Simulation Technology with Application to Biomechanical Problems

SimTech Cluster of Excellence

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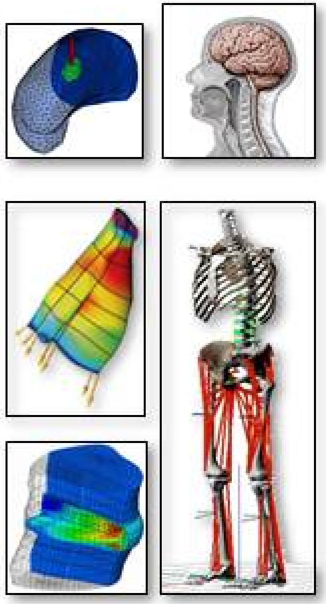


GAMM Activity Group: Computational Science and Engineering (CSE)
Kick-off Meeting, Technische Universität München, 17 September 2012

International Association of Applied Mathematics and Mechanics (GAMM)

- **Objectives**
  - Promotes the scientific development in all areas of applied mathematics and mechanics
  - Constitutes *Activity Groups* for future-oriented fields in applied mathematics and mechanics
- **Foundation of Activity Groups**
  - Proposal by GAMM members
  - Decision by the *Executive and Managing Board* of the GAMM
- **Duration and Procedure**
  - Running time: 5 + (2 x 3) = 11 years (max.)
  - Annual reports (published in *GAMM-Rundbrief*)
  - 2 evaluations by the *Executive and Managing Board* of the GAMM

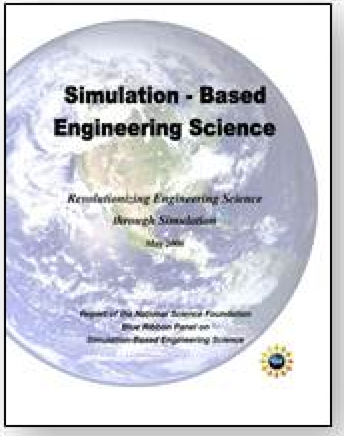
GAMM Activity Group: Computational Science and Engineering (CSE)

- **Aims and scopes**
  - Topic caused some controversial discussions in the GAMM boards
  - CSE is a very broad topic and, thus, seems to encompass the whole GAMM with all its members
  - CSE (as a part of Simulation Technology) as a *third column* (*"dritte Säule"*) of science (in addition to *theory* and *experiment*)
  - CSE as a rapidly emerging field of research seems to be not adequately represented within the German science community yet

- **Issues under discussion**
  - Settle the position of the activity group CSE within the GAMM
  - Constitution of the activity group CSE itself (membership, general assembly, elections, activities, etc.)

Simulation Technology: Motivation & Recognition

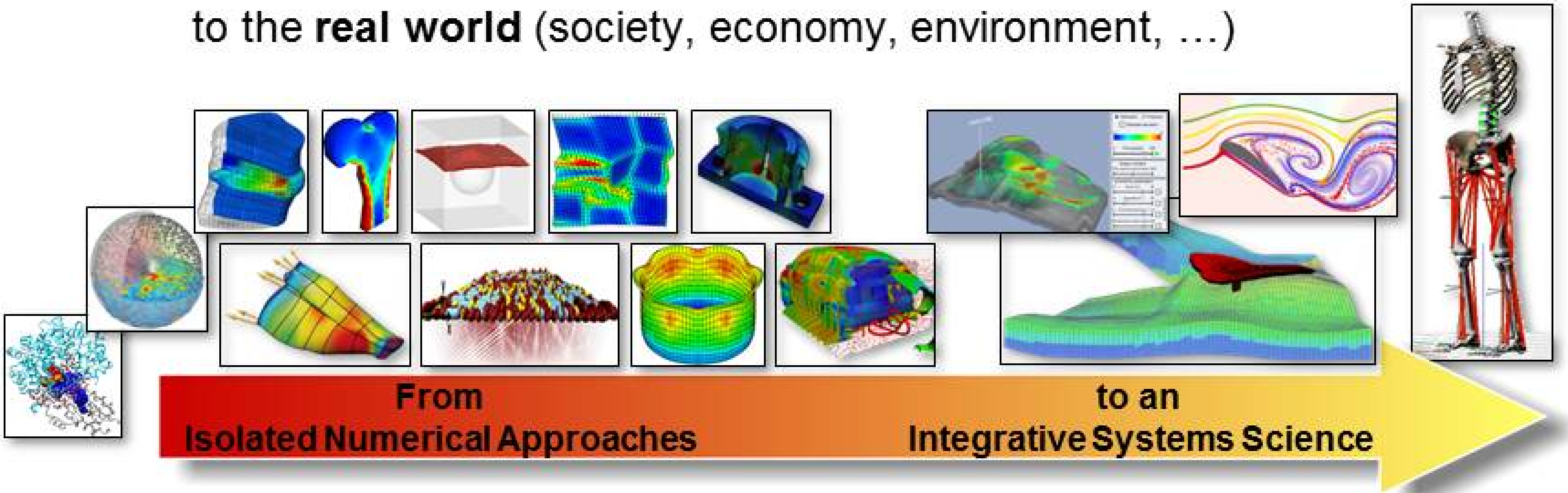
- Simulation Technology involves …
  - ✓ "… challenges in ***multi-scale, multi-physics modelling, model validation and verification, handling large data, visualisation, and CSE***."
  - ✓ "… a further challenge is the education of the ***next generation of engineers and scientists*** in the theory and practices of SBES."



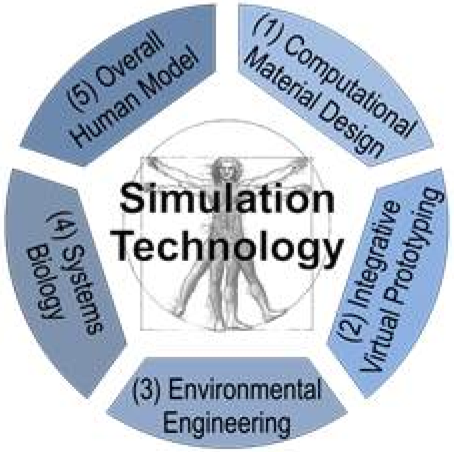
- Recognition by the ***World Technology Evaluation Center*** Simulation-Based Engineering and Science 2009:
  - ✓ "… ***pockets of excellence exist in Europe and Asia*** *that are more advanced than US groups, and* ***Europe is leading in training the next generation of engineering simulation experts***."
  - ✓ "... ***examples*** *of pockets* ***of excellence*** *in engineering simulation* ***include*** *… the* ***University of Stuttgart***."

SimTech and the Integrative Systems Science

- To combine a wide range of scientific disciplines into an **interdisciplinary effort to address new problem classes** which cannot be dealt with otherwise
- To **integrate disciplinary methods** into a new context giving rise to entirely **new solution strategies**
- To **form a new scientific field** by establishing a core of know how, a pool of techniques, a terminology, … and a curriculum
- To **reach out** from the **virtual world** (models and simulation) to the **real world** (society, economy, environment, …)



SimTech Visions – in 2007



From Empirical Material Description towards Computational Material Design

Towards Integrative Virtual Prototyping

Towards Interactive Environmental Engineering

From Classical Biology to Systems Biology

From Biomechanics towards the Overall Human Model

SimTech Visions – from 2012 on

From Empirical Material Description towards Computational Material Design

Towards Integrative Virtual Prototyping

Towards Interactive Environmental Engineering

Towards an Integrated Overall Human Model

Beyond a Simulation Cyber Infrastructure

Research Areas (RA)

- Our disciplinary core competences

A — **Molecular and Particle Simulations**

B — **Advanced Mechanics of Multi-scale and Multi-field Problems**

C — **Analysis, Design and Optimisation of Systems**

D — **Numerical and Computational Mathematics**

E — **Integrated Data Management and Interactive Visualisation**

F — **Hybrid High-performance Computing Systems and Simulation Software Engineering**

