Modelling in DCE-MRI

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Roadmap

- Gd leakage in multiple sclerosis and cancer – ‘Tofts model’
- A philosophy of quantification
- Gd uptake in kidney – simplifying the model
- Sensitivity analysis – effect of fixed parameters e.g. Hct
- 8 proposed principles for quantitative modelling
Modelling is in 2 parts

1) Gd concentration from signal
   - MRI – model

2) Tissue physiology from Gd concentration
   - pharmacokinetic model
Modelling 1a
Gd concentration from signal

dependence of signal on $T_1$:

(spoilt gradient echo, TE $<< T_2$)

$$S = S_0 \frac{\left(1 - e^{-\frac{TR}{T_1}}\right) \sin \theta}{1 - e^{-\frac{TR}{T_1}} \cos \theta}$$

$S$ = tissue signal

$S_0$ = relaxed tissue signal (TR $>> T_1$, $\theta=90^\circ$)

$\theta$ = flip angle FA

dependence of $T_1$ on Gd concentration $C$

$$\frac{1}{T_1} = \frac{1}{T_{10}} + r_1 C$$

$T_{10}$ = $T_1$ of tissue pre-Gd

$r_1$ = relaxivity of tissue

sometimes...

$$R_1 = \frac{1}{T_1} ; \quad R_1 = R_{10} + r_1 C$$

$R_1$ = relaxation rate
Modelling 1b
Gd concentration from signal

Signal enhancement ratio

\[
\frac{S(Gd)}{S(no Gd)} = \frac{1 - e^{-R_{10}TR+r_1C}}{1 - e^{-R_{10}TR}} \cdot \frac{1 - e^{-R_{10}TR} \cos \theta}{1 - e^{-R_{10}TR+r_1C} \cos \theta}
\]

We need to know the values of 3 parameters

- \( R_{10} \)  \( 1/T_1 \) of tissue
- \( \theta \) flip angle
- \( r_1 \) relaxivity (= increase in relaxation rate per unit concentration of Gd)

then there is a known relationship between C and enhancement
Modelling

2: physiology from Gd concentration

pharmacokinetics or compartmental modelling

- **Pharmacokinetics**: how a pharmaceutical moves around the body
- **Compartment**: a pool or reservoir of tracer (e.g. Gd) in which
  - i) the tracer is well mixed
    - (uniform concentration, same everywhere)
  - ii) weakly connected to its surroundings
    - (inflow or outflow too small to cause local change in concentration)
  - a BUCKET
Modelling 2: physiology from Gd concentration compartmental model for tumours

- **Bolus (short) injection into blood plasma compartment**
- **Reversible leak from capillaries into EES**
- **Concentrations $C_p$ and $C_e$ in plasma and EES compartments**
- **Plasma volume $v_p$**
  - $\sim 60\%$ in blood (Hct$\sim 40\%$)
  - $\sim 2$-10$\%$ in tissue
- **EES $v_e$**
  - Extracellular space outside vessels
  - 10-60\%
‘Tofts Model’ with variations

i) $v_p$ term included or not

- Tissue concentration = extravascular + intravascular contributions
- $v_p$ term describes IV contribution
- originally contribution of intravascular tracer to tissue concentration was ignored ($v_p \sim 2\%$ in brain)
- more recently it is often included ($v_p \sim 10\%$ in some tumours)

ii) $C_p(t)$ value – Arterial Input Function AIF

- Use population average or measure it
- Include first pass or not? (temporal resolution)
Modelling 2: physiology from Gd concentration mathematical model

- Flow of tracer from plasma to EES proportional to difference in concentrations
  - Passive, diffusive transport
  - No active mechanisms
  - Gd molecules all ~500-1000 daltons
- Key physiological parameters are:
  - $K_{\text{trans}}$ transfer constant
  - $v_e$ volume of EES
  - $k_{ep}$ rate constant
    - easier to measure than $K_{\text{trans}}$ and $v_e$, but less physiological; determines shape of response
    - independent of MRI technique e.g. 3T vs 1.5T
- Mathematical solution for tissue concentration
  - $v_p$ term IV tracer
  - $K_{\text{trans}} \times$ convolution of AIF and $\exp(-k_{ep}t)$

\[
\frac{dC_e}{dt} = K_{\text{trans}} (C_p(t) - C_e(t))
\]

\[
C_t(t) = v_p C_p(t) + K_{\text{trans}} \int_0^t C_p(\tau) e^{-k_{ep}(t-\tau)} d\tau
\]

\[
k_{ep} = \frac{K_{\text{trans}}}{v_e}
\]

