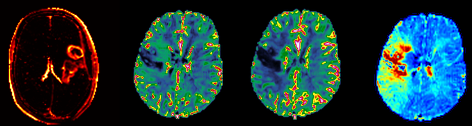

CONTRAST ENHANCED PERFUSION IMAGING

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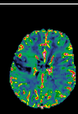
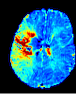
Oslo University Hospital

UNIVERSITY OF OSLO

Overview



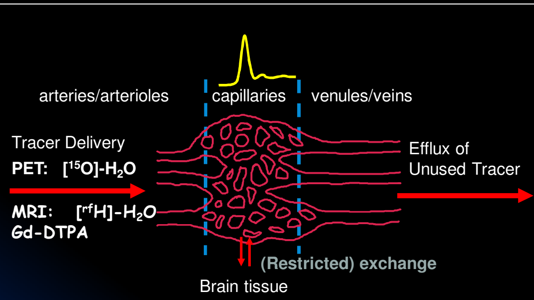
- Imaging methods:
  - T1- , T2 and T2* based analysis
  - Dose-response
- Kinetic modeling:
  - One- and two-compartments
  - 'Perfusion' and 'Permeability', DSC, DCE
- Arterial input function (AIF) and deconvolution
- 'Leakage' effects in tumor perfusion analysis
- Sequence considerations and protocol requirements



MR-based perfusion imaging Two approaches:

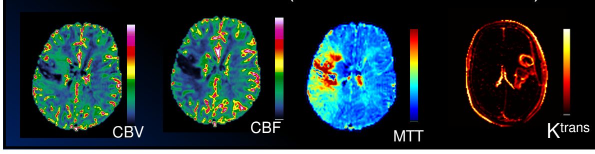
- Arterial spin labeling (ASL)
  - Use of blood as endogenous contrast agent (flow)
- Contrast-enhanced imaging
  - I.v. injection of gadolinium based contrast agents
    - VASO (volume)
    - Dynamic First-pass imaging (flow / volume)

Perfusion models



Biomarkers accessible through DCE and DSC analysis

- Tissue blood flow (perfusion, CBF)
- Tissue blood volume (CBV)
- Mean Transit Time (MTT)
- Capillary permeability (K^{trans})
- Extracellular volume (Ve, distribution volume)



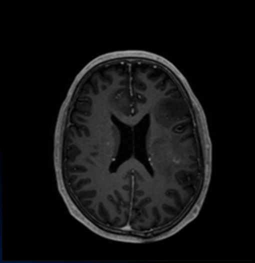
Perfusion MRI applications

- Acute stroke
  - CBV/CBF mismatch (MTT)
- Tumor imaging
  - Contrast agent permeability analysis (DCE)
  - Blood volume analysis (DSC)

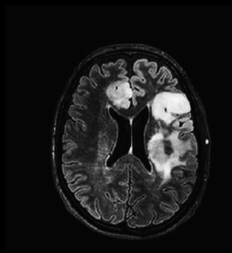
Two different kinetic models:

- I.V. effect: Central Volume Principle (flow/volume)
- E.V. leakage: Permeability analysis (Ktrans, EES, volume)

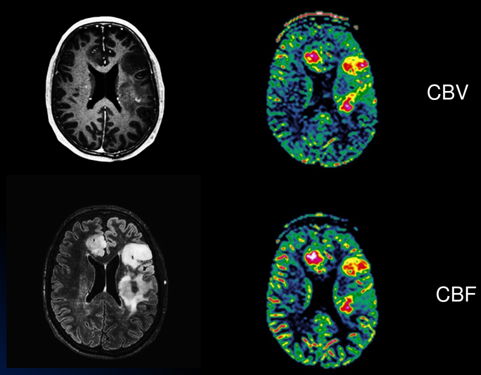
Grade IV gliomatosis cerebri



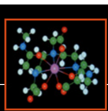
T1-w post contrast



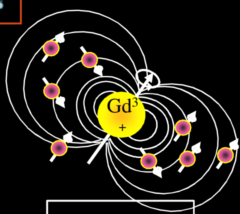
FLAIR

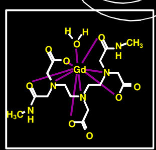


Paramagnetc ions



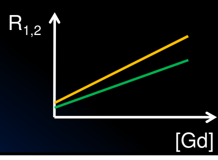
- Metal ions with unpaired electrons:
  - → gadolinium (Gd^{3+})
  - → iron (Fe^{2+} / Fe^{3+})
  - → manganese (Mn^{2+})
- Magnetic moment of unpaired electrons is >> magnetic moment of protons
- Dipolar magnetic interaction between electrons and water protons



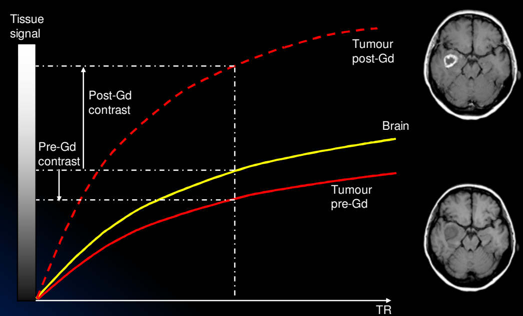


Important terms

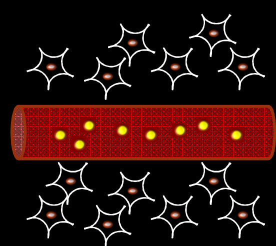
- Proton relaxation times: T_1, T_2, T_2^* [ms]
- Relaxation rates: R_1, R_2, $R_2^* = 1/T_1, 1/T_2, 1/T_2^*$ [1/s]
- Contrast agent relaxivity ($r_{1,2}$): ability of CA to increase relaxation rates
  - $R_{1,2}=R_{1,2}^0 + r_{1,2}[C]$; $r_{1,2}$ in $mM^{-1}s^{-1}$



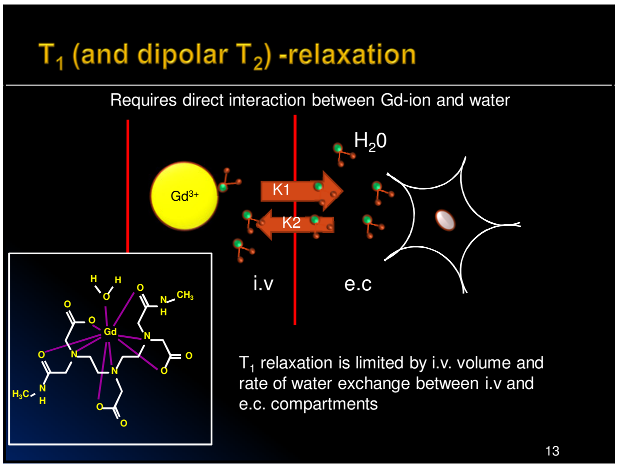
Paramagnetic agents in contrast enhanced MRI T1-weighted MR

