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Bioelectromagnetism in Neuroscience
(Gehirnstromkrams und so)

Skiseminar 2012

wissen.leben
WWU Münster

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Outline

“The human brain undoubtedly constitutes the most complex system in the known universe” (Wolf Singer, Director of the MPI for Brain Research)

Major branches of neuroscience (by Wikipedia):

- Affective neuroscience
- Behavioral neuroscience
- Cellular neuroscience
- Clinical neuroscience
- Cognitive neuroscience
- Computational neuroscience
- Cultural neuroscience
- Developmental neuroscience
- Molecular neuroscience
- Neuroengineering
- Neuroimaging
- Neuroinformatics
- Neurolinguistics
- Neurophysiology
- Paleoneurology
- Social neuroscience
- Systems neuroscience

Needs people from: Biology, chemistry, computer science, engineering, linguistics, mathematics, medicine, philosophy, physics and psychology.

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Major Modalities for Neuroimaging

X-ray imaging

- Projectional Radiography
- Computed Tomography (CT)

Nuclear imaging

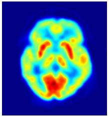
- Planar Scintigraphy
- Positron emission tomography (PET)
- Single photon emission computed tomography (SPECT)

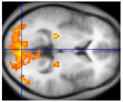
Magnetic resonance imaging (MRI)

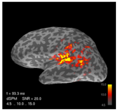
- Basic structural scans
- Functional (fMRI)
- Diffusion weighted (DW-MRI)

Bioelectromagnetic imaging:

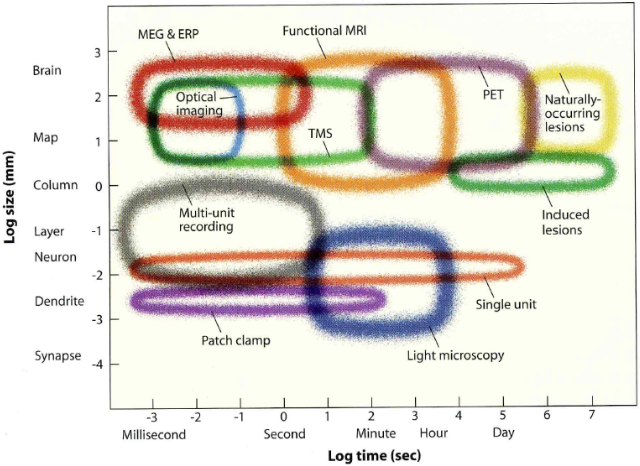
- Electroencephalography (EEG)
- Magnetoencephalography (MEG)







Spatio-Temporal Resolution in Neuroimaging



source: Gazzaniga, Ivry & Mangun, Cognitive Neuroscience, 2nd ed., W.W.Norton & Company, 2002

Electroencephalography (EEG) and Magnetoencephalography (MEG)

Aim: Reconstruction of brain activity by non-invasive measurement of induced electromagnetic fields (bioelectromagnetism) outside of the skull.

source: Wikimedia Commons

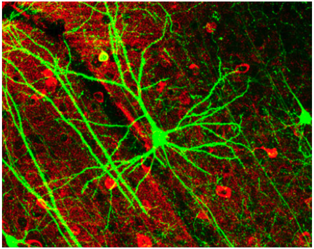
source: Wikimedia Commons

Neural Generators of EEG/MEG Signals

Signals derive from the net effect of ionic currents flowing in the dendrites of neurons during correlated synaptic transmission.

EEG: Extracellular volume currents produced by postsynaptic potentials.
→ strongly dependent on tissue's conductivity.

MEG: Intracellular currents associated with these postsynaptic potentials.
→ less dependent on tissue's conductivity.



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Basics of Mathematical Modeling I

Maxwell's equations (differential, microscopic form):

$$\mathrm{div}(\mathbf{E}) = \rho/\sigma \qquad \mathrm{rot}(\mathbf{E}) = -\partial_t \mathbf{B}$$

$$\mathrm{div}(\mathbf{B}) = 0 \qquad \mathrm{rot}(\mathbf{B}) = \mu_0 \cdot (\vec{j} - \sigma \partial_t \mathbf{E})$$

...4 coupled, (non-linear) time-dependent PDEs!

source: Wikimedia Commons

Simplifying assumptions:

- *Linearity:* Body ≈ passive conductor
- *Superposition:* Elementary sources don't interact.
- *Quasistatic approximation:* Temporal changes $<<$ spatial propagation velocity; Tissue is time-independent and has no inductance.
- *Charge-free:* No macroscopic charge aggregation.
- *Primary- and volume currents:* Separate current into a primary and resulting volume current.

Basics of Mathematical Modeling II

Forward/Direct Problem of EEG/MEG

Let $\sigma(\vec{r})$ be the conductivity and $\vec{j}^{pri}(\vec{r})$ a primary current density in $\Omega \subset \mathbb{R}^3$.
The electric potential u on $\partial\Omega$ is given by::

$$\begin{aligned} \nabla \cdot (\sigma \nabla u) &= \nabla \cdot \vec{j}^{pri} && \text{in } \Omega \\ n \cdot (\sigma \nabla u) &= 0 && \text{on } \partial\Omega \ (\textit{no-penetration condition}) \\ \int_{\partial\Omega} u \cdot dS &= 0 && (\textit{fix ground potential}) \end{aligned}$$

The magnetic field **B** can be conducted by (Biot-Savart):

$$\mathbf{B}(\vec{r}) = \frac{\mu_0}{4\pi} \int_{\Omega} \left\{ \vec{j}^{pri}(\vec{r}\,') - \sigma(\vec{r}\,') \cdot \nabla u(\vec{r}\,') \right\} \times \frac{\vec{r} - \vec{r}\,'}{\|\vec{r} - \vec{r}\,'\|^3} d\vec{r}\,' \qquad \text{for } \vec{r} \in \mathbb{R}^3 \backslash \bar{\Omega}$$

Solving the forward problem necessitates concerning 3 things:

- A source-model for $\vec{j}^{pri}$: How can we model the macroscopic current-flows?
- A volume-conductor-model of $\sigma(\vec{r})$: How can we model the dielectric properties of the different tissues?
- A numerical method for solving the PDE w.r.t. to source and volume conductor model; mostly FEM or BEM approaches.

Basics of Mathematical Modeling III

Inverse Problem of EEG/MEG Source Reconstruction

Given

- measurements b of the electric potential u and/or of the normal-component of the magnetic field $\langle n, \mathbf{B} \rangle$ on the surface $\partial\Omega$;
- a volume-conductor-model of $\sigma(\vec{r})$;
- a source model $\mathcal{J} \subset \mathcal{D}'(\Omega, \mathbb{R}^3)$;

estimate the primary current $\vec{j}^{pri} \in \mathcal{J}$ (source) that is consistent with b and the neurophysiological constrains of brain activity.

Solving the inverse problem (source reconstruction) necessitates concerning 3 things:

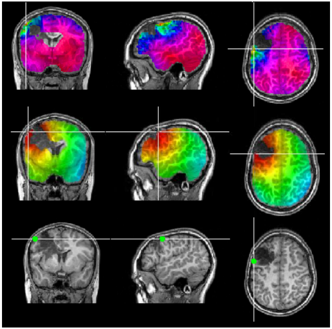
- Data preprocessing: How can we clean/filter the data from external sources (artifacts), noise, unwanted brain activity components?
- A-prior modeling: How much and which assumptions on brain activity do we need to incorporate and how do we model them to stabilize the inverse problem?
- Implementation: How do we solve the inverse problem practically?

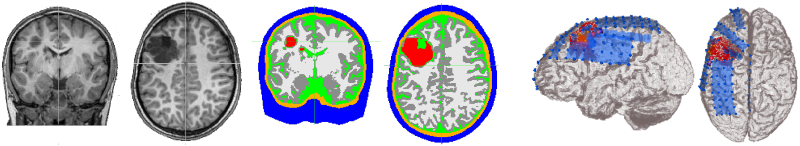
Work-flow in EEG/MEG Source Reconstruction

1. Head modeling;
2. Forward computation based on Head modeling;
3. Data preprocessing;
4. Source reconstruction based on forward computation and data preprocessing;

Applications of EEG/MEG

- Diagnostic tool in neurology, e.g., Epilepsy.
- Scientific applications:
  - Examination tool in several fields neuroscience.
  - Validation of therapeutic approaches in clinical neuroscience.
  - Examination tool for neurophysiology.





Institute for Biomagnetism and Biosignalanalysis

Focus on:

- Affective nsc
- Behavioral nsc
- Cognitive nsc
- Neuroimaging
- Clinical nsc
- Developmental nsc
- Neurolinguistics

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Experimental devices used:

- MEG & EEG
- Behavioral laboratory
- MRI (Basic, fMRI, DW-MRI)
- tDCS & TMS

Current fields of research:

- Auditory system: Tinnitus, neuroplasticity;
- Emotion, attention and affection;
- Language & speech: Plasticity, cochlea implantation, aphasia;
- Visual system: Conscious vision;
- Neuromuscular disorders in stroke patients.
- Methodical development

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Workgroup “Methods in Bioelectromagnetism”

Aim: Improve quality, applicability and reliability of EEG/MEG based source reconstruction in the presurgical diagnosis of epilepsy patients.

