Learning Goals

- introduction to perfusion imaging
  - basic MRI principles -> Physics of Imaging Techniques

- Goals:
  1. How does the technique work?
  2. What kind of images do we receive?
  3. Where is this applied to?

- Slides of the lectures at
  https://www.umm.uni-heidelberg.de/inst/cbtm/ckm/lehre/index.html
Reading

Content

- Principle of Diffusion
- Apparent Diffusion Coefficient (ADC)
- Diffusion Tensor Imaging (DTI)
- Intravoxel Incoherent Motion (IVIM)
- Diffusion Kurtosis Imaging (DKI)

Principle of Diffusion

- Diffusion: Random movement of molecules/atoms due to Brownian motion (temperature)

- Diffusion coefficient D:
  - Measure for amount of movement
  - $D_{\text{water}} = 10^{-3} \text{ mm}^2/\text{s}$  $\rightarrow$ 9 µm “wandering” in 40 ms

- Diffusion in tissue is complex and holds information about tissue structure and function

  Diagnostic value
Free Diffusion

• 1st Fick’s Law
  \[ J = -D \nabla C \]
  
  \( J \) = diffusion flux [mol/m\(^2\)/s]
  \( D \) = diffusion constant [m\(^2\)/s]
  \( C \) = concentration [mol/m\(^3\)]

• 2nd Fick’s Law (Diffusion)
  \[ \frac{\partial C}{\partial t} = \nabla (D \nabla C) \]

• mean square deviation
  \[ \langle x^2 \rangle = 6Dt \]

Principle of DWI by MRI

after 90° pulse

Phase in the rotating coordinate system is constant
Principle of DWI by MRI

1. Gradient → Spins acquire phase relative to the coordinate system

2. Gradient → Phase rephased → similar to gradient echo
Principle of DWI by MRI

Spin system with diffusion

1. Gradient → Spins acquire phase relative to rot. coordinate system

Diffusion occurs in between gradient playout → Spins change location
Principle of DWI by MRI

Spin system with diffusion

2. Gradient → Spins not completely rephased → Signal loss

Apparent Diffusion Coefficient (ADC) Model

• Gradients G make rotation frequency dependend on spatial position
  \[ \omega = \gamma \cdot (B + G \cdot x) \]
• If spins change position (diffusion) first and second gradient have different effects
  → Signal attenuation/loss
Bloch Equations with Diffusion

\[ \frac{\partial \vec{M}}{\partial t} = \gamma \vec{M} \times \vec{B} + D \Delta \vec{M} \]  
(without relaxation)

mit \( \vec{B}(\vec{r}, t) = (0, 0, \vec{G}(t)\vec{r} + B_0)^T \) und \( M_+ = M_x + iM_y \)

\[ \frac{\partial M_+}{\partial t} = -i\gamma G(t)\vec{r}M_+ + D \Delta M_+ \]  
(isotrop and homogen.)

Equation of transport

\[ M_+ = A(t)e^{-i\vec{r} \cdot \int \frac{\vec{G}(t)\vec{r}}{\vec{k}(t)} dt} \]

\[ A(t) = A(0)e^{-D \int_0^{TE} k^2(t) dt} \]

mit \( b = \int_0^{TE} k^2(t) dt \)

\[ S = S_0 e^{-bD} \Rightarrow \ln \left( \frac{S}{S_0} \right) = -bD \]
Signal loss and b-value

B-value a sequence parameter

\[ b = \int_0^{TE} \tilde{k}^2(t) dt \]

Integral divided into 3 parts

Strength of diffusion weighting:

\[ b = \gamma^2 G^2 \delta^2 (\Delta - \delta / 3) \]

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DWI Imaging Sequence

- Spin-echo sequence (a)
- Stimulated-echo sequence (b)
- Single-shot spin-echo EPI sequence (c)
- Single-shot FSE/TSE sequence (d)

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DWI Imaging Sequence - EPI

Friedli et al. Scientific Reports volume 6, 30088 (2016)
• Gradients $G$ make rotation frequency depend on spatial position
  \[
  \omega = \gamma \cdot (B + G \cdot x)
  \]
• If spins change position (diffusion) first and second gradient have different effects