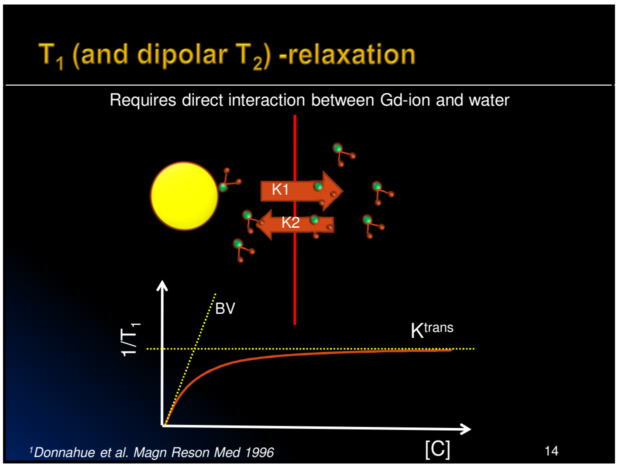


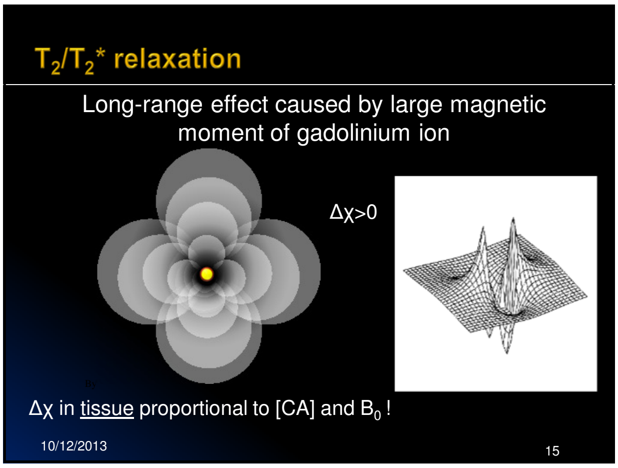
Gd-extracellular fluid (ECF) agents are intravascular in the brain (BBB)

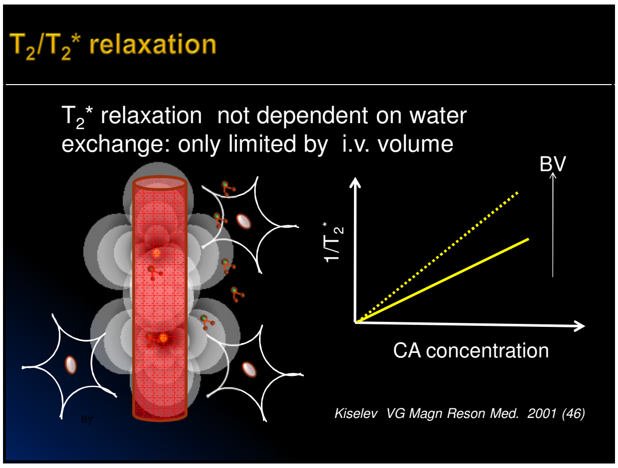


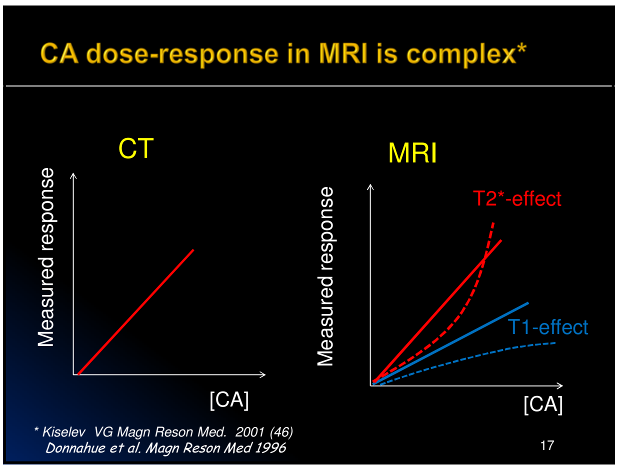
MW ≈ 900 D

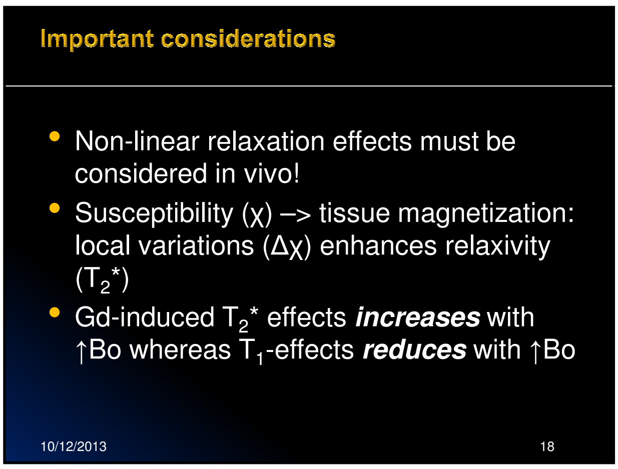

T1 (and dipolar T2) -relaxation
Requires direct interaction between Gd-ion and water
H20
Gd3+
K1
K2
i.v
e.c
Gd
T1 relaxation is limited by i.v. volume and rate of water exchange between i.v and e.c. compartments
13


T1 (and dipolar T2) -relaxation
Requires direct interaction between Gd-ion and water
K1
K2
BV
1/T1
Ktrans
[C]
1Donnahue et al. Magn Reson Med 1996
14

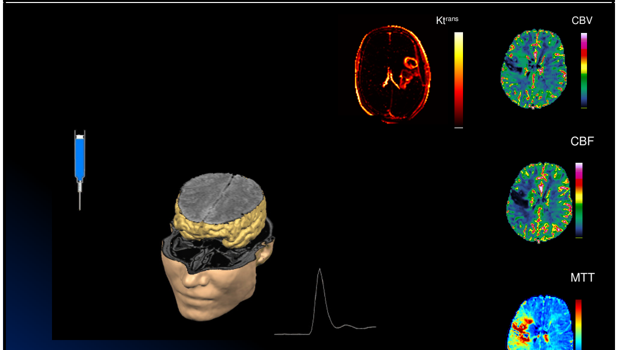

T2/T2* relaxation
Long-range effect caused by large magnetic moment of gadolinium ion
Δχ>0
Δχ in tissue proportional to [CA] and B0 !
10/12/2013
15


T2/T2* relaxation
T2* relaxation not dependent on water exchange: only limited by i.v. volume
BV
1/T2*
CA concentration
Kiselev VG Magn Reson Med. 2001 (46)


CA dose-response in MRI is complex*
CT
MRI
Measured response
T2*-effect
T1-effect
[CA]
[CA]
* Kiselev VG Magn Reson Med. 2001 (46)
Donnahue et al. Magn Reson Med 1996
17

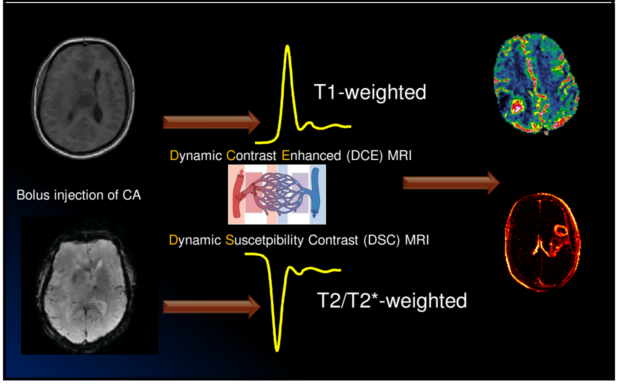

Important considerations
Non-linear relaxation effects must be considered in vivo!
Susceptibility (χ) –> tissue magnetization: local variations (Δχ) enhances relaxivity (T2*)
Gd-induced T2* effects increases with ↑Bo whereas T1-effects reduces with ↑Bo
10/12/2013
18

