Diffusion & Perfusion Weighted Imaging

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Introduction

This talk will shed some first light on the two imaging concepts *diffusion weighted imaging* (DWI) and *perfusion weighted imaging* (PWI). On the one side one may criticize that for the lecture time given, this will definitely be an incredible or even impossible task: To give sufficient credit to both of these importantant imaging concepts. On the other side one could say: 'Come on, let's talk about the basic ideas of both and why they often appear to be like brothers or sisters. Yet, they are two quite different aspects.' — And even until recently, the ISMRM society had a single study group called the *diffusion* ***and*** *perfusion study group ....*
Well, this syllabus belongs to a talk supporting the 'other side' ☺.

Diffusion

The Basic Physical Effect ...

Actually, 'diffusion' is a physical effect that is almost pervasive – yet, we just do not realize it, do not think about it or we simply do not know it. Anyone who ever in his or her life made a tea, for instance, encountered diffusion. After brewing up, 'tea' comes into existence around the leaves. Then these cords of tea turn up in the surrounding pure water and after a while of steeping there is 'just tea'. Observing this fascinating effect a bit more from a physical point of view, we recognize that with the steeping of tea leaves two phases become present, pure water and tea, which mix themselves 'automatically' within the time. The cause or reason for this is diffusion – also known as Brownian motion of (water) molecules.

What we, i.e. human beings, and other creatures perceive as temperature is in the factual world of physics nothing else but motion, rotation and vibration of atoms and molecules, observed on a microscopic scale. The higher the temperature is the faster the atoms and molecules move, rotate and vibrate in gases, liquids and even solids. But, let's keep the gases and solids aside here and stick to water and watery human tissue.

In our previous tea example – and this tea is really hot – the water molecules are in very fast motion (besides rotation and vibration). As a consequence both phases, still pure water and new existing tea, interfuse more and more over the time until there is a uniform distribution of 'water-tea', which is the final tea we want.

But why does it take a while? Admittedly, the molecules are quite small, but they are also very fast ... and close together. Thus, they constantly bump

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into each other, about 10^{21} times a second, and so they constantly change their direction and speed after these collisions. A closer look at a single molecule reveals that it therefore performs a *random walk* of independent radom steps over time, e.g. as shown in Fig. 1. Such trajectories are not deterministic due to the stochastic nature of the diffusion process.

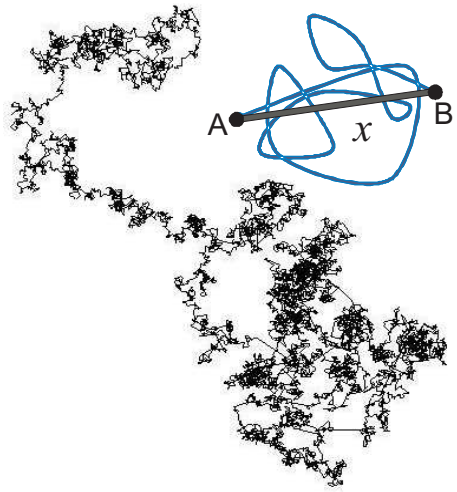

Figure 1: *Example for the stochastic trajectory of a water molecule. Statistics can predict the average net displacement.*

The mean displacement, however, can be calculated, which is the average net distance of the particles from their origin. Water can diffuse freely and isotropically in big pools, and approximately in a cup of tea (*free isotropic diffusion*). In the case of this free isotropic diffusion the Einstein-Smoluchowski relation quantifies the average net displacement $\overline{x}$ after the expired time Δ (Fig. 1):

$$\overline{x} = \sqrt{2\,n\,D\,\Delta} \quad , \tag{1}$$

with $n = 1, 2, 3$ being the number of spatial dimensions. Δ is usually called the *diffusion time*. With increasing diffusion time Δ the mean displacement $\overline{x}$ increases.

The proportionality factor D is the *diffusion coefficient*. It is a measure for the mobility of the diffusing molecules in the medium and it depends on the temperature. In MRI, its unit is usually $^{\mathrm{mm}^2}/_{\mathrm{ms}}$, less frequently $^{\mathrm{m}^2}/_{\mathrm{s}}$. A few values for water (H_2O) and cerebral gray matter (GM) at hand: $D_{H_2O}(20°\mathrm{C}) = 0.002\,^{\mathrm{mm}^2}/_{\mathrm{ms}}$, $D_{H_2O}(37°\mathrm{C}) = 0.003\,^{\mathrm{mm}^2}/_{\mathrm{ms}}$, $D_{\mathrm{GM}}(37°\mathrm{C}) = 0.0008\,^{\mathrm{mm}^2}/_{\mathrm{ms}}$.

In tissue, water molecules basically behave the same way, they are in permanent diffusional motion due to their thermal energy. But is it free diffusion? No! The existence of compartments such as extracellular spaces, intracellular spaces, intravascular spaces and cell membranes restrict diffusion (*restricted diffusion*). Thus, the characteristics of diffusional motion in tissue may considerably differ from the characteristics of diffusional motion in pure liquid.