G — **Integrative Platform of Reflection and Contextualisation**

Towards an Integrated Overall Human Model

Wolfgang Ehlers

Oliver Röhrle

- Essential Research Areas:

A Molecular and Particle Simulations

B Advanced Mechanics of Multi-scale and Multi-field Problems

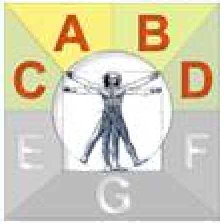
C Analysis, Design and Optimisation of Systems

D Numerical and Computational Mathematics

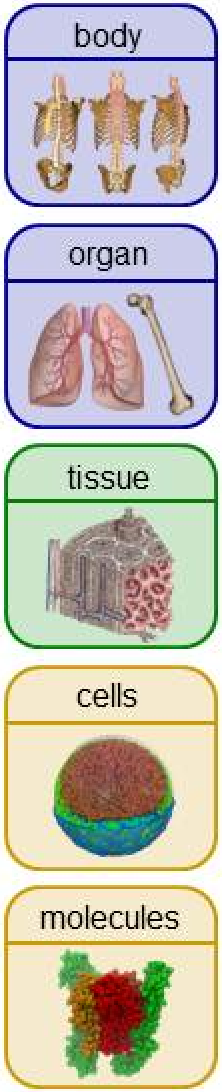
E Integrated Data Management and Interactive Visualisation

F Hybrid High-performance Computing Systems and Simulation Software Engineering

G Integrative Platform of Reflection and Contextualisation



Integrated Overall Human Model



Discrete Biomechanics:

- Sports and movement science
- Multi-body Systems, Robotics, etc.

Continuum Biomechanics:

- Solid Mechanics
- Fluid Mechanics
- Fluid-Structure Interaction
- Theory of Porous Media
- Multi-phase Flow
- Multi-component Transport

Systems Biology:

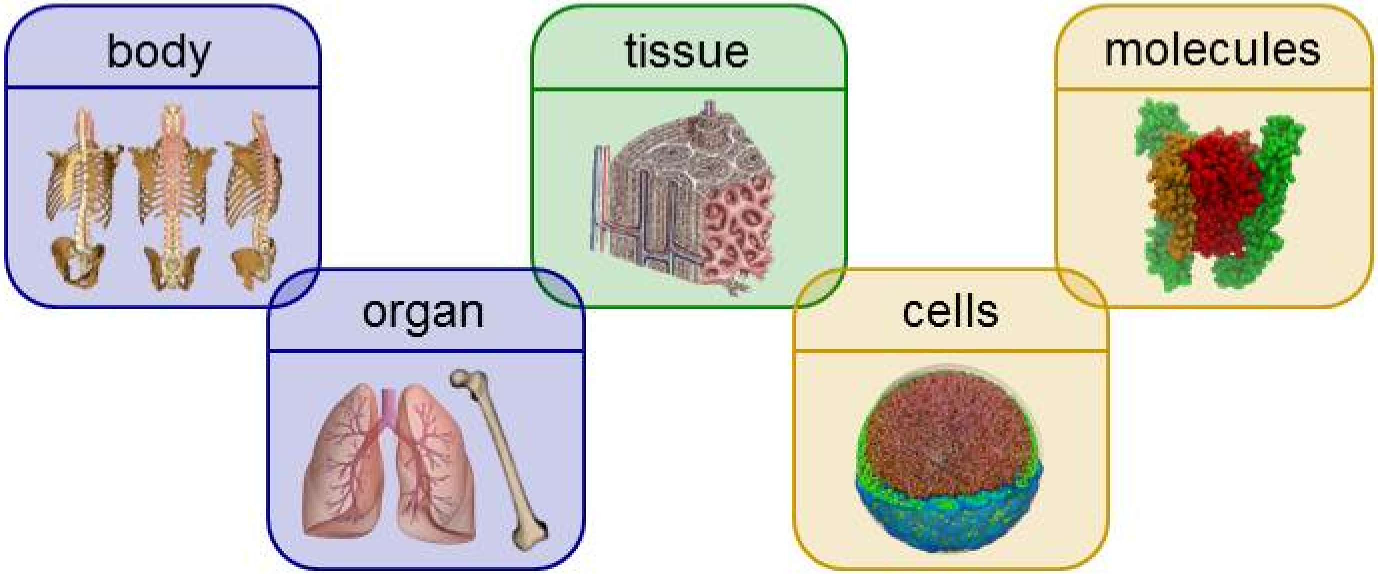
- Chemical Reaction Kinetics
- Signal Transduction Pathways
- Heterogeneous Cell Populations
- Statistical Methods

Molecular Biology, Biochemistry:

