QUANTITATIVE IMAGING, PHYSIOLOGICAL MODELS, AND PERFUSION

DIFFERENCES BETWEEN ANIMAL AND HUMAN STUDIES. TECHNICAL ASPECTS OF ANIMAL STUDIES

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OUTLINE

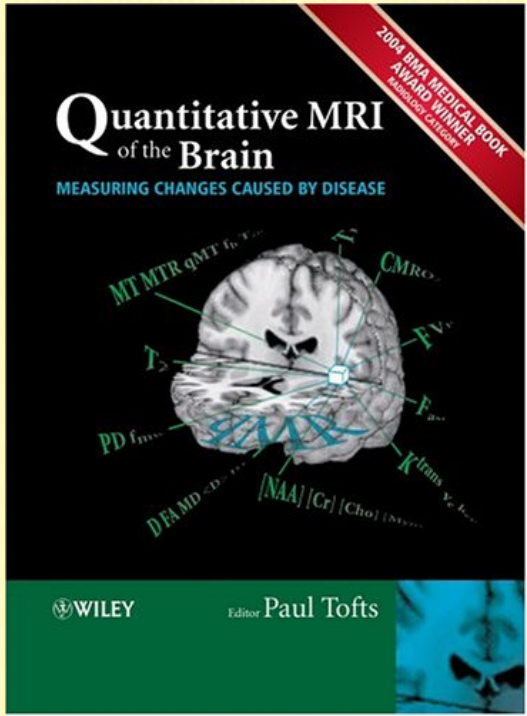
1. Quantitative imaging
2. Perfusion imaging (tumor-bearing mice)
3. T1 quantification (rat myocardium)

(Differences between animal and human studies.
technical aspects of animal studies)

1. QUANTITATIVE IMAGING

„Quantitative MRI“ (qMRI)

- first in the 1980’s – physicists measured the NMR properties of tissue (PD, T1 and T2) – to characterize biological tissue – to differentiate different tissues
- MRI scanner is no **longer a camera**, but a **scientific measuring instrument**
- common (T1w, T2w, PDw, DWI, PWI, …) images
  - signal intensity in arbitrary units
  - cannot be compared across sites or even scanning sessions
- quantitative imaging
  - biomarkers in physical units (s, mm2/s, ml/min/g, …)
  - absolute measures comparable across imaging sites and time points



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

1. QUANTITATIVE IMAGING

- Proton Density (PD) - water content
- T1, T2 –size of the molecule, tumbling of spins, mobility of 1H, water content
- diffusion and its tensor – microscopic details about tissue architecture
- Magnetization transfer – macromolecules (e.g. demyelination in multiple sclerosis)
- spectroscopy – concentrations of metabolites
- dynamic T1-weighted MRI (DCE-MRI) – vessel permeability
- dynamic T2 (*) - weighted MRI (DCE-MRI) – blood flow and volume
- Arterial Spin Labelling (ASL) – blood flow

2. PERFUSION IMAGING

Oncology

- tumor characterization
- grading
- treatment monitoring
- pseudo-progression vs. recurrence

Neurology

- stroke treatment: delay from stroke onset => individualized decision based on the tissue status
- penumbra – salvageable brain tissue, viable brain tissue with reduced perfusion
- based on perfusion and diffusion imaging

2. PERFUSION IMAGING

Cardiology

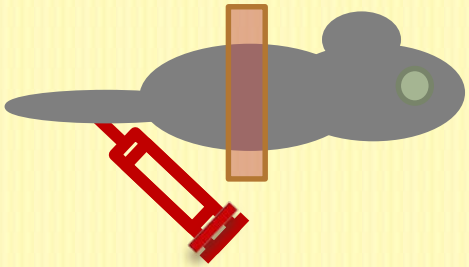
- ischemic diseases – diagnosis
- treatment monitoring

Preclinical studies

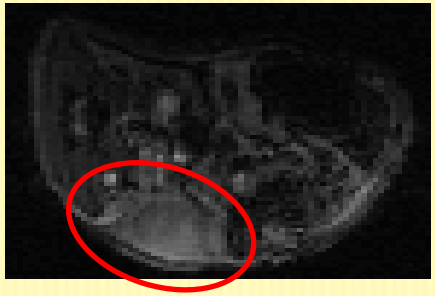
- validation of animal models
- test of BBB opening
- testing of nanoparticle carriers of imaging markers and drugs -> pharmacokinetics, pharmacodynamics
- development of new drugs
- ...

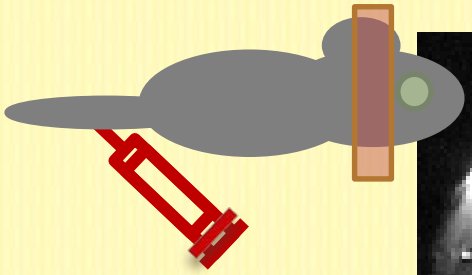
2. PERFUSION IMAGING

Imaging of contrast-agent distribution in the tissue

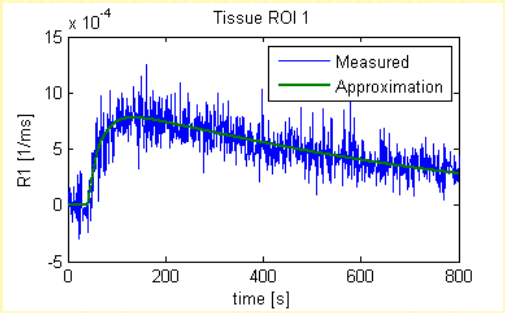


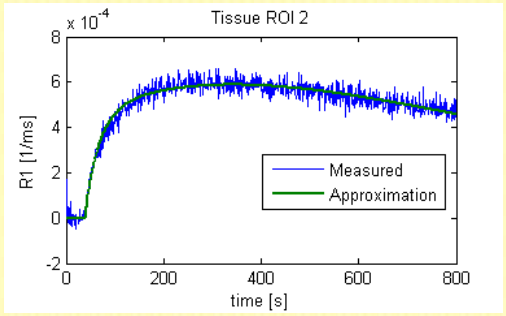
DCE-MRI
mouse
subcut. CT26 tumor





DCE-MRI
rat
glioblastoma





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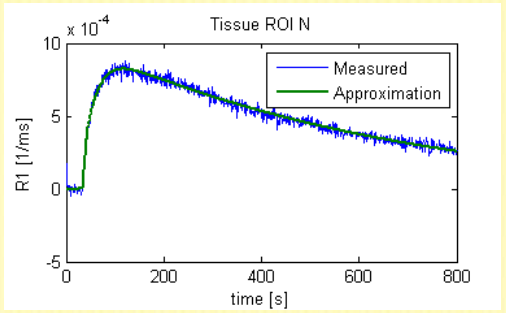
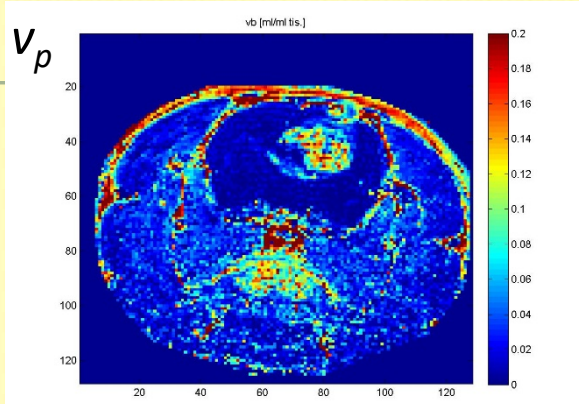


