TECHNISCHE UNIVERSITÄT DARMSTADT
FACHBEREICH MATHEMATIK

TECHNISCHE UNIVERSITÄT DARMSTADT

International Workshop

Multiscale Models in Mechano and Tumor Biology
Modeling, Homogenization, and Applications

Monday 28 September 2015
to
Wednesday 30 September 2015

Lecture Room S4|10 – 001
Dolivostr. 15
Darmstadt (Germany)

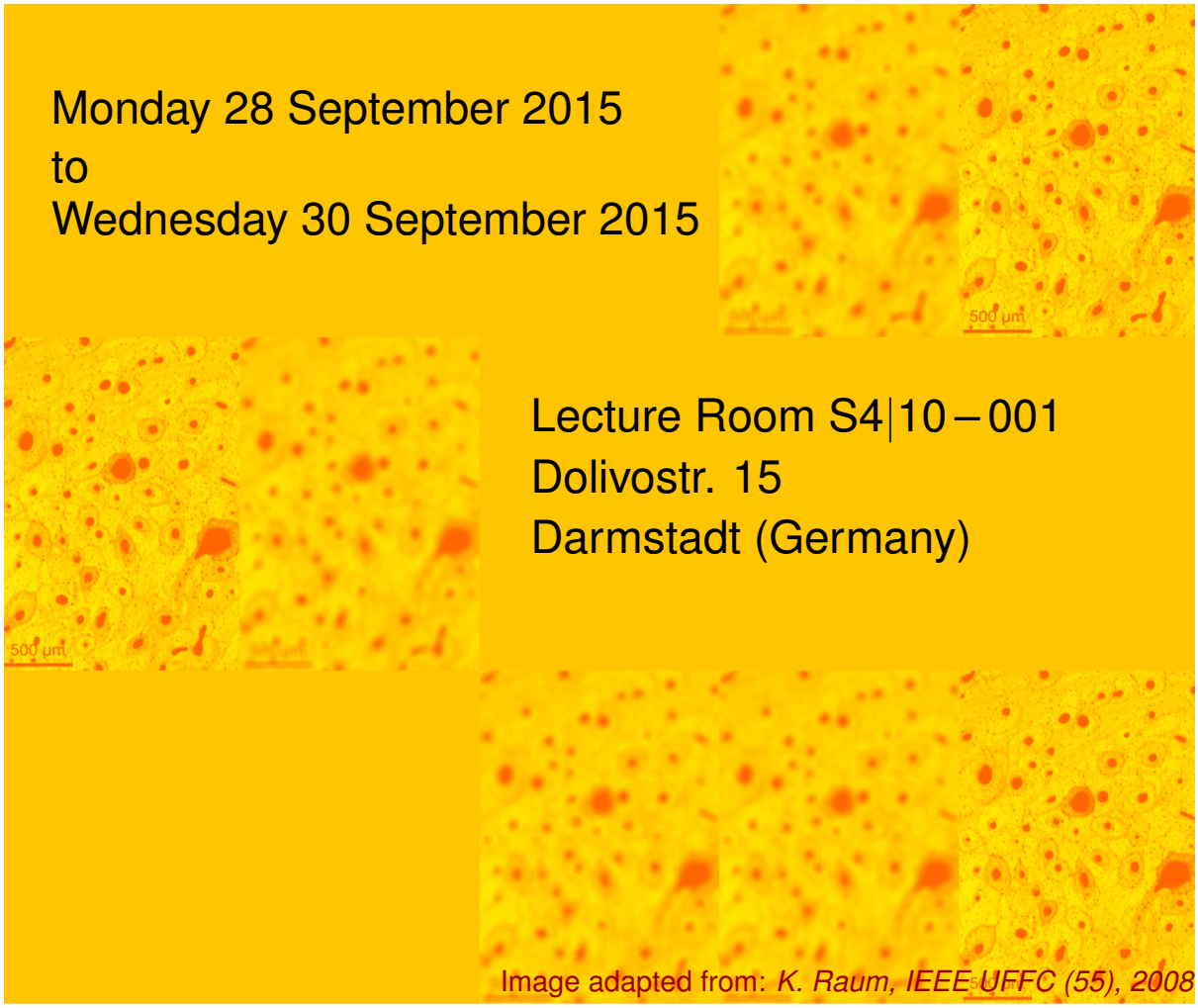

Image adapted from: *K. Raum, IEEE UFFC (55), 2008*

Workshop Booklet

Information, Programme, Abstracts, Participants

The international workshop *Multiscale Models in Mechano and Tumor Biology: Modeling, Homogenization, and Applications* is organized by the research group *Numerical Analysis and Scientific Computing* of the *Department of Mathematics* at *Technische Universität Darmstadt*.

The members of the Organizing Committee are

- Alf Gerisch
- Jens Lang
- Raimondo Penta

The Organizing Committee would like to thank

- Elke Dehnert
- Sigrid Hartmann
- Ursula Röder

for their committed assistance in preparing the workshop.

The workshop is generously supported by the Graduate School of Excellence *Computational Engineering* at Technische Universität Darmstadt and by the DFG Priority Program SPP 1420 *Biomimetic Materials Research: Functionality by Hierarchical Structuring of Materials*. We are indebted to the Technische Universität Darmstadt for making available various university facilities throughout the workshop days.

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1 General Information

1. **Workshop Venue**
   All scientific events of the workshop, including Welcome Reception and Poster Session, take place in the lecture room 001 at Dolivostr. 15, 64293 Darmstadt (S4|10, Room 001). This building also houses the Numerical Analysis and Scientific Computing Group of the Department of Mathematics at TU Darmstadt. The lecture room is signposted inside the building. Dolivostr. 15 is located a 15 minute walk from the Welcome Hotel and also a 15 minute walk from Darmstadt main train station.

2. **Registration Desk and Contact**
   The registration desk is located in the lecture room at Dolivostr. 15. It is staffed on Monday, September 28, 2015 from 8:30 to 19:00, on Tuesday, September 29, 2015 from 9:00 to 14:45, and on Wednesday, September 30, 2015 from 9:00 to 16:00.