- Molecular Dynamics
- Phenomics, Genomics

Integrated Overall Human Model

- From isolated numerical approaches to an integrative systems science



length scales span over 10 orders of magnitude

time scales span over 15 orders of magnitude

Biomechanics

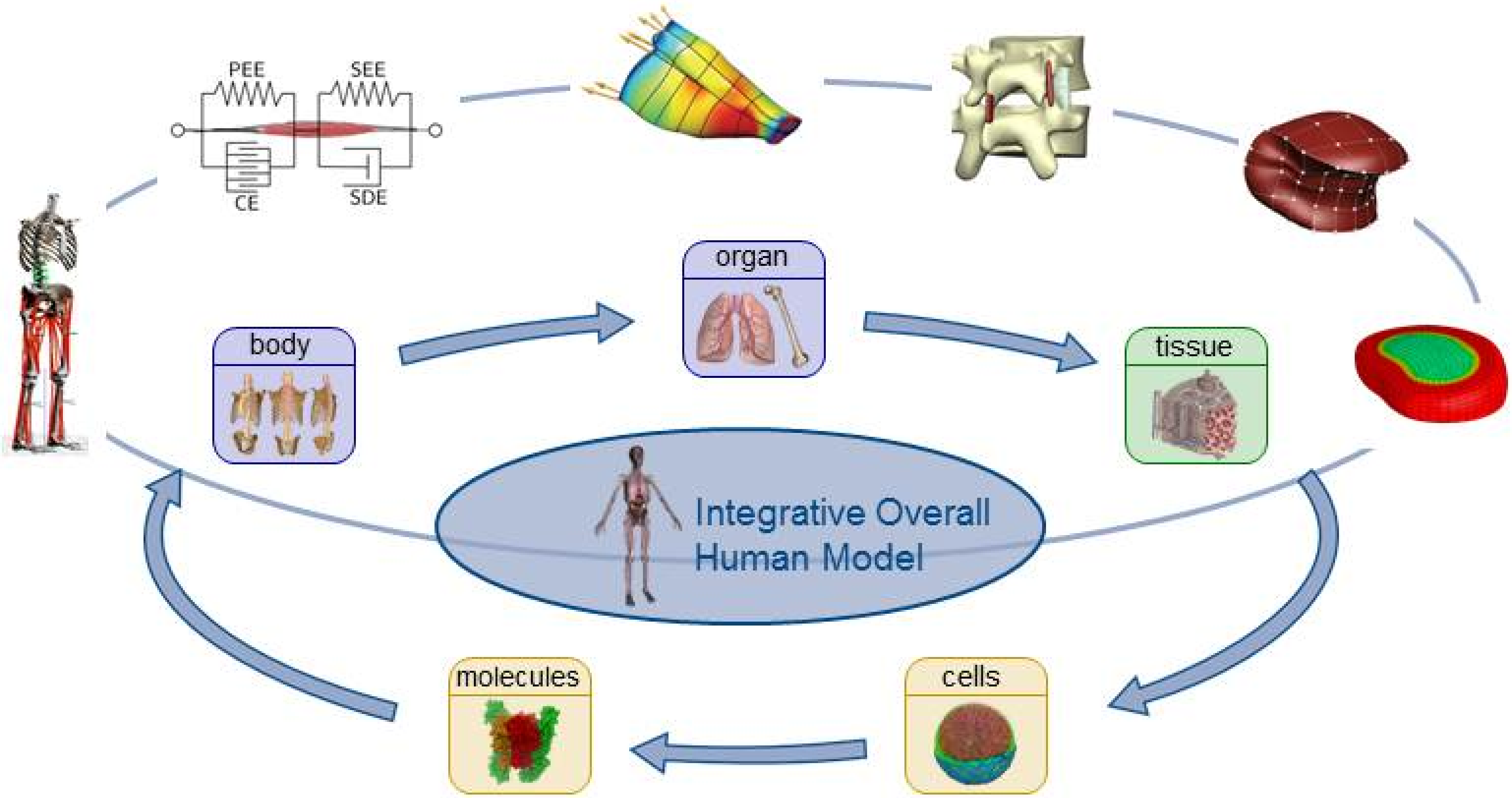
Systems Biology

GAMM & FA CSE

Simulation Technology

Exemplary Applications

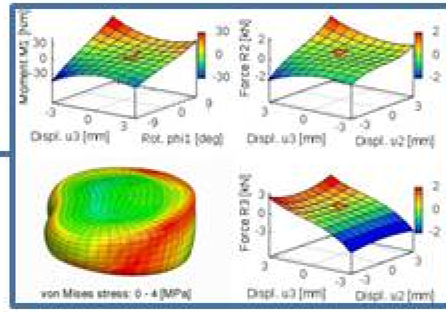
Integrated Overall Human Model



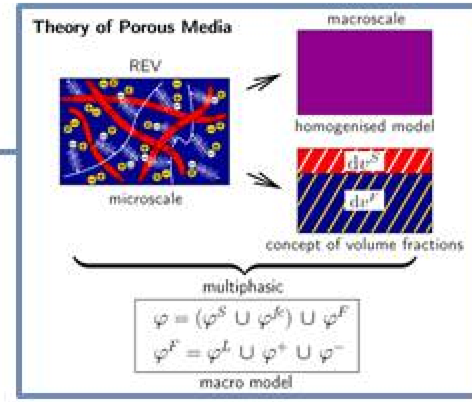
- **The Integrative Overall Human Model** is a toolbox of multi-physical models ranging from the molecular to the full body scale. It provides bridging information on the coupled driving quantities to generate a custom model for a specific application.

Integrated Overall Human Model

- Multi-scale simulation of the dynamic loads on the lumbar spine

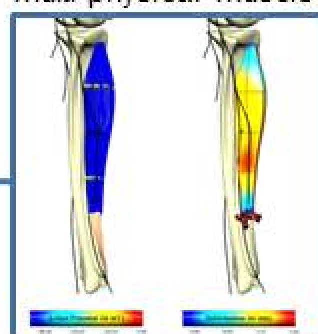


bridge from the continuum

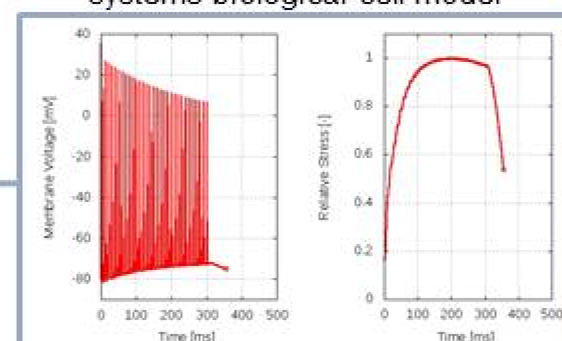


volumetric homogenisation

multi-physical muscle



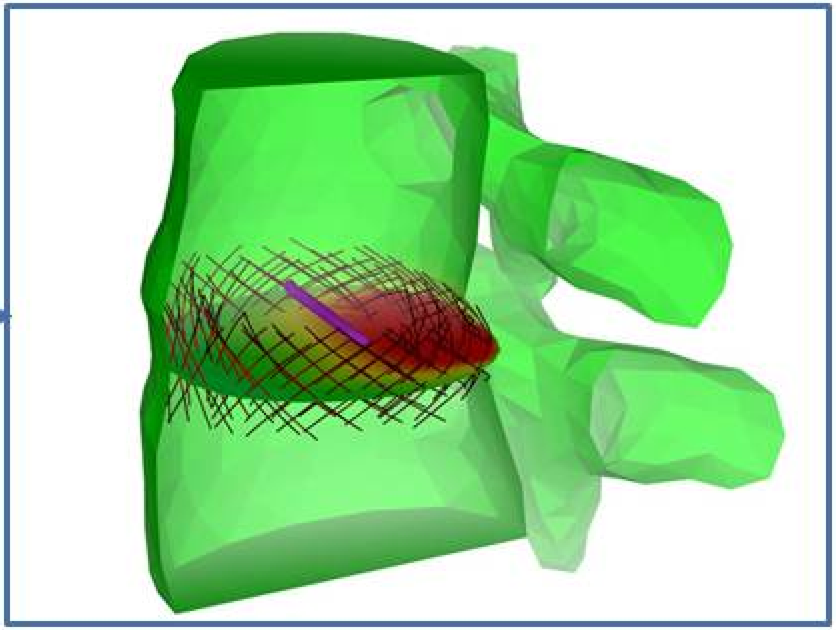
systems-biological cell model



Integrated Overall Human Model

- Multi-scale simulation of the dynamic loads on the lumbar spine

application of dynamic loading conditions



to recover local stresses and strains

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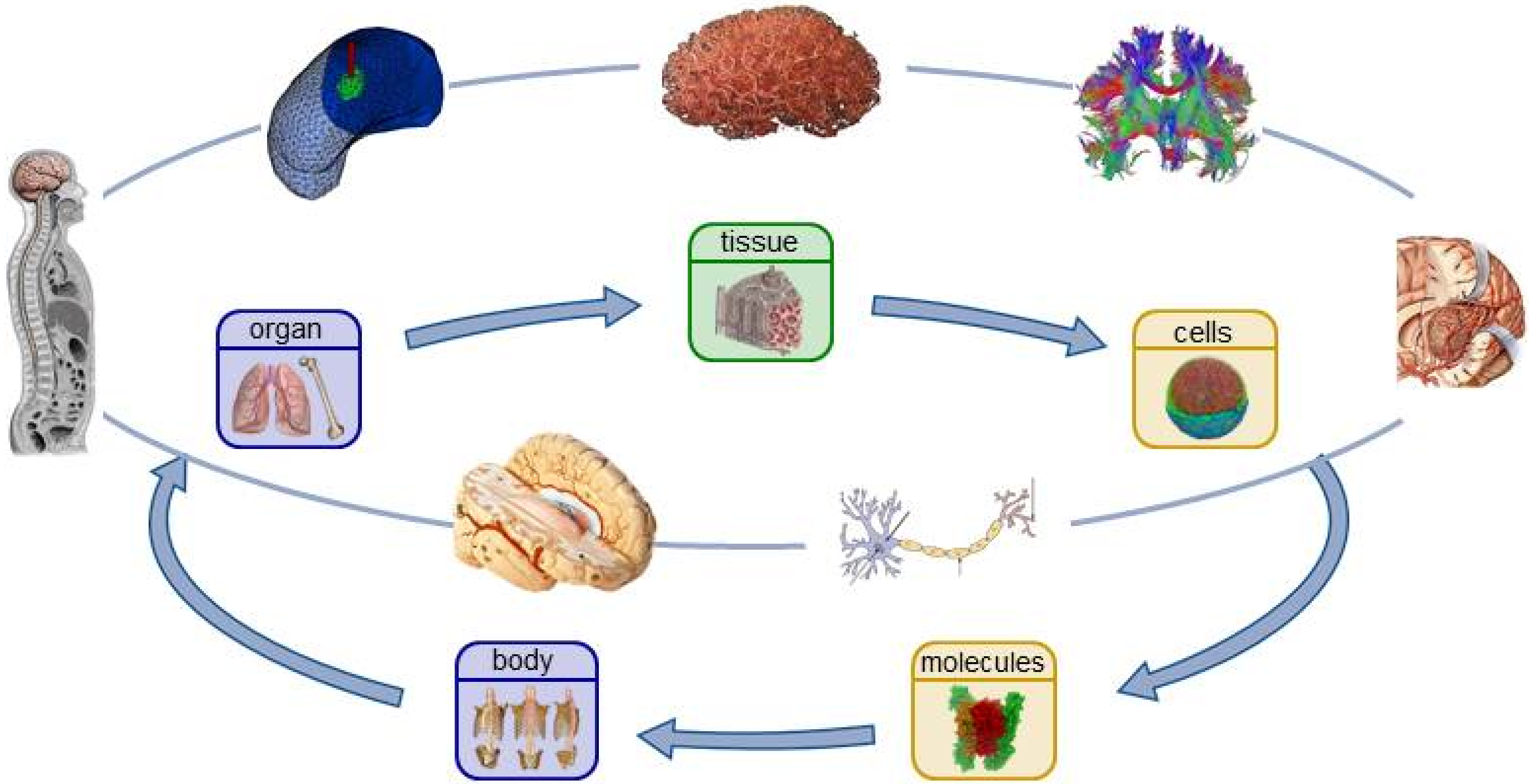
Simulation Technology