2. PERFUSION IMAGING

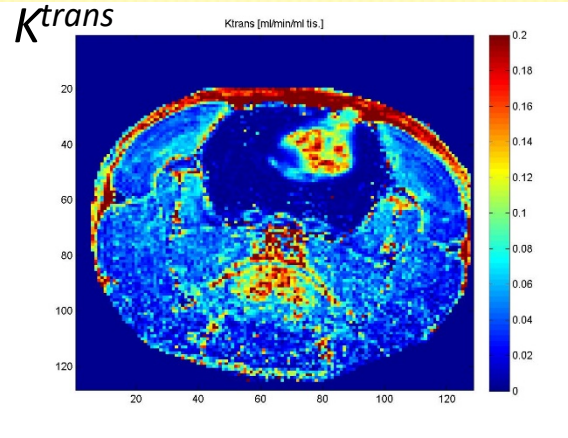
perfusion-parameter maps

- F_p - plasma flow [ml/min/100ml tis.]
- v_p - plasma volume [ml/100 ml tis.]
- v_e - EES volume [ml/100 ml tis.]
- PS - permeability-surface product [ml/min/100ml tis.]
- ...

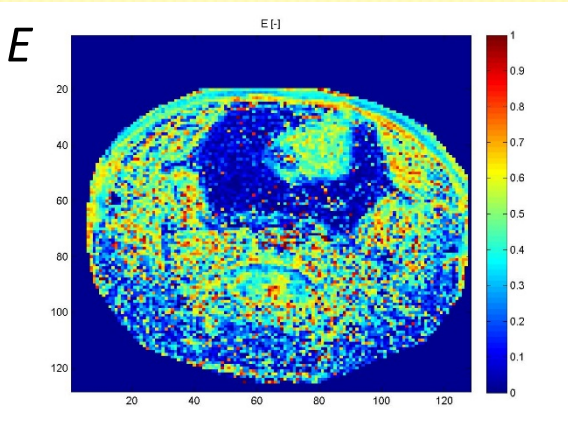
v_p



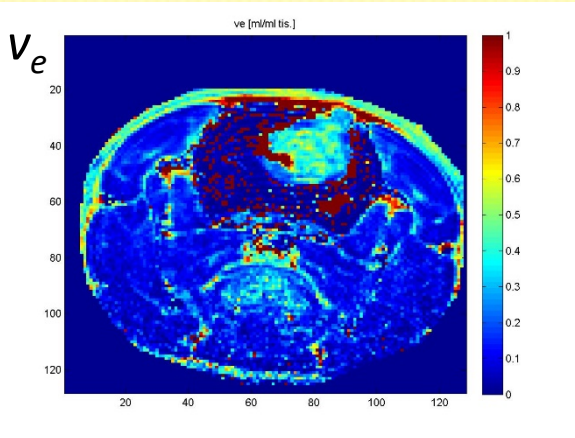
K^{trans}



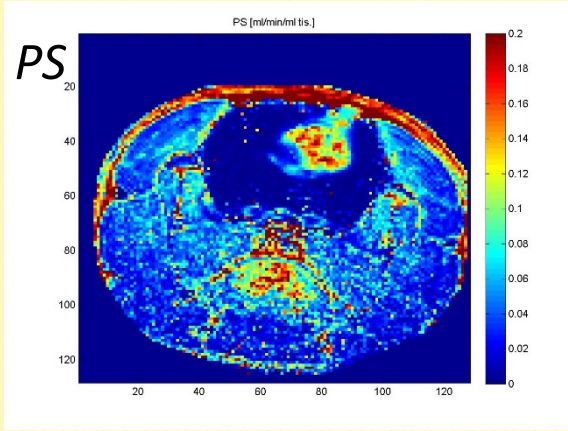
E



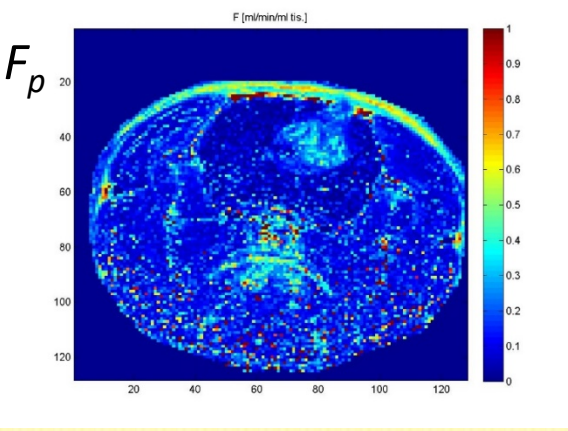
v_e



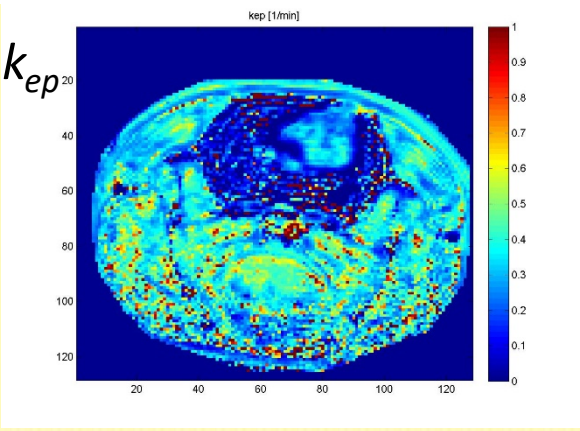
PS



F_p



k_{ep}

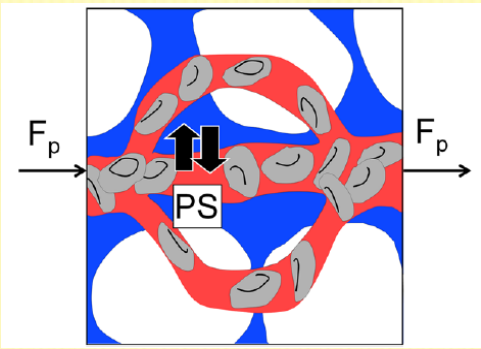


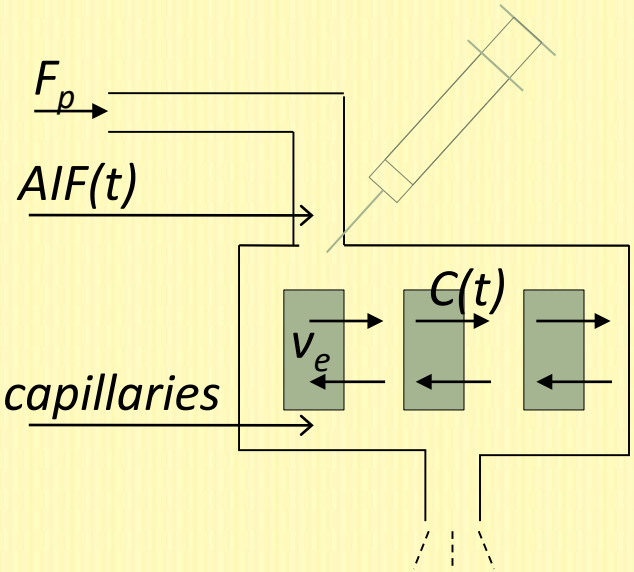
2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