   Please contact the staff at the registration desk after your arrival in order to receive your workshop documents.

   You can reach the workshop office by email (M3TB@mathematik.tu-darmstadt.de), by phone (+49 6151 16-4687), and by fax (+49 6151 16-2747).

3. **Time of Lectures and Discussion**
   Please note that the lecture times as given in the programme already include discussion time of 5 minutes.

4. **Coffee Breaks**
   Coffee, tea, and refreshments are provided during the morning and afternoon breaks.

5. **Lunch Breaks**
   There are some restaurants around the workshop location, for more details ask local participants or see the staff at the registration desk. We have also arranged for tables in a different restaurant each day so that we can have lunch (individual payments) together. Please indicate as early as possible at the registration desk when you plan to participate such that we can arrange for sufficiently many seats.

6. **Computer Access, WiFi, and Printer**
   Wifi access via Eduroam is available in the whole of the building and you can use the Eduroam login credentials from your home institution. If you need a temporary Eduroam account then please contact the staff at the registration desk.

   For those who do not have laptops, a PC with internet access is available in Room 20.

   If you require printed boarding passes or the like for your return journey then please send them as pdf-files to `M3TB@mathematik.tu-darmstadt.de` and we will print them for you.

7. **Welcome Reception and Poster Session**
   The Welcome Reception and Poster Session will take place in the lecture room from 17:30 to 19:00 on Monday, September 30, 2015. We will provide some drinks and finger food to stimulate and encourage discussions.

8. **Workshop Dinner**
   The Workshop Dinner will be held in the Restaurant Mezzo (Frankfurter Straße 67) on Tuesday, September 29, 2015 starting at 19:00. The meal is included in the workshop fee. If you bring a partner to the dinner then please contact the registration desk for details.

9. **Guided Tour along Mathildenhöhe on Tuesday afternoon**
   There are no scientific sessions on Tuesday afternoon past 14:40.

   Instead we offer a visit of the Mathildenhöhe in Darmstadt. We meet at 14:50 at the entrance of Dolivostr. 15 and then go to the Mathildenhöhe together, enjoy a guided tour there, have some time for a drink, and will return to the Welcome Hotel at about 17:00.

   You can also use this afternoon to explore the city and its surrounding area with your friends or by yourself.

10. **Recommended travel and walking routes**
    The Airliner Bus, see `http://goo.gl/9ypwJ0`, connects the Airport Frankfurt with Darmstadt Main Train Station.

    To get from Darmstadt Main Train Station to the Welcome Hotel, we recommend to use Bus H in direction *Alfred-Messel-Weg / Kesselhutweg*. The bus stop is in front of the main entrance of the train station, close to where the Airliner Bus arrives and departs. Take this bus to stop *Alexanderstraße / TU* and walk back for about 200 metre and find the hotel on the other side of the street. For the bus time table, see `http://goo.gl/jwxgDi`.

    The map on last page of this booklet shows recommended walking routes between Welcome Hotel, the workshop location at Dolivostr., the train station, and the Restaurant Mezzo.

2 Programme

Monday, September 28, 2015

9:00 – 10:30 **Raimondo Penta**
Introductory Course *Asymptotic Homogenization*, Lecture 1.

10:30 – 11:00 **— Coffee —**

11:00 – 12:30 **Raimondo Penta**
Introductory Course *Asymptotic Homogenization*, Lecture 2.

12:30 – 14:15 **— Lunch —**

14:15 – 14:45 **Workshop Opening Address and Presentation of Challenges**

14:50 – 15:30 **Alessandro Musesti**, Giulia Giantesio
On the mathematical modeling of ageing in skeletal muscle tissue

15:30 – 16:00 **— Coffee —**

16:00 – 16:40 **Rebecca Shipley**
Development and Testing of New Mathematical Models for Tissue Blood Flow and Mass Transport using Asymptotic Homogenisation

16:45 – 17:05 **Paolo Zunino**, L. Cattaneo, P. Decuzzi, M. Nabil, P. Zunino
An embedded multiscale approach for blood perfusion, drug and heat transport in tumors

17:10 – 17:30 **Elena Danesi**, C. de Falco, M. Taffetani
Multiscale Numerical Modeling of Nanoparticle Transport and Absorption in Biological Tissues

17:30 – 19:00 **Welcome Reception and Poster Session**

Tuesday, September 29, 2015

9:30 – 10:10 **Raimondo Penta**, Alf Gerisch
Investigation of multiphase composites via asymptotic homogenization and its application to the bone hierarchical structure

10:10 – 10:30 **— Coffee —**

10:30 – 10:50 **Mohit Dalwadi**, Maria Bruna, Ian Griffiths
An efficient asymptotic homogenization method for problems with a near-periodic microstructure

10:55 – 11:15 **Stefan Scheiner**, Peter Pivonka, Christian Hellmich
Poromicromechanics reveals that physiological bone strain induces osteocyte-stimulating lacunar pressure

Tuesday, September 29, 2015 (continued)

11:20 – 11:40 **Marta Zoppello**, L. Giraldi, P. Martinon
Modelization, controllability and optimal strokes for N-link Microswimmer

11:45 – 12:05 **Niklas Kolbe**, Maria Lukacova, Nikolaos Sfakianakis, Nadja Hellmann
Modeling and Numerical study of an Epithelial-Mesanchymal like transition in cancer cell communities

12:10 – 14:00 **— Lunch —**

14:00 – 14:40 **Quentin Grimal**
Modeling apparent elastic properties of cortical bone at the millimeter scale for in vivo applications

14:40 – 17:00 **— Excursion to Mathildenhöhe —**

19:00 – 22:00 **— Workshop Dinner —**

Wednesday, September 30, 2015

9:30 – 10:10 **Alfio Grillo**
Mechanical and Transport Properties of Biological Systems: Microstructural-Based Constitutive Models and Inelastic Phenomena

10:10 – 10:30 **— Coffee —**

10:30 – 10:50 **Melania Carfagna**, Alberto Stracuzzi, Alfio Grillo
Remodeling in Fibre-Reinforced Multiphasic Biological Materials