### Apparent Diffusion Coefficient (ADC) Model

- \textit{\textbf{b-value}} $= b(G, \delta, \Delta)$ determines impact of signal loss due to diffusion
- assuming equal diffusion in all directions (isotropic)

\[
S = S_0 \cdot e^{-b \cdot \text{ADC}}
\]

\[
\ln(S/S_0) = -b \cdot \text{ADC}
\]
Anisotropic Diffusion

White Matter

- Consists of highly directional neuron fibres (anisotropic)

White Matter

- Diffusion along fibres easier than across myelin sheath
Diffusion Tensor Imaging (DTI)

**Diffusion Tensor**

\[
\begin{pmatrix}
D_x & 0 & 0 \\
0 & D_y & 0 \\
0 & 0 & D_z \\
\end{pmatrix}
\]

\[\text{ADC} = \frac{1}{3} (D_x + D_y + D_z)\]

Fractional Anisotropy (FA):
- Amount of anisotropy
- Main direction
- \(0 \leq FA \leq 1\)

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Diffusion Tensor Model

**DTI equation**
\[
\langle x^2 \rangle = \bar{g}^T D \bar{g}
\]

**Isotropic diffusion**
\[
D = \begin{pmatrix}
1 & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & 1
\end{pmatrix}
\]

**Anisotropic diffusion**
\[
D = \begin{pmatrix}
3 & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & 1
\end{pmatrix}
\]

coordinate system, Eigen system

Diffusions - Tensor Model

**In general:**

world coordinate system \(
\neq
\)

Eigensystem
Diffusions - Tensor Modell

- Eigen system

\[ \mathbf{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} = \begin{pmatrix} V_{1x} & V_{1y} & V_{1z} \\ V_{2x} & V_{2y} & V_{2z} \\ V_{3x} & V_{3y} & V_{3z} \end{pmatrix} \cdot \begin{pmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \end{pmatrix} \cdot \begin{pmatrix} V_{1x} & V_{2x} & V_{3x} \\ V_{1y} & V_{2y} & V_{3y} \\ V_{1z} & V_{2z} & V_{3z} \end{pmatrix} \]

- major Eigen value: \( \lambda_1 \)
- major Eigen vector: \([V_1, V_2, V_3]\)

Diffusions – Tensor Modell

rotation matrix

\[ A \rightarrow \tilde{g} = A \tilde{g} \rightarrow D' = A^T DA \]

\[ D' = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} \]

Eigenvectors \( \lambda_1, \lambda_2, \lambda_3 \) invariant to rotation

- derived quantities (z.B. Trace, fractional anisotropy (FA))

\[ ADC = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \]

\[ FA = \frac{\sqrt{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}}{\sqrt{6\bar{\lambda}}} \]
Fractional anisotropy

FA

Colormap

DTI Fibretracking

- Investigation of main diffusion axis of neighbouring voxels
- Similar directions can indicate fibre structures

**Fiber tracking (naive approach)**

- Fiber tracking using the given 3D vector field
- Start at (1,1)
- Discrete iteration of the fibers voxel by voxel

> too simple, not working

**FACT Algorithmus**

- FACT = fibre assignment by continuous tracking
- Start at (1.5,1.5)
- Continuous iteration
- Stopping criteria
  - Border of image reached
  - FA < 0.2 ~ FA of grey matter
  - Curvature too big

Rong et al., _JMRM 42:1123-1127_ (1999)
Euler und Runge-Kutta Algorithmen

Given: discrete stationary image, vector field / Tensor field

- Fiber track trajectories represented as 3D space curve
- Vector \( r(s) \) parametrised by the arc length \( s \)
- Evolution of \( r(s) \) by Frenet equation \( dr(r(s)) = t(s) \)
- \( T(s) \) identified by the largest eigenvector \( \epsilon(r(s)) \)

Associated with the largest eigenvalue of \( D \)

\[
\mathbf{r}(s_1) \sim \mathbf{r}(s_0) + \alpha \mathbf{\epsilon}_1(\mathbf{r}(s_0))
\]

Basser et al., MRM 44:625-632 (2000)

