Quantitative MRI – how difficult is it?

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Overview

1. What do we mean by qMRI?
   1. What can make it difficult?
   2. FA, unstable receiver, segmentation ...
   3. Why might we want to do it anyway?
2. An example of qMRI – kidney DCE
   1. Measuring renal filtration and vascularity using Gd
   2. Precision and accuracy
3. Conclusion
   1. How difficult is it? What do you think?

Overview - qMRI

1. Quantification: the word
2. Paradigm shift
3. Measurement
4. Sensitivity & reproducibility
5. Sensitivity & biology
6. Specificity & biology
7. Tissue parameters
8. Accuracy
9. Ideal biomarker
10. More..

This talk is on: http://qmri.org

1. Quantification: the words

Quantify means 'to measure'

Quantitative Analysis was first used in a chemical context, meaning 'analysis designed to determine the amounts or proportions of the components of a substance'

Quantity: the thing we are measuring e.g. volume, T_1, permeability

Quantification – the operation of quantifying

(also Quantitation – means the same)

Quantitate – is not a word! (Oxford English Dictionary)

- is a 'back formation' (Webster USA)

2. 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

To: *scientific instrument*, set up by physicists, images analysed by neuroscientists, psychologists

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

3. three components of good quantification

could a quantity be useful?

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

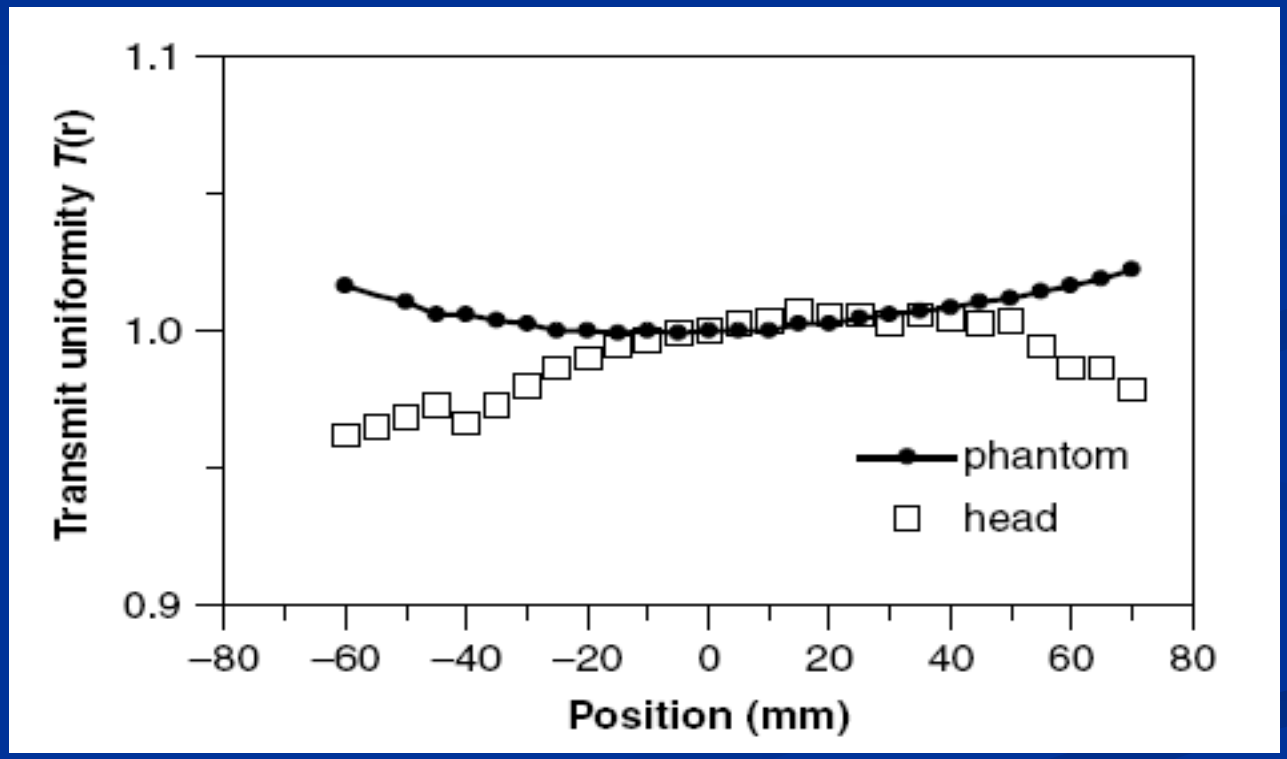
Hardware (coils), Pulse sequence, Subject positioning, Subject variation, any subjective elements of scanning, FA variation, receive variation, image noise

***Image data analysis* – the retrospective measurement**

Software, subjective components, can be automated

- *Radiofrequency transmit field* B_1
  - B_1 *and flip angle (FA) errors* are the largest source of error in qMR.
    - Magnetisation Transfer – saturation power
    - T_1 measurement (inversion pulse).
  - *Absolute (global) value* is set by APS (auto pre scan)
  - *RF transmit coil nonuniformity* causes B_1 to vary with position
  - $B_1(r)$ can be mapped
    - worst for small transmit/receive coil (e.g. head coil)
    - best for body transmit coil
      - often with multi-array receiver coil
  - *Residual nonuniformity* caused by subject
    - increases with field (3T..).

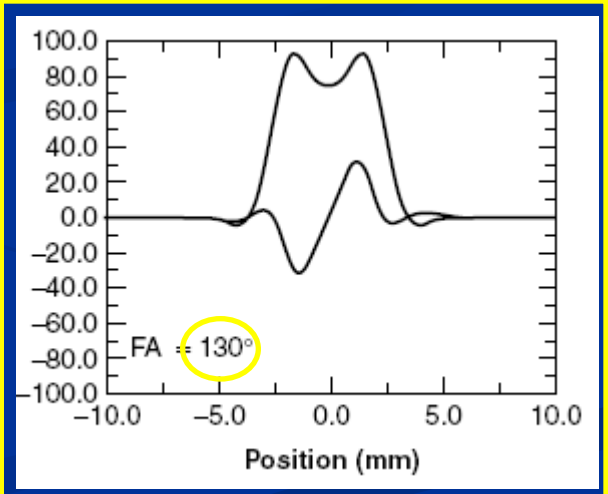
- 1.5T birdcage coil – transmit field
  - Transverse sensitivity
  - oil phantom – increase in sensitivity near bars of birdcage
  - Head – dielectric resonance gives 'doming'



Barker 1998

It gets worse.....

- *Slice selection*
  - In 2D sequences
    - FA varies across slice profile
    - slice profile varies with position (if B_1 is nonuniform).
    - Poor slice profile can degrade quantification.
    - correction using knowledge of selective pulse and $B_1(r)$
  - $B_1(r)$ mapping is a growing subject
  - 3D sequences preferred
    - harder, broadly-selective RF pulse.