Exemplary Applications

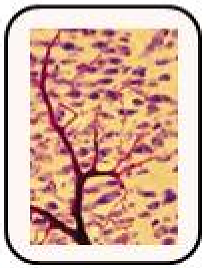
Integrated Overall Human Model



- **Show Case: human brain**

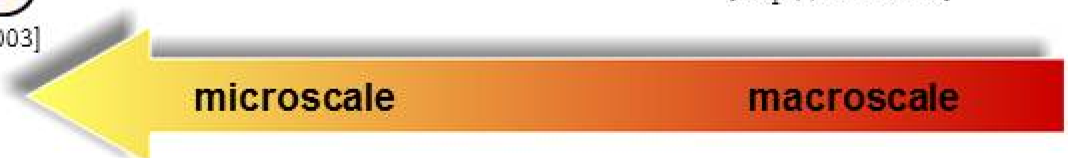
  addressing coupled biomechanical problems that span from the organ over the tissue to the cellular scale.

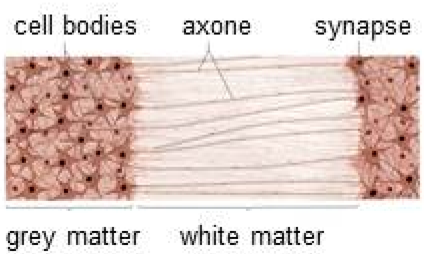
Modelling and Simulation of Human Brain Tissue



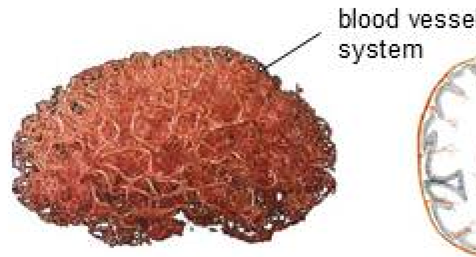
[*Thompson* 2003]

[http://brata.com]

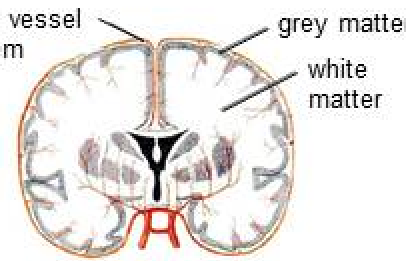




[*Prometheus*: Lernatlas der Anatomie]



[*Zlokovic & Apuzzo* 1998]



[*Lippert*: Lehrbuch Anatomie]

- Macroscopic modelling of the multi-component and multi-physical human brain tissue for clinical studies

Innovative Treatment Options for Brain Tumours

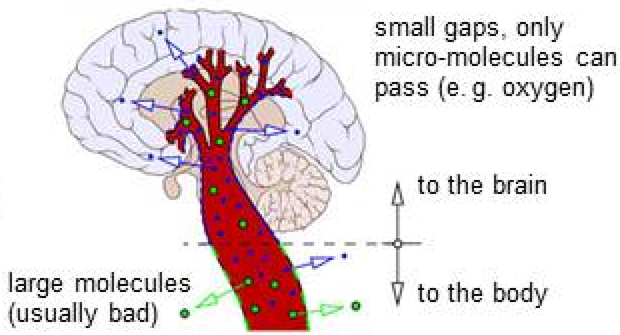
- **Conventional treatment**

  Complete removal of the tumour, combined with radiotherapy/chemotherapy

  › **highly invasive** and often **insufficient** (regrow)

- **Intra-vascular medication**
  - Distribution by the blood circulation
  - Large therapeutic macro-molecules cannot pass the blood-brain barrier (BBB)

  › **efficient treatment impossible**

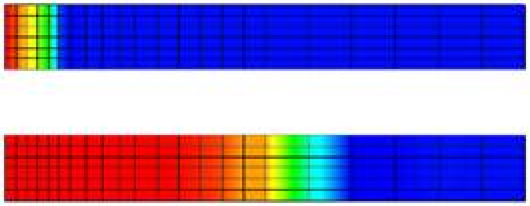


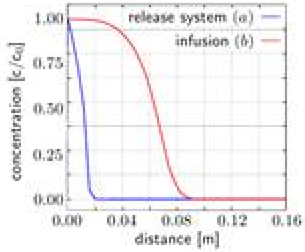
- **Extra-vascular medication**

  (a) implantation of release systems → diffusion-driven distribution

  (b) intracerebral infusion → distribution by diffusion and convection

(a)
(b)

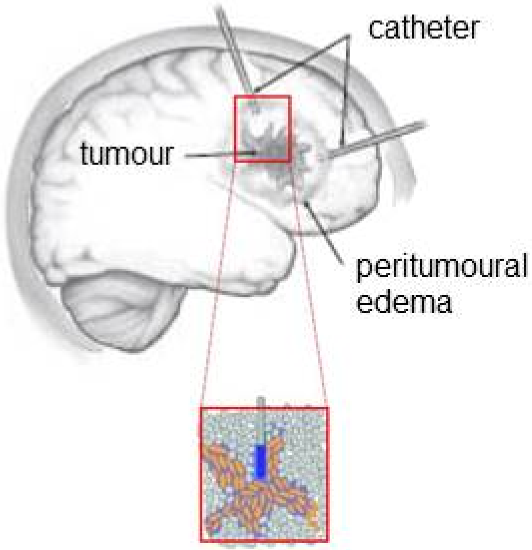




› intracerebral **infusion** promises an **effective distribution of molecules**

Convection-Enhanced Drug Delivery (CED)

- Continuous slow infusion of a dilute drug solution into the nervous brain tissue (extra-vascular space) via infusion catheters $\rightarrow$ bypassing the BBB
- Drug dispersion within the brain's extra-cellular space is due to diffusion and convection, mainly driven by pressure gradients and chemical effects
- Spreading is influenced by anatomical boundaries, white-matter alignment, deformation and the application dose
- Deep penetration of large compounds is possible and a selective targeting can be realised