The ‘contrast enhanced perfusion’ procedure

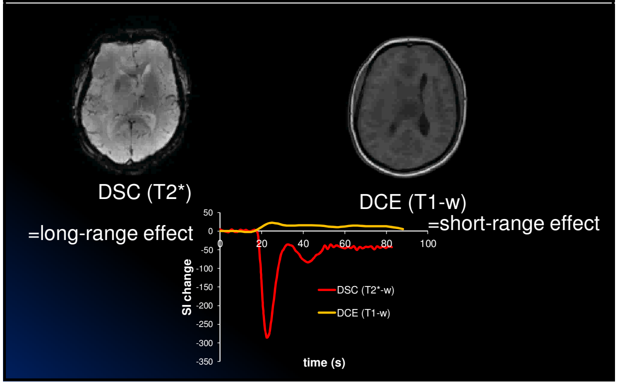


Courtesy of Dr. Kyrre Emblem, OuH

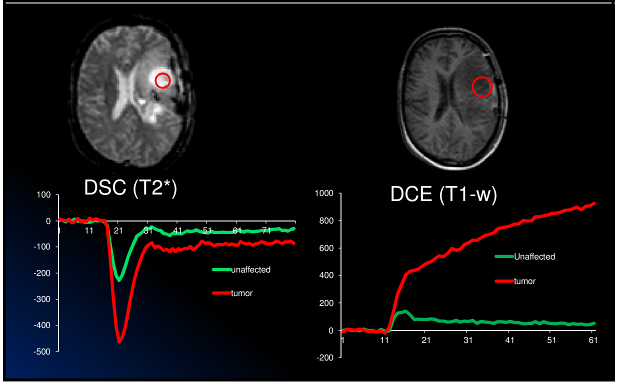
T1-w versus T2/T2*-w perfusion imaging



Normal brain: dynamic T1 vs T2*-effects



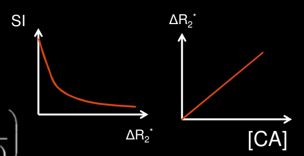
Tumors: dynamic T1- vs T2* effects

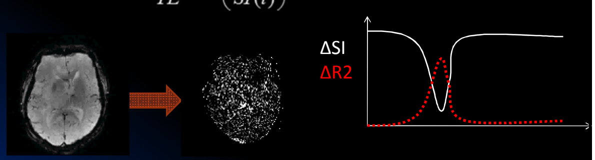


DSC (T2/T2*) dose-response

- DSC assumptions:
  - $SI = SI_0 \exp(-TE \cdot \Delta R_2^*)$
  - $[CA] = k \cdot \Delta R_2^*$

$$C(t) = k \cdot \Delta R_2^* = \frac{k}{TE} \log_e \left(\frac{SI_0}{SI(t)} \right)$$

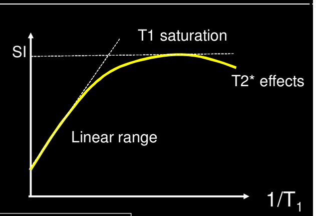


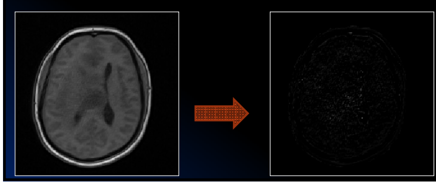


T1-weighted dose-response

$$R_1(t) = 1/T_{1,0} + r_1[CA(t)] \Rightarrow [CA] = \frac{\Delta R_1}{r_1}$$

$$\Delta R_1(t) = f(T_1(0), \alpha, TR/TD)$$





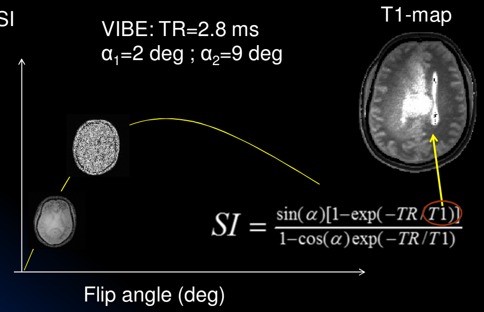
Basline T1-map

- Conversion of SI change to absolute change in 1/T1 requires knowledge of baseline T1
- Different from DSC (T2*) where baseline T2* is not required
- Two methods used for T1-calculation:
  - Inversion/saturation recovery with multiple delay times
  - GRE with multiple flip angles
- HOWEVER: question whether baseline T1 estimation improves accuracy...[1]

[1] Haacke et al. Magn Reson Med 2007

Baseline T1-mapping: multi-flip

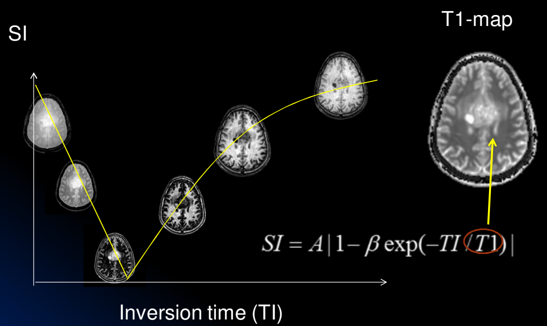
VIBE: TR=2.8 ms
α_1=2 deg ; α_2=9 deg



$$SI = \frac{\sin(\alpha)[1-\exp(-TR/T1)]}{1-\cos(\alpha)\exp(-TR/T1)}$$

NB: B1-effects (errors in flip angle)

Baseline T1-mapping: multi-inversion ('Look-Locker')



$$SI = A\,|1-\beta\exp(-TI/T1)|$$

Perfusion analysis T1- vs T2/T2* pros and cons

T1-weighted:

- ✓ Better image quality (GRE vs EPI)
- ✓ More linear dose-response (?)
- ✗ Poorer CA sensitivity in brain
- ✗ Poorer temp res / coverage
- ✗ Requires baseline T1-map (?)