Current Major Projects

- Cooperation with epilepsy centers in Erlangen, Bochum, Kiel.
- COMESAPED: Reconstruction of epilepsy-characteristic sources by means of a simultaneous evaluation of EEG- and MEG- data using calibrated realistic head models.
- KONNEKFEM: Development, validation and application of methods for the determination of connectivity between brain structures.
- Cooperation with BESA: Integration of realistic head modeling and FEM computation into "end user" software.
- Hierarchical Bayesian modeling for EEG/MEG source reconstruction of brain networks involving deep-lying sources using multimodal integration.

Current Cooperations with Mathematical/Physical Departments of the WWU

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theoretische physik

- Co-supervision of Diploma/Master/PhD thesis by Martin Burger.
- Lectures/seminars in applied mathematics.
- Dynamical causal modeling with Christian Himpe / Mario Ohlberger.
- Modeling of brain tumor cell dynamics with Markus Knappitsch / Christina Surulescu
- FEM mesh adaptation techniques (in DUNE?) with Mario Ohlberger.
- Nonlinear dynamics of epileptic activity with Rudolf Friedrich.

Epilepsy

- Epileptic seizures: Transient symptoms of "abnormal excessive or synchronous neuronal activity in the brain" (prevalence: 4%).
- Epilepsy: Long term risk of recurrent seizures (prevalence: 0.5-1%).
- No "standard" type of seizure, no "standard" respond to treatment.
- 30% of patients are resistant to medication
  $\Longrightarrow$ Surgery may be considered for *focal* epilepsies.

source: Wikimedia Commons

Presurgical Epilepsy Diagnosis

- Aim: Localize epileptic zones. Focal *irritative/seizure-onset zone*?
- Basic diagnostics: EEG, (MEG), MRI, PET, SPECT, neuropsychology.
- Phase 1, non-invasive: Video EEG-monitoring, ictal/interictal EEG/MEG, ictal SPECT.
- Phase 2, invasive: Subdural depth-recording (ECoG), WADA test, angiography

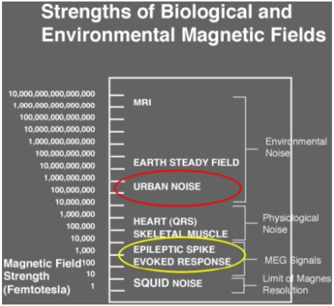
$\Longrightarrow$ Interdisciplinary case conference $\Longrightarrow$ Surgery decision.

source: Wikimedia Commons

EEG & MEG in Presurgical Epilepsy Diagnosis

EEG and MEG are non-invasive but direct measurements of epileptic activity.

- EEG is standard for various diagnosis tasks.
- MEG is expensive.
- MEG data processing is as complicated as for EEG.
- The health insurance in Germany does not cover MEG (contrary to USA).



EEG & MEG in Presurgical Epilepsy Diagnosis

So why should MEG be used in presurgical epilepsy diagnosis?

- EEG and MEG are complementary to each other.
- Different sensitivity profiles.
- Recent studies: Stefan et al. 2003, Iwasaki et al. 2005, Knake et al. 2006).

modality	**sensitivity to**		
	tissue geometry & conductivity	superficial sources	deep sources
EEG	high	tang: moderate radial: high	moderate
MEG	low	tang: very high radial: very low	low

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Even better than retrospective comparison (*converging evidence*):

Symmetric data fusion of simultaneous measurements.

Challenges of Combined EEG/MEG Source Reconstruction

- Practical and technical challenges.
- Different noise characteristics.
- Different sensitivity to tissue conductivity/forward modeling.

$\Longrightarrow$ We need:

- Realistic and individual modeling of the electrophysiological properties of the human head.
- Fast and accurate numerical forward computation methods.
- Advanced data preprocessing techniques and inverse methods for symmetric data fusion.

Outline

Introduction

Forward Computation

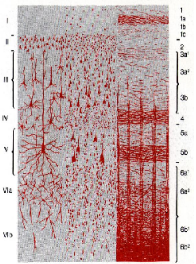
Head Model Generation

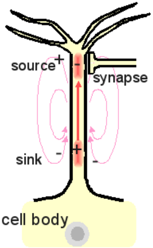
Data Analysis / Inverse Problem

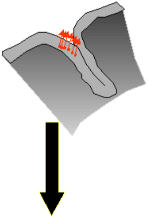
Forward Computation I: Source Model

Reminder: We need 3 things: A source-model for $\vec{j}^{pri}$, a volume-conductor-model of $\sigma(\vec{r})$ and numerical method for solving the PDE w.r.t. to source and volume conductor model.

Common source model: Equivalent current dipoles, $\vec{j}^{pri}(x) = \sum_i M_i \delta(x - x_i)$



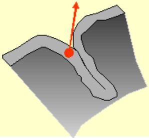




Equivalent Current Dipole (Primary current) (~50 nAm)

parameters:

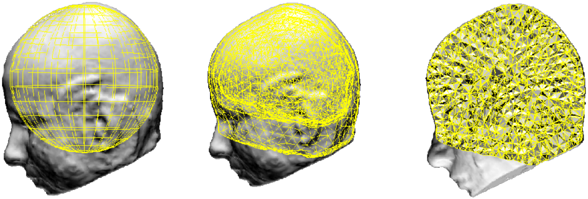
position : x_0
moment : M



Size of Macroscopic Neural Activity

~30 mm² = **5.5×5.5 mm²**

Forward Computation II: Numerical Methods



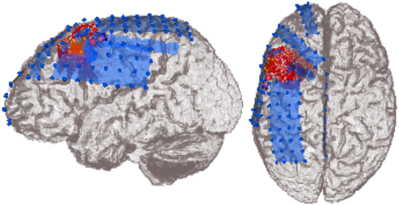
Sphere: Under the assumption of modeling the head by a multi-layer sphere model, a (quasi-)analytic solution exists.

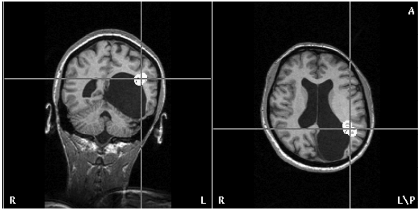
BEM: Assuming a nested shell topography boundary element methods can be used, demanding the discretization of the compartment boundaries.

FEM: Finite element methods are based upon a discretization of the whole volume conductor.

Why FEM?

- Possibility to incorporate nearly arbitrary complex geometries and arbitrary number of compartments:
  - CSF, gray/white matter, cerebellum, brain steam, muscles, dura mater, blood vessels;
  - Realistic skull modeling: Skull holes, three-layeredness.
  - Anatomical anomalies from surgeries / brain damages.
- Modeling of invasive recording devices (ECoG, depth-electrodes)
- Inclusion of anisotropic conductivities, e.g., white matter anisotropy





FE Forward Approaches

Problem: Singular source model; $D^{\alpha}\delta(r) \in H^{-3/2-|\alpha|-\varepsilon}(\Omega)\ \forall \varepsilon > 0$

FEM approaches to deal with this:

- Subtraction approach
- Venant approach
- Partial Integration approach

Alternatives: Source model $j^{imp}(r) \in H(\mathrm{div}, \Omega, ; \mathbb{R}^3)$ and use **Whitney elements** for FEM.

Subtraction Approach

Split the potential and the conductivity into two parts:

$$u = u^{\infty} + u^{cor}, \tag{1}$$

$$\sigma = \sigma^{\infty} + \sigma^{cor}. \tag{2}$$

Now calculate the analytic solution u^{∞} for a source in a medium with constant homogeneous conductivity σ^{∞}. Afterwards, only a correction potential has to be calculated numerically:

$$-\nabla \cdot (\sigma \nabla u^{cor}) = f \quad \text{in } \Omega, \qquad f := \nabla \cdot (\sigma^{cor} \nabla u^{\infty}), \tag{3}$$

$$\sigma \partial_{\mathbf{n}} u^{cor} = g \quad \text{on } \Gamma, \qquad g := -\sigma \partial_{\mathbf{n}} u^{\infty}. \tag{4}$$

This equation can now be discretized and solved without having to deal with the singularity numerically.

Venant Approach

Approximation of the dipolar source by a distribution of electrical monopoles (i.e., current sinks and sources/electrical charges), placed on the FE-nodes in the vicinity of the source position.
Then, try to match the moments of the distribution to those of a dipolar source:

$$({}^{l}T)_j = \sum_{i=1}^{k} (\Delta x_i)_j^l \, q_i, \qquad j = 1, 2, 3. \tag{5}$$

For $l = 0, 1, 2$ we have

$$^{l}T = \frac{1 - (-1)^l}{2^l} \cdot p. \tag{6}$$

This leads to a sparse RHS-vector (≈ 30 non-zero entries).