Tofts JMRI 1997
Modelling 2: physiology from Gd concentration

first application - multiple sclerosis

- First applications had low temporal resolution
- Rapid enhancement $\rightarrow$ high $K_{\text{trans}}$
- High $v_c$ lesions take longer to reach peak
- Sample enhancement curve to beyond peak to measure $v_c$

**Fig. 4.** Signal enhancement (1R1020/40/500) after injection of 0.1 mM/kg Gd-DTPA at time zero into a patient with active multiple sclerosis. The broken lines are fitted curves. (a) A rapidly enhancing lesion $k = 0.050$ min$^{-1}$, $v_1 = 21\%$. (b) A slowly enhancing lesion $k = 0.013$ min$^{-1}$, $v_1 = 49\%$. 


P. S. Tofts and A. G. Kermode

Modelling 2: physiology from Gd concentration simulated enhancement curves


Paul S. Tofts and Allan G. Kermode

Magnetic Resonance in Medicine 17, 357–367 (1991)

- Varying $K_{\text{trans}}$ controls initial slope (upper plot)

- Varying $v_e$ does not affect initial slope (lower plot) but
  - does affect peak enhancement and time to peak
  - need to sample up to peak to get $v_e$

- In tumours it happens much faster!

**Fig. 3.** Model triexponential lesion concentration curves, following a bolus injection of 0.1 mM/kg of Gd-DTPA. (a) Fixed leakage space $v_l = 20\%$, varying permeability $k$. (b) Fixed permeability $k = 0.01\ min^{-1}$, varying leakage space $v_l$. 
Prostate DCE
Siemens tissue 4D - prostate

- model fits data (apart from movement!); no $v_p$ term
- high and low $K_{\text{trans}}$ values (LHS: 0.5 min$^{-1}$, RHS: 0.1 min$^{-1}$)
- $v_e$ unreliable if peak of curve not sampled (RHS $v_e = 1.02$ !)

Suspicious apex gland lesion

Medial gland

(Esmi Les Houches April 16-20 2012)
Modelling 2: physiology from Gd concentration: what does $K_{\text{trans}}$ mean?

- Flow of tracer from plasma to EES is $K_{\text{trans}} \times$ concentration difference

- For small leak (e.g. MS),
  - tracer transport $\propto$ PS
  - PS = Permeability surface area product
  - permeability–limited situation $K_{\text{trans}} = \text{PS}$ ($F \gg \text{PS}$) ‘permeability imaging’

- Large leak (many tumours),
  - tracer transport $\propto$ local blood flow
  - flow–limited situation $K_{\text{trans}} = \text{flow}$ ($F \ll \text{PS}$) ‘perfusion imaging’

- Tumours - often mixed PS- and F- limiting – hard to interpret
  - Though $F$ can sometimes be estimated using faster data

Tofts Brix et al JMRI 1999
Modelling 2: physiology from Gd concentration
advanced models - 1

• Tissue homogeneity model (St Lawrence and Lee). Distributed model; not a compartmental model

• Accounts for inflow effects during bolus arrival.

• In principle gives flow from the bolus arrival portion and PS from the later portion

• However good temporal resolution is required.

Figure 10.4. Components of the tissue homogeneity model (after St Lawrence and Lee, 1998). The components are equivalent to the compartments in Figure 10.1. The major difference between the assumptions of the models is that the tissue homogeneity model attempts to account for the fact that contrast agent (small grey circles) concentration within the capillary is likely to decrease with position, $x$, along the capillary of length, $L$, during the vascular stage (see text) of a bolus contrast enhancement study. This leads to a concentration gradient between the arterial ($C_a$) and venous ($C_v$) ends of the capillary. Contrast agent is assumed to be evenly mixed in the EES ($v_c$)
Two compartment exchange model. 2CXM
- Can fit better than standard ‘Tofts model’
- Recognise that capillary bed is distinct from arterial supply
- Gives perfusion and $v_p$ from bolus arrival portion and PS from later portion
- Important when:
  - High $v_p$ (11% in this example)
  - longer bolus arrival time in vascular bed
  - Needs good temporal resolution
Tissue4D - ROI and maps of $K_{\text{trans}}$
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- 8 proposed principles for quantitative modelling
Quantitative imaging – a paradigm shift

