Basic (physics) principles of quantification using MR

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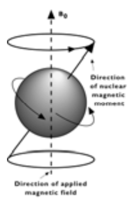
Basics of Nuclear Magnetic Resonance

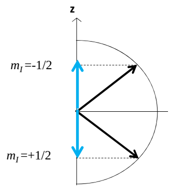
Nuclei with odd number of protons and/or neutrons possess a nuclear spin $\vec{I}$ and an associated magnetic moment $\vec{\mu}$.

For MRI the most important nucleus is the hydrogen nucleus. MRI images show therefore the weighted distribution of water and body lipids.

Nuclear magnets follow the laws of Quantum Mechanics:
For a nuclear spin $\vec{I}$ (I=1/2,1,…) $\rightarrow$ $2I+1$ discrete energy states $E_{I,m_I} = -\gamma \cdot \hbar \cdot B_0 \cdot m_I$
with m_I = $-I,-I+1,\ldots,+I$

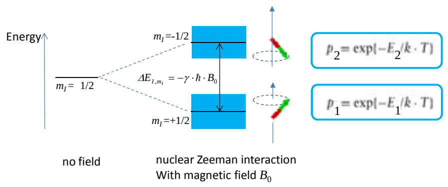
For protons I=1/2: $\rightarrow$ 2 discrete states in presence of magnetic field (parallel, antiparallel)



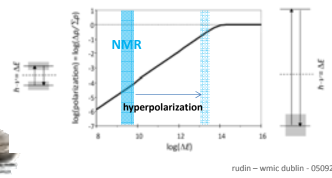


Sensitivity

Population of energy levels: Boltzmann distrubution



Polarization: population difference between energy levels involved



$$P = \frac{p_1 - p_2}{p_1 + p_2} = \tanh\left(-\frac{\Delta E}{2 \cdot k \cdot T}\right)$$

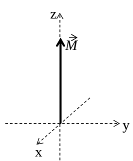
NMR/MRI: $P \approx 10^{-5}$

NMR (MRI/MRS) is inherently insensitve

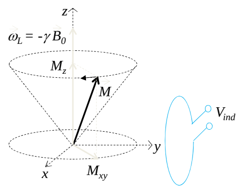
Macroscopic sample in magnetic field

Macroscopic magnetization = sum of all nuclear magnets, i.e. $\vec{M} = \gamma \cdot \hbar \cdot \sum_k \vec{I}^{(k)}$

Equilibrium



Non-equilibrium



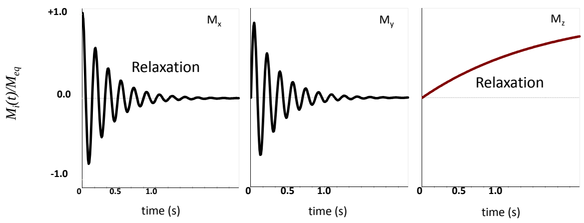
Equation of motion for magnetization:

$$\frac{d}{dt}\vec{M} = \gamma \cdot \vec{M} \times \vec{B}_0$$

$\rightarrow$ **precession around $\vec{B}_0$ with Larmor frequency $\omega_L = \gamma \cdot B_0$, which is proportional to the magnetic field**

Non-equilibrium magnetization in real system

Solution of the equation of motion including relaxation effects



Transverse relaxation
$R_2 = 1/T_2$

Longitudinal relaxation
$R_1 = 1/T_1$

MRI: Spatial encoding

Resonance requency depends linearly on magnetic flux: $\omega_0 = \gamma \cdot \hbar \cdot B_0$

No magnetic field gradient

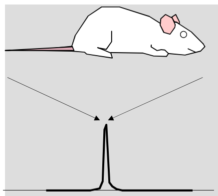
$G=0$

$B=B_0$

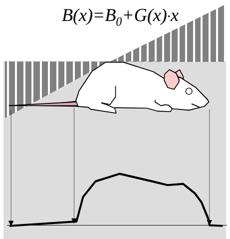
Magnetic field gradient

$G=G(r)$ (e.g. $G(x)$)