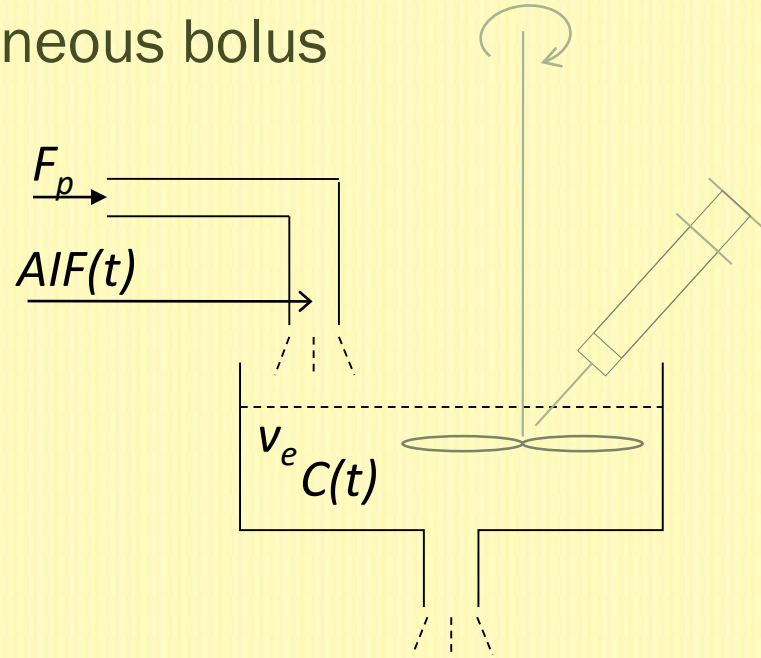
Impulse residual function (IRF) – *R(t)*

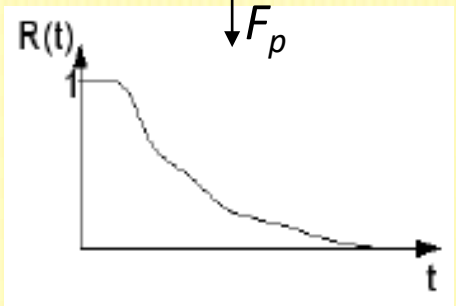
$$C(t) = c_0 R(t)$$

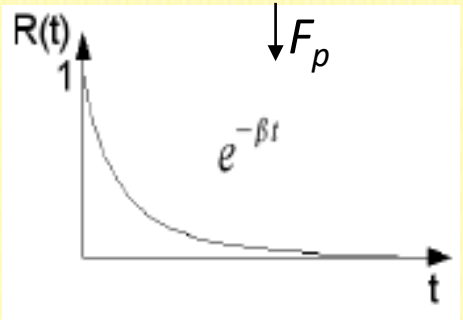
- Characteristics of a tissue ROI
- Normalized response to an instantaneous bolus