- Paradigm = a way of viewing the world, a mindset
- Paradigm shift: e.g. Newtonian physics to Quantum Physics
- MR imager: ‘happy snappy camera’, images reported by radiologists (‘qualitative mode’)
- To: scientific instrument, set up by physicists, images analysed by neuroscientists, psychologists (‘quantitative mode’)
- Traditions to guide us: astronomy, measurement science, school science
- New concepts: accuracy = systematic error
- Precision = random error (reproducibility)
- Within-individual variation: instrumental, biological
- (all a long way from traditional radiology) accessing the invisible
Everyday examples of quantification

Body mass

Blood test

We expect: reliable, accurate, reproducible, easy

We hope that instrumental variation « biological variation
Three components of good quantification:

Could a quantity be a useful biomarker?

Sensitivity: how small a biological change can be measured? 
random error; precision

Specificity: what kind of biological change took place? 
patients or histology

Accuracy: how close is the measurement to the true value? 
systematic error

Need to: Understand the Process of Measurement
The Measurement Process

**Data collection** – the Scan

Hardware (coils), Pulse sequence, Subject positioning, Subject variation, any subjective elements of scanning, FA variation, receive variation, image noise

**Image data analysis** – the retrospective measurement

Software, subjective components, can be automated

**Aim:** refine process until instrumental variation ≪ biological variation

- ‘the perfect quantitative imaging machine’
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Renal model - overview

A simple model of the renal uptake curve enables four key physiological parameters to be accessed.

\[ K_{\text{trans}} \] filtration (GFR/unit volume) \rightarrow GFR

\[ v_b \] blood volume \hspace{1cm} \% 

\[ F \] perfusion \hspace{1cm} ml blood (100 ml tissue) min\(^{-1}\)

\[ FF \] filtration fraction \hspace{1cm} FF = \frac{K_{\text{trans}}}{((1-Hct)\times F)}

MAT: \hspace{1cm} Mean Arrival Time

15 normal subjects were each imaged twice, to enable reproducibility to be measured (Bland-Altman analysis)

Estimate accuracy by comparison with published values
MRI Acquisition

- Siemens Avanto 1.5 T scanner
- Abdominal TIM coil
- Gradient-echo 3D-FLASH pulse-sequence
- TR = 1.63 ms; TE = 0.53 ms
- Flip angle = 17°
- Strong fat saturation; PAT factor = 2 (GRAPPA)
- FOV = 400 x 325 mm²
- 18 x 7.5 mm coronal slices covering entire kidney (no gap)
- Voxel size = 3.1 x 3.1 x 7.5 mm³
- Frames acquired every 2.5 s
- Gd dose = 0.05 mmole/kg (half dose)
Kidney model

Uptake mode

no efflux from tubules (t<90s)

\( K_{\text{trans}} = \) transfer constant from plasma to kidney

(=GFR per unit volume of tissue)

IV plasma

\( g(t) = \) Vascular Input Response Function

EV tracer \( C_d \)

total tracer \( C_t \)

\[ C_{p}^{\text{kid}}(t) = C_{p}^{\text{art}}(t) \otimes g(t) = \int_{0}^{t} C_{p}^{\text{art}}(t - \tau) g(\tau) d\tau \]

\[ \nu_d \frac{dC_d(t)}{dt} = F_1 = K_{\text{trans}} C_{p}^{\text{kid}}(t) \]

\[ \nu_d C_d(t) = K_{\text{trans}} \int_{0}^{t} C_{p}^{\text{kid}}(\tau) d\tau \]

\[ C_t(t) = \nu_b (1 - Hct_{\text{small}}) C_{p}^{\text{kid}} + \nu_d C_d(t) \]
Fit parenchymal ROI
(uptake mode – no efflux)

- Spreadsheet implementation
  - uses solver; ROI fits in 5s
- blood and kidney signals
  - red circles; blue circles
- Fit up to 90s
  - green line
  - residuals RMS < 3%;
    - model errors are small
    - contributions from movement
    - contribution from blood signal noise?
  - efflux visible after 100s
    - kidney signal < model
- plot shows Gd in two compartments:
  - IV (~glomerular) (red line; delayed AIF)
  - EV (~tubular) (green line; shows uptake)
## Normal values