Partial Integration Approach

Take the weak formulation of the PDE and apply integration by parts to both sides:

$$\int_\Omega \nabla(\sigma\nabla u)\cdot\phi_i dx = \int_\Omega f\cdot\phi_i dx = \int_\Omega \nabla j^{imp}\cdot\phi_i dx. \tag{7}$$

$$-\int_\Omega (\sigma\nabla u)\cdot\nabla\phi_i dx + \int_{\partial\Omega} \sigma\partial_{\mathbf{n}} u\cdot\phi_i d\gamma(x) = -\int_\Omega j^{imp}\cdot\nabla\phi_i dx + \int_{\partial\Omega} \partial_{\mathbf{n}} j^{imp}\cdot\phi_i d\gamma(x). \tag{8}$$

We use the Neumann boundary condition and the fact that the current density vanishes at the head surface and obtain

$$\int_\Omega (\sigma\nabla u)\cdot\nabla\phi_i dx = \int_\Omega j^{imp}\cdot\nabla\phi_i dx = p\nabla\phi_i(x_0), \tag{9}$$

which yields a sparse RHS again (4 non-zero entries for tetrahedral, 8 non-zero entries for hexahedral meshes).

Pros and Cons of Approaches

Direct Approaches (Venant, Partial Integration, Whitney)

- ✓ Extremely fast computation after unique setup of a lead-field basis (some ms per RHS)
- ! Achieved accuracy depends on local mesh structure
- ! Only heuristic derivation (esp. Partial Integration)

Subtraction Approach

- ✓ Mathematically well-understood; existence, uniqueness and convergence of a solution can be proven
- ! High computational effort for the setup of a single RHS (some s)

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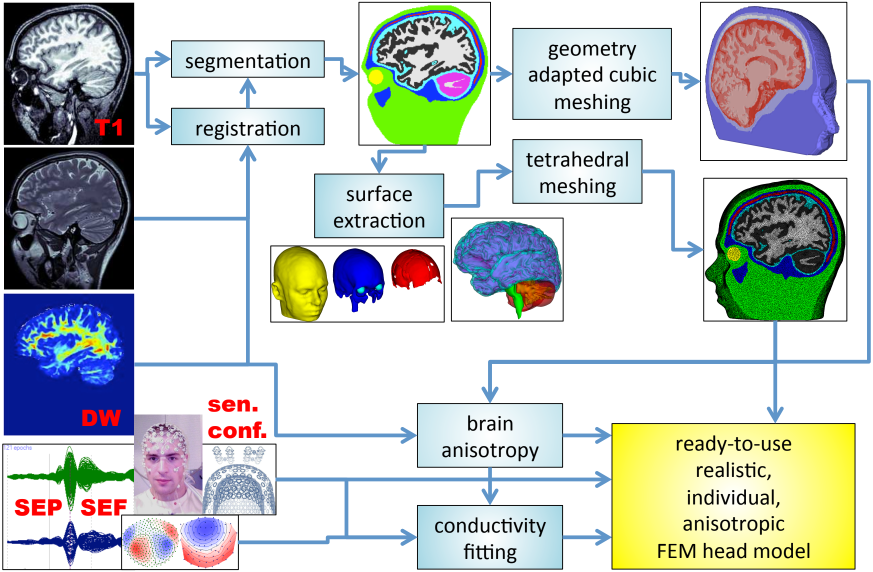
Realistic, individual head modeling for bioelectromagnetic applications



segmentation

registration

geometry adapted cubic meshing

surface extraction

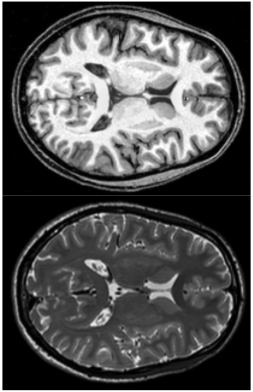
tetrahedral meshing

brain anisotropy

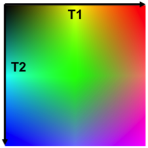
conductivity fitting

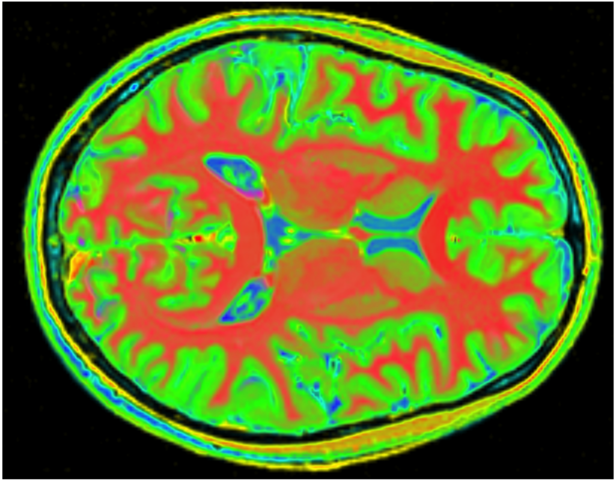
ready-to-use
realistic,
individual,
anisotropic
FEM head model

Part 1: MRI Processing, Structural Scans



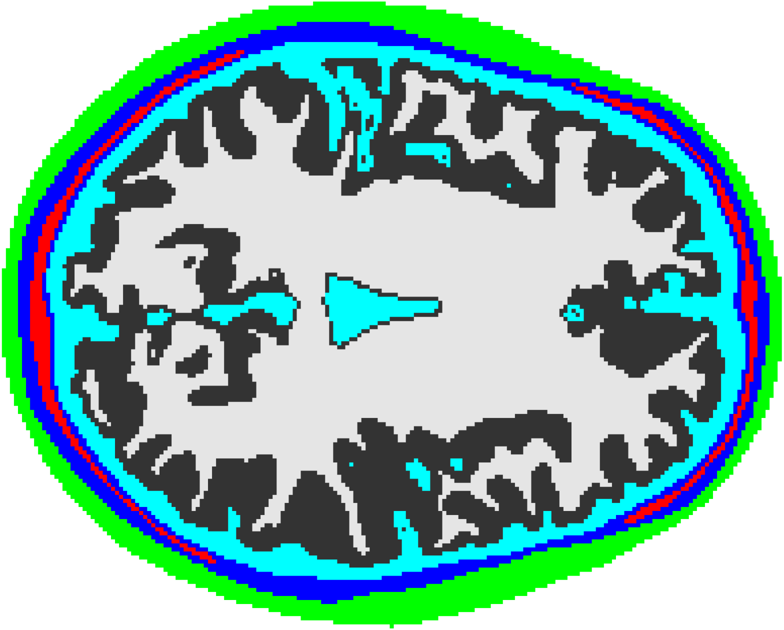
RGB map



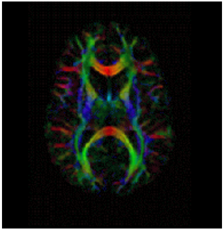


RGB composite of T1 and T2 MRI scan

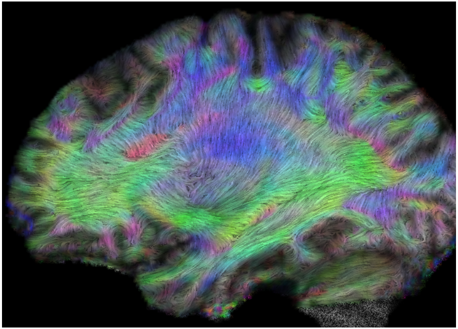
Part 1: MRI Processing, Segmentation

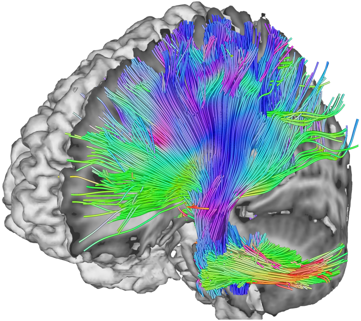


Part 1: MRI Processing, Diffusion Weighted MRI



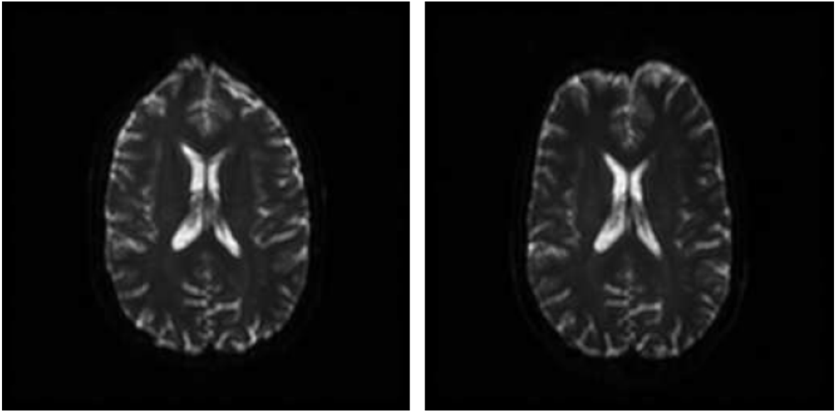
- DW-MRI allows the mapping of diffusion processes of molecules in biological tissues, in vivo.
- Clinical application: Localization of white matter lesions in stroke patients, surgical planning.
- Key imaging modality to assess connectivity via tractography .
- We use it to compute conductivity tensors.