$B(x)=B_0+G(x)\cdot x$

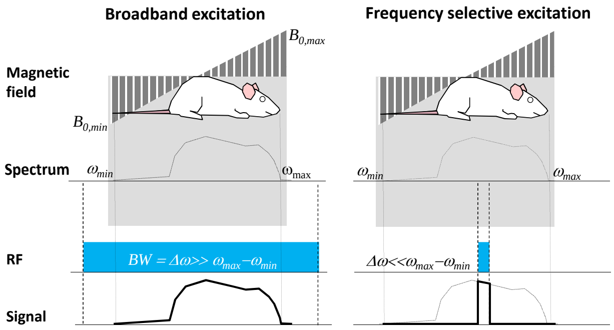


Frequency $\omega(x)=\omega_0$



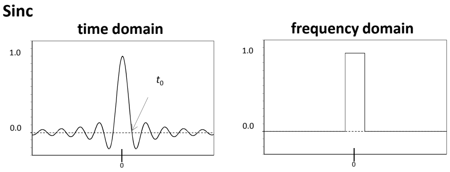
Frequency $\omega(x)=\omega_0+\gamma\cdot\hbar\cdot G(x)\cdot x$

Slice selection

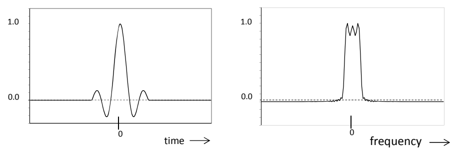


Frequency selective RF pulses

Ideal pulse: Sinc

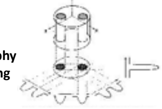


Practical pulse: Sinc3

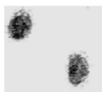


Two-dimensional encoding

1973
Zeugmatography
Radial sampling

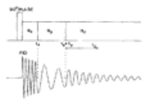


PR



Lauterbur PC
Nature 1973

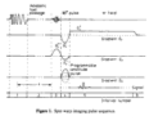
1975
Fourier
Zeugmatography



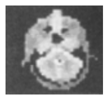
2/3D FT

Kumar A, Welti D, Ernst RR
J Magn Reson 1975

1980
Spin Warp



2/3D FT



Edelstein WA, Hutchison WMS, Johnson G, Redpath T
Phys Med Biol 1980

Encoding in two dimensions: Fourier imaging

Rendering the field location dependent by application of a magnetic field gradient $G_x(t)$ along x

$$B(x,t) = B_0 + G_x(t)\cdot x$$
$$\omega(x,t) = \omega_0 + \gamma \cdot G_x(t)\cdot x$$

Signal corresponding to projection along x

$$s(t) = \int_{x_{min}}^{x_{max}} M_{xy}(x)\cdot \exp\left\{-i\cdot\gamma\cdot\int_0^t G_x(t')\cdot x\cdot dt'\right\}dx$$

Introducing the variable $k_x(t)$

$$\boxed{k_x(t) = \frac{\gamma}{2\pi}\int_0^t G_x(t')\cdot dt'}$$

yields

$$\boxed{s(k_x) = \int M_{xy}(x)\cdot \exp\{-i\cdot 2\pi\cdot k_x\cdot x\}\cdot dx}$$

The MRI signal in k-space and the magnetization distribution are related through the Fourier Transformation

Encoding in 2D: incomplete k-space sampling

k-space

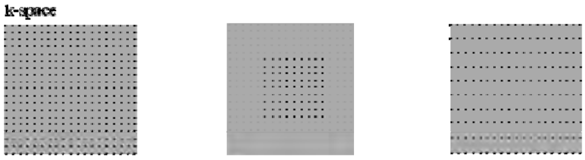
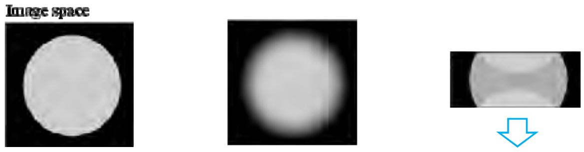
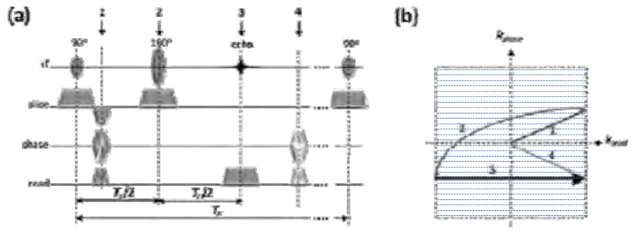


