraint counting [4], we obtain valid results for both regular and singular configurations. In addition, our geometric approach provides an explicit basis for motions along floppy modes, resulting in an efficient procedure to probe conformational space. We show how singularities can affect molecular rigidity and identify singular motions that remain undetected with combinatorial approaches. Our kinematic analysis can provide high-level insights into dynamic processes beyond the reach of MD simulations, with broad implications for drug design, protein engineering and human health.

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Computational simulation of piezoelectric coating surrounding activated tooth implant

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Since the natural ligament responsible for the fixation of teeth in jawbone is destroyed when artificial replacements are implanted, the mechanical stimulation of the bone is reversed. Idea of this research project is the development of active implants which provide additional electrical stimulation for bone adaption.

The electric properties of bone material have been widely investigated, when Fukada and Yasuda in 1957 [1] discovered that bone exhibits piezoelectric behavior. A clinical study demonstrated that a local electromagnetic field accelerates the healing process after bone fracture [2]. Ramtani [2] presented a mathematical model relating to the benefit of the electric field in the repair and maintenance of the solid matrix of bone. Garzon-Alvardo [3] has developed a new electro-mechanical bone remodeling model using the remodeling model of Nackenhorst[4] as a starting point. The electro-mechanical model of bone remodeling that involves mechanical and electrical stimuli can be written, hypothetically, as follows

$$\frac{d\rho}{dt} = g_{mech}(\rho, W_{mech}(\rho)) + g_{elect}(\rho, W_{elect}(\epsilon(\rho))) \tag{1}$$

Where W_{mech} and W_{elect} are the mechanical strain energy and the electrical field potentioal, respectively. The bone mass density variation over time depends on the electrical and mechanical stimulus that exists at every spatial point of the bone.

In this research project, 3D-finite element model of lower mandible has been reconstructed from a CT data set of a 63 years old male patient using segmentation techniques. Furthermore, the implant used in this project is a conical endosseous implant and is placed as a incisor tooth at the ventral part of the mandible. The implant, consists of a conical part with a screw thread, an abutment and a crown. In addition, to investigate the effect of electrical field with in the bone matrix, a thin piezoelectric layer of 3D contact elements is inserted between implant and bone. This FEM model totally consist of about 20.000 nodes and 100.000 elements. As Dirichlet boundary conditions the models are fixed at the medial and dorsal ends. The crown is loaded with about 45N which this load was calculated for a single tooth according to biting force statistics of people in this age. The results indicate the distribution of stress, electric potentioal and electrical field in each elements of the interface layer, the implant and the jawbone.

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Coupling an active middle ear implant to the round window of the cochlea

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The inner ear or cochlea is composed of a bone structure of spiral shape which is separated into two chambers by a soft membrane, the basilar membrane. These chambers or scalae are closed by the stapes footplate and the round window membrane. In a normal ear, sound is received by the eardrum and is transmitted through the middle ear ossicular chain and excites the inner ear fluid through the vibration of the stapes footplate. The pressure changes in the inner ear fluid excite the basilar membrane and the displacement is the major phenomenon eventually resulting in hearing impression. The function of the round window is mainly pressure compensation in the scalae.

Pathological changes can result in conductive hearing loss. This is most often caused by a reduced elasticity of the stapedial annular ligament and thus a reduced amplitude of the stapes footplate. In contrast to classical hearing aids or passive protheses, one way to reconstruct hearing is to couple an active implant to the round window membrane to drive the basilar membrane to compensate the conductive hearing loss. The transfer behavior of the coupled system not only depends on the dynamics of the actuator and the mechanical characteristics of the round window membrane, but also on the interface between middle ear implant and round window membrane. To transfer the vibrations of the implant to the round window membrane with a minimum of distortions, several requirements, such as preload, transversal guidance, and an elastic suspension are necessary. However, these parameters have a significant impact on the transfer behavior of the entire coupled system, investigated in this study using an active middle ear implant, the Floating Mass Transducer (FMT).

In order to address these requirements, laboratory experiments were performed to analyze the dynamic behavior of the separated actuator and the coupled system. To reduce experiments on real human temporal bones, laboratory experiments on a technical inner ear model have been performed. The technical model consists of a fluid column enclosed by two silicone membranes. The vibration of the active implant and the membranes were measured by Laser Doppler Vibrometers. First, it will be shown that special membranes had to be developed to describe the mechanical characteristics of the round window membrane and the stapedial annular ligament. Then, the coupled system will be investigated with respect to preload, transversal guidance and distortion. Also, the experimental results from the technical model will be compared to measurements performed on a real temporal bone as well as with simple mechanical models.

Eigenfrequencies of the reconstructed middle ear after tympanoplasty and stapedotomy corresponding to the case when the prosthesis is fixed

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The normal middle ear consists of the tympanic membrane (TM) and three hinged bones: the malleus, the incus, and the steps, which are connected to each other by small joints and suspended by ligaments and muscles in the middle ear cavity. The ossicular chain begins at the malleus, which is attached to the eardrum, and ends at the stapes footplate, which vibrates with a small amplitude through the oval window into the inner ear vestibule. The vestibule is filled with the perilymphatic fluid. The vibration of the stapes footplate transmits pressure waves into the cochlea to activate the hearing nerves.

Mechanical injuries of the middle ear elements, pathologic changes and different diseases of the middle-ear structures can result in a hearing loss. Common treatment for the pathological diseases is the surgical reconstruction of the middle. The most rare and worst case of similar procedure consists in replacement of all elements of the middle ear. This surgery is performed in two steps: at the first stage, a surgeon performs tympanoplasty using cartilage transplants; and at the second step, he inserts the total ossicular replacement prosthesis (TORP) bridging a gap in the ossicular chain [1]. If the stapes footplate is immobilized by bone growth around the oval window, a small hole is drilled in the footplate (stapedotomy). Then the piston-like total cylindrical prosthesis is glued by its plate on the restored TM, and inserted into the vestibule through the drilled hole.

The negative consequence of the stapedotomy surgery is a reduction in the total stiffness of the middle-ear structure and, as a result, a drop in the natural frequencies of the biomechanical oscillating system [2]. For these type of reconstructions, including tympanoplasty and stapedectomy, the outcome is influenced by the cartilage transplant thickness, the prosthesis mass and geometrical design [2], and its position with respect to the TM [1].

This study relates to the case when the middle ear is subjected to both tympanoplasty and stapedotomy. The main goal is to study the natural frequencies of the eardrum, which do not stimulate oscillations of the adjoint prosthesis. These modes of the reconstructed TM was called the dead ones in [3]. And also to study the dependence of the plate vibration forms on a position of the prosthesis at the eardrum.

The reconstructed TM will be considered as a plate close to an ellipse. The prosthesis consists of the pliable shaft and the plate, which can be positioned according to the plane of the reconstructed TM. The prosthesis plate is treated as a perfectly rigid thin circular plate. We assume also rigid coupling between the prosthesis plate and the reconstructed TM.

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