For very short diffusion times tissue diffusion may still be regarded as *quasi free*, however, for longer diffusion times more and more molecules will collide with barriers: Then diffusion is not free, Eq. (1) is not valid anymore.

Diffusion in biological tissue is not only restricted but also often anisotropic, i.e. its magnitude depends on the direction. Typical examples are orientated micro structures like fiber bundles in cerebral white matter (WM). Diffusion parallel to such a fiber bundle is almost free, whereas diffusion perpendicular to the fiber bundle is considerably restricted due to the confinement of the fibers' membranes: $D_{\parallel\,\mathrm{WM}}(37°\mathrm{C}) = 0.002\,^{\mathrm{mm}^2}/_{\mathrm{ms}}$, $D_{\perp\,\mathrm{WM}}(37°\mathrm{C}) = 0.0002\,^{\mathrm{mm}^2}/_{\mathrm{ms}}$. The most common mathematical model in MRI to describe this effect is the *diffusion tensor*.

As we have seen, diffusion depends on restrictions, anisotropy, diffusion times, and a multitude of other factors that have not been mentioned, yet. Thus, any experiment will measure an average diffusion effect, since diffusion takes place on a microscopic scale but the voxel size of MRI diffusion measurements is on the order of 1mm or 2mm. Hence, any measured diffusion coefficient is usually called an *apparent diffusion coefficient ADC*, implying that a multitude of

factors influences the measured parameter in a voxel, Fig. 2. This challenge is at the same time also a major reason for the fascination that users perceive in diffusion imaging methods: *Diffusion is a very sensitive marker for morphological and functional (metabolic) changes on the cellular level. It gives a deep insight into tissue micro structure.*

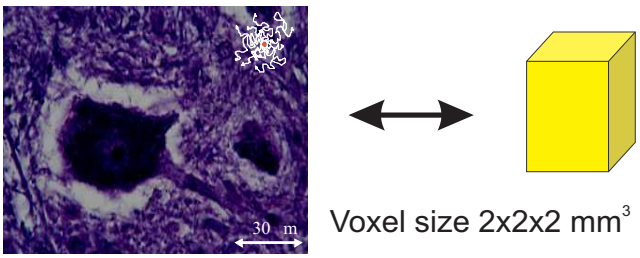

Figure 2: *Experiments assess an apparent diffusion coefficient (ADC).*

How to Image it ...

MRI images the presence of hydrogen nuclei (protons) in the tissue. Thus, MR imaging methods based on diffusion weighting will be particularly sensitive to the diffusion of water molecules in the biological tissue. — How does it work?

So called *diffusion imaging pulse sequences* use *motion sensitizing gradients* to produce signal attenuation which is directly related to the present diffusion coefficient in the tissue. The most popular diffusion preparation experiment is the pulsed gradient spin echo (PGSE) or so called Stejskal-Tanner sequence, Fig. 3. The PGSE sequence consists of a conventional spin echo with two symmetric, monopolar gradients added. Without motion, the phase shift introduced by each gradient is the same, but with opposite sign. Thus, they compensate each other. With motion present, a net phase shift results that is proportional to the speed of the spin. This effect is actually also exploited in phase contrast based flow measurement techniques. Whereas there a coherent macroscopic flow is imaged, which results in a net phase shift of the total magnetization vector, the stochastic nature of diffusion causes different phase shifts for each spin. A diffusion correlated dephasing of the magnetization results, i.e. signal attenuation. The signal attenuation is therefore directly diffusion dependent. The dephasing caused by the diffusion is irreversible.

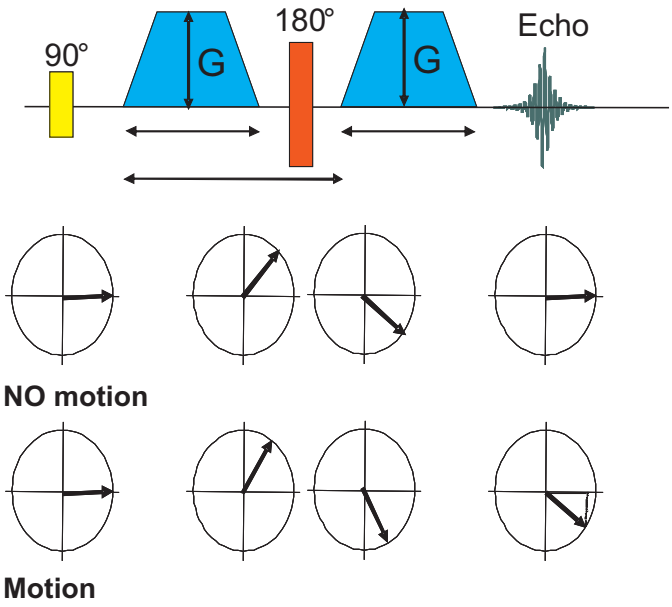

Figure 3: *The PGSE sequence. Motion sensitzing gradients produce a phase shift for moving spins, which results in a net signal attenuation due to the stochastic nature of diffusional motion (diffusion weighting).*

The diffusional signal attenuation obeys a mono-exponential decay in the simplest cases:

$$\frac{SI(b)}{SI_0} = \exp(-b \cdot D) \quad , \tag{2}$$

where D signifies the diffusion coefficient, $S(b)$ the signal measured with diffusion weighting gradients turned on and S_0 the signal without any diffusion weighting gradients.