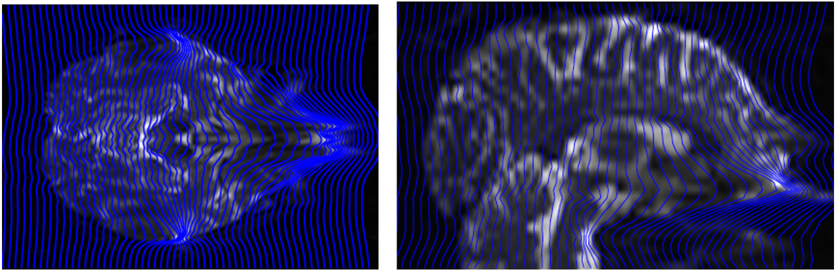
Part 1: MRI Processing, Diffusion Weighted MRI

Fast Echo-Planar Imaging (EPI)



Part 1: MRI Processing, Diffusion Weighted MRI

New, non-linear, variational registration approach (DA and PhD by Lars Ruthotto):



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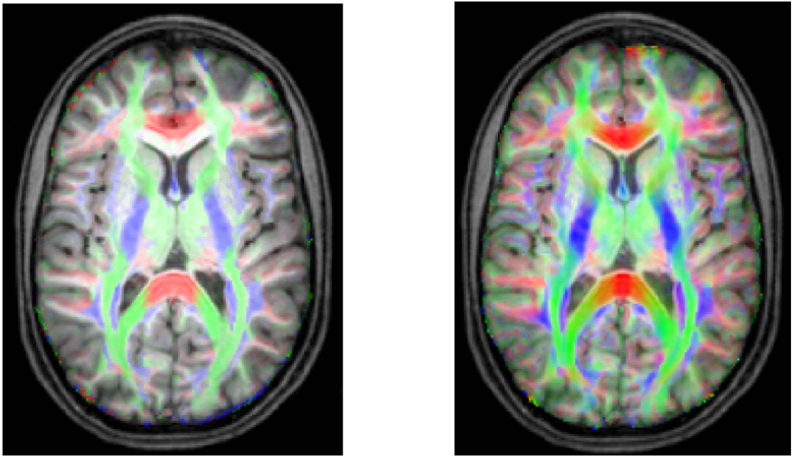

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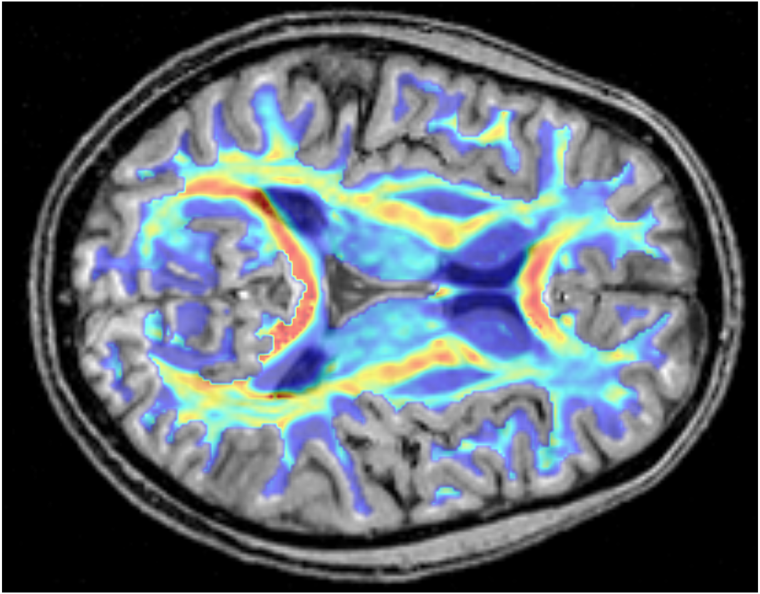

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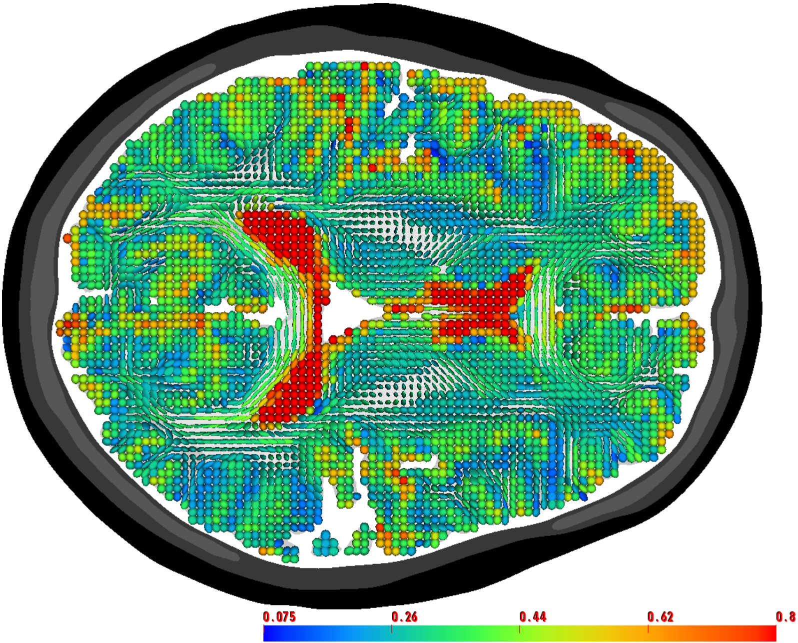

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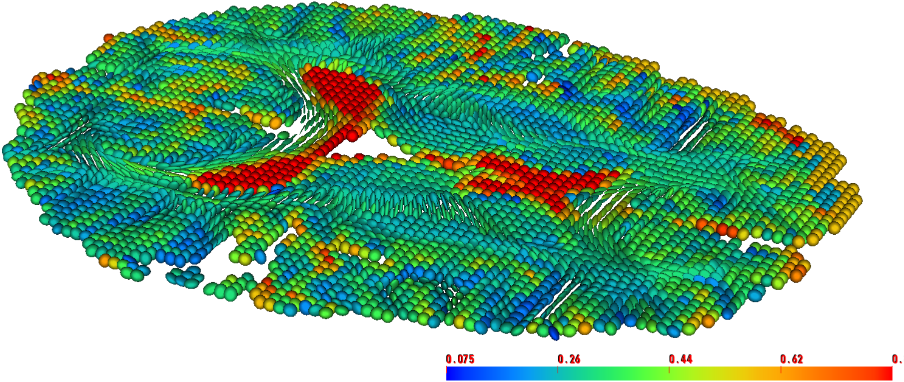
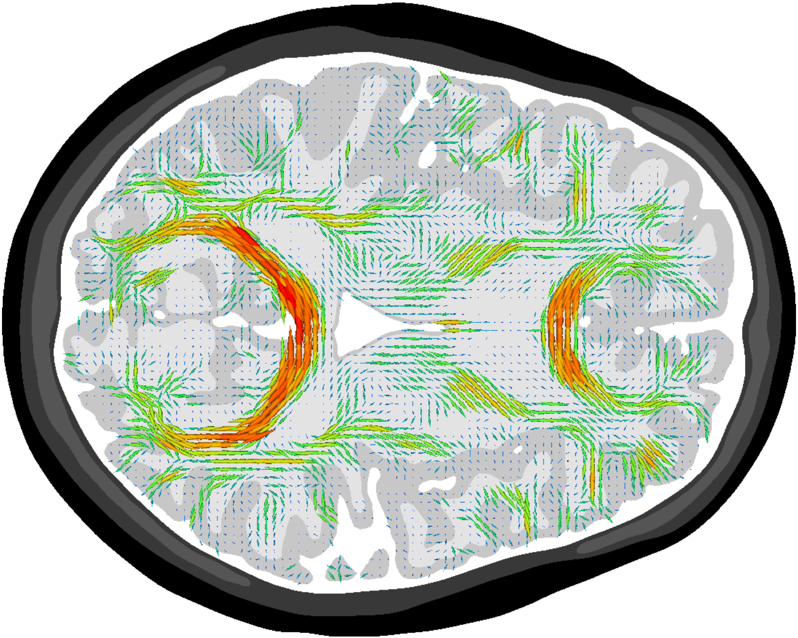