### parenchymal ROIs in uptake mode

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MRI Hct\text{small} =41% mean (sd)</th>
<th>instrumental sd (CV)</th>
<th>literature value</th>
<th>MRI Hct\text{small} =24% mean (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filtration (min\textsuperscript{-1})</td>
<td>(K^{\text{trans}})</td>
<td>0.25 (0.05)</td>
<td>0.04 (18%)</td>
<td>0.28\textsuperscript{a}</td>
</tr>
<tr>
<td>Mean Arrival Time (s)</td>
<td>(MAT)</td>
<td>5.5 (0.7)</td>
<td>0.4 (7%)</td>
<td>6.5\textsuperscript{b}</td>
</tr>
<tr>
<td>blood volume (%)</td>
<td>(v_b)</td>
<td>44 (11)</td>
<td>8 (18%)</td>
<td>35\textsuperscript{c}</td>
</tr>
<tr>
<td>perfusion\textsuperscript{d} (ml blood min\textsuperscript{-1} (100 ml tissue))\textsuperscript{-1}</td>
<td>(F)</td>
<td>284 (89)</td>
<td>72 (14%)\textsuperscript{e}</td>
<td>264\textsuperscript{f}</td>
</tr>
<tr>
<td>filtration fraction (%) \textsuperscript{g}</td>
<td>(FF)</td>
<td>15.5 (2.9)</td>
<td>1.5 (9%)</td>
<td>15-20\textsuperscript{h}</td>
</tr>
<tr>
<td>absolute single kidney volume (ml)</td>
<td>(V_{\text{kid}})</td>
<td>230 (28)</td>
<td>not measured</td>
<td>213\textsuperscript{i}</td>
</tr>
<tr>
<td>standardised single kidney volume (ml)\textsuperscript{j}</td>
<td>(V_{\text{kid}})</td>
<td>214 (20)</td>
<td>not measured</td>
<td>213\textsuperscript{i}</td>
</tr>
<tr>
<td>total GFR (ml min\textsuperscript{-1})</td>
<td>GFR</td>
<td>115 (27)\textsuperscript{k}</td>
<td>not measured</td>
<td>125\textsuperscript{h}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} = \(GFR/(2V_{\text{kid}})\) \textsuperscript{k} measured using MRI by Sourbron\textsuperscript{6}; ‘plasma transit time TP'; SD=1.3s \textsuperscript{c} from CT\textsuperscript{50} \textsuperscript{d} from peak of gaussian VIRF \(F_{\text{gauss peak}}\); average perfusion over parenchymal ROI \textsuperscript{e} ISD of cortical perfusion is better (14%). \textsuperscript{f} mean parenchymal perfusion = RBF/2*\(V_{\text{kid}}\); RBF = 1.1 litre min\textsuperscript{-1} (Eaton\textsuperscript{51}) \textsuperscript{g} using eqn 10. \textsuperscript{h} typical for young adult male\textsuperscript{51} \textsuperscript{i} estimated using mass=150g (see text) \textsuperscript{j} i.e. corrected for body surface area \textsuperscript{k} 2 \(K^{\text{trans}} V_{\text{kid}}\)

**CONCLUSION:** our values for **four physiological parameters** **may be accurate**  (and FF and MAT are precise and could be useful)
Increasing ROI size

In a central kidney slice, GFR in progressively larger ROI’s increases to a plateau value of about 11 mL min⁻¹; for 5 slices per kidney this gives a total GFR of 110 mL min⁻¹ (single kidney GFR=55). Nominal cortical (C = 350 pixels) and parenchymal (P = 600 pixels) ROI’s are shown. Mean $K_{\text{trans}}$ values for small cortical ROI’s vary, then decrease progressively for ROI’s larger than the cortex.
Vascular Impulse Response Functions

- Fig. 6 Vascular impulse response functions (VIRFs). All fitted the data shown in Fig. 3a (parenchymal ROI, uptake phase) and have unit area. The instant exponential VIRF modelled the delayed perfusion peak badly. Differing peak values give rather different estimates for perfusion (see Table 2), although mean residence times are similar for both delayed VIRFs.