Euler / Runge-Kutta algorithm

Comparison of Fiber Tracking approaches

Figure 22.2: Illustration of DTI tractography using different fiber integration methods. FACT (Mori et al., 1999) and Euler (EUL) are piecewise linear methods. FACT changes the direction at the junctions between voxels, whereas Euler uses a fixed step size. The Runge-Kutta (RK) method is also a stepwise integration method that yields a non-linear and more accurate solution to curved trajectories. In general, the RK methods yield smoother solutions, although all approaches generate similar solutions. Smoother trajectories can also be generated with Euler using smaller step sizes.
Fiber tracking

In Vivo DTI  Post mortem Atlas

Stieltjes et al, Neuroimage, 2001

Corpus Callosum
Fornix

Fiber tracks in Tumors

Schlüter et al., CURAC 2005

Capsula interna anterior
Risk assessment of structures?

Problems of Fiber Tracking

- Fiberkissing/Crossing
- Fibertracking: choice of parameters

Stieltjes B et al., Neuroimage, 2001
Noise & Accuracy of Fiber tracks

- Image data generally noisy
- Errors of noise add up
- Smoothing reduces noise but blurs the image

(Basser et al., MRM 44:625-632 (2000))

Fiber Tractography: Seeding points

- Seed location
  - Regional seed methods
    To extract a specific pathway or mapping tracts from a specific region
  - Whole-brain seed methods
    To generate nearly all possible pathways
    Higher redundancy in the pathways
Qunatification in DTI

- Histogram analysis
- Voxel based analysis (VBA)
- ROI analysis

ROI-Analyse (1)

+ meaningful, if it is known where the pathology is to be expected
+ can be used for well delimited structures
+ simple, transparent methodology

- a lot of work for larger patient groups/cohorts
- structures are not always easy to define
- poor reproducibility, inter- and intrareader variability
ROI-Analyse (2)

- $\text{FA} = 0.76$
- $\text{FA} = 0.64$

Semi-automatic ROI-Analysis

- Multivariate Gaussian
- Equally distributed linear mixture
- Multivariate Gaussian

Schlüter et al., IEEE 2004
fiber density at CC (1)

Schlüter et al., IEEE 2004

fiber density in CC (2)

Stieltjes et al., ECR 2005
Intravoxel Incoherent Motion (IVIM) Model

Water moves inside capillary bed (perfusion)

Randomly oriented capillaries

Same effect on the MRI signal as diffusion in the tissue

- Two compartments: inside and outside vascular system (both free diffusion)
- Resulting motion referred to as pseudo-diffusion ($D^* > \text{ADC}$)

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Effect primarily present for low $b$-values
IVIM (Intravoxel Incoherent Motion) theory

- perfusion influences the DWI signal decay
- IVIM: Perfusion can be described as a pseudo diffusion process
- under following conditions:
  - several capillaries in a voxel
  - random orientation of the capillaries
  - long diffusion time compared to the travel time in a capillary segment

IVIM in the past

- The IVIM theory was first introduced in 1988 by Le Bihan
- Studies were focused on the brain and the IVIM effect was minimal (low perfusion fraction f≈5 %)
- The origin of the biexponential signal decay was discussed controversially
- “Diffusion, Perfusion=Confusion?”
IVIM in the present

The question of the optimal b-value distribution is not answered yet.

IVIM technique can help differentiating lesions from benign tissue in the abdomen, however.

IVIM perfusion parameters are not in agreement with parameters obtained from other imaging techniques (DCE, Ultrasound, CT).

IVIM equation

- both the diffusion and the pseudodiffusion due to perfusion contribute to the signal attenuation

\[
\frac{S}{S_0} = (1 - f)e^{-bD} + fe^{-bD^*}
\]

D: Diffusion constant
D*: Pseudodiffusion coefficient due to perfusion
f: Perfusion fraction
IVIM in the abdomen

Blood Suppression

Lemke et al., submitted. in MRM

IVIM in pancreas carcinoma

Healthy pancreas:

Patient with pancreas carcinoma:

Lemke et al., Invest. Radiology, 2009
Errors due to bad choice of b-values

b-values too low:
- Curve “fits well to data”, but only because of extra degree of freedom
- No reasonable signal course
- Fit parameters strongly deviate from ground truth