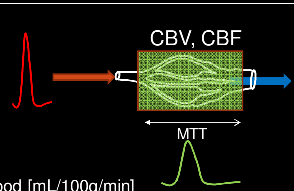
T2/T2*-weighted (DSC):

- ✓ Higher CA sensitivity in brain
- ✓ Higher temp resolution
- ✓ Increasing CA sensitivity with Bo
- ✗ Poorer image quality
- ✗ More geometric distortions
- ✗ Complex leakage effects (tumor CBV)
- ✗ Non-linear dose response (quantification)

Kinetic modeling

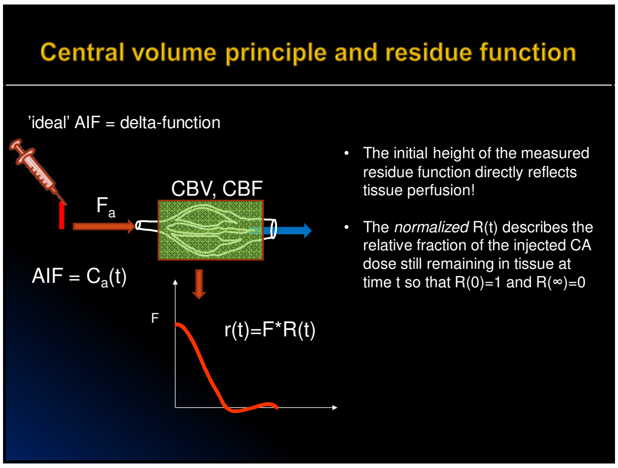
Perfusion analysis

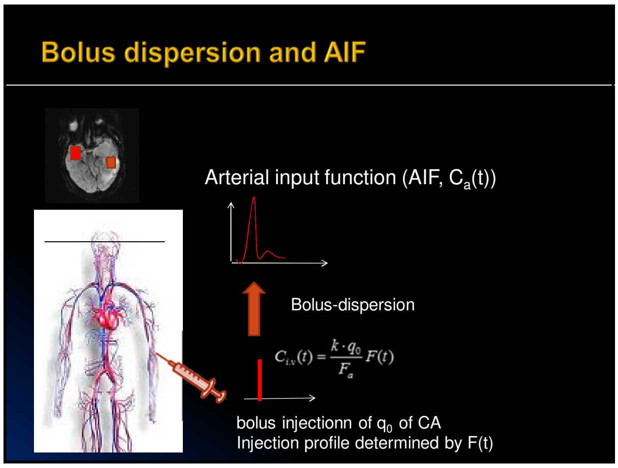
Perfusion definitions

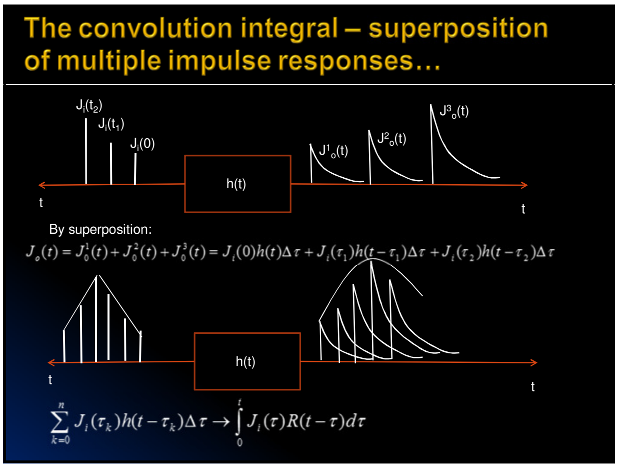


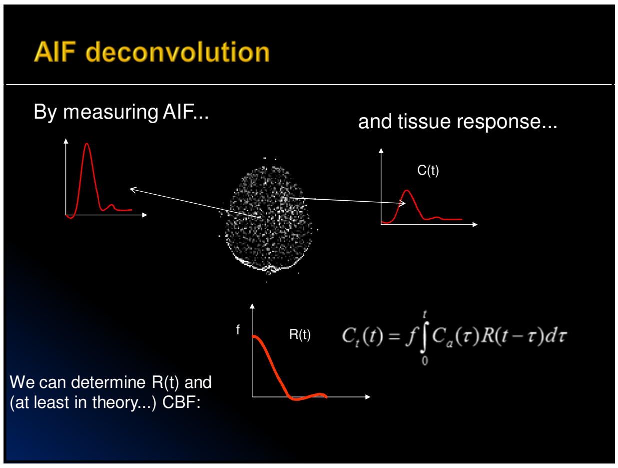
- CBF = tissue supply of blood [mL/100g/min]
- CBV= volume of blood in tissue [mL/100 g]
- Mean transit time (MTT) [seconds]
- Central volume principle*:
  - Volume = Flow x MTT

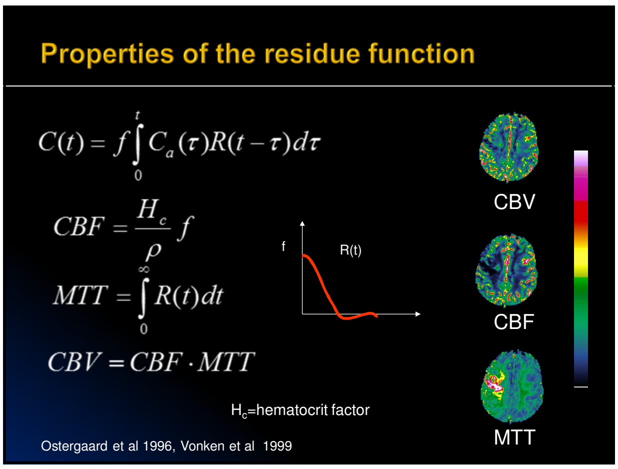
*Meier & Zieler. On the theory of Indicator-Dilution method for measurement of blood flow and volume. J Appl Physiol. 1954

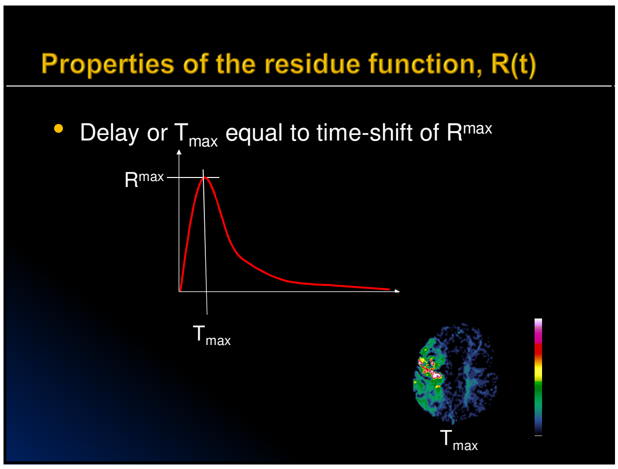

Central volume principle and residue function
'ideal' AIF = delta-function
CBV, CBF
F_a
AIF = $C_a(t)$
F
r(t)=F*R(t)
The initial height of the measured residue function directly reflects tissue perfusion!
The *normalized* R(t) describes the relative fraction of the injected CA dose still remaining in tissue at time t so that R(0)=1 and R(∞)=0


Bolus dispersion and AIF
Arterial input function (AIF, $C_a(t)$)
Bolus-dispersion
$C_{i.v.}(t) = \frac{k \cdot q_0}{F_a} F(t)$
bolus injectionn of q_0 of CA
Injection profile determined by F(t)

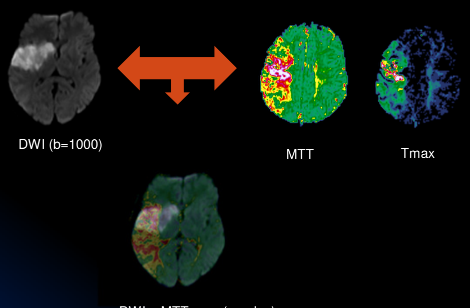

The convolution integral – superposition of multiple impulse responses…
$J_i(t_2)$
$J_i(t_1)$
$J_i(0)$
h(t)
$J^1_o(t)$
$J^2_o(t)$
$J^3_o(t)$
t
t
By superposition:
$J_o(t) = J_o^1(t) + J_o^2(t) + J_o^3(t) = J_i(0)h(t)\Delta\tau + J_i(\tau_1)h(t-\tau_1)\Delta\tau + J_i(\tau_2)h(t-\tau_2)\Delta\tau$
h(t)
t
t
$\sum_{k=0}^{n} J_i(\tau_k)h(t-\tau_k)\Delta\tau \rightarrow \int_0^t J_i(\tau)R(t-\tau)d\tau$