- From: Tofts European Radiology 2012

- Work in progress: flat topped function
  - DHE2: Delay top Hat Exponential decay; decay portion constrained to have same area as top-hat portion
Summary

- Use uptake phase, parenchymal ROI’s and incorporate delay and dispersion in the model.
- Can fit longer dataset using complete model (with efflux); $K_{\text{trans}}$ is more variable (~40% more).
- Filtration and vascular parameters can be estimated with acceptable precision (9-18%).
- Accuracy may be good (normal values in agreement with literature).
- Accurate perfusion from peak of gaussian Vascular Impulse Response Function.
- Accurate blood volume using small vessel haematocrit (24%).
- The perfect biomarker! Biologically relevant, precise and (maybe) accurate.
- Total GFR seems accurate and could be used clinically to measure single kidney GFR.
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Error Propagation and choice of fixed parameters

• How sensitive are the fitted parameters (filtration, vascularity) to the fixed parameters (haematocrit, relaxivity, $T_{10}$)?

• Error Propagation Ratio
  % change in fitted parameter for 1% change in fixed parameter

• Reducing Hct$^\text{small}$ from 41% to 24% reduces $v_b$, $F$ improves accuracy

• Reducing tubular relaxivity $r_{1d}^\text{blood}$ from 4 s$^{-1}$ mM$^{-1}$ to 1 s$^{-1}$ mM$^{-1}$ (suggested by rat work) increases $K^{\text{trans}} \times 4$
  implausibly high $K^{\text{trans}}$
  unresolved mystery – true value of $r_{1d}^\text{blood}$?

• Increasing kidney $T_{10}$ reduces filtration and $F$ estimates
  measure $T_{10}$ if disease is present

• Mean Arrival Time MAT is robust unaffected by choice of fixed parameters

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Table: error propagation ratios

<table>
<thead>
<tr>
<th></th>
<th>$K^{\text{trans}}$</th>
<th>$v_b$</th>
<th>$F$</th>
<th>MAT</th>
<th>FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed tissue parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Hct^{\text{large}}$</td>
<td>-0.72</td>
<td>-0.69</td>
<td>-0.70</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$Hct^{\text{small}}$</td>
<td>0</td>
<td>+0.69</td>
<td>+0.69</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$r_{1d}^\text{blood}$</td>
<td>+0.98</td>
<td>+1.03</td>
<td>+1.03</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$r_{1d}^\text{d}$</td>
<td>-0.97</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-0.99</td>
</tr>
<tr>
<td>$r_{1d}^\text{glom}$</td>
<td>0</td>
<td>-0.98</td>
<td>-0.98</td>
<td>0</td>
<td>+0.99</td>
</tr>
<tr>
<td>$r_{1d}^\text{glom} = r_{1d}^\text{blood}$</td>
<td>+0.99$^c$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+0.99</td>
</tr>
<tr>
<td>$T_{10}^\text{blood}$</td>
<td>+1.04</td>
<td>+1.24</td>
<td>+1.29</td>
<td>0.02</td>
<td>-0.22</td>
</tr>
<tr>
<td>$T_{10}^\text{kidney}$</td>
<td>-1.06</td>
<td>-1.08</td>
<td>-1.14</td>
<td>0</td>
<td>+0.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fixed instrumental parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta$</td>
</tr>
<tr>
<td>$TR$</td>
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</table>

ESMI Les Houches

April 16-20 2012
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Hypothesis for scientific medical imaging

- Unless we are (contributing to) developing a biomarker we are wasting our talents

- Biomarker: sensitive to biological changes
  - reproducible (and reliable)
  - accurate (phantoms or other physiological measurement)
  - biologically relevant - responds to disease or interventions (normal physiology or treatment)
Principles for quantitative modelling

1. relate the model to the known tissue physiology
2. use the simplest possible model that fits the data
3. ensure the fit is reliable (e.g. independent of starting values; use constraints)
4. identify the influential fixed parameters (related to the instrument, CA and tissue) and measure the sensitivity of the fitted parameters to these.
5. use repeated imaging (if possible) to estimate measurement variance
6. use phantoms (if possible) to measure accuracy
7. output goodness-of-fit parameters (e.g. rms residual) and exclude fit failures
8. estimate (if possible) fitted parameter variance from Hessian (beware parameter covariance).