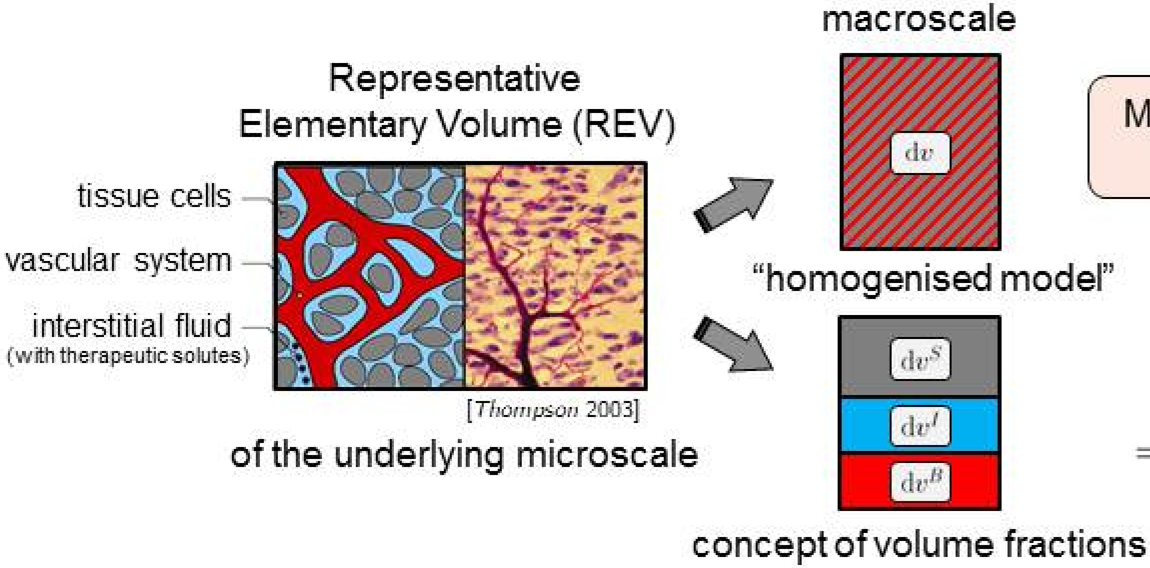


- Established by researchers from the US National Institutes of Health in the early 1990s [*Bobo et al.* 1994]
- Despite tumour treatment, new treatment options arise for epilepsy, stroke and Parkinson's disease

Fundamentals of the Theory of Porous Media

[*Bowen* 1980, *Lewis & Schrefler* 1998, *Ehlers* 1989, 1993, 2002, 2009]

- **Homogenisation of human brain tissue**



Macroscopic multi-phasic modelling approach

$$\varphi = \bigcup_\alpha \varphi^\alpha$$
$$= \varphi^S \cup \varphi^B \cup \varphi^I$$
$$= \varphi^S \cup \varphi^B \cup (\varphi^L \cup \varphi^D)$$

- **Ternary model for drug infusion studies**
  - Hyperelastic solid skeleton φ^S (tissue cells and vascular walls)
  - Two mobile pore-liquid constituents (blood φ^B and interstitial fluid φ^I)
  - Overall interstitial fluid φ^I as a real mixture of two components: Liquid solvent φ^L and dissolved therapeutic solute φ^D

Balance Relations for the Drug-Infusion Model

- **Concentration balance of the therapeutic agent**
  - MB of the therapeutic agent φ^D expressed in c_m^D

$$0 = (n^I c_m^D)'_S + n^I c_m^D \operatorname{div} (\mathbf{u}_S)'_S + \operatorname{div} (n^I c_m^D \mathbf{w}_D)$$

- **Volume balance of the overall interstitial fluid**
  - MB of the liquid solvent φ^L with $n^L \approx n^I$ and $\overset{\prime}{\mathbf{x}}_L \approx \overset{\prime}{\mathbf{x}}_I$

$$0 = (n^I)'_S + n^I \operatorname{div} (\mathbf{u}_S)'_S + \operatorname{div} (n^I \mathbf{w}_I)$$

- **Volume balance of the blood plasma**

$$0 = (n^B)'_S + n^B \operatorname{div} (\mathbf{u}_S)'_S + \operatorname{div} (n^B \mathbf{w}_B)$$

- **Momentum balance of the overall aggregate**
  - summation of all particular MMB of the constituents

$$\mathbf{0} = \operatorname{div} \mathbf{T} + \rho\, \mathbf{b}\,, \qquad \text{where} \quad \left\{ \begin{array}{rcl} \mathbf{T} & = & \mathbf{T}^S + \mathbf{T}^B + \mathbf{T}^I \\ \rho & = & n^S \rho^{SR} + n^B \rho^{BR} + n^I \rho^{IR} \end{array} \right.$$

Primary variables of initial-boundary value problems: $\mathbf{u}_S$, p^{BR}, p^{IR}, c_m^D

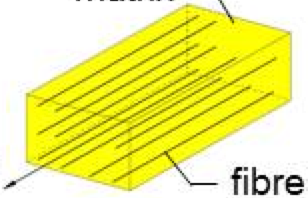
Constitutive Settings

- **Evaluation of the entropy principle**
  [*Bowen* 1980, *Ehlers* 1993, 2002, 2009]
  - Helmholtz free energies: $\psi^S = \psi^S(\mathbf{F}_S)\,,\ \psi^B = \psi^B(s^B)\,,\ \psi_I^\gamma = \psi_I^\gamma(c_m^\gamma)$

- **Overall Cauchy stress**

$$\mathbf{T} = \mathbf{T}^S_{E\,\text{mech.}} - p\,\mathbf{I}\,, \quad \text{with} \begin{cases} p = s^B\,p^{BR} + s^I\,p^{IR} & : \text{pore pressure} \\ \mathbf{T}^B_E \approx \mathbf{0},\ \mathbf{T}^I_E \approx \mathbf{0} & : \text{liquid extra stresses} \end{cases}$$

- **Hyperelastic brain's solid skeleton**
  [*Eipper* 1998, *Markert et al.* 2005, *Karajan* 2009]



$$\mathbf{T}^S_{E\,\text{mech.}} = 2\,J_S^{-1}\,\mathbf{F}_S\,\frac{\partial W^S}{\partial \mathbf{C}_S}\,\mathbf{F}_S^T = \mathbf{T}^S_{E,\,iso} + \mathbf{T}^S_{E,\,aniso}$$

$$\text{where} \begin{cases} \mathbf{T}^S_{E,\,iso} = \dfrac{\mu_0^S}{J_S}\,(\mathbf{B}_S - \mathbf{I}) + \lambda_0^S\,(1 - n_{0S}^S)^2\Big(\dfrac{1}{1 - n_{0S}^S} - \dfrac{1}{J_S - n_{0S}^S}\Big)\,\mathbf{I} \\ \mathbf{T}^S_{E,\,aniso} = \dfrac{\tilde{\mu}_1^S}{J_S\,(\mathbf{a}^S\cdot\mathbf{a}^S)}\,\Big((\mathbf{a}^S\cdot\mathbf{a}^S)^{\tilde{\gamma}_1^S/2} - 1\Big)\,(\mathbf{a}^S\otimes\mathbf{a}^S) \end{cases}$$

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Exemplary Applications

- **Pore-liquid seepage velocities**

$$n^I \mathbf{w}_I = -\frac{\mathbf{K}^{SI}}{\mu^{IR}} [\operatorname{grad} p^{IR} - \rho^{IR} \mathbf{g}]$$

$$n^B \mathbf{w}_B = -\frac{\mathbf{K}^{SB}}{\mu^{IR}} [\operatorname{grad} p^{BR} - \rho^{BR} \mathbf{g} + \frac{p^{BR} - p^{IR}}{s^B} \operatorname{grad} s^B]$$

Separated pore spaces → different (anisotropic) initial permeabilities $\mathbf{K}^{S\xi}$

- **Pore-diffusion velocity of the therapeutic agent**

$n^I c^D_m \mathbf{d}_{DI} = -\mathbf{D}^D \operatorname{grad} c^D_m$, where $\mathbf{D}^D$ is the diffusivity tensor

- **Determination of volume fractions**

$\sum_\alpha n^\alpha = n^S + n^B + n^I = 1$ where $\begin{cases} n^S = n^S_{0S} (\det \mathbf{F}_S)^{-1} \\ n^D \approx 0 \quad \rightarrow \quad n^L \approx n^I \end{cases}$

› additional constitutive equation

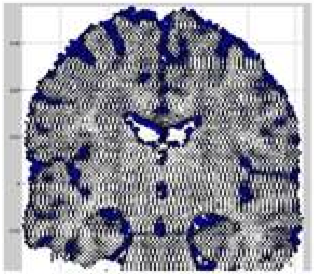
- Constant blood volume fraction: $n^B = n^B_{0S} = 0.05 \rightarrow n^I = 1 - n^S - n^B_{0S}$
- Pressure-saturation relation → partitioning via pressure difference

