Basic (physics) principles of quantification using MR

Markus Rudin

Institute for Biomedical Engineering UZH/ETH
Institute of Pharmaceutics and Toxicology UZH
Zürich, Switzerland

Contents

Principles of detection
Spatial resolution
Temporal resolution
Sensitivity
Quantification of signal
Correction factors for quantification
Contrast agents

Basics of Nuclear Magnetic Resonance

Nuclei with odd number of protons and/or neutrons possess a nuclear spin \( I \) and an associated magnetic moment \( \mu \).

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 \( I (I = 1/2, 1, \ldots) \) \( \rightarrow 2I + 1 \) discrete energy states

with \( m_I = -I, -I+1, \ldots, +I \)

\[ \mathbf{E}_{m_I} = -\gamma \mathbf{B}_0 \cdot \mathbf{m}_I \]

Population of energy levels: Boltzmann distribution

Energy

Population difference between energy levels involved

Polarization: population difference between energy levels involved

Equation of motion for magnetization:

\[ \frac{d}{dt} \mathbf{M} = -\gamma \mathbf{M} \times \mathbf{B}_0 \]

Transverse relaxation \( R_2 \equiv 1/T_2 \)

Longitudinal relaxation \( R_1 \equiv 1/T_1 \)

Non-equilibrium magnetization in real system

Solution of the equation of motion including relaxation effects

Macroscopic muegnetization = sum of all nuclear magnets, i.e.

Equilibrium

Non-equilibrium

\[ \mathbf{M} = \mathbf{y} \cdot \mathbf{B}_0 \sum \mathbf{I}^{(i)} \]

\[ \mathbf{M} = \mathbf{M}_0 e^{-t/T_2} \]

\[ \mathbf{M} = \mathbf{M}_0 e^{-t/T_1} \]

NMR/MRI: \( P = 10^{-5} \)

NMR (MRI/MRS) is inherently insensitive
Resonance frequency depends linearly on magnetic flux:

\[ \omega_0 = \gamma \cdot B_0 \]

No magnetic field gradient

\[ G = 0 \]

\[ B = B_0 \]

Magnetic field gradient

\[ G \neq 0 \] (e.g. \( G(x) \))

\[ B(x) = B_0 + G(x) \cdot x \]

Frequency selective RF pulses

Ideal pulse: Sinc

Practical pulse: Sinc3

Two-dimensional encoding

1973
Zeugmatography
Radial sampling

1975
Fourier Zeugmatography

1980
Spin Warp

Parallel acquisition

Encoding in two dimensions: Fourier imaging

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

\[ B(x,t) = B_0 + G_x(t) \cdot x \]

\[ \alpha(x,t) = \omega_0 + \gamma \cdot G_x(t) \cdot x \]

Signal corresponding to projection along \( x \):

\[ s(t) = \int M_x(x) \cdot \exp \left( -i \frac{\gamma}{2} \int G_y(t') \cdot x' \cdot dt' \right) dx \]

Introducing the variable \( k_x(t) \):

\[ k_x(t) = \frac{\gamma}{2 \pi} \int G_y(t') \cdot dt' \]

yields

\[ s(k_x) = \int M_x(x) \cdot \exp \left( -i 2 \pi k_x \cdot x \right) dx \]

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

MRI contrast parameters

Relaxation times:

$T_1$: Spin-lattice relaxation time (longitudinal relaxation time)

$T_2$: Spin-spin relaxation time (transverse relaxation time)

$T_2^*$: Decay time of free induction decay

Relaxation $R_1$ and $R_2$: two fundamentally different processes

ADC: Apparent diffusion coefficient

$\lambda$: water exchange rate

Excitation relaxation: energy dissipation

Loss of phase coherence
**Measurement of \( R_1 \) Relaxation**

1. generate non-equilibrium \( z \)-magnetization: \( M_z(0) \neq M_0 \)
2. wait: \( M_z(t) \)
3. generate detectable transverse magnetization: \( M_z(t) = M_x(t_0) \)

Inversion recovery equation:

\[
M_z(t) = M_0 \cdot (1 - e^{-R_1 t/2})
\]

Analysis of recovery curve \( M_z(x,y,z)(t) \)/\( M_z(x,y,z)(t_0) \) yields relaxation rate (or time) \( R_1(x,y,z) \).

**Measurement of \( R_2 \) Relaxation**

Spin-echo experiment to account for any static susceptibility differences

Analysis of echo amplitude decay \( M_{xy}(x,y,z; TE) \) yields transverse relaxation rate (or time) \( T_2(x,y,z) \).