Selective pulse designed to give 5mm slice with 90^0

Parker 2001

- *Receive sensitivity*
  - *depends on Coil loading*
    - depends on subject
    - electrical losses reduce Q.
  - *and on Receiver gain* **(adjusted by Auto Pre Scan or manually)**
    - ***R1 R2* on a GE**
  - **Control receiver gain in serial scans e.g. DCE-MRI**

Receive sensitivity (more)

- *Image noise*
  - measure in surrounding air
    - sd_air = 0.6 sd_subject. ; mean_air = 1.2 sd_subject
  - SNR can be increased
    - at expense of imaging time, spatial resolution, unwanted T_1-w

- *Receive nonuniformity*
  - can degrade qualitative appearance (*close fitting coils* for high SNR)
  - often does not degrade qMR, since *ratios* of images are used
  - exceptions: PD and spectroscopy (*absolute* signal is important).
  - Sometimes corrected in software: usually only qualitative
  - Can be (partially) corrected using phantom scan or B_1 map

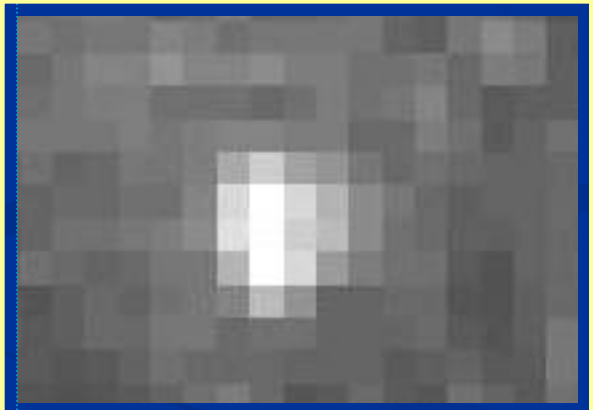
image analysis includes….

- *ROI analysis*
- *Histogram analysis*
- *Voxel-based group mapping*
- *Statistical analysis*
  - *Negative results (FN → TP?)*
  - *False positive results*
  - *Correlation*
  - *Classification*

- Region of Interest (ROI)
  - *simplest*: locate in various parts of the body.
  - *measure* mean value, sd and number of pixels (area in mm^2)
  - Can be *2D* (single slice) or *3D* (VOI, several slices).
  - manual or semi-automatic *generation*.
  - *Check adjacent slices* for partial volume errors (if measuring mean)
  - *Location of ROI* is source of variation in repeats
    - near edge of tissue
    - in heterogeneous location
    - If defined manually (auto segmentation is better)

ROI analysis

- **Partial volume effects (voxel too large or elongated) often prevent us measuring a pure tissue (e.g. grey matter).**
  - **Use small isotropic voxels where possible (compromise with SNR).**



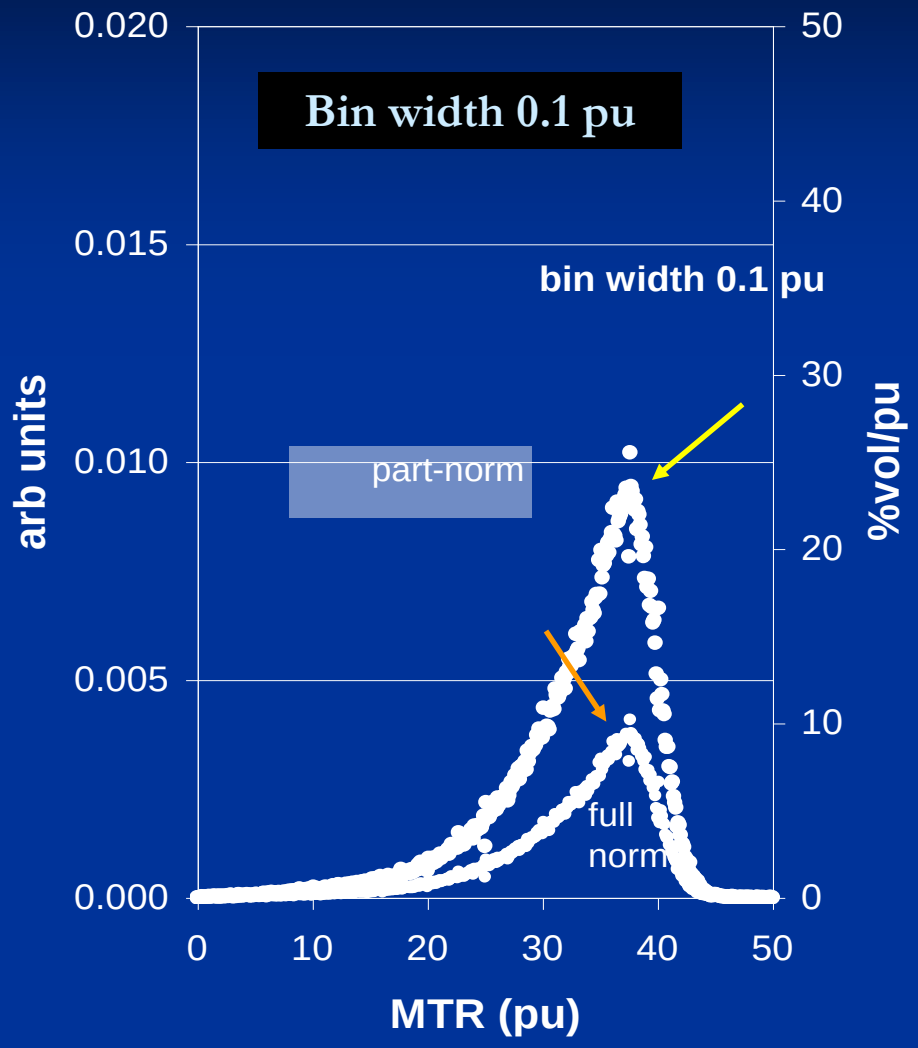
Small MS lesion.

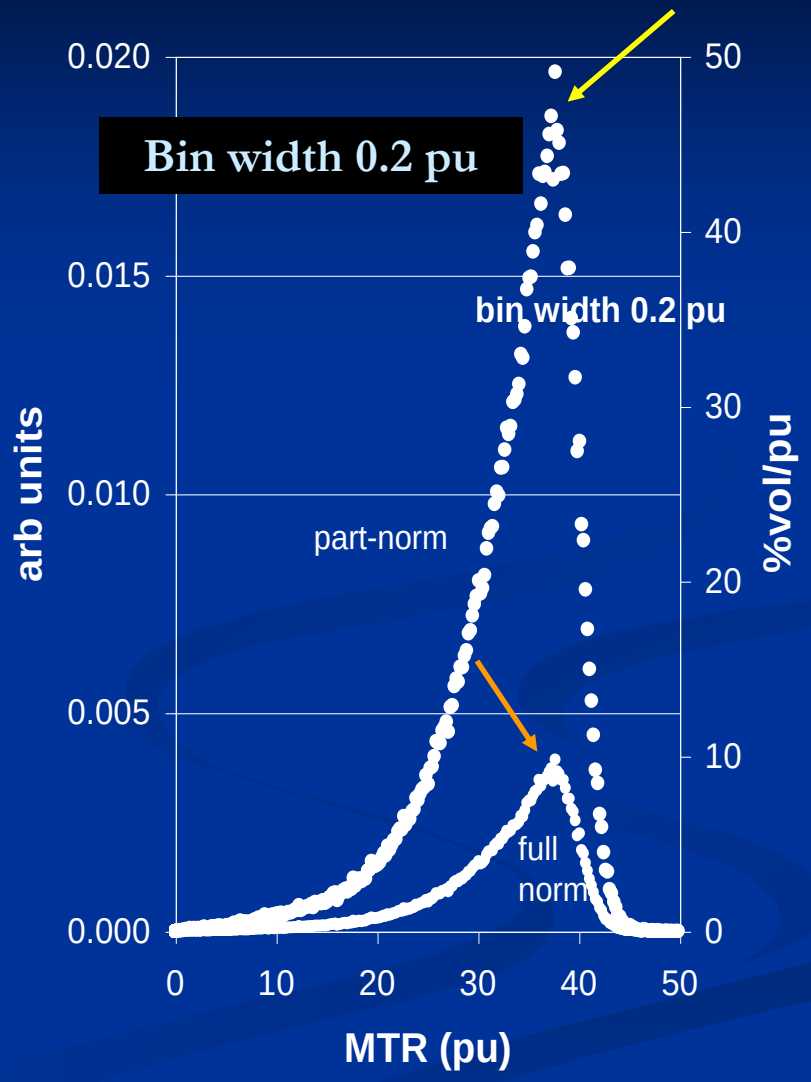
mean intensity?

size?