AIF deconvolution
By measuring AIF...
and tissue response...
C(t)
f
R(t)
$C_t(t) = f\int_0^t C_a(\tau)R(t-\tau)d\tau$
We can determine R(t) and (at least in theory...) CBF:


Properties of the residue function
$C(t) = f\int_0^t C_a(\tau)R(t-\tau)d\tau$
$CBF = \frac{H_c}{\rho} f$
$MTT = \int_0^\infty R(t)dt$
$CBV = CBF \cdot MTT$
f
R(t)
CBV
CBF
MTT
H_c=hematocrit factor
Ostergaard et al 1996, Vonken et al 1999


Properties of the residue function, R(t)
Delay or T_{max} equal to time-shift of R^{max}
R^{max}
T_{max}
T_{max}

Perfusion / diffusion mismatch in stroke



The deconvolution problem

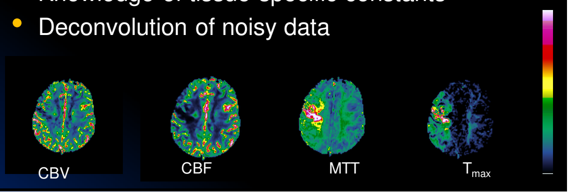
$$C(t) = CBF \cdot C_a(t) \otimes R(t)$$

- Can be solved for R(t) using standard deconvolution methods like:
  - Singular value decomposition (SVD)[1]
  - Fourier (FFT) based deconvolution[2]
- NOTE: For some deconvolution methods CBF estimates are sensitive to T_{max}.
- Delay-insensitive deconvolution methods exist like block-circulant SVD[2] or FFT-based methods[3]

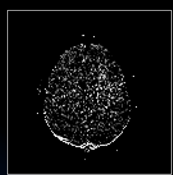
[1] Osteergaard et al. Magn Reson Med. 1996; 36(5):715-25
[2] Wu et al. Magn Reson Med 2003; 50:164-174
[3] Salluzzi M. Magn Reson Imaging. 2005 ;23(3):481-92

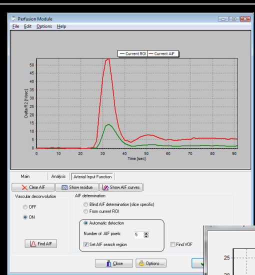
CBF quantification from DSC - Challenges:

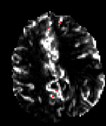
- AIF:
  - Correct identification
  - Dispersion effects
  - Non-linear dose-response
  - Partial volume effects
- Knowledge of tissue-specific constants
- Deconvolution of noisy data

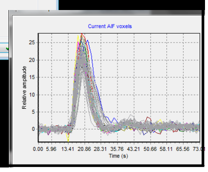


AIF determination[1,2,3,4 etc..]









[1] Mouridsen et al Magn Reson Med 2006;55(3):524-31
[2] Caroll et al. Radiology 2003;227(2):593-600
[3] Bjørnerud and Emblem, JCBFB 2010
[4] Knutsson et al JMRI 2006

Do we really need to quantify perfusion?

- Tumor perfusion: most studies based on normalized CBV analysis. A few studies on quantitative analysis but with lower specificity[1]
- In acute stroke, T_{max} may be the most sensitive parameter[2]
- In longitudinal studies (e.g. treatment response) quantitative analysis may have merit[3]
- AIF determination or tissue normalization may be required in most cases

[1] Law et al. Am J Neuroradiol 27:1975– 82 ; 2006
[2] Christensen S et al. Stroke. 2009;40(6):2055-61; 2009
[3] Sorensen et al . Cancer Res 72(2) 2012

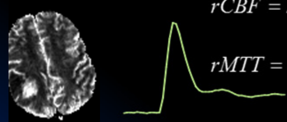
Relative, vs normalized vs absolute perfusion values...

- Relative: rCBV, rCBF*
  - commonly used for parameters derived without deconvolution or normalization

$$rCBV = \int \Delta R_2^*(t)dt$$

$$rCBF = \Delta R_2^{*max} \quad or \quad \frac{\int t\Delta R_2^*(t)dt}{\int \Delta R_2^*(t)dt}$$

$$rMTT = rCBV / rCBF$$

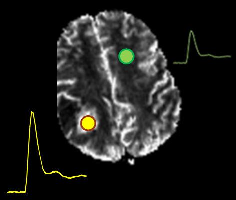


* Zierler. Circ Res 1965

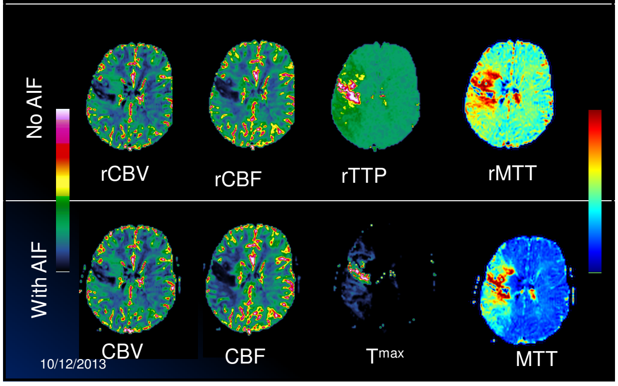
normalized (n)CBV

- Can estimate ratio of volume in two different regions (e.g. tumor vs WM)
- No need to determine AIF
- Assume similar dose-response in source and reference tissue..

$$nCBV = \frac{\int \Delta R_2^1(t)dt}{\int \Delta R_2^2 dt}$$

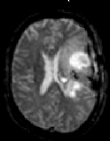


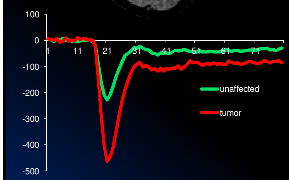
Relative vs 'absolute' analysis

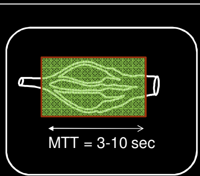


Perfusion analysis – time scale of effects

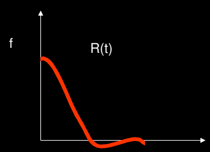
'Perfusion' (CBF/MTT)