Image space

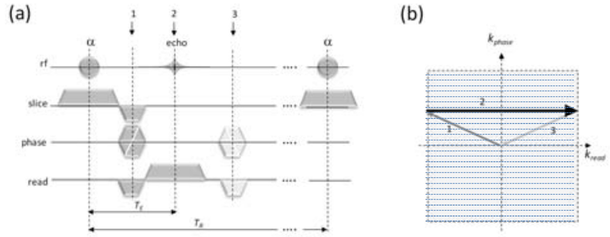


Parallel acquisition

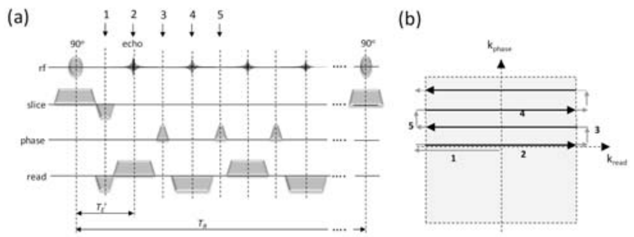
Sampling k-space: spin echo experiment



Sampling k-space: gradient echo experiment



Sampling k-space: echo planar imaging



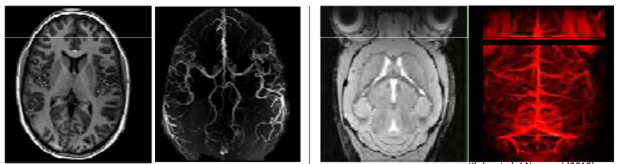
Resolution

Spatial resolution is dependent on signal-to-noise ratio (SNR) and acquisition time

electronics rf coil B_0

$$SNR = A^{-1/2}\cdot\frac{\omega\cdot(B_1/I)}{\sqrt{4\cdot k_B\cdot R_{eq}\cdot T_{eq}}}\cdot M_T\cdot V_{voxel}\cdot\sqrt{\frac{N_{FE}}{BW}}\cdot\sqrt{N_{PE}}\cdot\sqrt{N_A}$$

sensitivity spatial resolution temporal resolution



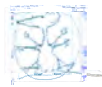
Courtesy K Pruessmann, ETHZ

Klohs et al, J Neurosci (2012)

Leonardo da vinci

Voxel:	1x1x1 mm³
rel V_{voxel}:	4000 (~BW: 80kg)
rel SNR:	63

Voxel:	63x63x63 μm³
rel V_{voxel}:	1 (~BW: 20g)
rel SNR:	1



unknown artist

MRI contrast parameters

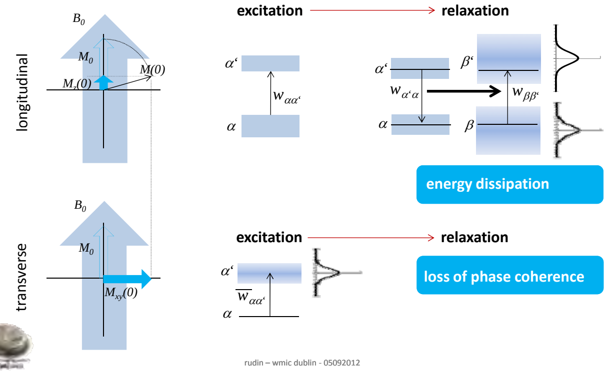
Relaxation times:

- *T_1* — **Spin-lattice relaxation time (longitudinal relaxation time)**
  Return of spin system to equilibrium state
- *T_2* — **Spin-spin relaxation time (transverse relaxation time)**
  Loss of phase coherence due to fluctuations of interacting spins ('phase memory time')
- *T_2** — **Decay time of free induction decay**
  Signal loss due to magnetic field inhomogeneity (difference in magnetic susceptibility)
- *ADC* — **Apparant diffusion coefficient**
  Signal loss due to diffusion of water molecules in an inhomogeneous magnetic field
- *k* — **water exchange rate**
  Exchange of water between macromolecul bound fraction and bulk (free) water

etc.

Relaxation

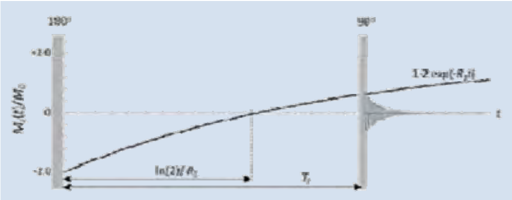
R_1 and R_2 relaxation: two fundamentally different processes



Measurement of R_1 Relaxation

1. generate non-equilibrium z-magnetization: $M_z(0) \neq M_0$
2. wait: $M_z(\tau)$
3. generate detectable transverse magnetization: $M_z(\tau) = M_{xy}(0)$

Inversion recovery $M_z(t) = M_0 \cdot \{1 - 2 \cdot \exp(-R_1 \cdot t)\}$.