10:55 – 11:15 **Sandesh Hiremath**, Christina Surulescu
A stochastic model featuring acid induced gaps during tumor progression

11:20 – 11:40 **Nikolaos Sfakianakis**, Chr. Schmeiser, D. Oelz, A. Manhart
Derivation and numerical simulations of the Filament Based Lamellipodium Model (FBLM)

11:45 – 12:05 **Anneke Nikolaus**, Paul Zaslansky, Claudia Fleck
Influence of soft layers on the deformation and stress state in the tooth-jaw complex during mastication: a finite element study

12:10 – 14:00 **— Lunch —**

14:00 – 14:40 **Kay Raum**, Bernhard Hesse, Peter Varga, Susanne Schrof, Hanna Isaksson, Quentin Grimal, Simon Bernard
Multimodal and multiscale assessment of bone properties

14:45 – 15:15 **Challenge Wrap-up and Closing of the Workshop**

15:15 – 16:00 **— Coffee —**

3 Abstracts of Invited and Contributed Talks

Remodeling in Fibre-Reinforced Multiphasic Biological Materials

Melania Carfagna, Alberto Stracuzzi, Alfio Grillo

DISMA, Politecnico di Torino, Italy

Soft biological tissues are often quite heterogeneous. In most of the cases, they can be considered as deformable, fibre-reinforced porous media. This is, for example, the case of arterial walls and articular cartilage.
Articular cartilage is usually modelled as a biphasic mixture, which consists of a deformable matrix, reinforced by collagen fibres, and an interstitial fluid flowing through and escaping from the tissue. The pathways followed by the interstitial fluid are influenced by the inhomogeneous behaviour of the solid matrix, and the preferential directions imposed by the local alignment of the fibres. The latter are statistically oriented in the tissue in such a way to optimize the mechanical loads. Indeed, three layers with distinct orientation of fibres can be experimentally found in articular cartilage. Fibres are aligned vertically where the tissue touches the bone, they are randomly distributed in the middle, and parallel in the upper boundary. Thus, a preferential angle of orientation can be defined for each of these three layers. If the material undergoes large and/or permanent distortions, a reorientation and a structural reorganization of the fibres may occur, thereby leading to structural changes. Hence, dealing with remodeling seems to be of crucial importance to describe the transient response of the tissue to both physiological and pathological Stimuli.
In the present work, we propose Finite Element simulations of unconfined compression of a sample of articular cartilage. The mechanical model accounts for the presence of anisotropy, due to presence of fibres, which are numerically treated by means of a Spherical Design algorithm [1,2]. Moreover, the possibility of a transient reorganization of the fibres is addressed by solving an evolution law for the most probable angle of orientation of the fibres [3]. Some peculiar outcomes of the considered benchmarks are exposed and discussed.

References

[1] Federico, S., Gasser, T.C., Nonlinear elasticity of biological tissues with statistical fibre orientation. *J. R. Soc. Interface*, **7**, 955–966 (2010)

[2] Tomic, A., Grillo, A., Federico, S., Poroelastic materials reinforced by statistically oriented fibres—numerical implementation and application to articular cartilage. *IMA Journal of Applied Mathematics*, **79(5)**, page 1027–1059 (2014)

[3] Grillo, A., Wittum, G., Tomic, A., Federico, S., Remodelling in statistically oriented fibre-reinforced materials and biological tissues. *Mathematics and Mechanics of Solids*, DOI: 10.1177/1081286513515265 (2014).

An efficient asymptotic homogenization method for problems with a near-periodic microstructure

Mohit Dalwadi, Maria Bruna, Ian Griffiths

University of Oxford, United Kingdom

Recent work has extended classical asymptotic homogenization theory, which relies on a strictly periodic microstructure, to allow for a *near*-periodic microstructure. This procedure now enables homogenization to be carried out on geometries with a slow (macroscale) variation in their microstructure, and is a powerful new tool. However, whilst this extension is certainly a significant advancement to the field, its generality means that, usually, the cell problem must be solved at every point in the macroscale.

In this talk we show how to bypass this issue by imposing a specific one-parameter form on the microstructure. This reduces the additional computational cost to simply solving a one-parameter family of cell problems, whilst still being able to capture a three-dimensional variation in the underlying microstructure of the problem. As a result, we are able to obtain a macroscale equation with explicit coefficients that contain information about the underlying varying microstructure.

We end by presenting an example of this technique in action; a model of fluid and drug transport through heterogeneous tissue. The drug is dissolved within the fluid, which flows past spherical inclusions (modelling the tissue) whose radii vary slowly in both the macroscale and time. The drug is absorbed by the underlying tissue, which causes a prescribed change in the size of the tissue. A surprising result of this formal procedure is that a varying microstructure induces additional advection in the macroscale.

A major reason to perform an asymptotic homogenization is to reduce the computational expense of solving problems in complicated geometries. Motivated by the spirit of this statement, our work provides an efficient way to homogenize problems whose microstructure geometry varies in the macroscale, thus extending the scope of homogenization to a wide range of heterogeneous problems.

Multiscale Numerical Modeling of Nanoparticle Transport and Absorption in Biological Tissues