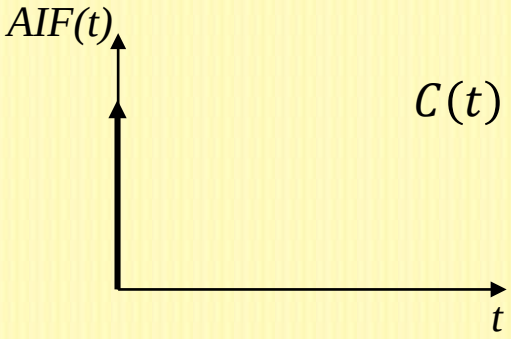




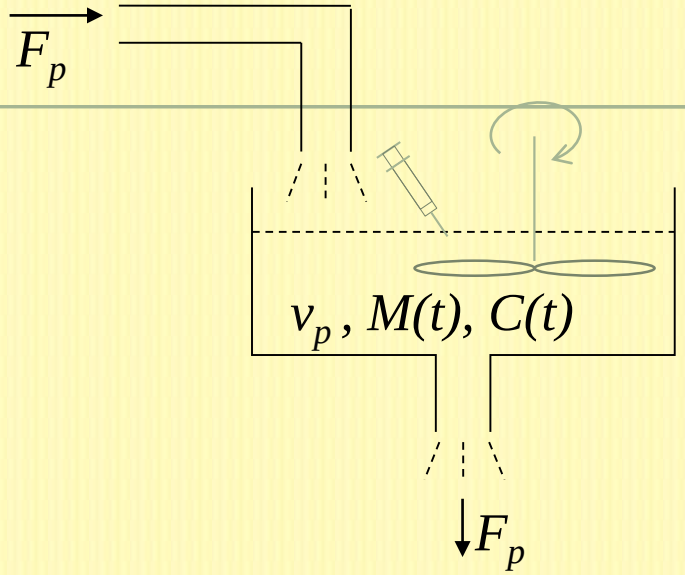


2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

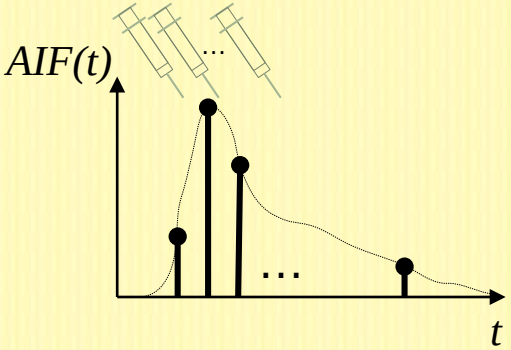
instantaneous CA bolus

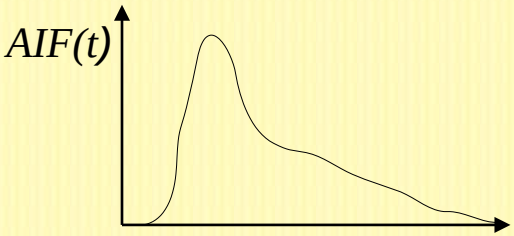


$$C(t) = c_0 R(t)$$



general CA bolus

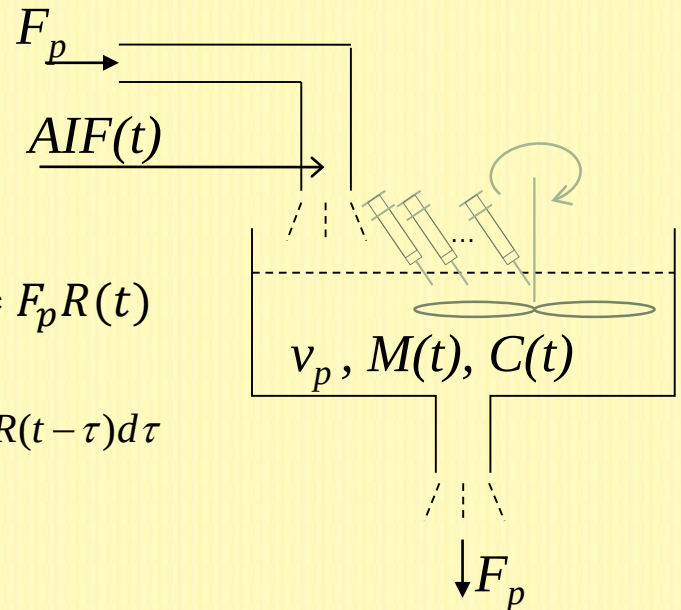




convolution

$$C(t) = AIF(t) * F_p R(t)$$

$$C(t) = F_p \int_0^t AIF(\tau) R(t-\tau) d\tau$$

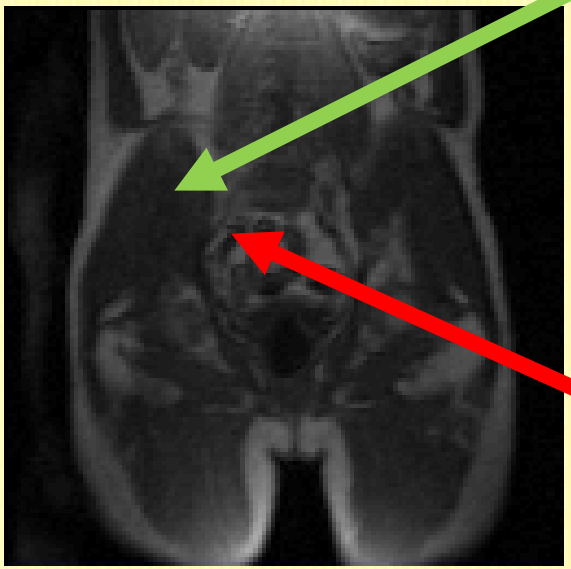


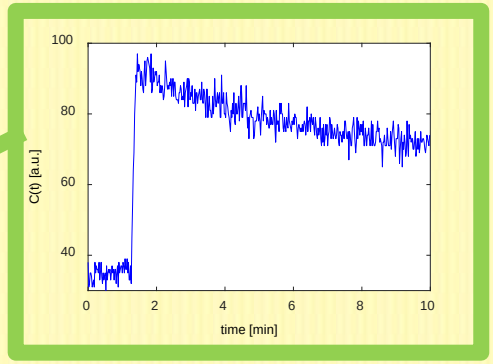
2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

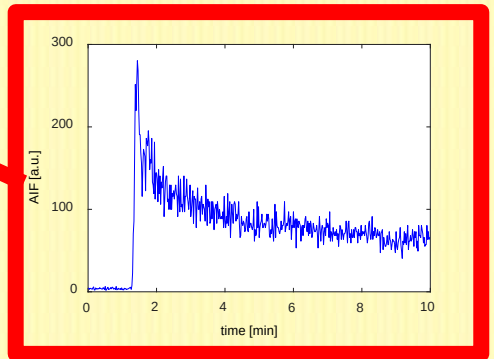
Standard approach:

1. Data acquisition
2. SI -> C(t) conversion
3. AIF selection (*C(t)* in an artery)
4. Tissue ROI / voxel
5. Deconvolution => perfusion parameters e.g. F_p, PS, v_p, v_e (K^{trans}, k_{ep}, E, T_c)

$$C(t) = AIF(t) * F_p R(t)$$



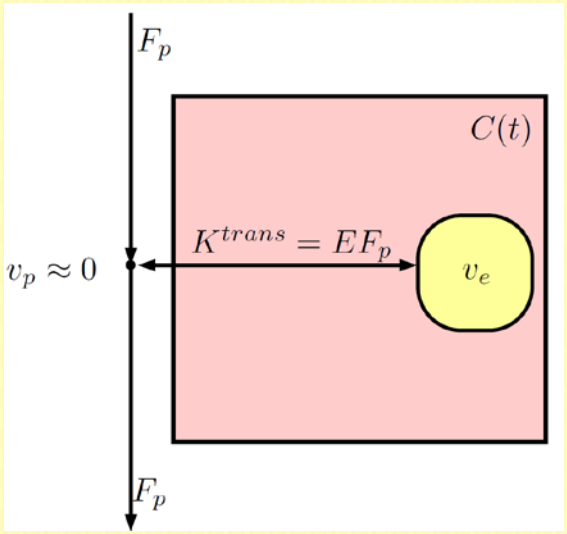




2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

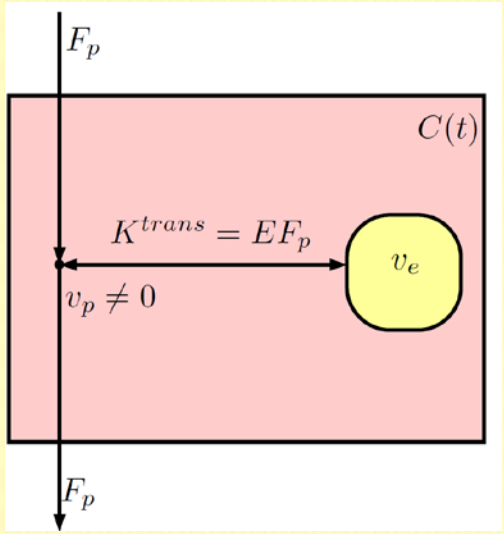
$$C(t) = AIF(t) * F_p R(t)$$

Tofts

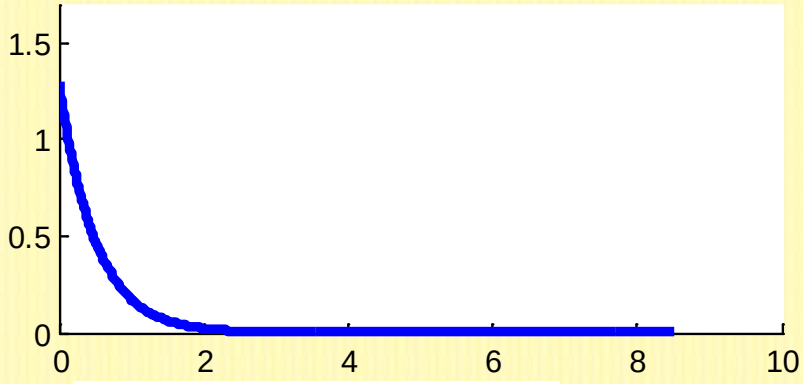


- o plasma – neglected
- o EES – compartment
- o K^{trans}, v_e ($k_{ep} = K^{trans}/v_e$)
- o *Ktrans* combination of F_p and *PS*