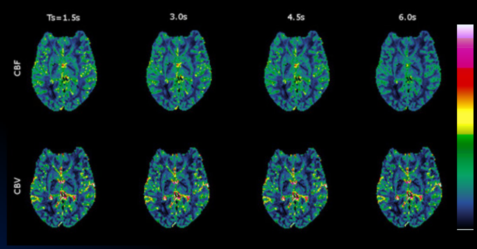




Time-scale: seconds

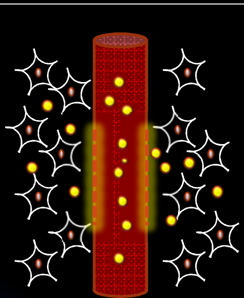


Temporal resolution requirements in DSC*

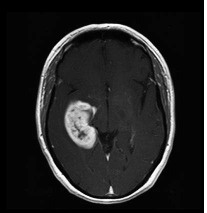


* Bakke and Bjørnerud; Proc ESMRMB 2012

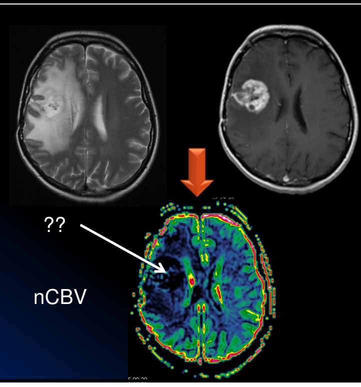
Extravasation effects in perfusion analysis



capillary



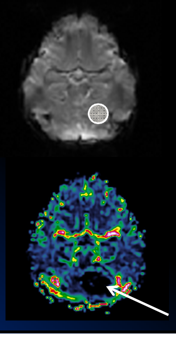
Effect of CA extravasation

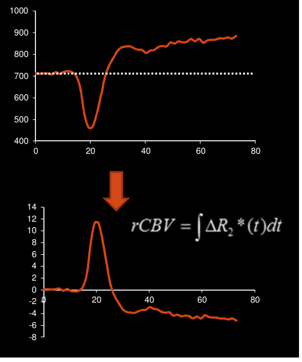


Glioblastoma

CA Extravasation (glioma)

GRE-EPI (3 T)
TR/TE/flip = 1200ms/30ms/60 deg



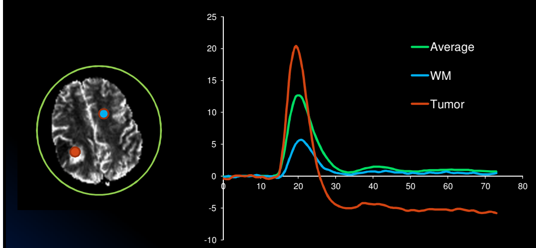


CA extravasation issues

- EITHER:
  - Attempt to minimize effect (sequence, predose) OR
  - Correct for effect
- Sequence optimization
- Correction schemes:
  - Gamma variate fitting
  - Pre-bolus (T1-saturation)[4]
  - Correction algorithms[1,2,3]

[1]Weisskoff et al. Proc ISMRM 1994
[2]Quarles et al. Magn Reson Med 2005
[3] Bjørnerud et al. JCBFM 2011
[4] Hu et al. AJNR 2010

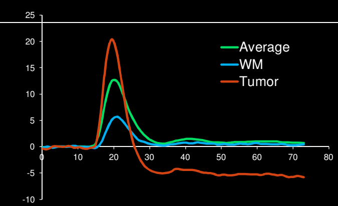
CA leakage correction based on kinetic modelling*



Assumptions: i.v. T_2^* effect; e.v. T_1-effects

[1] Weisskoff et al, *Proc SMRM (1994)*

CA leakage correction (II)

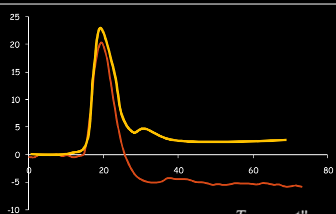


No leakage: $\Delta R_2^*(t) \approx K_1 \cdot \overline{\Delta R_2^*(t)}$

Leakage:

$$\Delta R_2^*(t) \approx K_1 \overline{\Delta R_2^*(t)} - K_2 \int_0^t \overline{\Delta R_2^*(t')}dt'$$

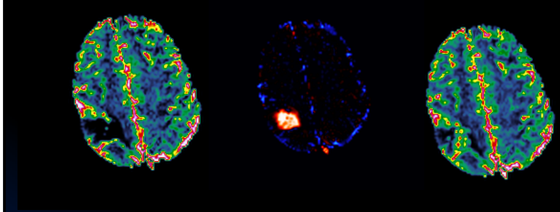
CA leakage correction



$$rCBV_{corr} = rCBV + K_2 \int_0^T dt'' \int_0^{t''} dt'$$

- K_2 is related to Permeability Surface area (PS) product.

Leakage correction

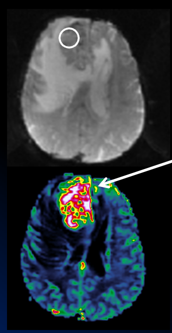


uncorrected $\quad$ K_2 map $\quad$ corrected

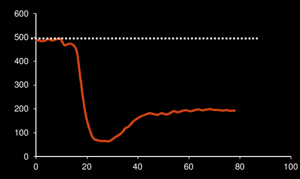
Limitations of 'Weisskoff' leakage correction method

- Only corrects for T1-dominant leakage
  - Can be overcome by letting leakage constant assume both positive (T2) and negative (T1) values
- Assumes MTT in tumor to be equal to MTT in reference tissue (unaffected brain)
  - Inherent limitation which will result in over-estimation of (T2-dominant) leakage and consequent under-estimation of (corrected) CBV in regions of elevated MTT.

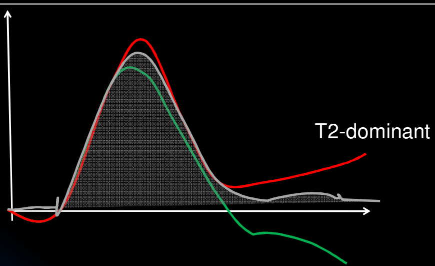
CA Extravasation (metastasis)



GRE-EPI (1.5 T)
TR/TE/flip = 1500ms/40ms/90 deg



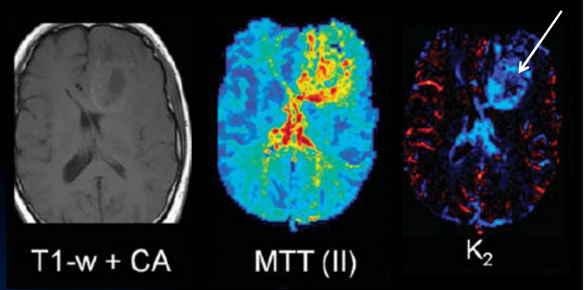
CA leakage: over- or under estimation of rCBV*



- Sequence parameters
- Tumor type and malignancy
- CA dose
- Field strength

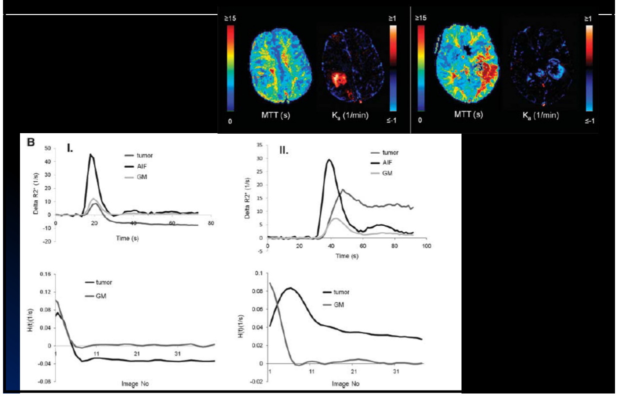
Bjørnerud et al. JCBFM 2011

MTT effects (anaplastic astrocytoma)