Elena Danesi, C. de Falco, M. Taffetani

MOX - Dipartimento di Matematica - Politecnico di Milano, Italy

Nanoparticles represent a promising tool for cancer therapy either as a device for drug delivery or for hypertermia treatment, but their limited ability in penetrating within the tumor tissue may hinder their therapeutic effictiveness. The use of mathematical modeling for analysing the diffusion of nanoparticles in tumour tissue and their absorption by cells, recently emerged as a tool for calibrating parameters of the nanoparticle injection process in order to optimise its effectiveness. This phenomenon depends on physiological properties of the tissue as well as chemical and mechanical properties of the nanoparticles, and given the multiple time and space scales involved clearly demands for a multi-scale modeling approach. At the Macroscale tumor tissue may be modeled as a homogenized porous medium of varying permeability, where the fluid flow is modeled by Darcy's equation and nanoparticle transport is described by a continuum Diffusion-Reaction-Advection equation. The tissue permeability as well as the value of the coefficients for the nanoparticle transport equation may be determined by means

of simulations at the microscale. In such simulations the complex geometry of the extracellular domain must be directly taken into account when solving Stokes' equation for the fluid flow. The transport of nanoparticles at the microscale may be modeled either by the stochastic Langevin equation or by its continuum limit, considering in both cases short distance interacion forces such as Coulomb and van der Waals interactions between particles and collecting cells as well as disturbances of the fluid velocity field induced by the presence of nanoparticles. In this communication we study procedures for determining particle diffusion and convection velocities as well ad deposition rates by means either of Kinetic Monte Carlo (KMC) microscale simulations or by Finite Volume Method (FVM) applied to continuum Partial Derivative Equation (PDE) models. We then derive macroscale equation coefficients from the results of microscale simulations by means of a suitable Upscaling technique and, finally, study the effect of microscale geometrical properties of the tissue as well as nanoparticle size and charge on the macroscale tissue penetration and deposition efficiency of the nanofluid.

Mechanical and Transport Properties of Biological Systems: Microstructural-Based Constitutive Models and Inelastic Phenomena

Alfio Grillo

DISMA "G.L. Lagrange", Politecnico di Torino, Italy

In this contribution[1], I report on some recent results about the characterisation of the mechanical and transport properties of biological systems. In particular, I focus on articular cartilage and tumour masses. Within a purely mechanical approach, biological systems of this kind are often studied as biphasic media consisting of one or more solid constituents and an interstitial fluid.

I divide my talk into three parts. In the first one, I review the mathematical model developed in [1], in which the effect of collagen fibres on the elasticity and permeability of articular cartilage has been investigated. The model, which is an extension to the large deformation framework of the theory presented in [2], relies on two hypotheses: (i) the collagen fibres are oriented statistically, and (ii) the tissue's permeability tensor and hyperelastic strain energy density can be computed by performing directional averages of physical quantities defined as functions of the local fibre alignment. The effectiveness of these assumptions has been tested in [3], where it has been demonstrated that, in articular cartilage, the motion of the interstitial fluid along the fibres is faster than that occurring across the fibres, which are regarded as impermeable. Finally, I show some comparisons with other models of permeability available in the literature [4,5]. In the second part of this contribution, I discuss some implications of describing the flow of the interstitial fluid by means of the Darcy-Forchheimer law [6]. This is a correction to the standard Darcy's law that accounts for both pore scale inertial effects and solid-fluid interactions, thereby leading to a non-linear relation between the fluid filtration velocity and the pressure gradient in the system. To highlight the implications of the Darcy-Forchheimer law,

[1]This contribution summarises joint works with Melania Carfagna, Marco Scianna (Dept of Mathematical Sciences, DISMA, "G.L. Lagrange", Politecnico di Torino, Torino, Italy), Chiara Giverso (Dept of Mathematics, Modelling and Scientific Computing, MOX, Politecnico di Milano, Italy), Salvatore Federico (Dept of Mechanical and Manufacturing Engineering, The University of Calgary, Calgary, AB, Canada), Raphael Prohl (Steinbeis Center, Simulation in Technology, Wiernsheim, Germany), Alexandar Tomic (former student of Mechanical Engineering at the Dept of Mechanical and Manufacturing Engineering, The University of Calgary, Calgary, AB, Canada), and Gabriel Wittum (Goethe Center for Scientific Computing, G-CSC, Goethe Universität Frankfurt, Frankfurt am Main, Germany).

I review the fundamental hypotheses characterising the Darcian dynamic regime, and I show how correcting Darcy's law yields a further coupling between the deformation of the system and the motion of the interstitial fluid. In the third part of my contribution, I speak of growth and remodelling. I present a recently developed model of tumour growth based on the concept of evolving natural configurations [7], and then I discuss some preliminary results expressing the influence of remodelling (intended as "plastic" reorganisation of the internal structure of a biological system) on the flow and mechanical properties of a biological system [8].

References

[1] Federico, S., Grillo, A., Elasticity and permeability of porous fibre-reinforced materials under large deformations. *Mech. Mat.*, **44** (2012), pp. 58–71.

[2] Federico, S., Herzog, W., On the permeability of fibre-reinforced porous materials. *Int. J. Solids Struct.*, **45** (2008), pp. 2160–2172.

[3] Tomic, A., Grillo, A., Federico, S., Poroelastic materials reinforced by statistically oriented fibres—numerical implementation and application to articular cartilage. *IMA J. Appl. Math.*, **79(5)** (2014), pp. 1027–1059.

[4] Holmes, M.H., Mow, V.C., The nonlinear characteristics of soft gels and hydrated connective tissues in ultrafiltration. *J. Biomech.*, **23** (1990), pp. 1145–1156.

[5] Ateshian, G.A., Weiss, J.A., Anisotropic hydraulic permeability under finite deformation. *J. Biomech. Eng.*, **132** (2010), pp. 111004-1–111004-7.

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[7] Giverso, C., Scianna, M., Grillo, A., Growing avascular tumours as elasto-plastic bodies by the theory of evolving natural configurations. *Mech. Re. Comm.* (2015), http://dx.doi.org/10.1016/j.mechrescom.2015.04.004

[8] Grillo, A., Prohl, R., Wittum, G., A poroplastic model of structural reorganisation in porous media of biomechanical interest. *Submitted*.

Modeling apparent elastic properties of cortical bone at the millimeter scale for in vivo applications

Quentin Grimal

LIB (UPMC - CNRS - INSERM), France

An evidence gap exists in fully understanding and reliably modeling the variations in elastic anisotropy that are observed at the millimeter scale in human cortical bone. The porosity (pore volume fraction) is known to account for a large part, but not all, of the elasticity variations. This effect may be modeled by a two-phase micromechanical model consisting of a homogeneous matrix pervaded by vascular pores. Here, the 'matrix' is a mixture of small pores containing the cells and their processes and of the extracellular matrix. The variability of the anisotropic elastic properties of the matrix likely contribute to the apparent elastic properties at the millimeter scale, although to an unknown extent.