SNR for high b-values not sufficient:
- No reasonable signal course (noise corrupts fit)
- Fit parameters strongly deviate from ground truth

Optimization of the b-value distribution

- IVIM parameters of the liver, kidney, brain were used
- Rician noise was added to the simulated signal
- Process was repeated $N=5000$ times and $\sigma$ was calculated
  $$\sigma = \sqrt{\frac{\sum (f - \bar{f})^2}{f} + \frac{\sum (D - \bar{D})^2}{D} + \frac{\sum (D' - \bar{D}')^2}{D'}}$$
  
  - serial optimization approach starting with 3 b-values ($b=0, 40, 1000$ s/mm$^2$)
  - distribution with minimal $\sigma$ was chosen as the new optimal distribution and iterated consecutively up to 100 b-values
Comparison to recently used b-value distributions (in vivo)

<table>
<thead>
<tr>
<th>b=0 s/mm²</th>
<th>D</th>
<th>f</th>
<th>D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>![image]</td>
<td>![image]</td>
<td>![image]</td>
<td>![image]</td>
</tr>
</tbody>
</table>

- In agreement with the simulations, the D*-map suffers from low image quality due to a high variance.
- However, the image quality of the D-, f-, and D*-map calculated from the distribution $b_{\text{sum}}$ show an improved image quality compared to the corresponding maps calculated from $b_{\text{lit}}$.

Diffusion Kurtosis Imaging (DKI)

- Standard diffusion weighted imaging (DWI) assume that diffusion water molecules follow a Gaussian (normal) distribution.
- True for pure liquids and gels.
- Incorrect for complex biological tissues with cell membranes that create compartments and barriers to diffusion.
- Non-Gaussian behavior becomes more noticeable when stronger gradients (higher $b$-values) and longer echo times are used.
Diffusion Kurtosis Imaging (DKI)

- Non-Gaussian behavior becomes more noticeable when stronger gradients (higher $b$-values) and longer echo times are used

- Dimensionless parameter $K$, is a long recognized statistical metric for quantifying the shape of a probability distribution
  - Gaussian distribution has $K = 0$
  - More "peaked" and with less weight on their "shoulders" typically have a positive kurtosis ($K > 0$)

![Diagram showing Gaussian and positive kurtosis distributions]

Diffusion Kurtosis Imaging (DKI)

- Comparison of $b$-value range for different DWI measurements

![Graph showing signal attenuation vs. b-value with "Traditional" ADC and Kurtosis effect]
Diffusion Kurtosis Imaging (DKI)

- Imaging procedure
  - similar to DWI, but employ higher b-values $\geq 1500$ s/mm$^2$
  - SNR an issue at high b-values -> averaging
  - increased TEs needed to run diffusion gradients

- Data processing

\[ S = S_0 e^{-bD} + \frac{b^2D^2K}{6} \]

Clinical Application of ADC Model

Stroke
DWI of pancreas – healthy volunteer

\[ b = 0 \text{ s/mm}^2 \quad b = 400 \text{ s/mm}^2 \]

\[ \text{ADC} = 1650 \mu\text{m}^2/\text{s} \]

DWI of patient with pancreas ca
IVIM Application - Brain

**Stroke**

**Cancer: Glioblastoma**

Applications of IVIM - Body

- **Pancreatitis**
- **Prostate**

**Registration**

**Segmentation**
DKI Application - Brain

- traumatic brain injury
- Grade 2 astrocytoma (AS 2), grade 3 astrocytoma (AS 3), and glioblastoma multiforme (GBM)

Steven et al. Am J Roentgen 2014

DKI Application - Body

- Prostate
- bladder CA

Summary

- DWI measures water movement in tissue by MRI
  - change in signal due to uncomplete rephasing of the moving spins
  - structural restrictions reflected by higher signal loss
  - properties of DW gradients given by b-value ("diffusion strength")
- different models to evaluate the diffusion
  - ADC
  - IVIM
  - Kurtosis
- choice of b-values must match quantification
- DTI, diffusion weighted imaging combined with weighting of spatial direction
  - allows to tract structures
- broad range of clinical applications