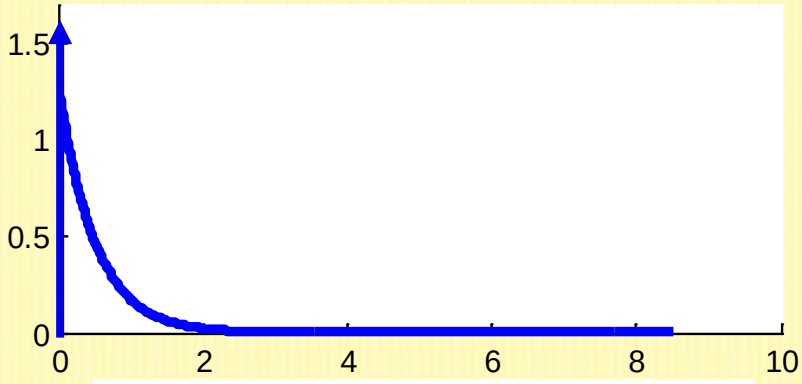
Extended Tofts



- o plasma – equal to AIF
- o EES – compartment
- o K^{trans}, v_e, v_p ($k_{ep} = K^{trans}/v_e$)
- o *Ktrans* combination of F_p and *PS*



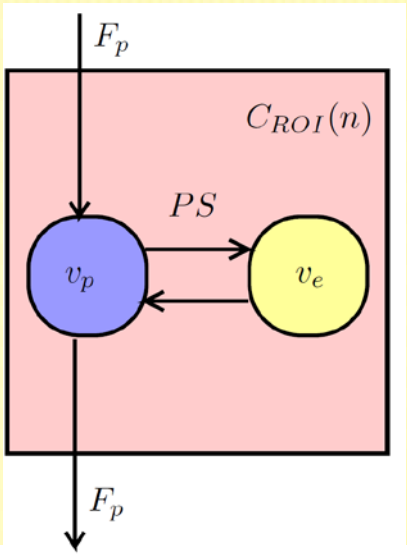
$$C(t) = K^{\mathrm{trans}} e^{-k_{\mathrm{ep}} t} * c_{\mathrm{a}}(t)$$



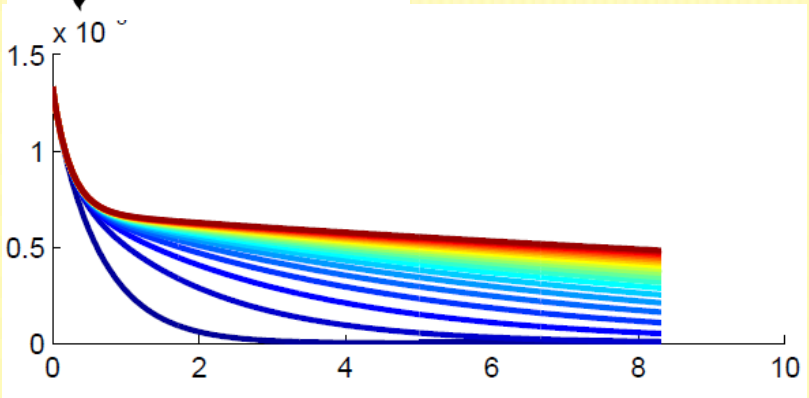
$$C(t) = \left(v_{\mathrm{p}}\delta(t) + K^{\mathrm{trans}} e^{-k_{\mathrm{ep}} t}\right) * c_{\mathrm{a}}(t)$$

2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

2CXM



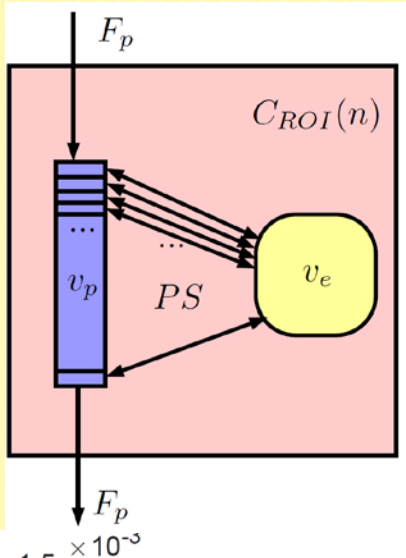
- plasma – compartment
- EES – compartment



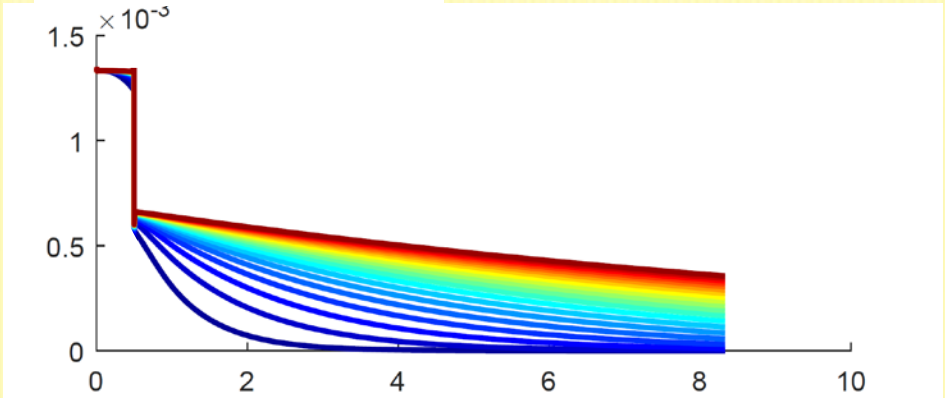
$$C(t) = \frac{(T\,\alpha_- - 1)\,\alpha_- e^{-t\,\alpha_-} + (1 - T\,\alpha_-)\,\alpha_+ e^{-t\,\alpha_+}}{\alpha_+ - \alpha_-} * c_a(t)$$

$$where: \alpha_\pm = \frac{T + T_e \pm \sqrt{(T + T_e)^2 - 4\,T_c T_e}}{2 T_c T_e}.$$

TH



- plasma – plug flow
- EES – compartment
- no analytical solution in the time domain