In the talk, we will give an overview of homogenization methods commonly used to predict the apparent elastic properties of cortical bone at the millimeter scale. Will we discuss the ability of a simple model, where the vascular porosity is accounted for by a periodic, or random, array of cylindrical pores, to match experimental data (transverse isotropic stiffness tensor).
The simplicity of such a model is a major advantage for a use in in vivo applications. We will present recent applications of the model to the prediction of the macroscopic behavior of bones and to the in vivo characterization of bone properties with ultrasound methods for the diagnosis of osteoporosis.

A stochastic model featuring acid induced gaps during tumor progression

Sandesh Hiremath, Christina Surulescu

TU Kaiserslautern, Germany

In this paper we propose a phenomenological model for the formation of an interstitial gap between the tumor and the stroma. The gap is mainly filled with acid produced by the progressing edge of the tumor front. Our setting extends existing models for acid-induced tumor invasion models to incorporate several features of local invasion like formation of gaps, spikes, buds, islands, and cavities. These behaviors are obtained mainly due to the random dynamics at the intracellular level, the go-or-grow-or-recede dynamics on the population scale, together with the nonlinear coupling between the microscopic (intracellular) and macroscopic (population) levels. The wellposedness of the model is proved using the semigroup technique and 1D and 2D numerical simulations are performed to illustrate model predictions and draw conclusions based on the observed behavior.

Modeling and Numerical study of an Epithelial-Mesanchymal like transition in cancer cell communities

Niklas Kolbe, Maria Lukacova, Nikolaos Sfakianakis, Nadja Hellmann

Johannes Gutenberg-Universität Mainz, Germany

Recent biological work has revealed the existence of multiple types of cancer cells within the body of a tumour that are of different levels of differentiation. Compared to the more usual differentiated cancer cells, less differentiated cancer cells exhibit higher motility, they are more resilient to therapy, and are able to metastasize to secondary locations within the organism. They seem to transition from the differentiated cancer cells via a (de-)differentiation process, termed Epithelial-Mesanchymal Transition, which can also be found in normal tissue. The compound of the tumour as well as its internal dynamics affect the extracellular environment, in particular the invasion of the Extracellular Matrix.
In this contribution we introduce a model that combines the transition between the aforementioned types of cancer cells based on the (microscopic) dynamics of the Epidermal Growth Factors, and the (macroscopic) invasion of the Extracellular Matrix by the cancer cell ensemble. We present numerical experiments exhibiting the dynamics of two and more types of cancer cells of different differentiation levels. In order to reduce the computational costs of the complex invasion dynamics, we apply Adaptive Mesh Refinement techniques on which we also elaborate.

On the mathematical modeling of ageing in skeletal muscle tissue

Alessandro Musesti, Giulia Giantesio

Università Cattolica del Sacro Cuore, Italy

One of the main consequences of ageing is a progressive loss of skeletal muscle mass and a worsening of the performance of muscle tissue, a syndrome termed "sarcopenia". The reason of such a deterioration, although being the subject of several studies, up to now have been considered only from a clinical and a statistical viewpoint. However, the construction of a sound mathematical model of the muscle tissue, accounting for the changes due to ageing, can provide a more refined quantitative tool. In the talk we will present some results obtained in the project "Active Ageing and Healthy Living" of the Università Cattolica del Sacro Cuore. In particular, considering the muscle as a fiber-reinforced material, we improve some existing hyperelastic models of active muscle tissue by introducing a damage in the activation parameter.

Influence of soft layers on the deformation and stress state in the tooth-jaw complex during mastication: a finite element study

Anneke Nikolaus, Paul Zaslansky, Claudia Fleck

Technische Universität Berlin, Germany

Teeth are stiff objects, suspended in soft tissue in sockets in the jaw where they successfully function for many years of harsh mechanical loading [1]. The relations between geometry and function of this complex are not fully understood. Enamel and dentine are connected through a 200-300 μm thick softer zone, the sub dentine-enamel-junction (sub-DEJ) dentine [2]. The dentine roots are encased by a layer of cementum and connected through the periodontal ligament (PDL) to the bone. Various finite element models reproduce deformation and motion related to the distribution of loads in the tooth-PDL-jaw-complex. Here we report on simulations where the geometry is based on 3D-reconstructions of micro-computer tomography measurements of the whole tooth-PDL-jaw complex. The model comprises all mechanically different components of the tooth-PDL-jaw complex. This includes also the layers sub-DEJ dentine, cementum and PDL. Being softer than the other tooth components, the sub DEJ dentine and the cementum locally reduce the stresses at the interfaces between the stiff enamel and the less stiff dentin and between the root dentine and the PDL. Our model further reproduces the real, uneven PDL geometry, and it uses hyperelastic material properties of the PDL coupled with uniaxial stress-strain data [3] from in vitro experiments. To validate our model a fresh pig molar was loaded in compression while mounted in its native condition in the jaw bone. We show that the elastic movement of teeth during chewing is strongly affected by the deformation of the PDL which itself strongly depends on the PDL geometry. By considering the non-linear elastic behaviour of the PDL we obtain a very good agreement between the load-displacement responses measured during the mechanical tests and the results predicted by simulation.