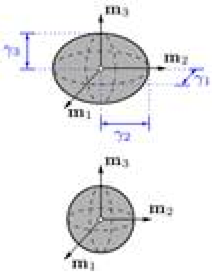
Inclusion of Anisotropic Tissue Properties

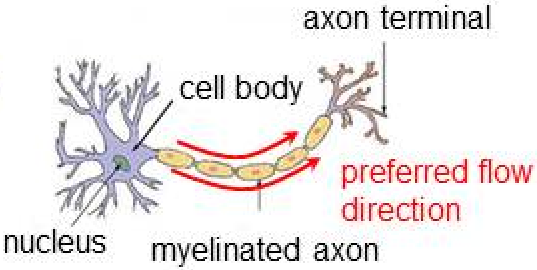
- **Diffusion Tensor Imaging (DTI)**
  - *In vivo* diffusion-weighted images
  - Measurement of the restricted motion of water molecules in biological tissue
  - Extended scans are sufficient to compute the self-diffusion tensor

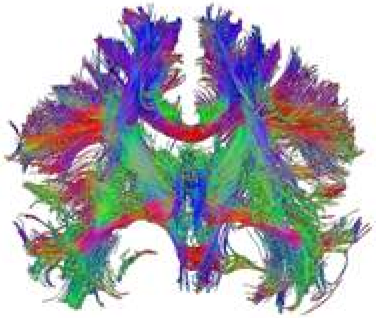
[http://tnp.wayne.edu/research/facilities.php]

- **Medical imaging techniques**
  - Microstructural characteristics
  - Diffusion tensor as ellipsoid
  - White matter, grey matter or cerebrospinal fluid
  - Identification of white-matter fibres
  - Corresponding eigenvector of the largest eigenvalue provides the fibre direction









[http://www.biomed.ee.ethz.ch/research/bioimaging/brain]

- **Apparent water-diffusion tensor at each evaluated voxel**

$$\mathbf{D}^{\mathrm{n}}_{\mathrm{awd}} = \begin{bmatrix} D^{\mathrm{n}}_{11} & D^{\mathrm{n}}_{12} & D^{\mathrm{n}}_{13} \\ D^{\mathrm{n}}_{21} & D^{\mathrm{n}}_{22} & D^{\mathrm{n}}_{23} \\ D^{\mathrm{n}}_{31} & D^{\mathrm{n}}_{32} & D^{\mathrm{n}}_{33} \end{bmatrix} \mathbf{e}_i \otimes \mathbf{e}_k = \begin{bmatrix} \gamma^{\mathrm{n}}_{1\,\mathrm{awd}} & 0 & 0 \\ 0 & \gamma^{\mathrm{n}}_{2\,\mathrm{awd}} & 0 \\ 0 & 0 & \gamma^{\mathrm{n}}_{3\,\mathrm{awd}} \end{bmatrix} \mathbf{m}^{\mathrm{n}}_i \otimes \mathbf{m}^{\mathrm{n}}_i$$

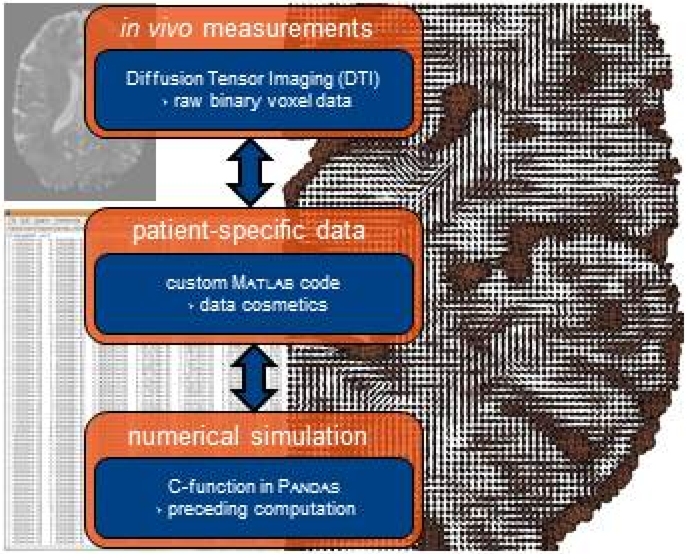
- **Estimation of corresponding permeability characteristics**
  [*Basser et al.* 1994, *Tuch et al.* 2001, *Linninger* 2008]

  Basic assumption: same set of eigenvectors

$$\gamma^{\mathrm{n}}_{i,\mathbf{D}_0^{\mathrm{D,n}}} = \bar{D}^{\mathrm{D}}_0 \frac{\gamma^{\mathrm{n}}_{i,\mathrm{awd}}}{\bar{\gamma}^{\mathrm{n}}_{\mathrm{awd}}}, \quad \gamma^{\mathrm{n}}_{i,\mathbf{K}_{0S}^{SI,\mathrm{n}}} = \bar{K}^{SI}_{0S} \frac{\gamma^{\mathrm{n}}_{i,\mathrm{awd}}}{\bar{\gamma}^{\mathrm{n}}_{\mathrm{awd}}},$$

  where $\begin{cases} \bar{D}^{\mathrm{D}}_0, \bar{K}^{SI}_{0S} & : \text{reference values} \\ \bar{\gamma}^{\mathrm{n}}_{\mathrm{awd}} & : \text{mean of eigenvalues} \end{cases}$

- **Specific tissue characteristics**
  - Effective diffusion tensor $\mathbf{D}_0^{\mathrm{D,n}}$ of the therapeutic agent
  - Intrinsic permeability tensor $\mathbf{K}_{0S}^{SI,\mathrm{n}}$ of the interstitial fluid
  - Fibre direction $\mathbf{a}_0^{S,\mathrm{n}}$ (eigenvector of the largest eigenvalue)



DTI-data by courtesy of G. Kindlmann and A. Alexander [www.sci.utah.edu/~gk/DTI-data]

Numerical Implementation

[*Sandhu & Wilson* 1969, *Ellsiepen* 1999]

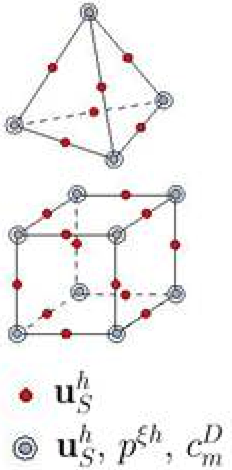
- **Weak formulations of governing balance equations**

$$\mathcal{G}_{\mathbf{u}_S}(\delta\mathbf{u}_S, \mathbf{u}_S, p^{BR}, p^{IR}) \equiv \int_\Omega \mathbf{T} \cdot \operatorname{grad} \delta\mathbf{u}_S \, dv - \int_\Omega \rho \, \mathbf{b} \cdot \delta\mathbf{u}_S \, dv - \int_{\Gamma_t} \underbrace{\mathbf{T}\,\mathbf{n}}_{\bar{\mathbf{t}}} \cdot \delta\mathbf{u}_S \, da = 0$$

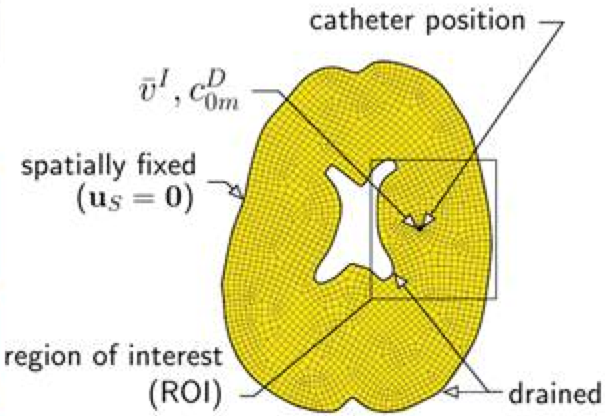
$$\mathcal{G}_{p^{\xi R}}(\delta p^{\xi R}, \mathbf{u}_S, p^{\xi R}) \equiv \int_\Omega \delta p^{\xi R} \, [(n^\xi)'_S + n^\xi \operatorname{div} (\mathbf{u}_S)'_S] \, dv - \int_\Omega n^\xi \mathbf{w}_\xi \cdot \operatorname{grad} \delta p^{\xi R} \, dv + \int_{\Gamma_{\bar{v}^\xi}} \delta p^{\xi R} \underbrace{n^\xi \mathbf{w}_\xi \cdot \mathbf{n}}_{\bar{v}^\xi} \, da = 0$$