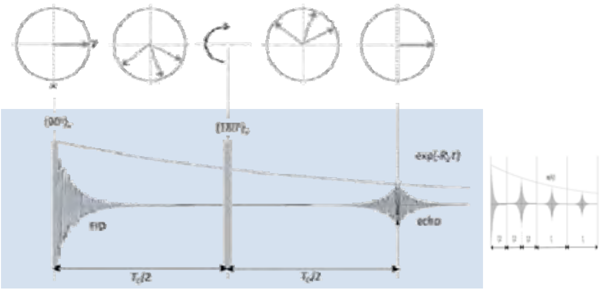


Analysis of recovery curve $M_{xy}(x,y,z;0)=M_z(x,y,z,t)$ yields relaxation rate (or time)

$R_1(x,y,z)$ $T_1(x,y,z) = 1/R_1(x,y,z)$

Measurement of R_2 Relaxation

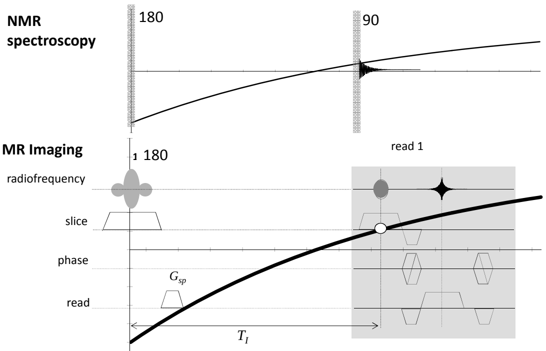
Spin-echo experiment to account for any static susceptibility differences



Analysis of echo amplitude decay $M_{xy}(x,y,z;n \cdot T_E)$ yields transverse relaxation rate (or time)

$R_2(x,y,z)$ $T_2(x,y,z) = 1/R_2(x,y,z)$

Incorporation of contrast generating modules into imaging



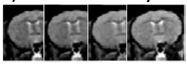
Contrast generation | Image acquisition

MRI parameter images

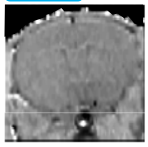
Tissue characterization

Prerequisite for deriving quantitative information

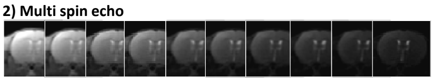
1) Saturation recovery



T_1 map



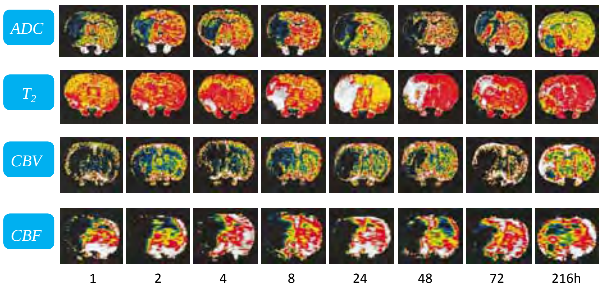
2) Multi spin echo



T_2 map

MRI parameter images

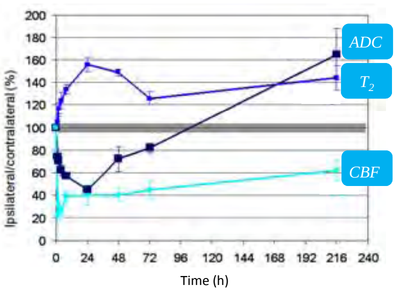
Tissue characterization: e.g. focal cerebral ischemia in rats



Rudin et al., Exp Neurol, 169: 56 (2001)

MRI parameter images

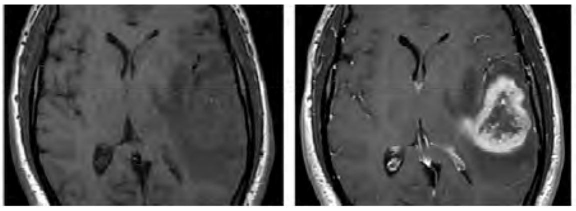
Tissue characterization: e.g. focal cerebral ischemia in rats



Rudin et al., Exp Neurol, 169: 56 (2001)