References

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[2] Zaslansky P, et al. Journal of Structural Biology. 2006;153:188-199

[3] Dorow C, et al. Journal of Orofacial Orthopedics / Fortschritte der Kieferorthopädie. 2003;64:100-107

Investigation of multiphase composites via asymptotic homogenization and its application to the bone hierarchical structure

Raimondo Penta, Alf Gerisch

TU Darmstadt, Germany

A multiscale approach is developed for three dimensional multiphase elastic composites via asymptotic homogenization (see, e.g., [1]). Each phase is assumed to behave as a linear, possibly anisotropic and inhomogeneous, elastic solid. Discontinuities of the elastic constants across the interface between the host medium (matrix) and any subphase interface are allowed. The classical stress balance equations are stated in each phase, where volume forces and inertia are neglected. Coupling among phases is enforced via continuity of stresses and displacements across every interface. Asymptotic expansion of the displacements is carried out to exploit the sharp length scale separation between the spatially periodic structure (*fine scale*) and the whole material (*coarse scale*).
The coarse scale mechanics is described by a standard anisotropic elastic model, where the role of the fine scale geometry is encoded in the effective elasticity tensor, which is to be computed solving elastic-type problems on the appropriate periodic cell. The model is general with respect to the number of subphases and periodic cell shapes. The cell problems are equipped with stress discontinuities, which are proportional to the jumps of the elastic constants across interfaces. The effective elasticity tensor and the auxiliary strains which arise from the cell problems computation are characterized by specific properties and representations which lead to a consistent effective elasticity tensor definition, in terms of symmetries and energetic bounds.
A novel three dimensional numerical study is performed assuming an isotropic and homogeneous linear elastic rheology for each phase. The periodic cell geometrical setup is chosen to properly compare the model response to that provided by Eshelby based techniques and point out analogies and differences between the two approaches. The model is benchmarked by comparing our method to well established semi-analytical schemes. An example of preliminary application to the hierarchical structure of the bone (see, e.g., [2]), where the host medium is identified with the collagen matrix and the subphases to the mineral inclusions is provided. We account for the formation of a continuous mineral foam, which is represented extending the mineral inclusions up to the periodic cell boundary. Such a physiological condition (which characterizes old bone tissue) cannot be captured by simple average field techniques, which are widely exploited in the bone literature (see, e.g., [3]).

References

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Multimodal and multiscale assessment of bone properties

Kay Raum, Bernhard Hesse, Peter Varga, Susanne Schrof, Hanna Isaksson, Quentin Grimal, Simon Bernard

Charité-Universitätsmedizin Berlin, Germany

Structure and elastic properties of the tissue matrix are keys to the mechanical function of musculoskeletal tissues. The elastic interaction of high frequency ultrasound waves with tissue offers a wide range of applications in research, diagnostics and therapy, from non-invasive, nondestructive, and multiscale elastic imaging to the controlled mechanical stimulation of cells by focused pulsed ultrasound. Moreover, electromagnetic waves (from the infrared to the x-ray range) provide insights into structure and chemical composition down to the nanoscale. The talk will review the status quo and challenges in the clinical diagnosis of bone and will present recent advances and future directions in the experimental and clinical assessment of bone quality using quantitative ultrasound and synchrotron radiation nanotomography with phase contrast.

Poromicromechanics reveals that physiological bone strain induces osteocyte-stimulating lacunar pressure

Stefan Scheiner, Peter Pivonka, Christian Hellmich

Vienna University of Technology, Austria

The mechanical loading that bone organs are subjected to is known to influence the activities of cells located in the pore spaces of bone. This concerns in particular the signalling and production processes mediated by osteocytes. The exact mechanism(s) by which osteocytes are actually able to feel the mechanical loading and changes thereof has been the subject of numerous studies, and while several hypotheses have been brought forth over time, has remained a matter of debate.

A recent experimental study (Gardinier et al., *Bone* 46: 1075-1081, 2010) revealed that due to the very narrow transport pathways in the lacunae-canaliculi system, when also taking into account that mechanical stimuli occur in transient fashion, substantial convective fluid flow, which has been suspected as prime candidate by a large part of the scientific community for causing osteocyte stimulation, is unlikely to take place in standard physiological load scenarios. Thus, revisiting the role of the pore pressure building up in the lacunar pore space, whose occurrence is at the same time confirmed in Gardinier's study, for osteocyte stimulation, is required. For this purpose, a thorough multiscale modeling approach is pursued. In particular, the proposed model is based on multiscale poroelasticity theory, able to account for a multiporous material such as bone, and combined with micromechanics-based homogenization. First, the model response is studied qualitatively, and distinctly non-linear dependencies of the resulting lacunar (and vascular) pore pressures on the underlying bone composition are revealed, highlighting the necessity of using a rigorous multiscale approach for computation of these pore pressures. Additionally, the pore pressures vary significantly between different load directions. Then, the derived equations are evaluated for macroscopic physiological strains. The resulting pore pressures agree well with the pressures that have been shown in vitro studies to be of adequate magnitude for modulating cell responses. Further numerical studies show how the lacunar pressure develops in the course of aging.

Thus, the important role of the hydrostatic pressure building up in the bone pore spaces in re-

sponse to macroscopically applied mechanical loading is corroborated, providing the incentive to further look into the mechanoregulatory role of the lacunar (and vascular) pore pressures in future research.

Derivation and numerical simulations of the Filament Based Lamellipodium Model (FBLM)

Nikolaos Sfakianakis, Chr. Schmeiser, D. Oelz, A. Manhart

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The cytoskeleton is a cellular skeleton inside the cytoplasm of living cells. The front of the cytoskeleton, also known as lamellipodium, is the driving mechanism of cell motility. The lamellipodium is comprised by long double helix polymers of actin protein termed actin-filaments that have one end (plus-end) at the cell membrane, and their other (minus-end) inside the cytoplasm. They polymerize by addition of actin monomers in their plus-end, depolymerize at their minus-end, and they exhibit a series of physical properties like elasticity, friction with the substrate, crosslink binding, repulsion, myosin-drive contractility, nucleation, fragmentation, capping and more.

In this talk we address the FBLM that describes the above mentioned (microspcopic) dynamics of the actin-filaments and results to the (macroscopic) movement of the cell, and introduce the Finite Element Method (FEM) used to simulate this system. We present numerical experiments exhibiting the motility and deformation) of the cells in a series biological scenaria (including chemotactic and haptotactic influence) and compare our results with on-vitro experiments.