Part 1: MRI Processing, Diffusion Weighted MRI



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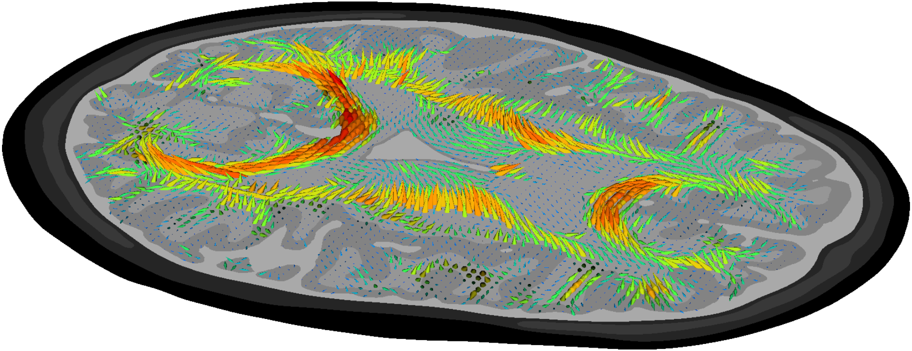

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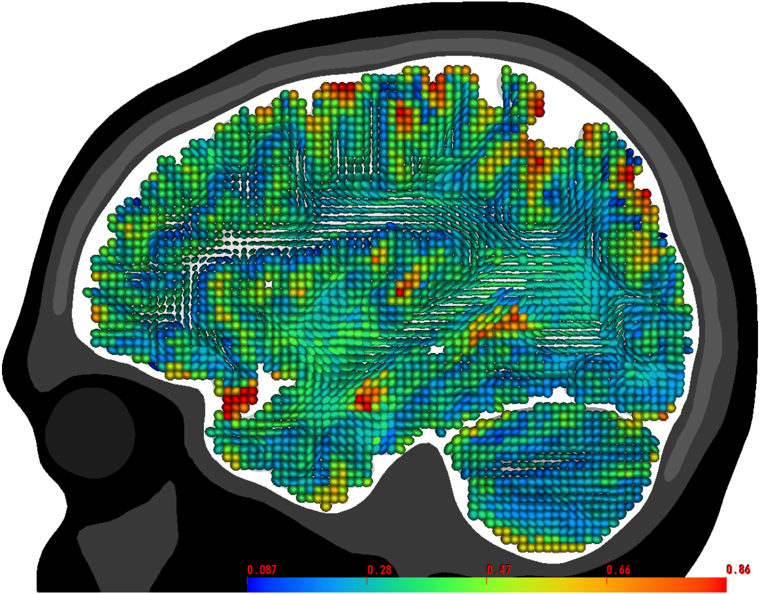

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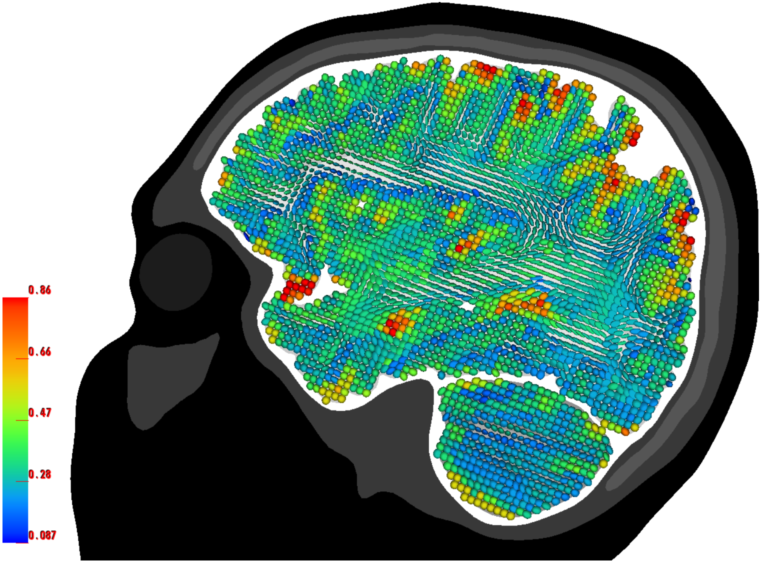

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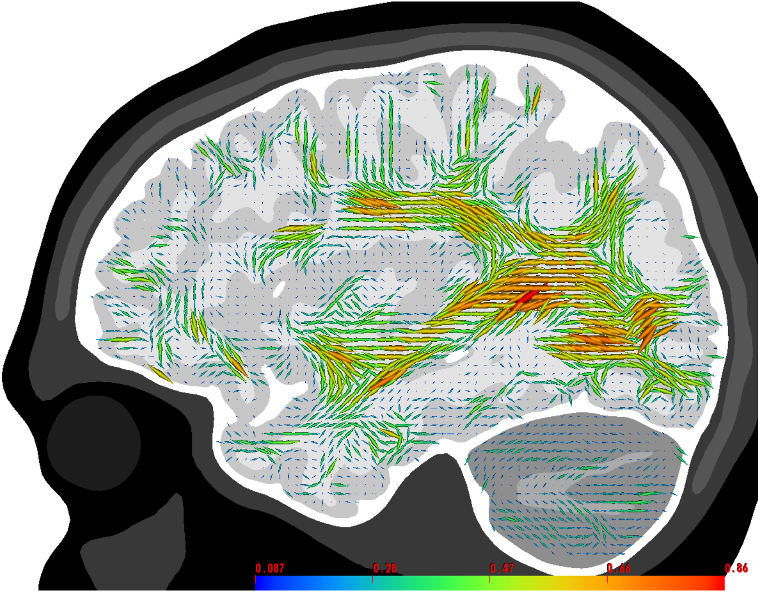

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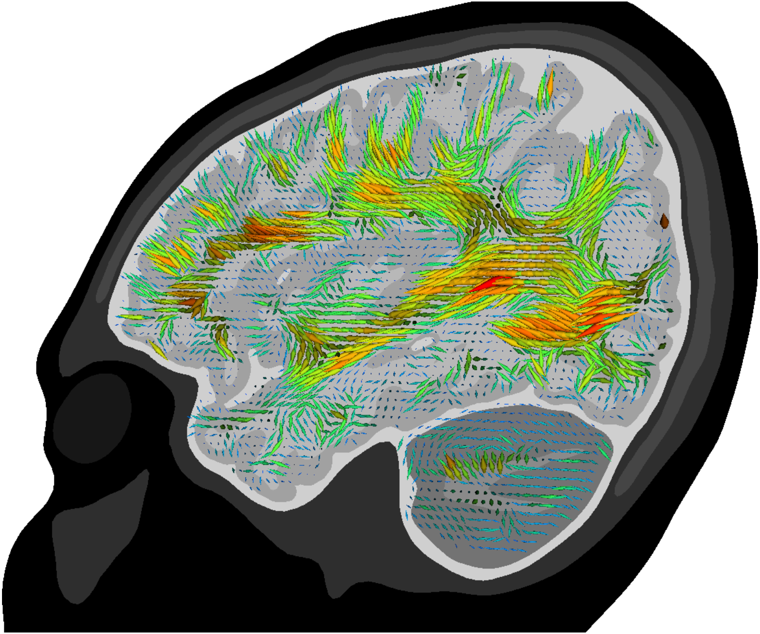
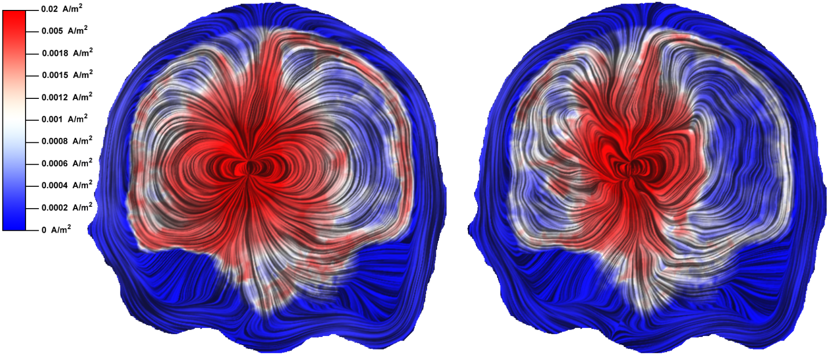
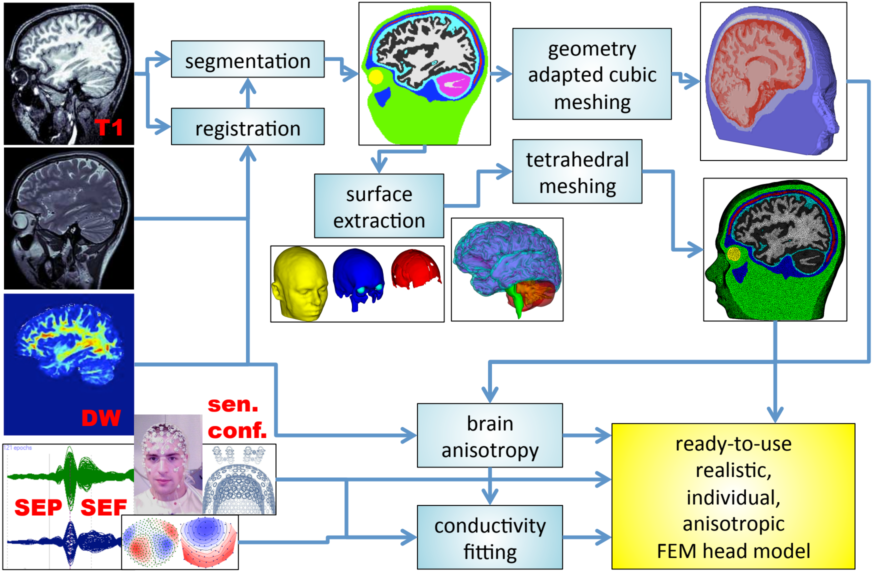