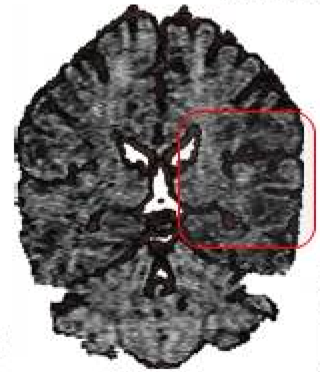
$$\mathcal{G}_{c_m^D}(\delta c_m^D, c_m^D, \mathbf{u}_S, p^{IR}) \equiv \int_\Omega \delta c_m^D \, [(n^I c_m^D)'_S + n^I c_m^D \operatorname{div} (\mathbf{u}_S)'_S] \, dv - \int_\Omega n^I c_m^D \mathbf{w}_D \cdot \operatorname{grad} \delta c_m^D \, dv + \int_{\Gamma_{\bar{j}^D}} \delta c_m^D \underbrace{n^I c_m^D \, \mathbf{w}_D \cdot \mathbf{n}}_{\bar{j}^D} \, da = 0$$

- **Mixed finite element formulation**
  - Simultaneously approximation of all primary unknowns
  - Quadratic approximation of the solid displacement and linear approximations for the pore-liquid pressures and the therapeutic agent concentration (uppc-formulation), LBB condition is fulfilled
  - Type of mixed finite elements (MFEM) is known as extended *Taylor-Hood* elements, fully integrated with 27 *Gauss* points
  - Temporal discretisation with an implicit *Euler* time-integration scheme

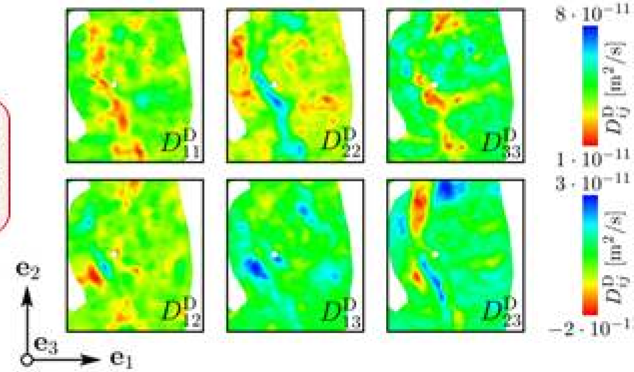


Simulation of CED: human brain slice

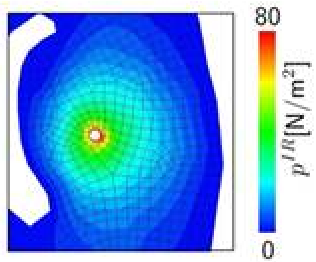




Inhomogeneous and anisotropic material parameters



interstitial fluid excess pressure



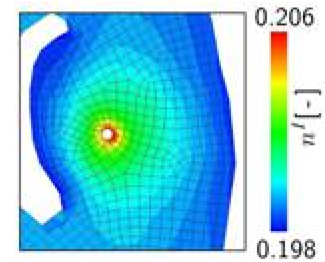
application rate solution

$\bar{v}^I = 3.33 \cdot 10^{-7}$ [m³/m²s]

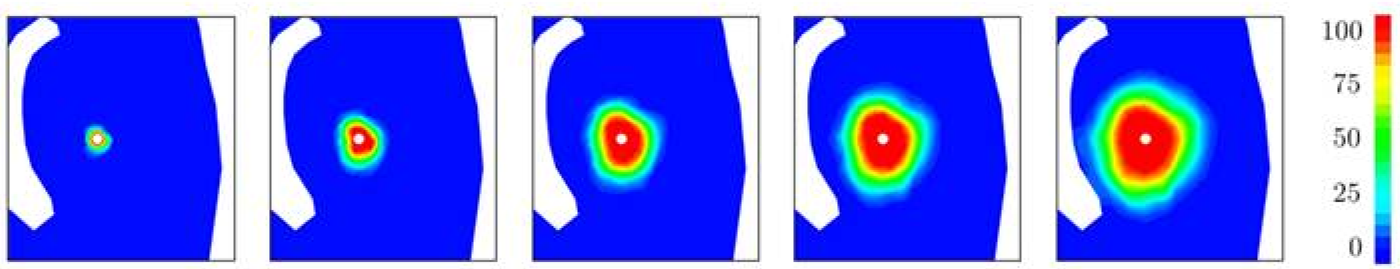
($\hat{=}\, Q = 2.5$ [μl/min])

$c^D_{0m} = 3.7 \cdot 10^{-3}$ [mol/l]

volume fraction interstitial fluid



therapeutic agent distribution



≈ 2 hours ≈ 12 hours ≈ 1 day ≈ 2 days ≈ 3 days

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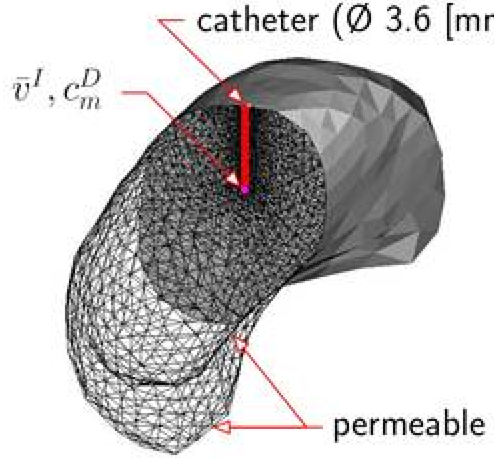
Simulation of CED: human brain hemisphere

- Mesh & boundary conditions



- 7462 elements, 37224 dof
- Brain cortex fixed, efflux permitted

Solution influx (application dose)

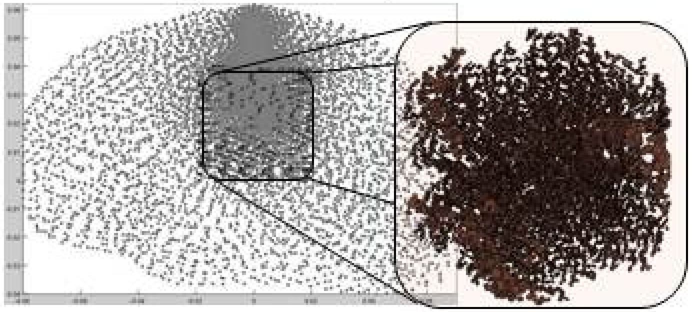
$$\bar{v}^I = 8.33 \cdot 10^{-6}\ [\mathrm{m}^3/\mathrm{m}^2\mathrm{s}]$$