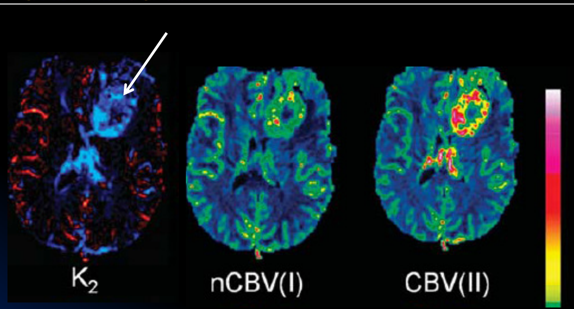


Bjørnerud et al; JCBFM (2011)

MTT-insensitive correction

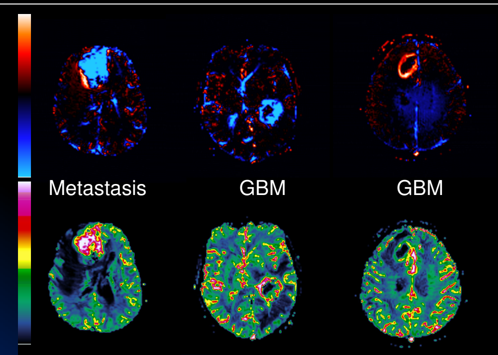


Elevated MTT leads to under-estimation of (corrected) CBV



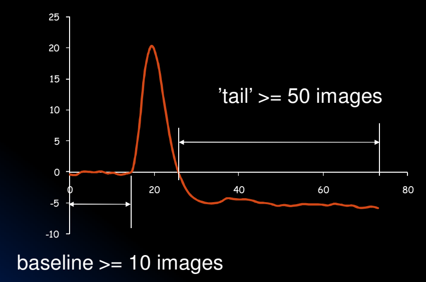
Bjørnerud et al; JCBFM (2011)

T1- vs T2*-dominant extravasation effects

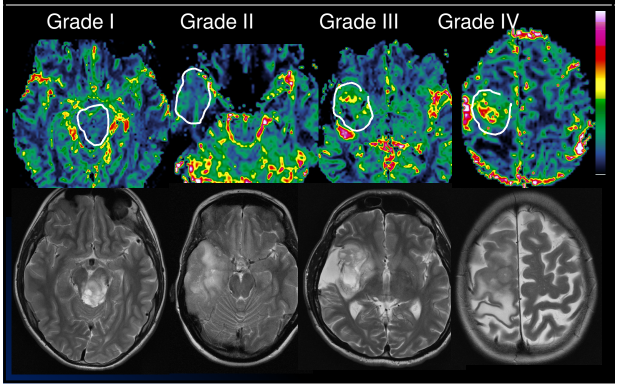


Bjørnerud et al. JCBFM 2011

Kinetic estimation of leakage requires acquisition of sufficiently long time-series



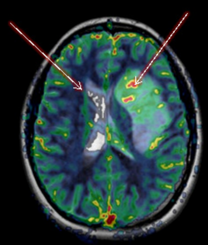
Glioma grading from nCBV



The 'hotspot' approach*

Normalised CBV (nCBV) = $CBV_{Hot\ Spot}$ / CBV_{Ref}

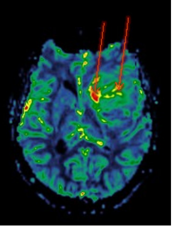
nCBV < ~2 : Low grade (grade I-II)
nCBV > ~2 : High grade (grade III-IV)



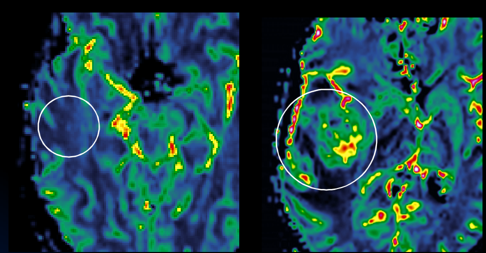
* Covarrubias et al, The Oncologist, 2004;9:528-537

Problems with the 'hot-spot' approach

- Differentiate tumour/ edema/ necrosis / blood
- What is the correct reference tissue? (WM vs GW)
- User dependence (def of hottest spot)
- Not all gliomas behave in the same way (astrocytomas vs oligodendrogliomas)



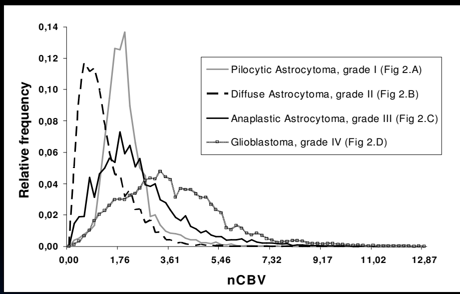
Tumor heterogeneity analysis



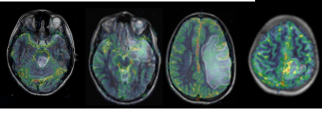
Low grade

High grade

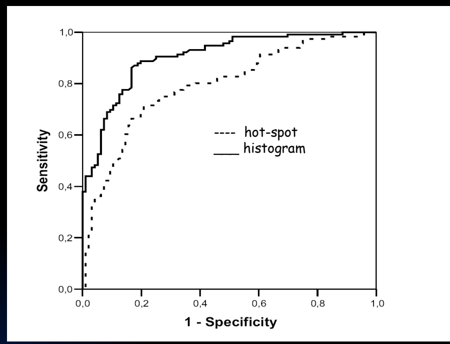
Tumor-grading with histogram-method*



*Emblem et al. In press. Radiology 2008

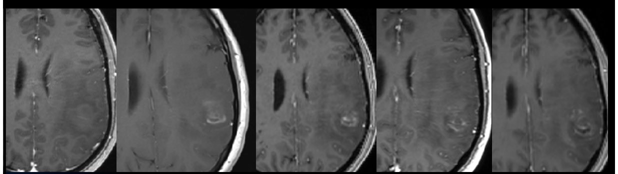


ROC curves (n=54, 4 observers)



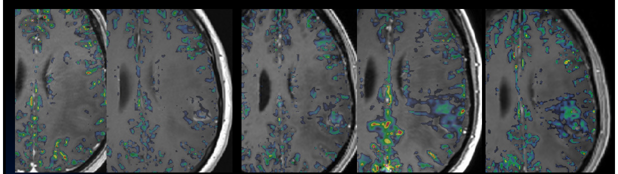
*Emblem et al. Radiology 2008

Longitudinal assessment of malignant glioma transformation



2007-09-18 2008-06-12 2009-01-21 2009-03-31 2009-06-30

Longitudinal assessment of malignant glioma transformation



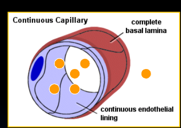
2007-09-18 2008-06-12 2009-01-21 2009-03-31 2009-06-30