Histogram normalisation – multicentre comparisons

Full-norm PH=10%vol/pu; fwhm≈10pu; area under histogram =100%vol





4. Sensitivity needs reproducibility

- We want instrumental sd ISD << biological variation
  - cross-sectional study :ISD << (normal) group variation
  - serial study: ISD << within-subject variation - harder
- Measure ISD by repeated imaging of normals (healthy volunteers)
  - Bland-Altman analysis: look at SD of difference of repeats
- Many clinical studies are limited in statistical power by the ISD

Cross-sectional study

effect of ISD on sample size; the perfect instrument

- Normal tissue value = 100
- sd_normal = 3
- *perfect instrument**:

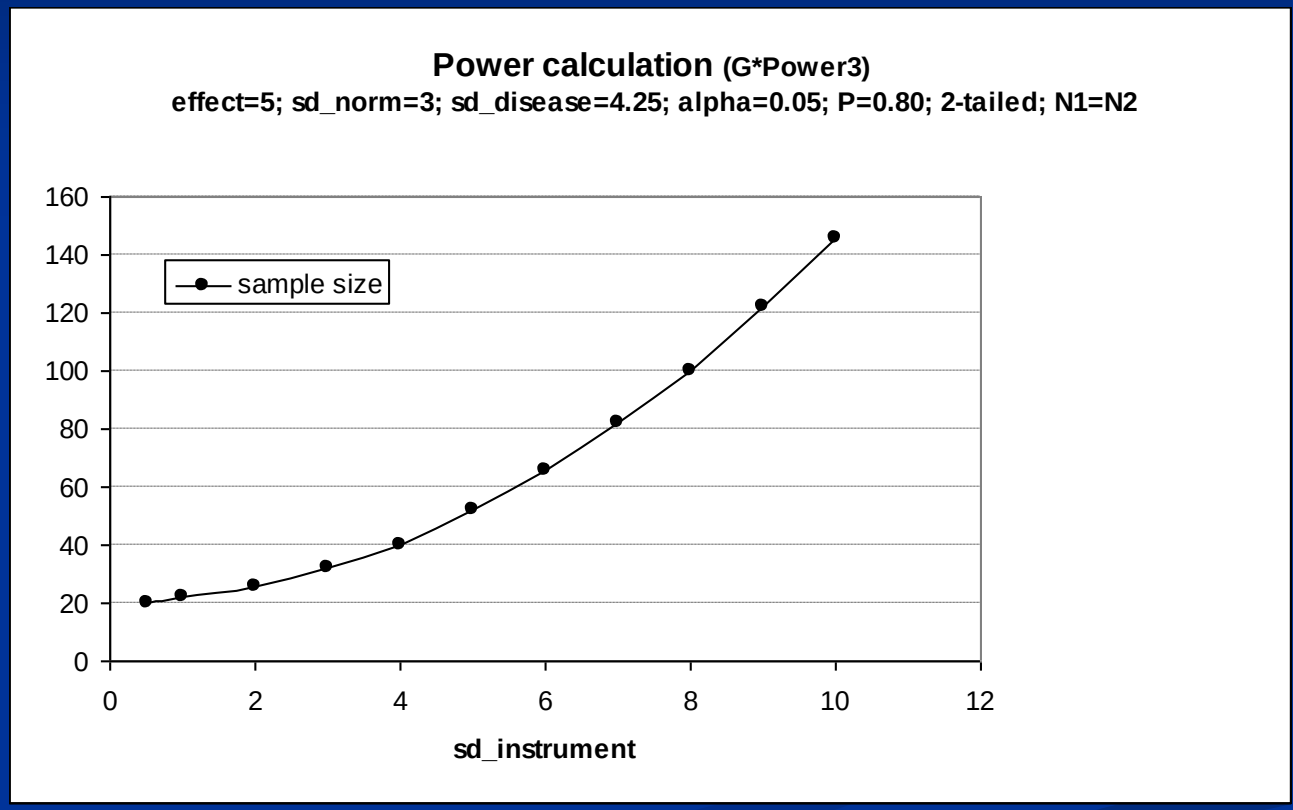
  isd << sd_normal

  isd << 3

- Serial study:
- ***perfect instrument ****

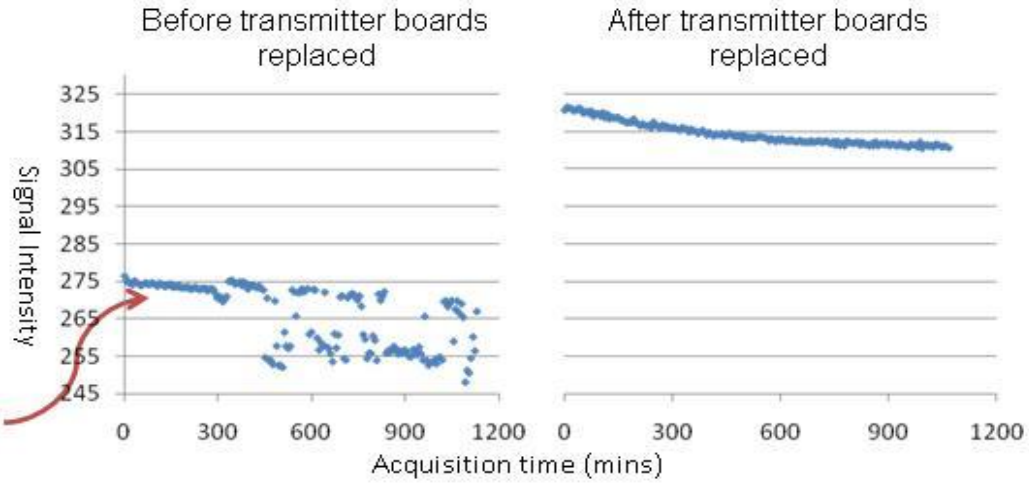
  isd << sd_within subject

  isd << 1

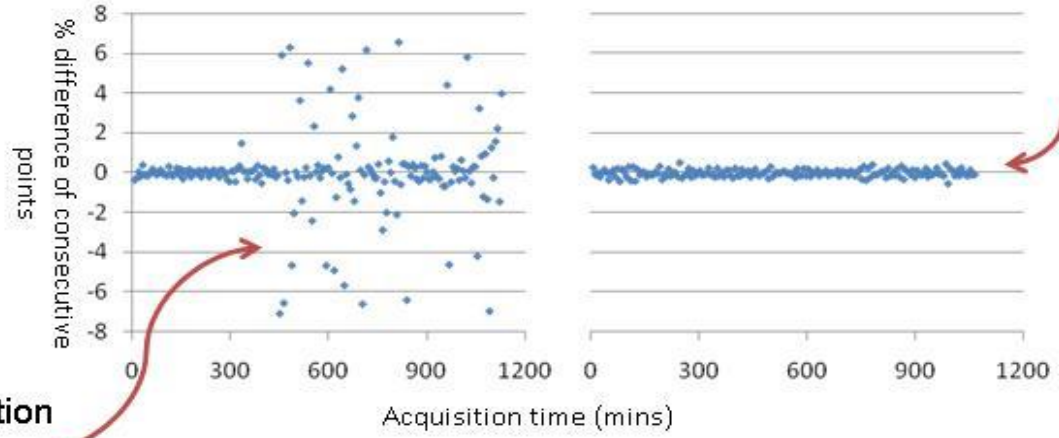


* *An instrument which is so precise that it does not introduce any significant variation to the existing biological variation*