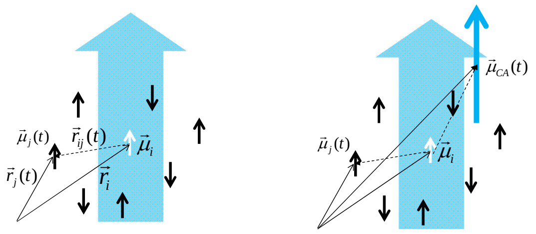
MRI contrast agents

Administration of contrast agent to enhance specific structure



MRI contras agent modify relaxation rates in a concentration dependent manner

MRI contrast agents



$$\vec{B}_i(\vec{x}_i,t) = \vec{B}_0 + \sum_{i\neq j} \vec{B}_j(\vec{x}_i;\vec{\mu}_j(t),\vec{r}_{ij}(t))$$

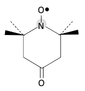
$$\vec{B}_i(\vec{x}_i,t) = \vec{B}_0 + \sum_{i\neq j} \vec{B}_j(\vec{x}_i;\vec{\mu}_j(t),\vec{r}_{ij}(t)) + \vec{B}_{CA}(x_i;\vec{\mu}_{CA}(t),\vec{r}_{i-CA}(t))$$

Criterion for effective change in local magnetic field: $|\vec{\mu}_{CA}| >> |\vec{\mu}_j|$

Electron magnetic moment >>proton magnetic moment, hence $\vec{\mu}_{CA} = \vec{\mu}_e$

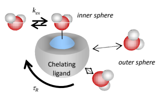
Types of MRI contrast agents

Paramagnetic compounds contain at least one unpaired electron: $S \geq 1/2$
electron magnetic moment $\mu_e \approx$ **650 x proton magnetic moment** μ_p



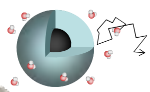
1) Stable free radicals (e.g. containing sterically protected nitroso group)

2) Transition metal complexes: d^n with n=1 to 9
expls: Fe(II), Fe(III), Mn(II), Cu(II)



3) Lanthanide complexes: f^n with n=1,13
expls: Gd(III), Dy(III)

Metal complexes are more efficient relaxation agents as they typically contain more than one unpaired electron



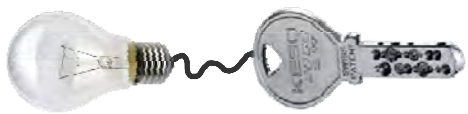
4) Superparamagnetic compounds
Iron oxide nanoparticles consisting of a Fe_xO_y core and organic coating to ensure biocompatibility and proper PK properties

Targeted contrast agents

Contrast behavior of non-specific CA is defined by the PK / biodistribution

Adding a target specific group will/should lead to specific accumulation at site expressing the molecular target

Direct targeting: Coupling of reporter to a target-specific moiety



Reporter group	Linker	Targeting moiety
MRI contrast agent:		**Antibody**
Paramagnetics		**Receptor ligand**
Superparamagnetics		**Peptide**
CEST ligands		**Enzyme substrate**
….		**Oligonucleotide**
		….

Estimate tracer concentration from MRI measurements

Overall relaxivity consists of two contribution:

- **intrinsic relaxivity of the tissue** R_{i0}
- **contribution due to the paramagnetic center** $R_{i,p}$

$$R_i = R_{i0} + R_{i,p}$$

Paramagnetic contribution is proportional to the local concentration of the CA in the tissue $c_{t,p}$ **and the CA's distribution volume (fractional volume** v**)**

$$R_{i,p} = r_i \cdot c_{t,p} \cdot v$$

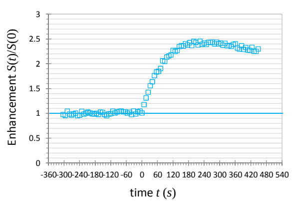
The proportionality factor r_i **is the molar relaxivity .**

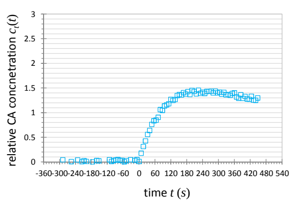
Estimation of local tissue concentration of CA

R_1 **in tissue in presence of** R_1 **relaxation agent** $R_1(t) = R_{10} + r_1 \cdot c_t(t) \cdot v_t(t)$

CA concentration assuming small changes in R_1 $(e^{-x} \approx 1\text{-}x)$

$$c_t(t) \approx \frac{R_{10}}{r_1 \cdot v_t(t)} \cdot \frac{S(t) - S(0)}{S(0)}$$