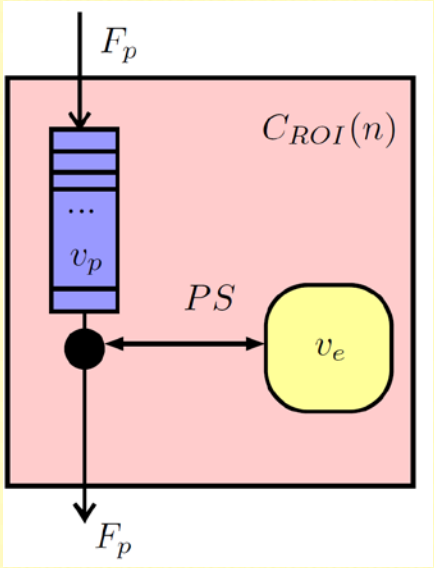


$$h_{TH}(s) = \frac{(T + s\,T_c T_e)(s\,T_c + a)\left(1 - e^{-(s\,T_c + a)}\right)}{s\,(T + s\,T_c T_e)(s\,T_c + a) + a\,(1 - e^{-(s\,T_c + a)})}$$

$$where: a = \frac{T - T_c}{T_e}.$$

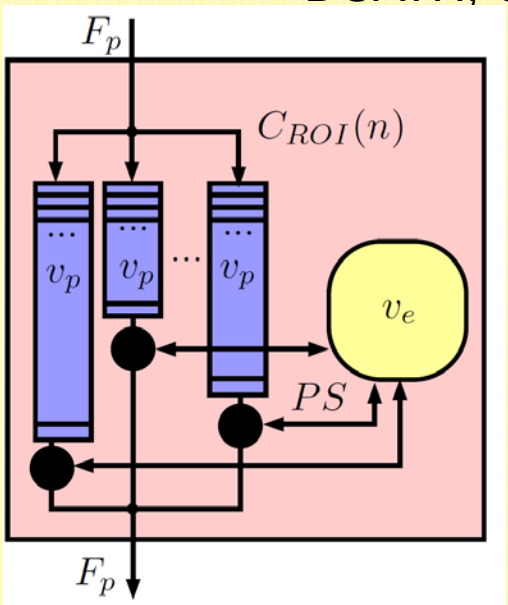
2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

ATH

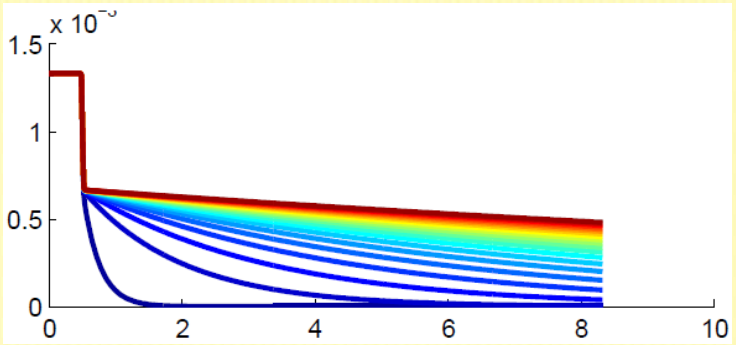


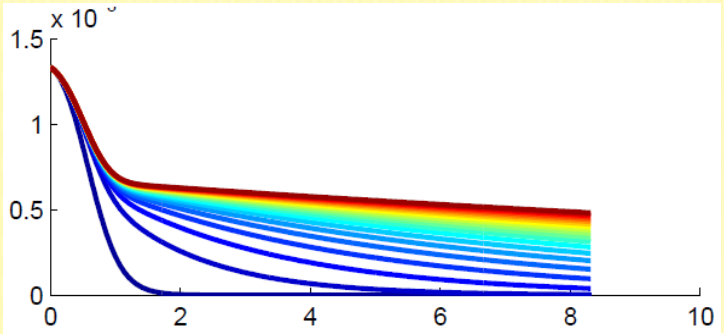
- plasma - plug flow
- EES – compartment
- analytical solution in the time domain
- much slower changes of $C_e(t)$ than $C_p(t)$

DCATH, GCCM



- several capillary paths
- distribution of *Tc:*
- DCATH: (truncated) normal, skewed Gaussian
- GCTT: gamma distribution
- additional perf. param.





$$h_{\mathrm{ATH}}(t) = F_{\mathrm{p}}\,\mathcal{H}(T_c - t) + \mathcal{H}(t - T_{\mathrm{c}})\,F_{\mathrm{p}}E\,e^{-\frac{F_{\mathrm{p}}E}{v_{\mathrm{e}}}t} = F_p\left(R_{\mathrm{p}}(t) + R_{\mathrm{e}}(t)\right)$$

$$R(\Psi,t) = R_v(\Psi,t) + R_p(\Psi,t),$$

$$R_v(\Psi,t) = 1 - \frac{\mathrm{erf}(\frac{t-\mu}{\sqrt{2}\sigma}) + \mathrm{erf}(\frac{\mu}{\sqrt{2}\sigma})}{1 + \mathrm{erf}(\frac{\mu}{\sqrt{2}\sigma})}$$

$$R_p(\Psi,t) = E\exp(\tfrac{1}{2}k_{ep}^2\sigma^2 + k_{ep}(\mu - t)) \cdot \frac{\mathrm{erf}(\frac{t-\mu}{\sqrt{2}\sigma} - \frac{k_{ep}\sigma}{\sqrt{2}}) + \mathrm{erf}(\frac{\mu}{\sqrt{2}\sigma} + \frac{k_{ep}\sigma}{\sqrt{2}})}{1 + \mathrm{erf}(\frac{\mu}{\sqrt{2}\sigma})}$$

2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

$$C(t) = AIF(t) * F_p R(t)$$

IRF model	Perf. farameters	Derived perf. parameters
Tofts	K^{trans}, v_e	k_{ep}
Extended Tofts	K^{trans}, v_e, v_p	k_{ep}
2CXM (2CCM)	F_p, PS, v_p, v_e	k_{ep}, K^{trans}
TH (tissue homogeneity)	F_p, PS, v_p, v_e	k_{ep}, K^{trans}
ATH (aaTH, aaJW)	F_p, PS, v_p, v_e	k_{ep}, K^{trans}
DCATH	F_p, PS, v_p, v_e, σ	k_{ep}, K^{trans}
GCTT	F_p, PS, v_p, v_e, α	k_{ep}, K^{trans}

2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

Which of the advanced pharmacokinetic models is more suitable for which application?

2CXM
- intravascular space – homogeneous well-mixed space
- for a chaotic spatial arrangement of capillaries, arterioles, venules and larger vascular-tree components

TH and ATH
- ”plug flow” of blood – red blood cells act as ”plugs”
- blood plasma between the red blood cells - same velocity
- for parallel vessels of the same length within the ROI

Both simplistic => DCATH and GCTT introduce a statistical distribution of the lengths of the plug-flow capillaries

2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

Which of the advanced pharmacokinetic models is more suitable for which application?