Variation in Phantom Signal Intensity



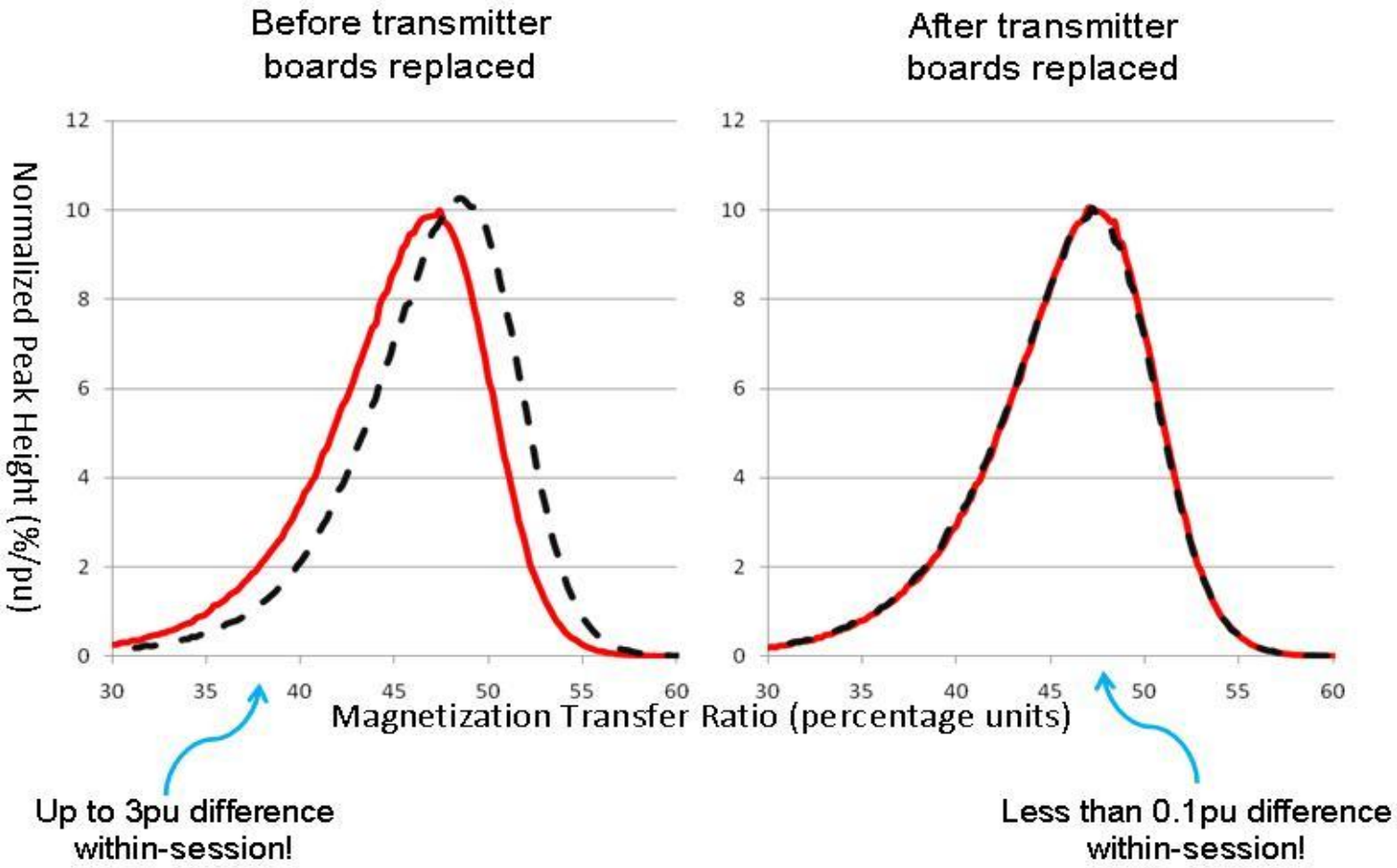
Short-lived stability



Less than 0.5% variation (SD <0.2%)

Up to 8% variation (SD >2.1%)

Whole-Brain MTR Histograms

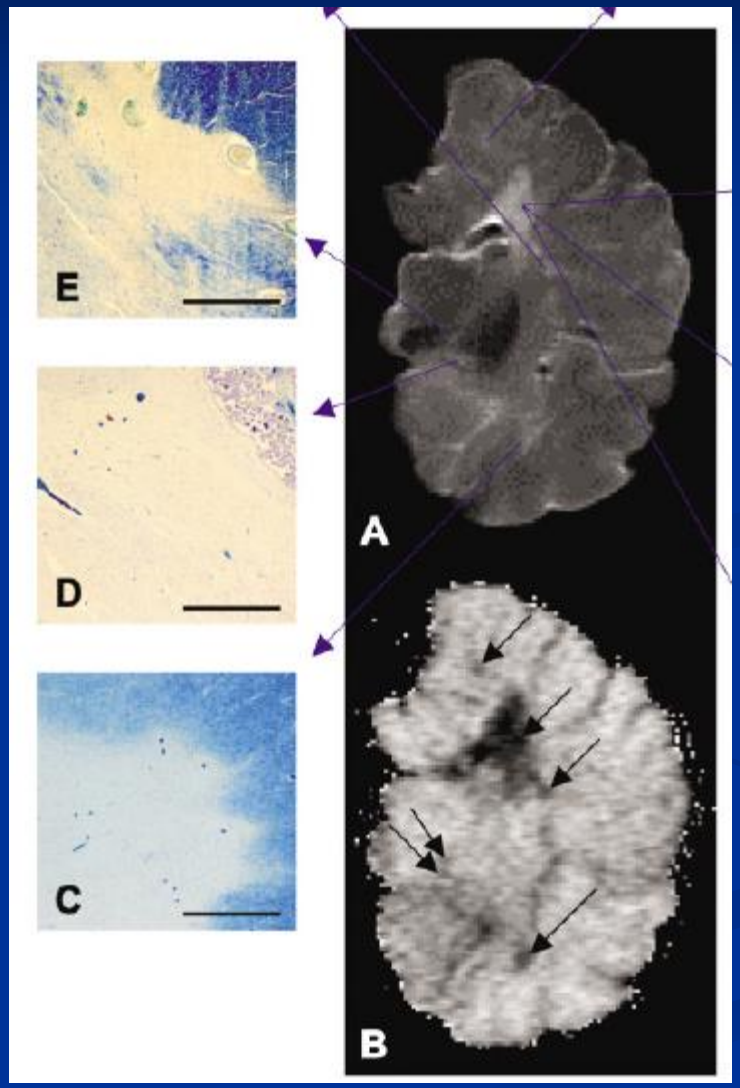


5. Sensitivity to biology

- A technique could be perfectly reproducible, yet completely insensitive to biological change (caused by for example disease).
- Thus after good reproducibility has been shown (often in healthy volunteers), sensitivity to biological change should be demonstrated. E.g. by:
- measuring *patients* in which a particular change is already known (e.g. reduction in renal function) or
- *Histo-pathological* studies (e.g. reduction in myelin in PM MS brain tissue samples seen with MTR) or
- in *healthy volunteers* where a particular change can ethically be brought about (e.g. increase in lactic acid concentration in muscle after application of a tourniquet).