Development and Testing of New Mathematical Models for Tissue Blood Flow and Mass Transport using Asymptotic Homogenisation

Rebecca Shipley

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The vasculature is a 3D multiscale network comprised of a hierarchy of vessels that is frequently categorized according to vessel size. Although the geometry and topology of the vasculature is organ-specic, blood ows into an organ from a feeding artery, through the arterioles into the microcirculation, and exits through the venules then veins. Gas exchange occurs primarily in the microcirculation and, indeed, the function of the vasculature is to bring oxygenated blood within a small distance of every tissue point in the body in order to meet metabolic demands. Modelling the ow of blood and solutes through these networks could play a crucial role in, for example, controlling drug dosage and predicting efficacy, as well as understanding pathological scenarios such as myocardial ischaemia or local tumour microenvironments.

Traditional modelling approaches have employed a discrete approach by solving equations for blood ow in each vessel of a network. However, recent advances in imaging methods have led to a wealth of data that describe vascular structure in a highly detailed way. As the resolution of this data increases, it is becoming too computationally intensive to simulate ow and mass transport in the complete vascular tree using a discrete approach. As such, continuum models must be developed that capture the key functional properties of blood ow.

Continuum multiscale models that describe blood flow in the microcirculation, derived using the mathematical process of asymptotic homogenization, will be discussed. These models include both vascular and interstitial fluid transport (as it pertinent for the leaky neovasculature

of solid tumours), as well as advective/diffusive/reactive transport of solutes. A strategy for combining discrete and continuum models to simulate transport in large network data sets will be presented, and results of testing this strategy on explicit examples of rat mesentery networks (with known flow solutions) will be demonstrated. Finally, applications of the modelling framework to large vascular data sets extracted using corrosion casting and micro-CT imaging will be presented.

Modelization, controllability and optimal strokes for N-link Microswimmer

Marta Zoppello, L. Giraldi, P. Martinon

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The study of the swimming strategies of micro-organisms is attracting increasing attention in the recent literature, moreover recently is emerging a connection between swimming and Control Theory. In fact, low Reynolds number swimming can be considered as a control problem which is linear in the control, and without drift.
We focus on the system of the N-link swimmer, a generalization of the classical Purcell swimmer [3], that was introduced in [1]. Of course one of the main difficulties in exploiting Control Theory in order to solve effectively motion planning or optimal control problems is the complexity of the hydrodynamic forces exerted by the fluid on the swimmer as a reaction to its shape changes. Whereas the N-link swimmer model introduced is simplified and explicit since Resistive Force Theory is used to couple the fluid and the swimmer. This leads to perform an optimal control study of such system; see [2].
After presenting the model, we validate it on some well known benchmarks, moreover we prove that the swimmer is controllable in the whole plane when it is composed by more than 3 links and for almost every set of links length. As a direct result, we show that there exists an optimal swimming strategy which leads to minimize the time to reach a desired target. Numerical experiments on the case of $N = 3$ (Purcell swimmer) suggest that the optimal strategy is periodic, i.e. composed of a sequence of identical strokes. Our results indicate that this candidate for an optimal stroke indeed gives a x-displacement twice better than the classical Purcell stroke.

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An embedded multiscale approach for blood perfusion, drug and heat transport in tumors

Paolo Zunino, L. Cattaneo, P. Decuzzi, M. Nabil, P. Zunino

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Reduced models of flow or mass transport in heterogeneous media are often adopted in the computational approach when the geometrical configuration of the system is too complex. A paradigmatic example in this respect is blood flow through a network of capillaries surrounded by a porous interstitium. We numerically address this biological system by a computational model based on a multiscale resolution of embedded domains. Exploiting their large aspect ratio, we avoid resolving the complex 3D geometry of the submerged vessels by representing them with a 1D geometrical description of their centerline and the resulting network [1,2].
Cancer employs mass transport as a fundamental mechanism of coordination and communication. The physics of mass transport within body compartments and across biological barriers differentiates cancer from healthy tissues [3]. Mass transport is also at the basis of cancer pharmacological treatment. Delivery of diagnostic and therapeutic agents differs dramatically between tumor and normal tissues. For example, tumors exhibit interstitial hypertension, which is caused by the high permeability of tumor vessels in combination with the lack of functional lymphatic vessels in the tumor interstitial space.
The analysis of fluid, drug and heat transport in vascularized tumors is a relevant application of the model proposed here. We will use it to study fluid, mass and heat exchange between the capillaries and the interstitial volume, as well as to compare different modalities to deliver chemotherapy and hyperthermia to the tumor mass, including using nanoparticles as delivery vectors [2,4,5,6].

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4 Abstracts of Contributed Posters

An Introduction to Measurements of Human Cortical Bone Elasticity using Resonant Ultrasound Spectroscopy

Xiran Cai, Simon Bernard, Johannes Schneider, Peter Varga, Kay Raum, Pascal Laugier, Quentin Grimal

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To understand the structure-function relationship of bone and to investigate bone fragility, a precise and practical way to measure cortical bone elasticity is important. Resonant Ultrasound Spectroscopy (RUS) has shown its accuracy and convenience in fully characterizing the stiffness coefficients of anisotropic solid materials. However, it was long believed that the method is not applicable to bone, a highly damping material. This poster reviews the basic concepts of RUS measurement and the recent progress of adapting this technique to the measurement of the elasticity tensor of highly damping materials. Meanwhile, a successful implementation of RUS with latest progress to measure the elasticity tensor of a collection of human tibia cortical bone specimens was demonstrated.

Structured models of cell migration incorporating membrane reactions

Pia Domschke, Dumitru Trucu, Alf Gerisch, Mark A.J. Chaplain

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In many enzymatic systems such as the uPA system, some processes take place on the surface of cells. For example, the uPA receptors are located on the cell membrane and bind uPA. To some extent, there is also free uPA in the system. Up to now, there is no difference between bound and free uPA in the models [1]. This neglects the fact that bound uPA, which catalyses plasminogen to plasmin, moves with the cells driven by diffusion, chemo- and haptotaxis, whereas free uPA follows its own Brownian motion.
In this approach, the modelling of surface-bound reactions is done via structured population models, where usually properties of species such as age, weight or size of cells are modelled via a structural variable, see e.g. [2]. Here, the amount of surface-bound molecular species is represented by a structural variable $y \in \mathcal{P}$, also called i-state variable. As a consequence, the surface-bound species move with the cells. The set $\mathcal{P}$ is defined as the set of all admissible structure states and is called the i-state space. The partial differential equation governing the *spatio-temporal-structural* distribution of the cells is given by

$$\frac{\partial}{\partial t}c(t,x,y) = S(t,x,y) - \nabla_x \cdot F(t,x,y) - \nabla_y \cdot G(t,x,y)\,,$$

where S denotes the source while F and G are the spatial and structural flux, respectively. The source S is given by the proliferation of the cells through cell division. The spatial flux F of the cells results from a combination of diffusion, taxis or adhesion. The flux G over the structural boundary originates from binding and unbinding of the molecules to the cell-surface.
The resulting model gives a more realistic description of surface-bound reactions on a tissue scale although it is computationally more expensive than unstructured models due to additional dimensions for the i-state space.