**Incorporation of contrast generating modules into imaging**

MRI parameter images

**Tissue characterization**

Prerequisite for deriving quantitative information

1) Saturation recovery

2) Multi-spin echo

**MRI parameter images**

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

**T2**

**ADC**

**CBF**

**Rudin et al., Exp Neurol, 169: 56 (2001)**
**MRI contrast agents**

Administration of contrast agent to enhance specific structure

MRI contrast agent modify relaxation rates in a concentration dependent manner

**Types of MRI contrast agents**

Paramagnetic compounds contain at least one unpaired electron: Si/2
- electron magnetic moment \( \mu_e \approx 6 \) proton magnetic moment \( \mu_p \)

1. Stable free radicals (e.g. containing sterically protected nitroso group)
2. Transition metal complexes: \( d^n \) with \( n=2 \) to \( 9 \)
   - examples: Fe(II), Fe(III), Mn(II), Cu(II)
3. Lanthanide complexes: \( f^n \) with \( n=1,13 \)
   - examples: 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 \( Fe_3O_4 \) 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

**Estimate tracer concentration from MRI measurements**

Overall relaxivity consists of two contributions:
- Intrinsic relaxivity of the tissue \( R_0 \)
- Contribution due to the paramagnetic center \( R_{P} \)

\[
R_s = R_0 + R_{P}
\]

Paramagnetic contribution is proportional to the local concentration of the CA in the tissue \( c_{CA} \) and the CA's distribution volume (fractional volume)

\[
R_{P} = \gamma_1 \cdot C_{P} \cdot V
\]

The proportionality factor \( \gamma_1 \) is the molar relaxivity.

**Estimation of local tissue concentration of CA**

\[
R_s(t) = R_{0} + R_{P}(c(t) + f(t))
\]

CA concentration assuming small changes in \( R_s \) \( (\Delta R_s = 1-\epsilon) \)

\[
c(t) = \frac{R_{P}}{R_{0} + y_1 c(t) + f(t)}
\]

[Graphical representation of relaxation rate vs time]

[Graphical representation of concentration vs time]
Estimation of local tissue concentration of CA

\[ R_1 \text{ in tissue in presence of } R_1 \text{ relaxation agent } \]

\[ R_1(t) = R_{10} + \frac{1}{T_1} \ln \left[ S(t)/S(0) \right] \]

CA concentration: mixed contrast

Increasing \( T_1 \) weighting

\[ \begin{align*}
T_1 &= 40\text{ms} \\
T_1 &= 100\text{ms} \\
T_1 &= 200\text{ms} \\
T_1 &= 400\text{ms} \\
T_1 &= 800\text{ms} \
\end{align*} \]

CA concentration in voxel

Voxel is composed of multiple compartments

Cell of different types

Interstitium space

Blood vessels

CA concentration in voxel: multiple compartments

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

\[ c_i(t) = \frac{1}{T_i} \sum v_i c_i(t) \]

Multicompartment models to deconvolve individual contributions

(a) Multicompartment model (a) \( c_i(t) \)

(b) Multicompartment model (b) \( c_i(t) \)

(c) Multicompartment model (c) \( c_i(t) \)

Determine \( c_i(t) \) for compartment of interest

CA concentration in voxel: multiple compartments

CA concentration: validity of linear approximation

\[ S(t)/S(0) = \frac{R_{10} + \frac{1}{T_1} \ln [S(t)/S(0)]}{R_{10} + \frac{1}{T_1} \ln [S(t)/S(0)]} \]

Gd(DOTA) clearance in kidney

Expl: kidney functional studied using GdDOTA

CA concentration: mixed contrast

Ambiguities in determination of CA concentration from signal enhancement values

0 2 4 6 8 10 12 14

0 2 4 6 8 10 12 14

0 2 4 6 8 10 12 14

CA concentration

Gd(DOTA) concentration [pmol/ml]
Summary

1H MRI images represent weighted distribution of water (and adipose tissue)

2 MRI is inherently insensitive.

3 Spatial resolution is linked to sensitivity (SNR) and temporal resolution

4 MRI data are acquired in k-space which is linked to the image space through a Fourier Transformation

5 The weighting factors (contrast parameters) are
   - relaxation times
   - microscopic motion (diffusion & perfusion)
   - spin exchange (chemical exchange, polarization transfer, spin diffusion)

6 MRI contrast parameters are tissue specific – generation of parameter maps as sequence independent tissue characteristic (yet dependent on $B_0$).

7 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.

8 Molecular information may be obtained by coupling CA to targeting moiety.