histopathology

- Luxol Fast Blue stain shows myelin
- areas with low MTR show less blue = low myelin concentration
- Myelin concentration correlates with MTR
  - (r=-0.84 from myelin transmission value)



T_2w image of brain slice

MTR map of brain slice; dark areas indicate demyelination

Schmierer Ann Neurol 2004;56:407

6. Specificity and biology

- *Specificity* is the ability to distinguish between several kinds of biological abnormality that may be present (e.g. In brain, oedema vs. demyelination)

- Sometimes this is an important reason for using a particular quantity

- E.g. When monitoring response of tumour to treatment,
  - Size is traditional measure (but cannot tell if tumour is alive or not)
  - Signal enhancement after Gd injection gives more idea (but qualitative; also depends on T_1 of tumour)
  - K^{trans} has a known dependence on blood perfusion and capillary wall permeability, and better indicates the tumour biology
  - Spectroscopy often very specific (but not reproducible or precise)

- Often hard to establish specificity for in-vivo studies:
  - Specificity is desirable but not always achievable

7. Tissue parameters

Principle quantities that are candidates for quantitative biomarkers are:

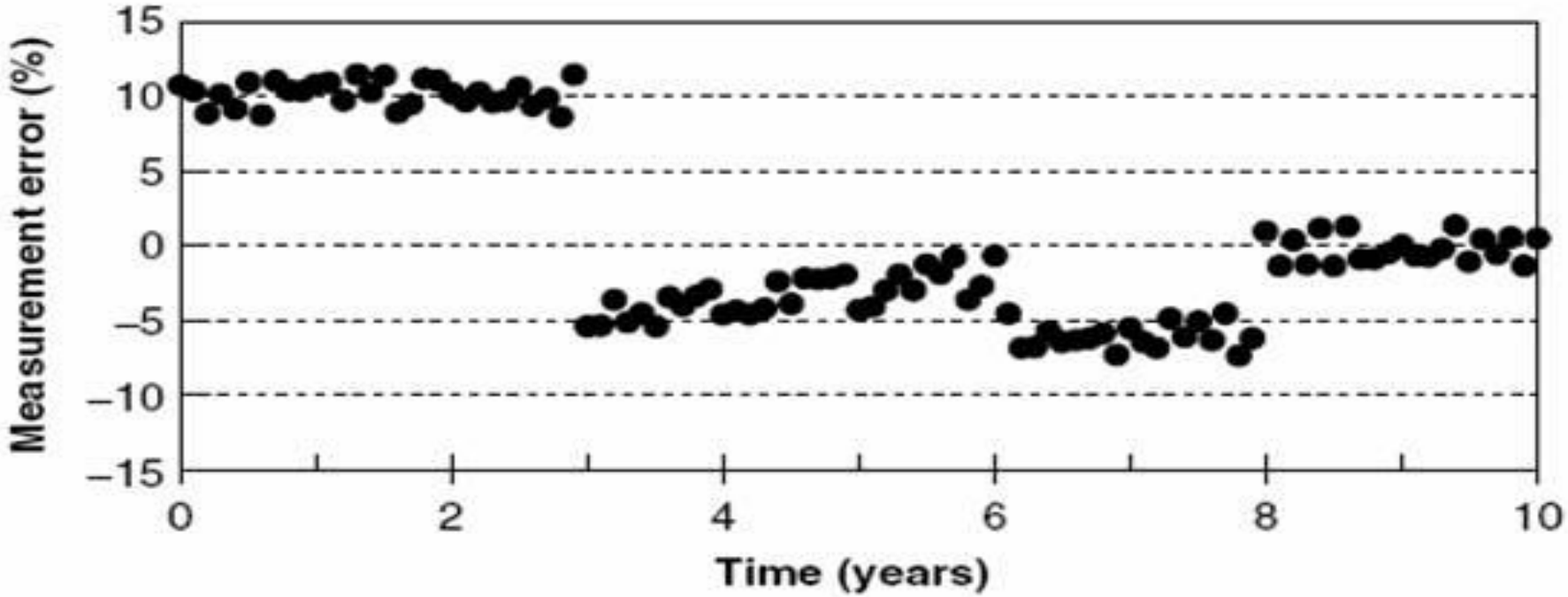
- Proton Density (PD) (gives water content)
- longitudinal relaxation time T_1
- transverse relaxation time T_2
- diffusion and its tensor
- magnetisation transfer: ratio (MTR) and 'quantitative MT'
- spectroscopy (gives metabolite concentrations)
- dynamic T_1-weighted MRI (measure transfer constant K^{trans} from uptake of contrast agent, particularly in tumours)
- dynamic $T_2^{(*)}$-weighted MRI (for blood flow and volume),
- blood perfusion (flow) using Arterial Spin Labelling (ASL).

Image analysis techniques include volume, histograms and texture (applied to any of the above).

8. Accuracy

- Accuracy (closeness to the truth) is often helpful:
  - Establishes credibility of the measure
  - Accuracy sometimes not vital
    - small systematic error can often be tolerated (in a single centre –short study), but…
  - Systematic errors are not usually stable
  - Comparison of studies, and multicentre studies are confounded by variable systematic error
- Measurement of accuracy:
  - Quality Assurance using phantoms (truth is known)
  - Humans good to establish accuracy by comparison with other studies
  - (Humans also good for stability)

- does systematic error matter?
  - In short-term single-centre study – NO
  - In multi-centre studies – YES
  - In long studies – PROBABLY
    - systematic error (if present, and not understood) can vary with centre and with time. BEWARE UPGRADES
    - Fictitious example: changes in systematic error wreck study



- Normal Controls vs phantoms (test objects)

	control	phantom
Stability over time	Good	Geometric good; **others poor (decay)**
Stable temperature?	Very good	**Often ±2°C (≈5%)**
realistic?	yes (but no pathology)	**no**
Truth known?	**No**	Yes
convenient?	**No**	Yes

- Use both, according to the MR quantity and purpose

- Phantoms exist for many MR quantities
  - but not all – use normal controls
  - Volume
    - easy – stable, well-defined geometric objects
    - Acrylic (perspex, plexiglass) and water
  - T_1 T_2
    - doped agarose gels - stability?
    - Ni T_1 is temperature independent
  - Diffusion
    - ADC: alkanes (although T_1 T_2 too long); iced water
    - DTI – hard. Need bundles of small fibres.
  - MT (MTR, qMT)
    - BSA (Bovine Serum Albumin) – stability?
  - Temperature
    - control and monitoring possible to 0.1°C (Jackson ismrm 2006)

9. Ideal biomarker

- Imaging biomarker (as defined by FDA) is similar to a quantitative measure
- Interest is increasing rapidly in the use of surrogate markers as primary measures of the effectiveness of investigational drugs in definitive drug trials. Many such surrogate markers have been proposed as potential candidates for use in definitive effectiveness trials of agents to treat neurologic or psychiatric disease, but as of this date, there are no such markers that have been adequately "validated," that is, shown to predict the effect of the treatment on the clinical outcome of interest. Katz 2004 (US Food and Drug Administration FDA)

- For any new proposed quantitative measure (biomarker), ask these questions!
- 1. Is it reproducible in-vivo? (precision)
  - What is the smallest change that can reliably be detected?
- 2. Is it accurate in-vivo?
  - Is it robust in the face of flip angle error and being off-resonance?
- 3. Is it specific to a particular aspect of the biology?