The new parameter b, called the *b-factor*, depicts the quantitative diffusion sensitivity of a DWI sequence in MRI. Its untis are the inverse of D, thus $^{\mathrm{ms}}/_{\mathrm{mm}^2}$.

For a PGSE sequence with the common simplification of ideal, rectangular diffusion gradient pulses of constant amplitude g and duration δ and with the temporal separation of Δ the resulting b-factor is:

$$b = \gamma^2 g^2 \delta^2 \left(\Delta - \frac{\delta}{3}\right) \quad , \tag{3}$$

where γ is the proton gyromagnetic ratio.

Any gradient in MRI, and therefore also any diffusion weighting gradient, posesses a defined direction in the coordinate system. As a result, diffusion weighting only takes place parallel to that direction. For an isotropically weighted diffusion image, hence, three images with perpendicular diffusion weighting have to be acquired and then combined.

For the read-out of the diffusion weighted echoes usually fast single-shot EPI sequences are employed.

Diffusion Applications

Today, common applications for DWI include:

- Diffusion-perfusion-mismatch for stroke imaging.
- Early detection / screening: Changed ADC due to cellularity or metabolism changes in metastases and micro fractures, for instance.
- Differential diagnosis: Differentiation of various pathologies by means of DWI and ADC, e.g. differentiation of benign and malign tumors.
- Monitoring of therapies: Nekrotic vs. vital tissue etc.
- Clinical basic research: Metabolism, structure, aging of cells etc.

Perfusion

What is it ?

Blood flow through the vasculature supplies the tissue with nutrients and oxygen in the human body. Thus, blood supply itself is an important measure for the vitality of tissue and it represents a key parameter. The knowledge of the dynamic properties of blood supply are of great diagnostic value.

One important parameter is the *regional blood volume* (RBV), which describes the subvolume occupied by blood within a volume of interest or in 100 g of tissue. This, basically, is equivalent to defining it as the percental volume fraction of blood in the tissue:

$$\mathrm{RBV} = \frac{V_{\mathrm{blood}}}{V_{\mathrm{voxel}}} \quad . \tag{4}$$

In the brain, the RBV is usually denoted as the *cerebral blood volume* (CBV). Unfortunately, the arbitrary units of the MRI signal do not allow a direct measurement of the RBV or CBV.

Blood supply of tissue is quantified via the parameters *blood flow rate* BF and *perfusion* P. In literature, these terms are often loosely defined as 'blood flow' or equivalent. It is:

$$P = \frac{\mathrm{BF}}{W} \quad . \tag{5}$$

W is the tissue mass in 100g. Thus, compared to the blood flow rate BF is the perfusion P a mass-specific parameter. The latter makes sense, because absolute blood flow rates have a quite limited value without knowing the mass of reference. For example, organs have quite different sizes.

BF is measured in milliliters of blood per minute ($^{mL}/_{min}$), therefore, P has the nominal unit milliliters of blood per minute per 100g ($^{mL}/_{min \cdot 100g}$).

To have some values for the human brain at hand: In healthy tissue the average brain perfusion equals to $(50-60)\,^{mL}/_{min \cdot 100g}$. However, it has to be considered that the brain perfusion is quite different from region to region. For example, the mean perfusion in gray matter is approximately $(80-130)\,^{mL}/_{min \cdot 100g}$, and $20\,^{mL}/_{min \cdot 100g}$ in white matter.

Another important parameter that depicts the dynamic properties of tissue blood supply is the *mean transit time* (MTT). MTT is the average time required for a given tracer to pass through the tissue.

As a rule of thumb, for agents that remain in the blood the MTT is typically a few seconds.

There is a direct relation between the parameters RBV, BF, and MTT for perfusion measurements using a contrast agent in MRI:

$$\mathrm{MTT} = \frac{\mathrm{RBV}}{\mathrm{BF}} \quad . \tag{6}$$

The MTT parameter is important since it demonstrates a very sensitive contrast between ischemic and healthy tissue, for instance.

How to Image it ...

In order to probe the properties of the blood circuit, tracers are injected into the blood and their passage is observed at a point of interest. For MRI, contrast agents that induce a strong local relaxation rate change and significant susceptibility effects are employed. Since dynamic acquisitions are performed, such methods are also denoted as *dynamic susceptibility* (DSC) perfusion measurements.

In order to achieve sufficient volume coverage combined with a temporal sampling rate that allows the determination of dynamic perfusion parameters, fast GE-EPI sequences with a repetition time TR of 1.5-2.0s are often used. After contrast agent administration, the signal time-course is investigated (bolus measurement). The strong susceptibility effects of the passing bolus of the contrast agent cause a significant drop in the T_2^* weighted signal of the GE-EPI sequence.

What do Diffusion and Perfusion have in Common ?

That is your homework ☺.