Part 1: MRI Processing, Diffusion Weighted MRI

Effects of white matter anisotropy on thalamic source:



Realistic, individual head modeling for bioelectromagnetic applications



segmentation

registration

geometry adapted cubic meshing

surface extraction

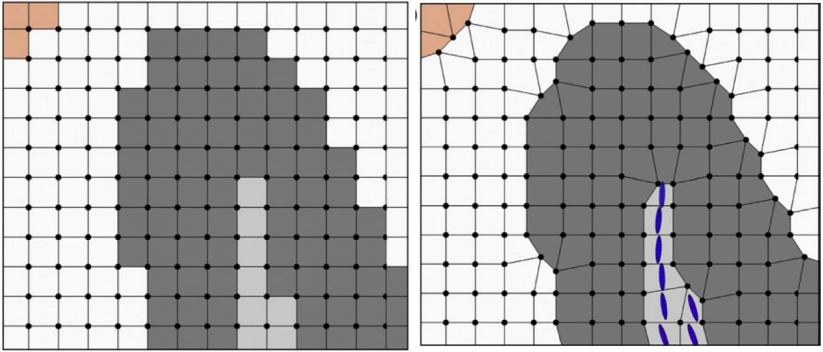
tetrahedral meshing

brain anisotropy

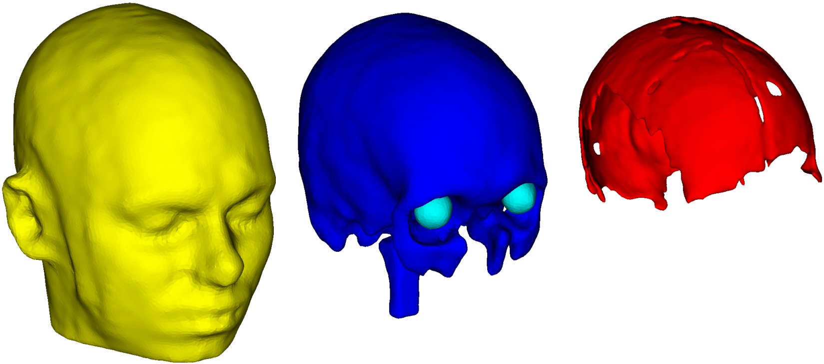
conductivity fitting

ready-to-use realistic, individual, anisotropic FEM head model

Part 2: FEM Meshing, the Cubic Way...



Part 2: FEM Meshing, the Tetrahedral Way...



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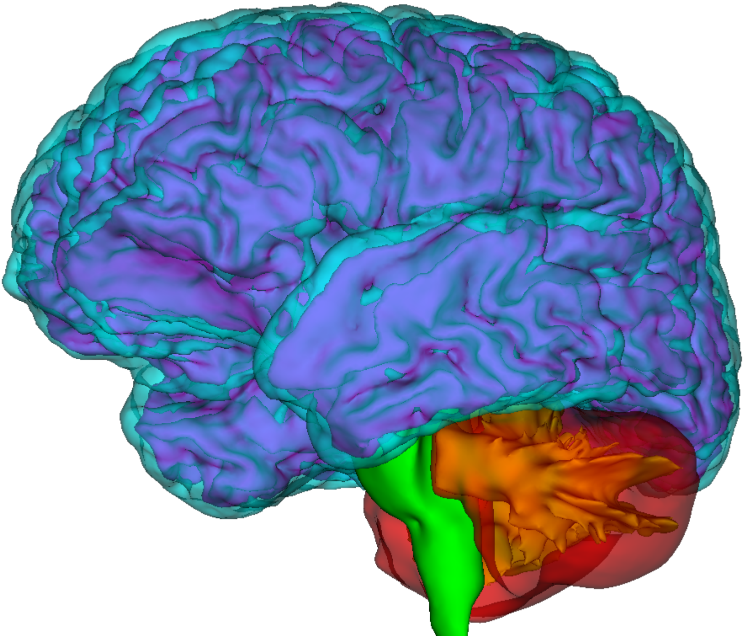

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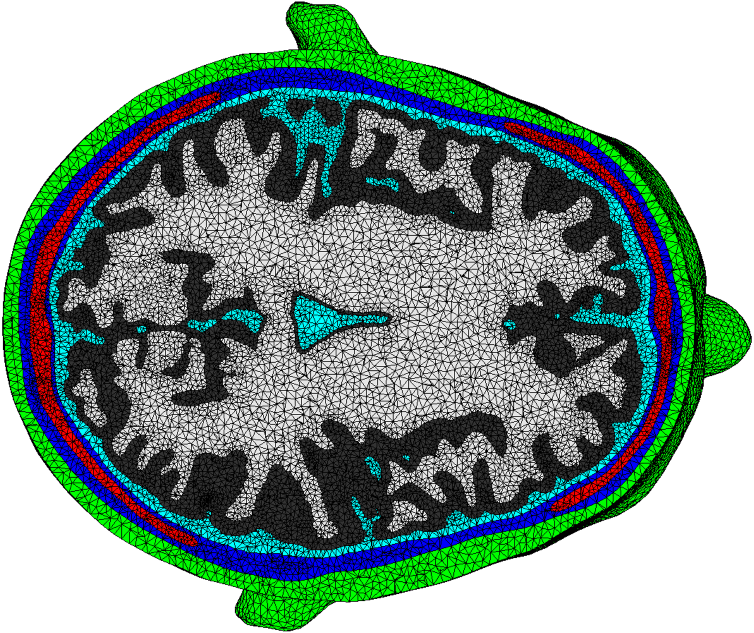

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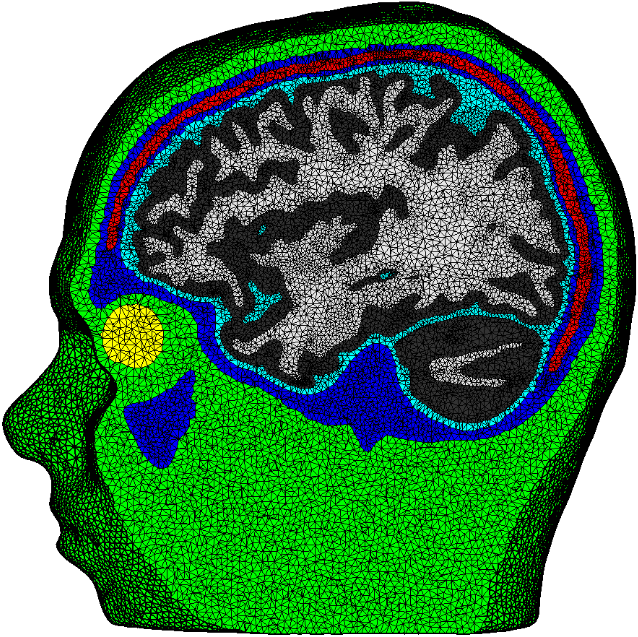
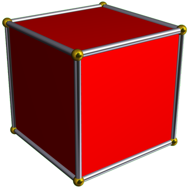
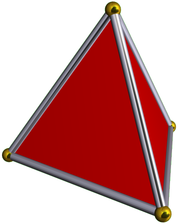


Part 2: FEM Meshing, Pros and Cons



Cubic meshing:

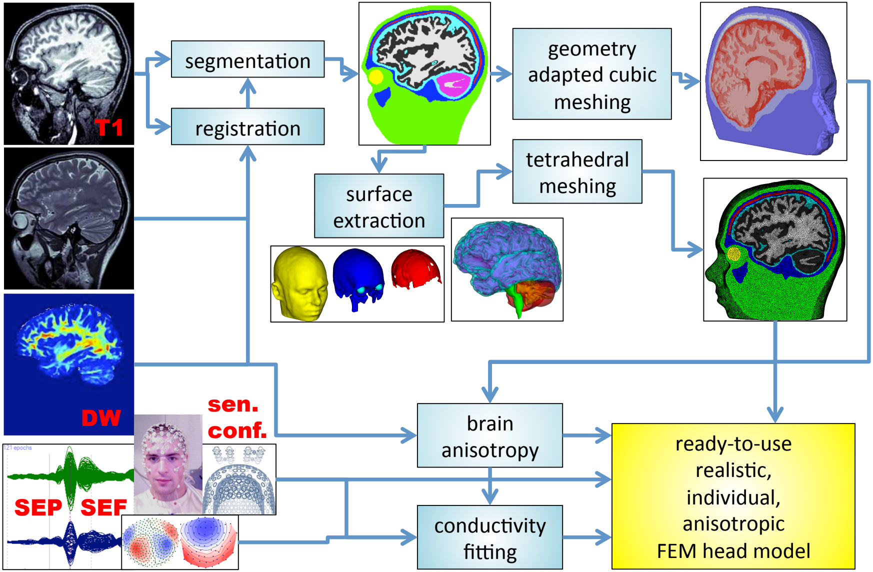
- ✓ Mesh generation is simple and fast.
- ! Surfaces are still “blocky”/“staircase like”.
- ! Mesh refinement is complicated; involves *hanging-nodes*.