General requirements

1. realistic
2. approximation problem should be
   - *well-posed* – unique solution,
   - *well-conditioned* – low sensitivity to noise

=> many vs. few model parameters

2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

1. Choice of a realistic model

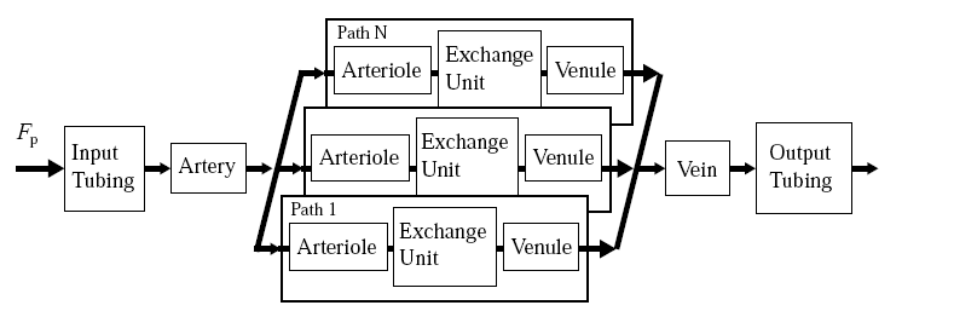
No ground truth available

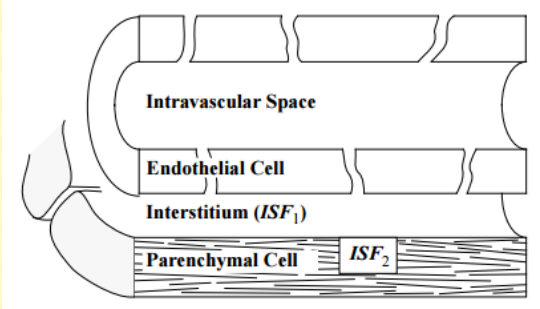
Simulation-based studies
MMID4

- Multiple path, Multiple tracer, Indicator Dilution, 4 region model
- Intravascular, extravascular, intracellular indicators
- partial differential equations
- up to 20 flow paths

MMID4 model:
http://physiome.org/jsim/models/webmodel/NSR/MMID4/

[1] BUCKLEY D. L.. Magnetic Resonance in Medicine 47 (3), 2002, 601–606.
[2] ZHANG J. et al. Magnetic Resonance in Medicine 72 (2), 2014, 534–545.





⇒ Tofts and extended Tofts too simplistic (besides impossible separation of PS and Fp) compared to ATH

2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

1. Choice of a realistic model

Real-data based

- quality of models considering their complexity and the goodness of fit
  - Akaike's information criterion (AIC)
  - F-test
- consistency of the estimated perfusion parameters with known assumptions (cervix carcinoma patients)

⇒ Tofts and extended Tofts too simplistic (besides impossible separation of PS and Fp) compared to 2CXM and ATH

[1] NAISH J. H., et al. Magnetic Resonance in Medicine 61(6), 2009, 1507– 1514
[2] DONALDSON S. B. et al. Magnetic Resonance in Medicine 63(3), 2010, 691–700

2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

$$C(t) = AIF(t) * F_p R(t)$$

IRF model	Perf. farameters	Derived perf. parameters
Tofts	K^{trans}, v_e	k_{ep}
Extended Tofts	K^{trans}, v_e, v_p	k_{ep}
2CXM (2CCM)	F_p, PS, v_p, v_e	k_{ep}, K^{trans}
TH (tissue homogeneity)	F_p, PS, v_p, v_e	k_{ep}, K^{trans}
ATH (aaTH, aaJW)	F_p, PS, v_p, v_e	k_{ep}, K^{trans}
DCATH	F_p, PS, v_p, v_e, σ	k_{ep}, K^{trans}
GCTT	F_p, PS, v_p, v_e, α	k_{ep}, K^{trans}

2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

2. Choice of a reliable model

Practical experience:

- problems with DCATH, GCTT (5 parameters) for realistic SNR
- 4-parameter models preferable
- **2CXM, ATH**
- TH (no analytical solution in the time domain) ???
- DP ???

M. Bartoš et al. *Magn. Reson. Imaging*, 32(5), 2014, 505–13.
M. C. Schabel, *Magn. Reson. Med.*, 68(5), 2012, 1632–1646.

2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

2CXM vs. ATH for mouse tumor

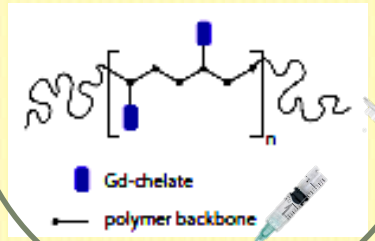
high- and low-molecular weight (MW) contrast-agents - consistency with assumed effects of MW:

- F_p, v_p, T_c: MW independent
- *PS* should decrease with increasing MW

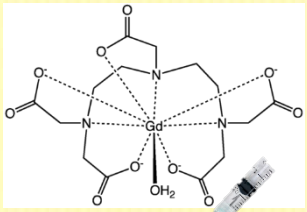
4 BALB/c mice (CT26 tumor)

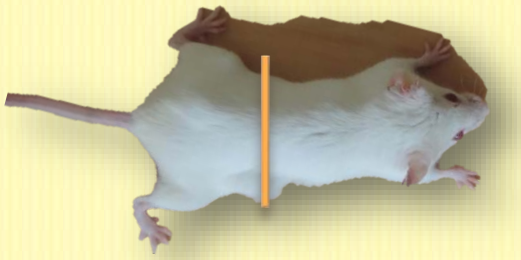
3 hours

GadoSpin P
200 kDa
(Miltenyi Biotec, Germany)