Overview

1. What do we mean by qMRI?
   1. What can make it difficult?
   2. FA, unstable receiver, segmentation ...
   3. Why might we want to do it anyway?
2. An example of qMRI
   1. Measuring renal filtration and vascularity using Gd
   2. Precision and accuracy
3. Conclusion
   1. How difficult is it?

Accurate and precise measurement of renal filtration and vascular parameters using DCE-MRI and a 3-compartment model.

P.S. Tofts[1,2], M. Cutajar[1,3], I. Mendichovszky[3,4], I. Gordon[3]

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[2]UCL Institute of Neurology, London, United Kingdom
[3]UCL Institute of Child Health, London, United Kingdom
[4]University of Manchester, Manchester, United Kingdom

Overview

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

K^{trans} filtration (GFR/unit volume) → GFR

v_b blood volume %

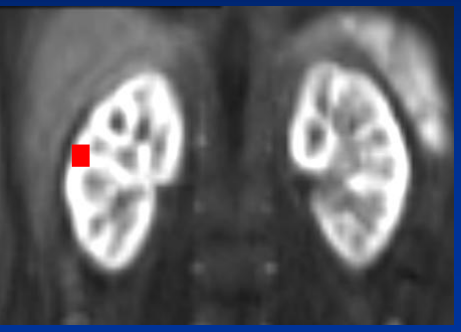
F perfusion ml blood (100 ml tissue) min-1

FF filtration fraction $FF = K^{trans} / ((1-Hct)*F)$

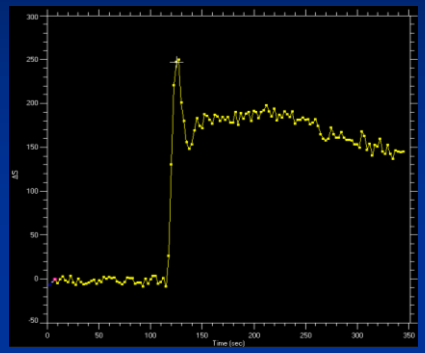
15 normal subjects were each imaged twice, to enable reproducibility to be measured (Bland-Altman analysis)

Accuracy by comparison with published values

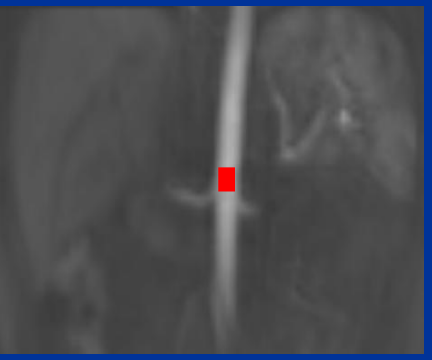
MRI Acquisition



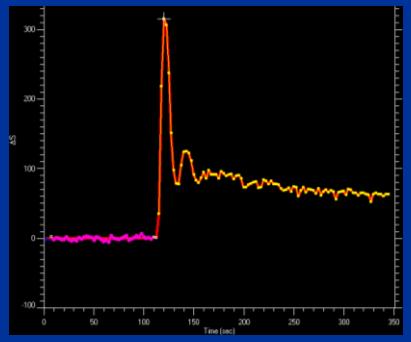
Cortical ROI



Time of peak



Arterial ROI



Arterial Input Function AIF

- 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 mm^2
- 18 x 7.5 mm **coronal slices** covering entire kidney (no gap)
- Voxel size = 3.1 × 3.1 × 7.5 mm^3
- Frames acquired every 2.5 s
- Gd dose = 0.05 mmole/kg (**half dose**)

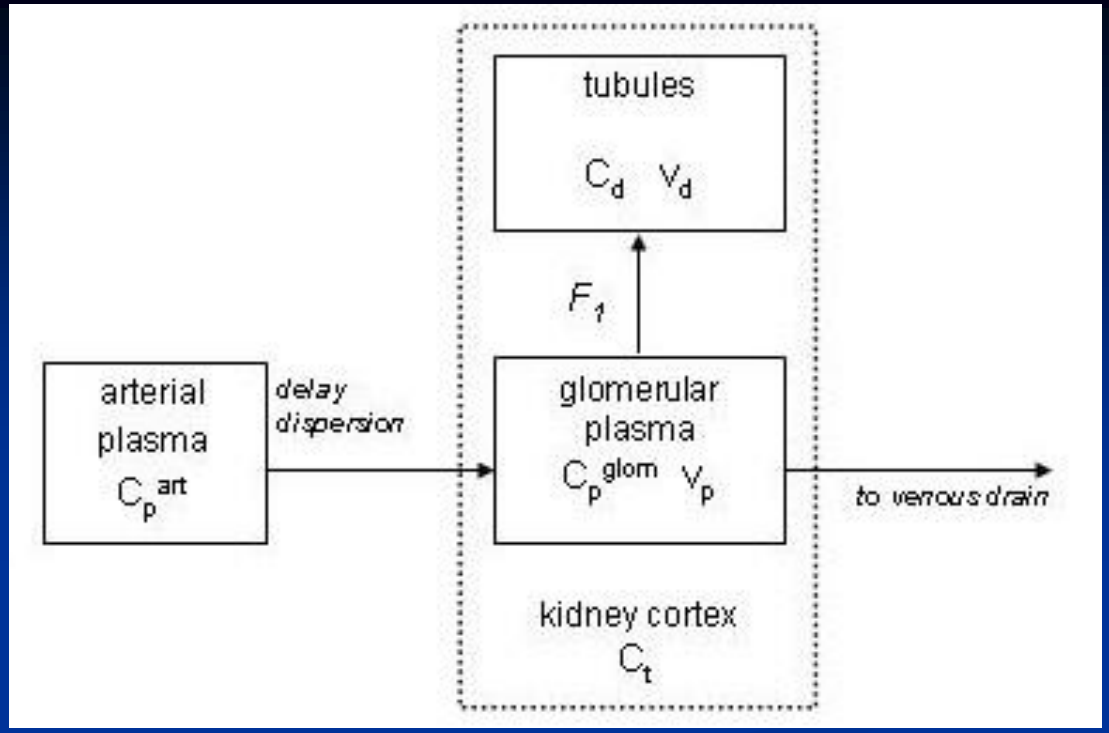
Kidney model

Uptake mode

no efflux from tubules (t<90s)