Post contrast T1-w + CBV maps

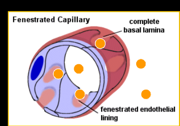
Kinetic modeling

Permeability analysis

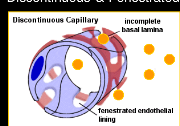
Permeability Surface Area product



Fenestrated



Discontinuous & Fenestrated



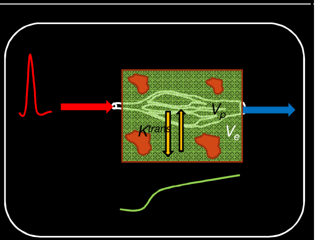
Slow

Limited by Permeability x Surface Area (P S product)

Fast

Permeability definitions*

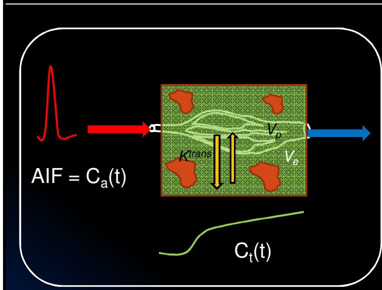
- K^{trans} = *Transfer constant*; Flux of CA from intravascular (iv) space to extravascular space (EES) [1/minutes] or [mL/100g/min]
- V_e = *distribution volume* of CA in EES [percent] or [mL/100g]
- $k_{ep}=K^{trans}/V_e$ = *rate constant* = Flux of CA from EES to iv space [1/minutes] or [mL/100g/min]
- V_p=*Plasma volume ; volume of plasma fraction in tissue [percent] or [mL/100g/min]*
- *K^{trans} is generally a function of perfusion!*



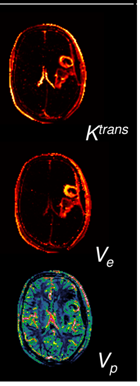
$$\frac{d}{dt}C_t(t)=K^{trans}C_a(t)-k_{ep}C_t(t)$$

*Tofts et al. JMRI 1999

Permeability analysis in MRI

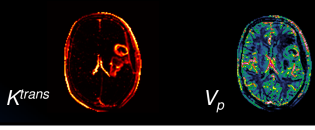


$$C_t(t)=K^{trans}C_a(t)\otimes\exp(-k_{ep}t)+V_pC_a(t)$$

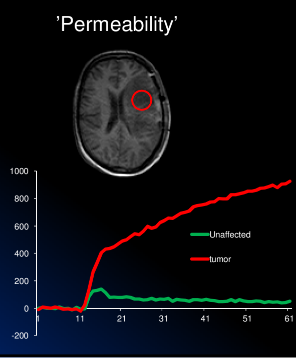


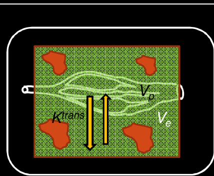
Permeability analysis

- Requires determination of AIF – usually better defined than in DSC
- Requires deconvolution but 'better behaved' since residue function is known (single exponential)
- Assume similar dose-response in source and reference tissue..(water exchange effects, T2*-effects)
- NB: CBV can be estimated from both one- and two-compartment models

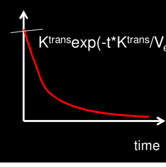


Permeability analysis- time-scale of effects

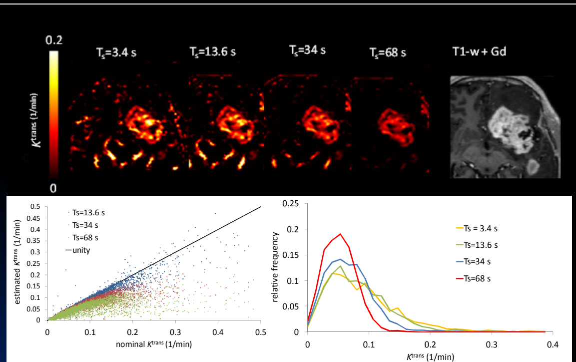




Time-scale: K^{trans}/Ve =minutes

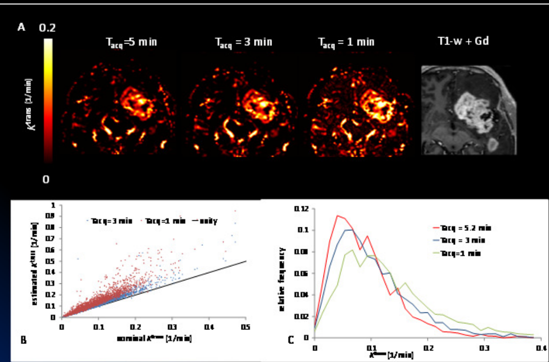


Temporal resolution requirements in DCE



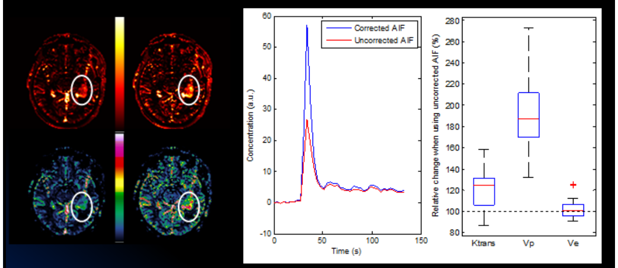
C. Larsson et al. JMRI 2012

Sampling duration requirements in DCE



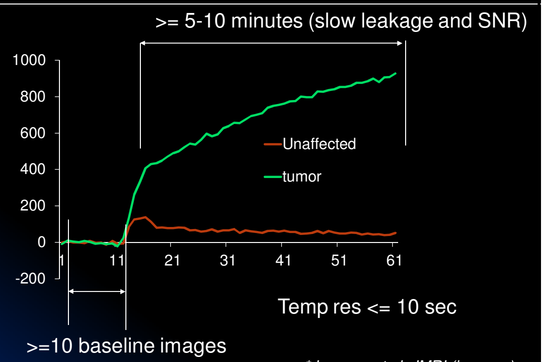
C. Larsson et al. JMRI 2012

T2*-effects in DCE*
(TE ≈ 1 ms to minimize)



*Kleppestø et al (JMRI in press)

DCE sequence requirements*
(brain tumors)



** Larsson et al. JMRI (in press)*

Summary (I)

- 'Perfusion-MRI' commonly used to refer to both CBF/CBV analysis (one-compartment) AND permeability analysis (two-compartment)
- CBV can be estimated from both models
- Perfusion analysis: T1-, T2- or **T2***-weighted
- Permeability analysis: T1-weighted
- DSC (T2/T2*)
  - High CA sensitivity in brain tissue
  - More sensitive to artifacts
  - Complex dose-response
- DCE (T1)
  - Low CA sensitivity in brain tissue
  - High sensitivity for extravasation
  - Less artifacts
  - Better AIF definition

Summary (II)

- DSC sequence considerations:
  - CA sensitivity: TE, Bo, dose, SE vs GRE-EPI
  - Higher Bo lower TE or CA dose
  - Capillary (T2) vs macrovessel (T2*) sensitivity
  - Leakage effects in DSC: sufficient scan-duration for leakage corection (2 min)
  - Temp res <= 1.5 sec

Summary (III)

- DCE /T1-w) sequence consideration
  - CA sensitivity: TR, TD, flip, dose, minimum TE
  - Baseline T1-map
    - Multi-flip
    - IR/SR
    - Added value in question..
  - Temp resolution (incl CBV) <= 10 s
  - Scan duration >= 5 minutes