$$(\widehat{=}\ Q = 0.3\ [\mathrm{ml/h}])$$

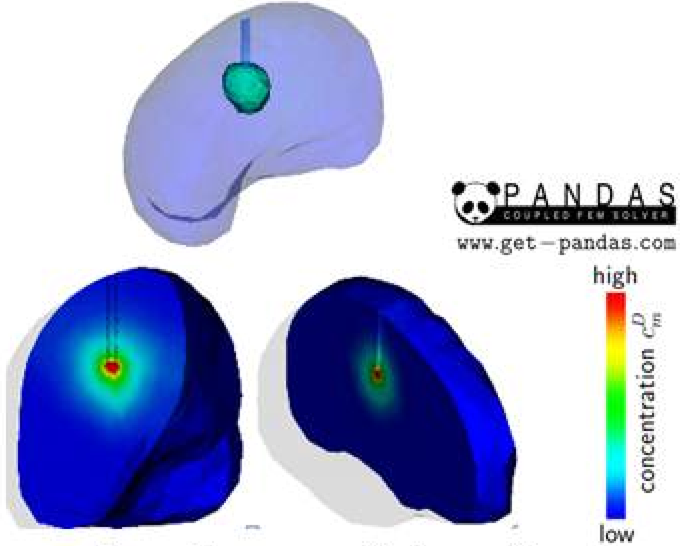
Concentration at the catheter tip

$$c_{0m}^D = 3.7 \cdot 10^{-3}\ [\mathrm{mol/l}]$$

- Inhomogeneous parameters

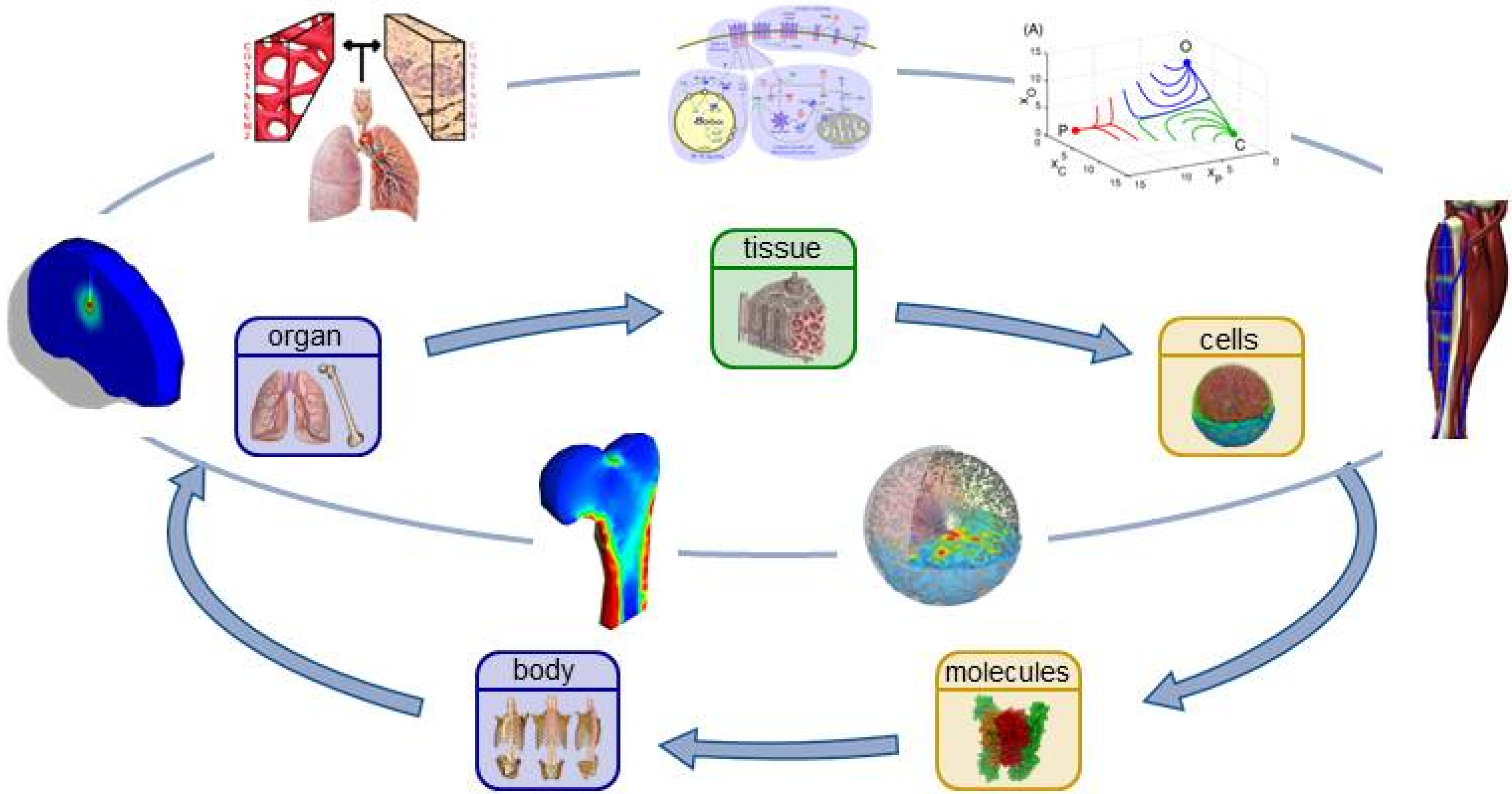


- Distribution of therapeutic agents



coronal section sagittal section

Integrated Overall Human Model



- **Show Case: bone remodelling process** addressing coupled biomechanical and systems-biological problems that span from the organ over the tissue to the cellular scale.

Simulation of a Bone Remodelling Process

- **Systems-biological model:**

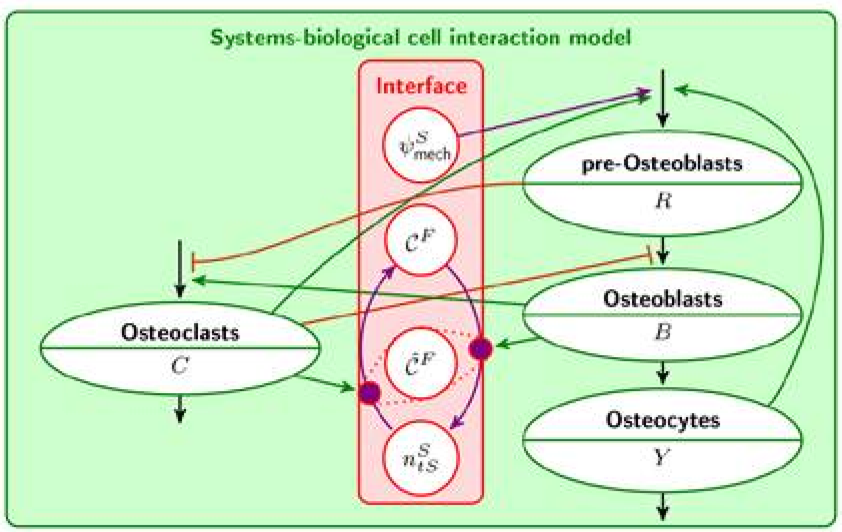
  model input: nutrient supply, mechanical stimulus

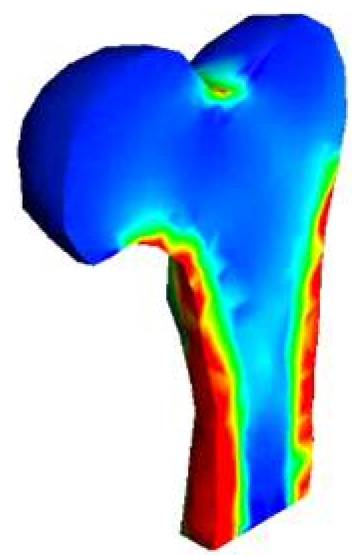
  model output: bone matrix turnover, nutrient evolution

- **Continuum-biomechanical model:**

  model input: bone density, nutrient consumption

  model output: nutrient diffusion, mechanical stimulus





volume fraction of the bone matrix

Simulation Technology with Application to Biomechanical Problems

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Stuttgart Research Centre for
Simulation Technology
www.simtech.uni-stuttgart.de

- **Summary**

  CSE within GAMM

  Simulation Technology
  - Generating an unique research and education infrastructure
  - Link to simulation-relevant areas by selected researchers
  - Establishing a transdisciplinary working research community

  Showcase Applications
  - Lumbar spine, Human brain tissue, Bone remodelling process
- **Future Aspects**
  - Vision of an integrative systems science