K^{trans} = transfer constant from plasma to kidney

(=GFR per unit volume of tissue)



glomerular plasma

g(t) = Glomerular Input Response Function

tubular tracer C_d

total tracer C_t

$$C_p^{glom}(t) = C_p^{art}(t) \otimes g(t) = \int_0^t C_p^{art}(t-\tau) g(\tau) d\tau$$

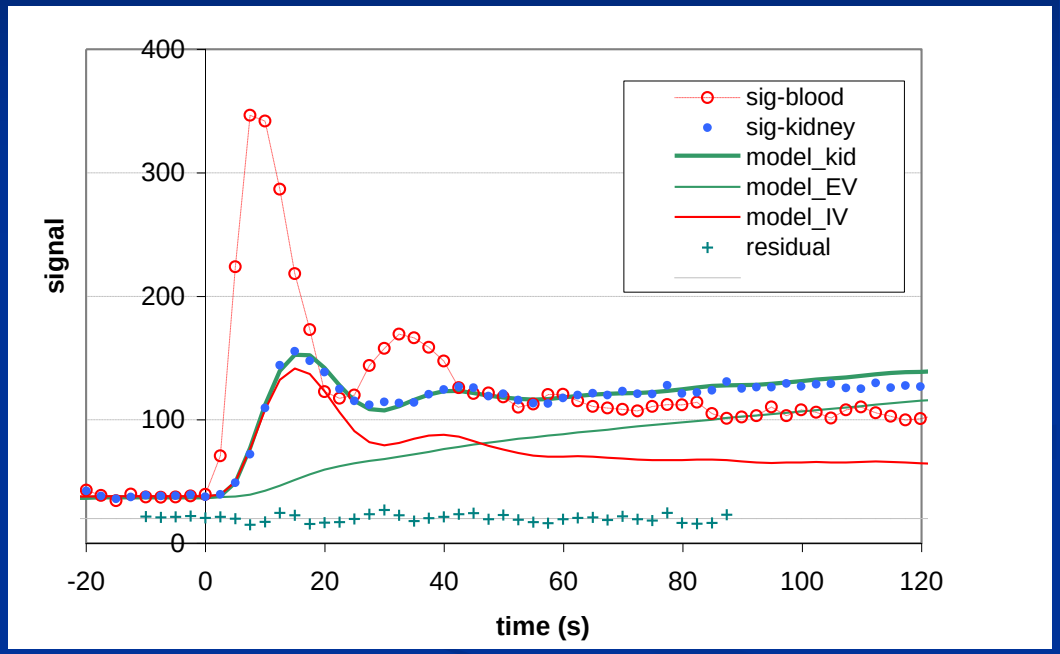
$$v_d \frac{dC_d}{dt} = F_1 = K^{trans} C_p^{glom}$$

$$v_d C_d(t) = K^{trans} \int_0^{\tau} C_p^{glom}(\tau) d\tau$$

$$C_t(t) = v_b (1 - Hct^{small}) C_p^{glom} + v_d C_d(t)$$

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)

Error Propagation and choice of fixed parameters

- How dependant are the *fitted* parameters (filtration, vascularity) on the *fixed* parameters (haematocrit, relaxivity, T_{10}) ?

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

- Reducing Hct^{small} from 41% to 24% reduces v_b, F
  improves accuracy

- Reducing tubular relaxivity r_1^d from 4 s^{-1} mM^{-1} to 1 s^{-1} mM^{-1} (suggested by rat work) increases K^{trans} ×4
  implausibly high K^{trans}
  unresolved mystery – true value of r_1^d ?

- Increasing kidneyT_{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

	K^{trans}	v_b	F	MAT	FF
Fixed tissue parameters					
Hct^{large}	-0.72	-0.69	-0.70	0	0
Hct^{small}	0	+0.69	+0.69	0	0
r_1^{blood}	+0.98	+1.03	+1.03	0	0
r_1^{d}	-0.97	0	0	0	-0.99
r_1^{glom}	0	-0.98	-0.98	0	+0.99
$r_1^{glom} = r_1^{blood}$	+0.99 [c]	0	0	0	+0.99
T_{10}^{blood}	+1.04	+1.24	+1.29	0.02	-0.22
T_{10}^{kidney}	-1.06	-1.08	-1.14	0	+0.22
Fixed instrumental parameters					
θ	-0.07	+0.25	+0.29	0.03	-0.38
TR	0	-0.13	-0.15	0	+0.16

Table: error propagation ratios

Estimation of Glomerular Impulse Response Function

- GIRF = Response in glomeruli to concentration spike in aorta

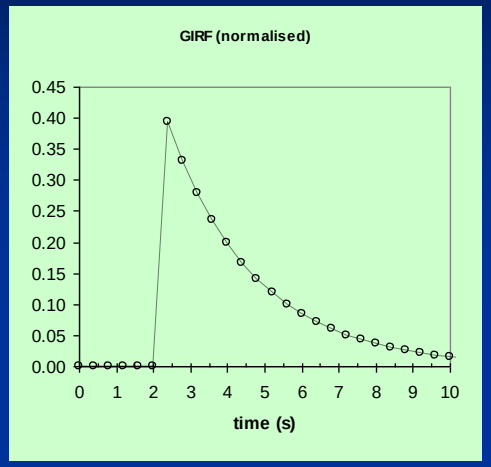
- Delayed exponential and delayed gaussian GIRFs fit well
  - Instant exponential GIRF fits worse

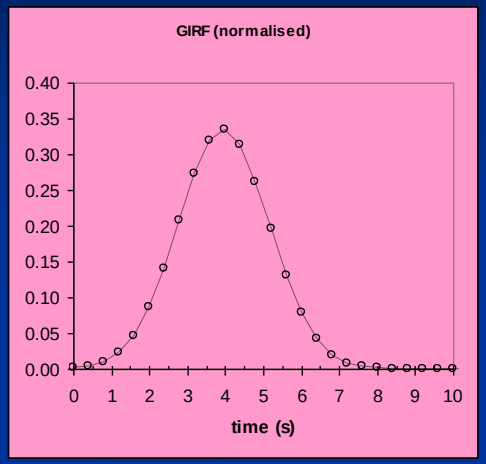
- Dispersion in vascular bed makes gaussian more plausible
  - Especially in large ROI
  - Tissue IRF measured by Sourbron; initial peak of this is vascular (i.e. GIRF) and looks gaussian

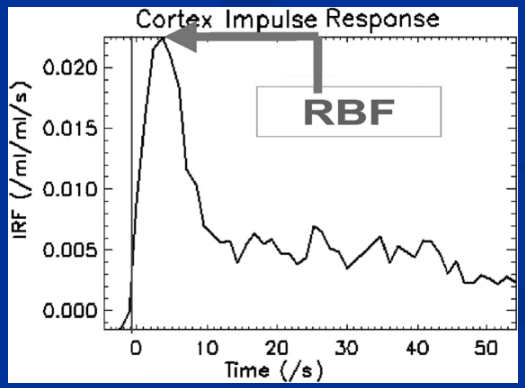
- Perfusion F estimation.. is tricky
  - From peak of exponential
    Valid for gaussian??
  - From Mean Arrival Time
    $F = v_b/MAT$?
  - All 4 methods have similar precision