Tetrahedral meshing:

- ✓ Possibility to model thin compartments.
- ✓ Better for complex geometries.
- ✓ Mesh refinement is simple.
- ! Mesh generation is complicated and time consuming.

Realistic, individual head modeling for bioelectromagnetic applications



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Part 3: Head Model Calibration

Problem: Tissue conductivity variations / uncertainty.

- Approximation error modeling / marginalization: Account for uncertainty explicitly (propagation of uncertainty, *Fehlerrechnung*).
- Model calibration: Reduce uncertainty by fitting model parameters to match known source and data.

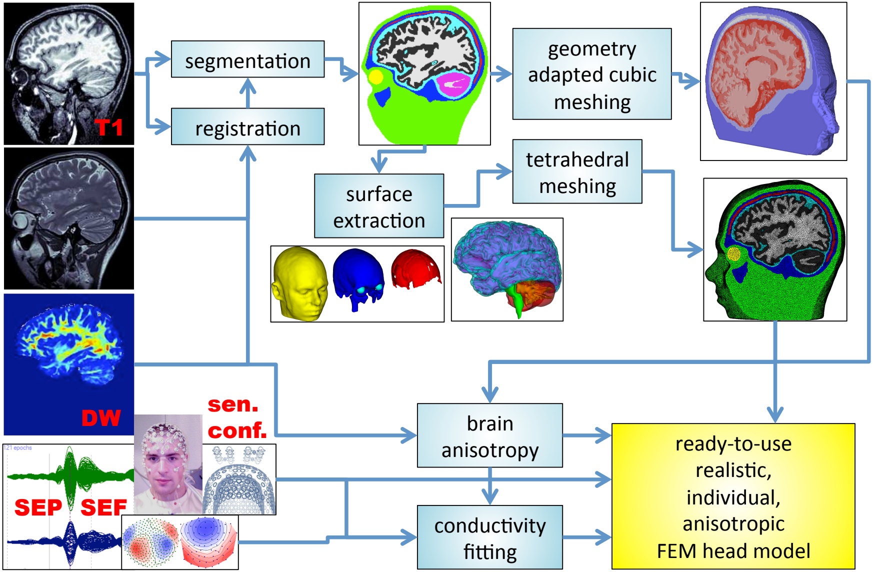
Problem for calibration: We don't really know the sources.

⇝ Use complementary characteristics of EEG and MEG?

modality	**sensitivity to** tissue geometry & conductivity	superficial sources	deep sources
EEG	high	tang: moderate radial: high	moderate
MEG	low	tang: very high radial: very low	low

- Low resolution conductivity estimation (LRCE) with SEP/SEF data.
- Work in progress: Bayesian approaches

Realistic, individual head modeling for bioelectromagnetic applications



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Modeling tDCS & TMS

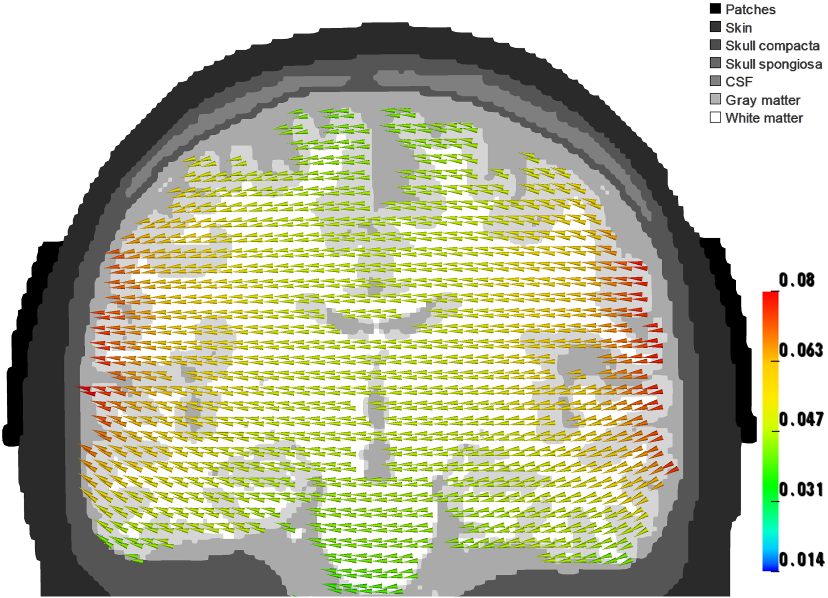
"Transcranial direct current stimulation" (tDCS) and "Transcranial Magnetic Stimulation" (TMS) $\Longrightarrow$ Means of non-invasive brain stimulation.

- Huge potential (alternative to invasive brain stimulation / hard medication) for therapeutic use in
  - Major depression
  - Chronic pain
  - Rehabilitation of aphasia and motor disability after stroke
  - Tinnitus
  - Parkinson's disease
  - Schizophrenia
- Neurophysiological effects are poorly understood.
- EEG/MEG source analysis and tDCS/TMS are linked via Helmholtz reciprocity.

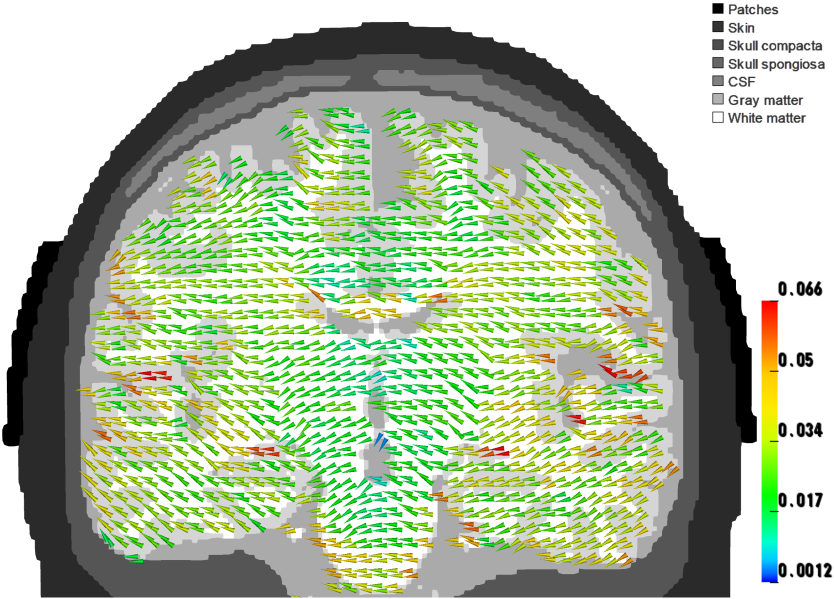
  $\Longrightarrow$ We can model it.

  $\Longrightarrow$ It helps to understand and visualize the effects of volume conduction and volume conductor modeling.