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Waveform Relaxation for the Computational Homogenization of Multiscale Magnetoquasistatic Problems

Innocent Niyonzima, Christophe Geuzaine, Sebastian Schöps

TU Darmstadt, Germany

This paper deals with the application of the waveform relaxation method for the homogenization of multiscale magnetoquasistatic problems. In the proposed approach, the macroscale problem and the mesoscale problems are solved separately using the finite element method on the entire time interval for each waveform relaxation iteration. The exchange of information between both problems is carried out using the heterogeneous multiscale method.

Multiscale structure-functional modeling of musculoskeletal mineralized tissues

Susanne Schrof, S. Tiburtius, F. Molnar, P. Varga, Q. Grimal, A. Gerisch, K. Raum

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No abstract.

Raman 3D Orientation Mapping of Collagen Fibrils in Human Osteonal Bone

Susanne Schrof, P. Varga, L. Galvis, K. Raum, A. Masic

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No abstract.

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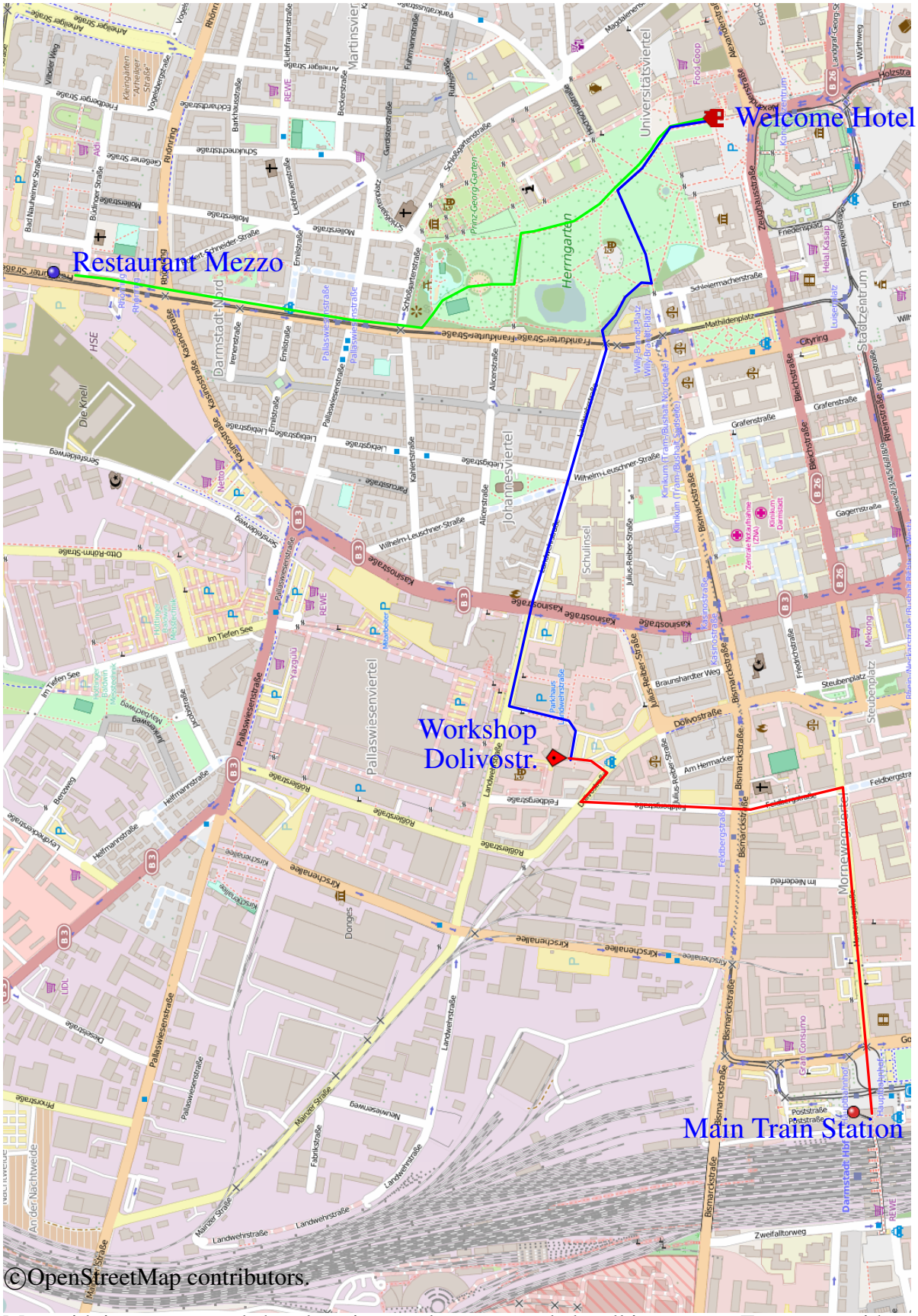

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International Workshop
Multiscale Models in Mechano and Tumor Biology: Modeling, Homogenization, and Applications

September 28 – 30, 2015

Technische Universität Darmstadt, Darmstadt, Germany

Topics

- *Multiscale modeling of hierarchical biological materials*
- *Innovative homogenization techniques for multiscale models*
- *Numerical challenges and methods in the simulation of multiscale models*

Invited Speakers

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