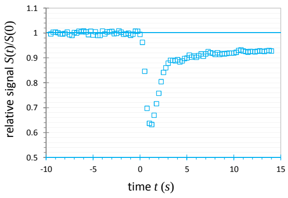


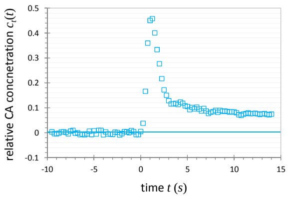
Estimation of local tissue concentration of CA

R_2 in tissue in presence of R_2 relaxation agent $R_2(t) = R_{20} + r_2 \cdot c_t(t) \cdot v_t(t)$

CA concentration

$$c_t(t) = -\frac{1}{r_2 \cdot v_t(t) \cdot T_E} \ln\{S(t)/S(0)\}$$

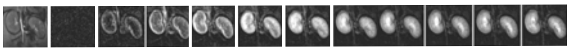


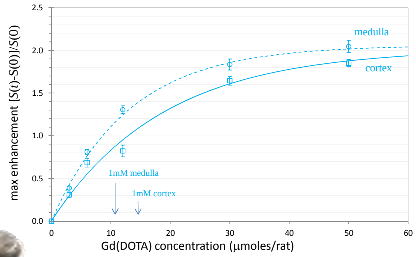


CA concentration: validity of linear approximation

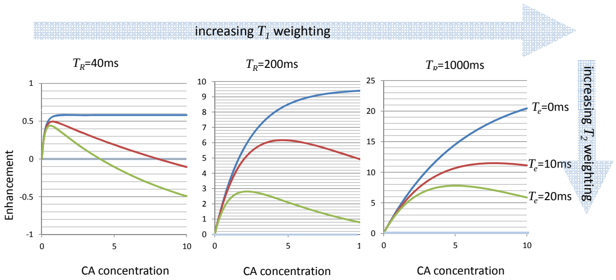
$$c_t(t) \approx \frac{R_{10}}{r_1 \cdot v_t(t)} \cdot \frac{S(t) - S(0)}{S(0)}$$

GdDOTA clearance in kidney

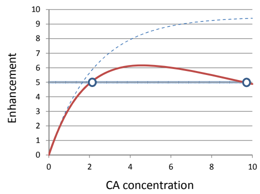




CA concentration: mixed contrast

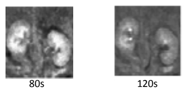


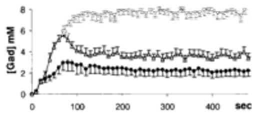
CA concentration: mixed contrast



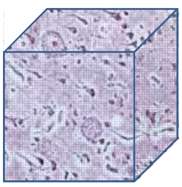
ambiguities in determination of CA concentration from signal enhancement values

Expl: kidney functional studied using GdDOTA





CA concentration in voxel



Voxel is composed of multiple compartments

cell of different types
interstitial space
blood vessels

CA is distributed into multiple compartments, therefore $c_t(t)$ corresponds to volume averaged concentration of CA across compartments, i.e.

$$c_t(t) = \frac{1}{V} \Sigma_i\ v_{ti} \cdot c_{ti}(t)$$

CA concentration in voxel: multiple compartments

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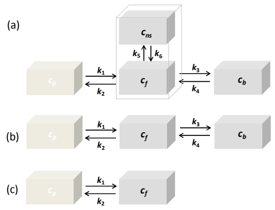
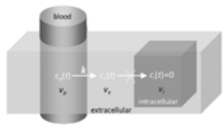
Multicompartment models to deconvolve individual contributions





Determine $c_{ti}(t)$ for compartment of interest

Summary

- ^{1}H MRI images represent weighted distribution of water (and adipose tissue)
- MRI is inherently insensitive.
- Spatial resolution is linked to sensitivity (SNR) and temporal resolution
- MRI data are acquired in k-space wihich is linked to the image space through a Fourier Transformation
- The weighting factors (contrast parameters) are
  - relaxation times
  - microscopic motion (diffusion & perfusion)
  - spin exchange (chemical exchange, polarization transfer, spin diffusion)
- MRI contrast parameters are tissue specific $\rightarrow$ generation of parameter maps as sequence independent tissue characteristic (yet dependent on B_0)
- Contrast may be enhanced through administration of contrast agents (CA) that contain unpaired electrons (transition metals, lanthanides). CA concentration may be estimated from local changes in relaxation properties.
- Molecular information may be obtained by coupling CA to targeting moiety.