Modeling tDCS & TMS: Skin, skull, brain



Modeling tDCS & TMS: Skin, skull comp., skull spon., CSF, GM, WM (aniso)



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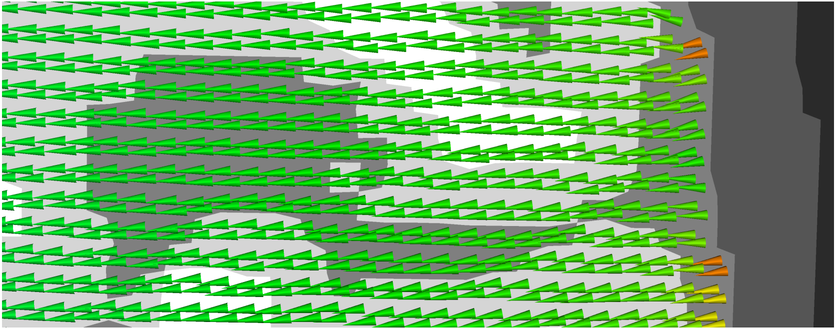

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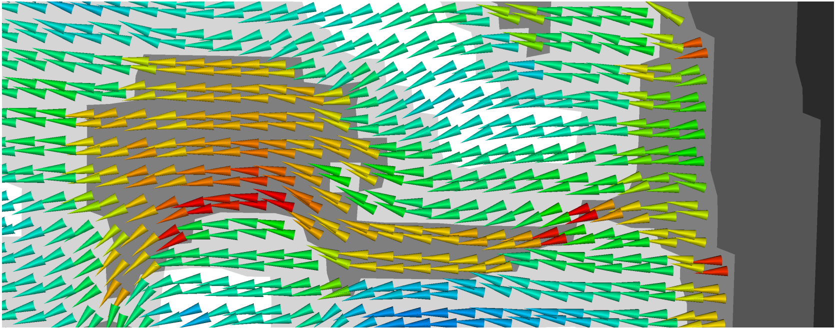

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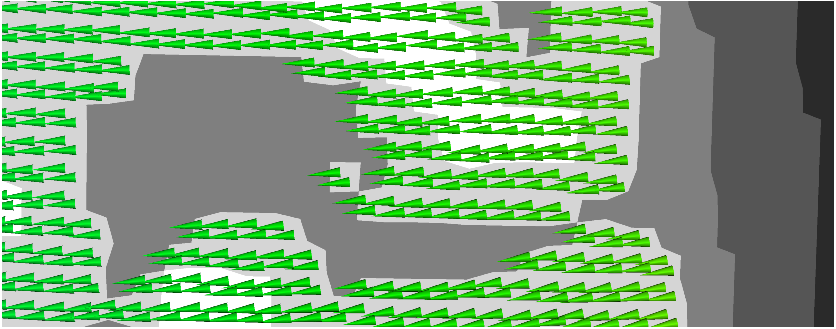

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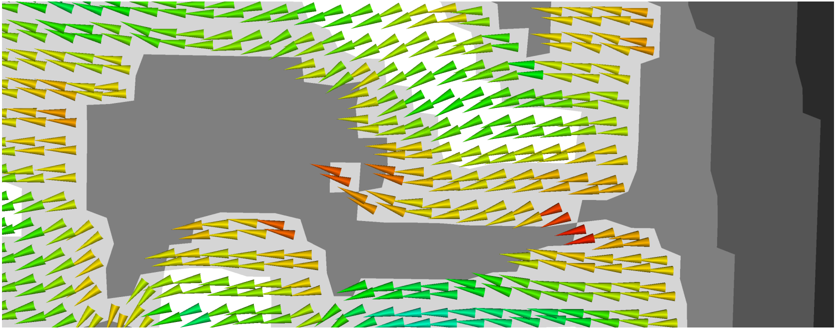


Outline

Introduction

Forward Computation

Head Model Generation

Data Analysis / Inverse Problem

Ways to use the EEG/MEG Data...

1. Analysis/preprocessing in sensor space: Infer information from indirect measurements.
2. Source reconstruction: Infer information about basic underlying activity from preprocessed sensor data.
3. Higher order analysis: Infer information about processes behind the reconstructed source activity.

Data Preprocessing

EEG/MEG measurements are a mixture of different signals:

- Signals from different brain activities: Task/stimulus related and periodic "background" activity in different frequency bands.
- Signals from muscular activity (eye blink, heart, swallowing).
- Signals from implants, piercings, make-up (e.g., magnetic nail polish)...
- Signals from measurement/stimulus devices.
- External fields like 50Hz fields or a helicopter flying over the building.

$\Longrightarrow$ Unmix by filtering, artifact removal, trial averaging, PCA, ICA, and activity specific detection algorithms (e.g., for automatic epileptic spike detection)

Then: Analysis in sensor space.
Examine event-related potentials/fields (ERP/ERF):

- Temporal latencies of components like N100, P200, ...
- Mismatch negativity (MMN)
- Group differences

But we want more!

Use the data to infer information about underlying brain activity in a more direct fashion.

Reminder:

Inverse Problem of EEG/MEG Source Reconstruction

Given

- measurements b of the electric potential u and/or of the normal-component of the magnetic field $\langle n, \mathbf{B} \rangle$ on the surface $\partial\Omega$;
- a volume-conductor-model of $\sigma(\vec{r})$;
- a source model $\mathcal{J} \subset \mathcal{D}'(\Omega, \mathbb{R}^3)$;

estimate the primary current $\vec{j}^{pri} \in \mathcal{J}$ (source) that is consistent with b and the neurophysiological constrains of brain activity.

Characteristic Features of Inverse Problems

Hadamard's definition of *well-posed* problems:

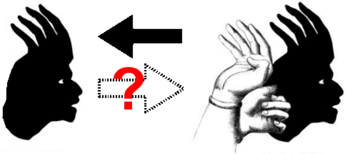
1. A solution exists.
2. The solution is unique.
3. The solution depends continuously on the data.

If one of the conditions does not hold, the problem is called ill-posed.

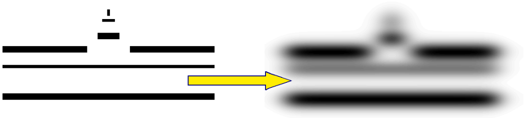
Inverse problems are typically ill-posed.

Jacques Salomon Hadamard
(1865-1963)

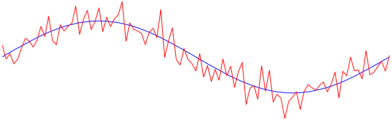
What About the Inverse Problem of EEG/MEG?



- (Presumably) under-determined



- Severely ill-conditioned



- Low SNRs

Summary: The problem is severely ill-posed.

Measurements alone are insufficient and unsuitable to determine solution.

$\Longrightarrow$ Incorporation of a-priori information about the solution in an explicit or implicit way:

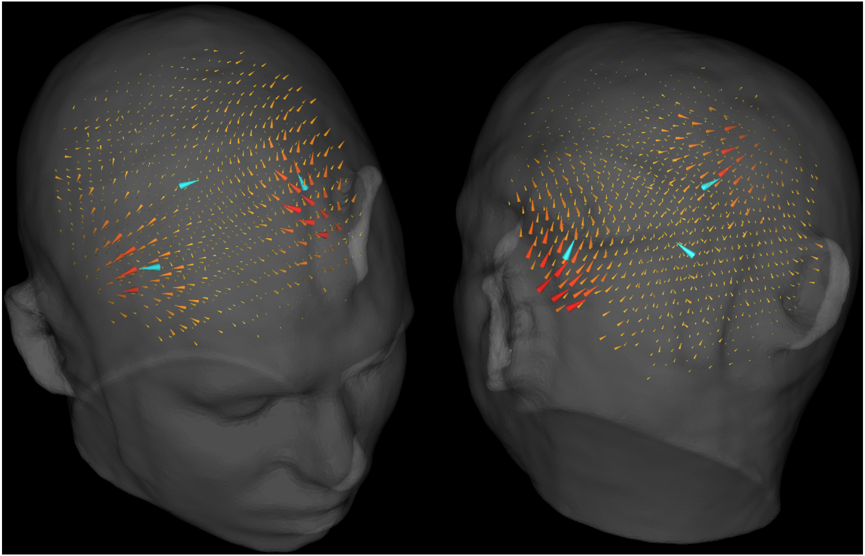
- Knowledge about general/specific brain activity?
- Integration of multimodal information (fMRI, DW-MRI, PET)?
- Mathematical formulation?
- Computational implementation?

$\Longrightarrow$ Variety of inverse methods for EEG/MEG

My focus: Hierarchical Bayesian inference for current density reconstruction (CDR).

Current Density Reconstruction

Discretization of an underlying continuous current distribution by large number of current dipoles with fixed location and orientation.



Current Density Reconstruction

Lead-field matrix concept:

- $L \in \mathbb{R}^{m \times n}$; columns represent measurements at m sensors caused by the n single current dipoles.
- Linear combination of the dipoles is represented by source vector $s \in \mathbb{R}^n$.
- Measurements $b \in \mathbb{R}^m$ caused by s can then be calculated via:

$$b = L\, s$$

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Infer s from b? Apparently ill-posed problem:

- $n \gg m. \implies b = L\,s$ is under-determined.
- L inherits the bad condition of the continuous problem.
- Noise $\mathcal{E} \sim \mathcal{N}(0, \sigma^2 \mathrm{Id})$ is added to signal.

Common approaches:

- Variational regularization
- (Hierarchical) Bayesian inference
- Spatial scanning methods/beamforming

We still want more! Dynamic causal modeling (DCM)

Christan Himpe oder Mario Ohlberger fragen.

Thank you for your attention!

Software used by our group:

- Registration: FSL,FAIR;
- Segmentation: FSL, CURRY;
- FEM Meshing: Tetgen, vgrid, iso2mesh;
- FEM Computation: SimBio;
- Data Preprocessing: CURRY, BESA;
- Inverse computation: Matlab;
- Volume Visualization: SCIRun;
- Everything else & software integration: Matlab;