- Accuracy is desirable
  - Gain clinical acceptance

- We have used peak of gaussian GIRF







Dujardin JMRI 2009

	peak	MAT
exponential	451	430
gaussian	282	450
literature	258	

F ml blood (100 ml tissue) $^{-1}$ min $^{-1}$
Parenchymal ROI; Hct=41%

ISMRM10 Stockholm

Normal values

parenchymal ROIs in uptake mode

		MRI mean±sd	instrumental sd	literature normal
filtration (min^{-1})	K^{trans}	0.25±0.05	0.04 (15%)	0.28(a)
blood volume (%)	v_b	34±8	6 (17%)	35 (c)
perfusion ml blood min^{-1} $(100\ ml)^{-1}$	F	219±53	26 (12%)	258(b)
filtration fraction (%)	FF	15.5±2.8	1.2 (8%)	15-20
Mean Arrival Time (s)	MAT	5.9±0.7	0.4 (6%)	6.5 (d)
absolute single kidney volume (ml)	V_{kid}	230±28	-	213
standardised kidney volume (ml)	V_{kid}^*	214±20		213
total GFR (ml min^{-1})	115	27		120

Values in yellow are updated from abstract values **(using F from peak of gaussian GIRF, and Hct^{small}=24%)**

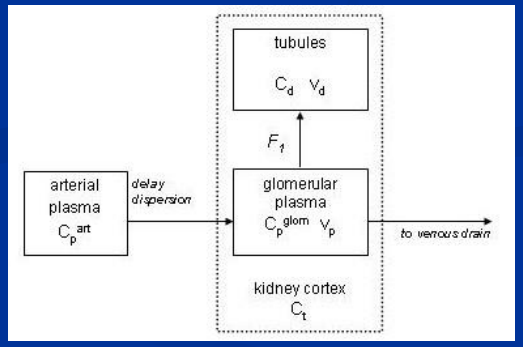
(a) = GFR/($2V_{kid}$*) **(b) using RBF = 1.1 litre min^{-1}** **(c) from CT** **(d) Sourbron Invest Radiol 2008**

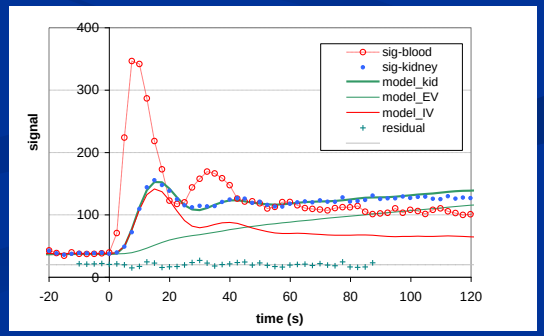
CONCLUSION: our values for four physiological parameters are accurate (and FF and MAT are precise and could be useful)

ISMRM10 Stockholm

Summary

- Use uptake phase, parenchymal ROI's and incorporate delay and dispersion in the model
- Filtration and vascular parameters can be estimated with acceptable precision (6-15%)
- Accuracy is good (in agreement with literature).
- Accurate perfusion from peak of gaussian Glomerular Impulse Response Function
- Accurate blood volume using small vessel haematocrit (24%)
- The perfect biomarker! Biologically relevant, precise and accurate
- Total GFR is accurate and could be used clinically to measure single kidney GFR
- This talk: on http://qmri.org
- Matlab GUI by Andy McGovern: http://www.mcgov.co.uk/toftsmodel



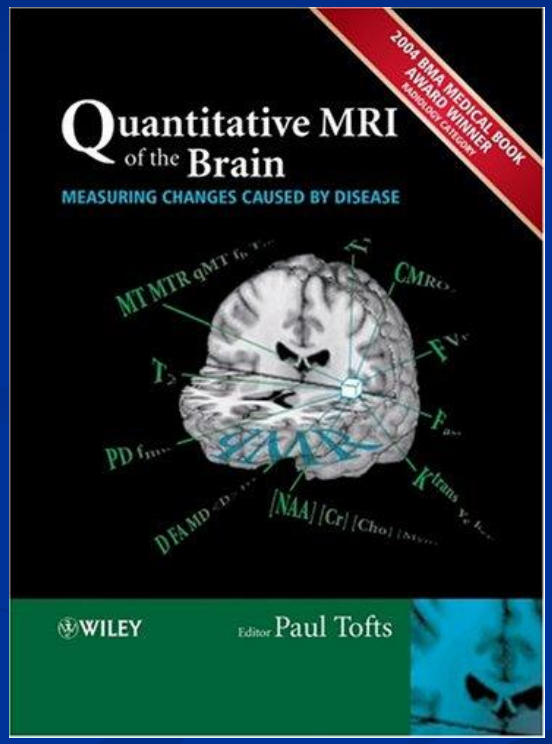


10. More....

This oral presentation is on
http://www.paul-tofts-phd.org.uk/talks/ and qmri.org

The qMRI site http://qmri.org has a variety of information and is growing.

The book [1] gives a comprehensive tour of the issues, and surveys the principle qMR tissue parameters
(although the clinical applications are now a little dated).



1. Tofts PS. Quantitative MRI of the brain: measuring changes caused by disease. John Wiley, 2003.

Is it worth it?

- Studies of white matter MTR show range of normal variation (2x)
- Contribution of instrumental variation
- Fixing our scanner reduced our normal variation SD from worst (1.0) to best (0.5)
- qMRI is
  - labour intensive, needs lots of physics input
  - Reduces sample size needed (saves lots of scans...)
  - 0.5 physicist-years vs. 50 patient scans vs. negative study result?
- Not so difficult!

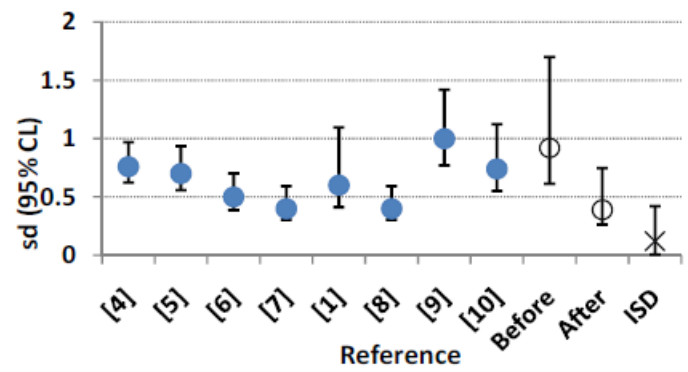
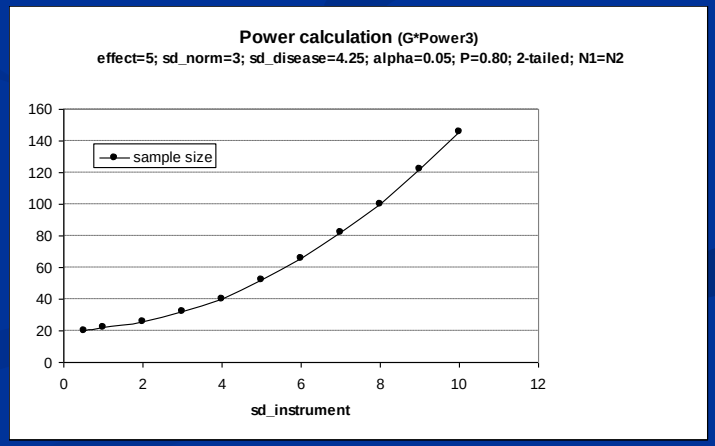



Figure 3: Normal variation (sd) for white matter MTR. Published values [1,4-10], measured values before and after changing the transmitter boards, and instrumental variation - ISD (after only).