Magnevist
0.9 kDa
(Bayer HealthCare, Germany



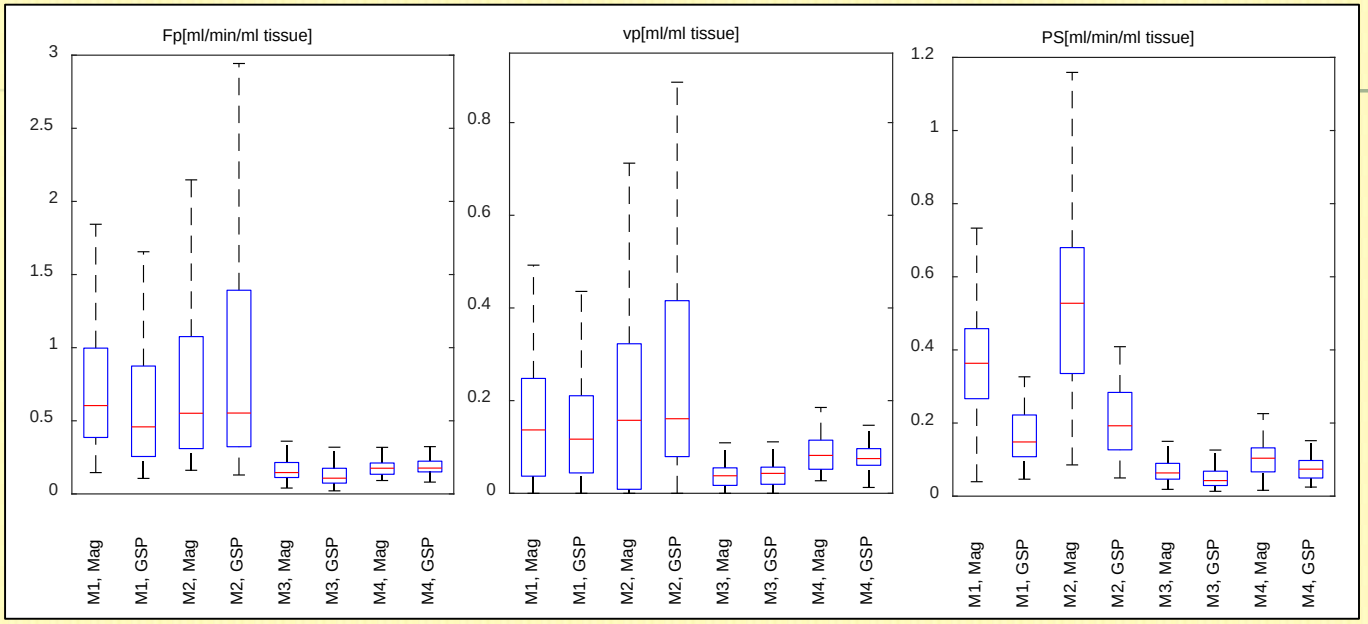


Loca-lizer	Anatomy	DCE-MRI	DCE-MRI 1	Anatomy	DCE-MRI 2
	T2w, T1w	Calibaration	GadoSpin P	post-con.	Magnevist
26 s	14 min	(milti-TR FLASH)	(FLASH)	T1w, T2w,	(FLASH)
		17 min	13 min	15 min	13 min

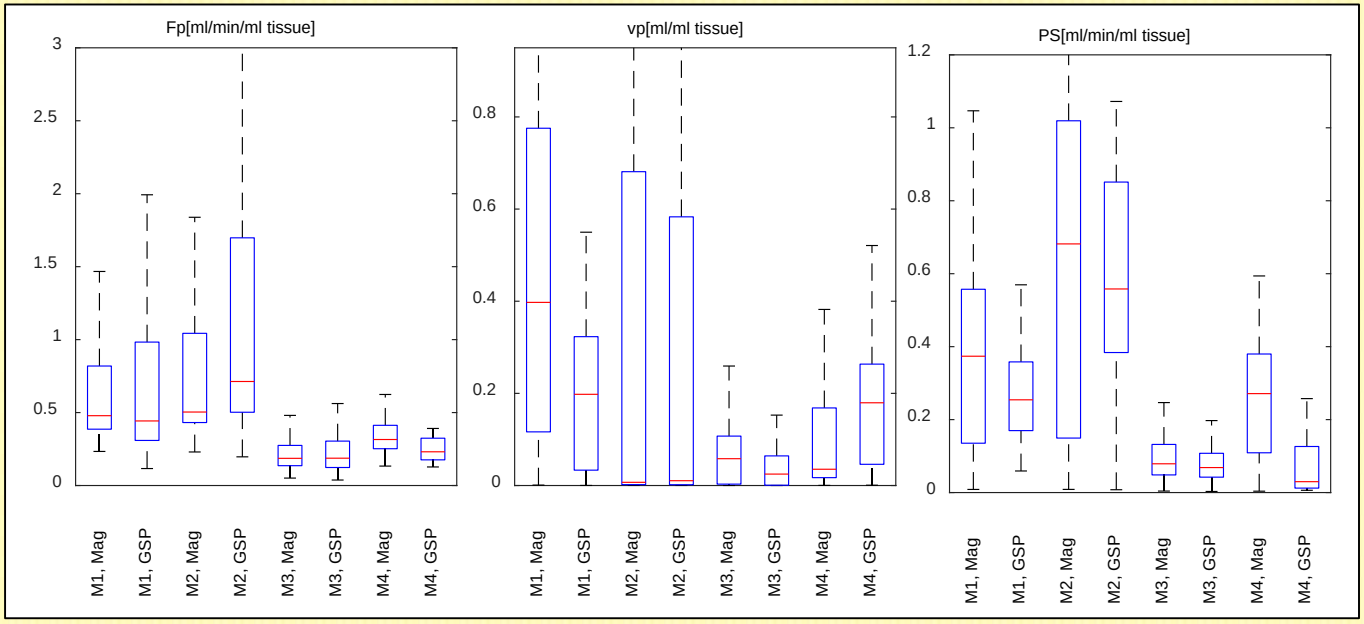
R. Jiřík et al. ESMRMB Conf. 2016

2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

ATH

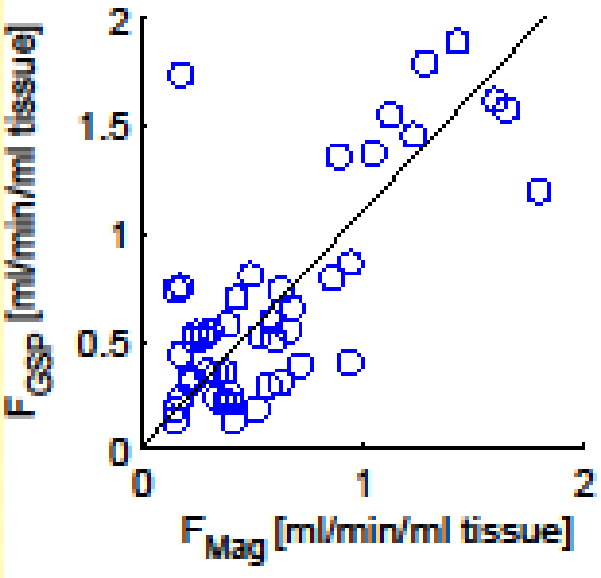


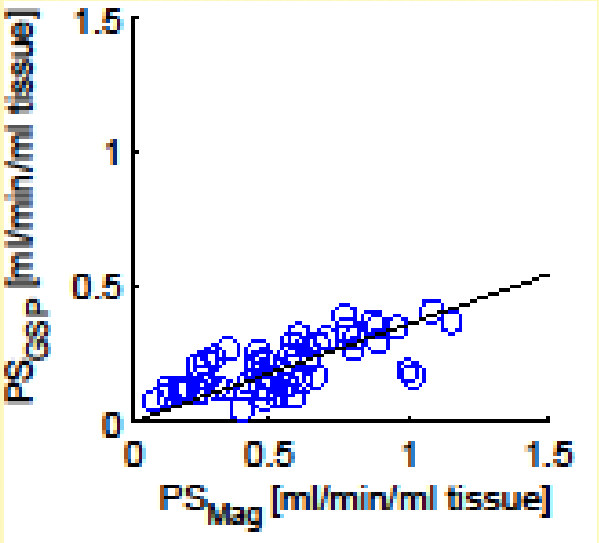
2CXM



⇒ ATH more consistent than 2CXM

2. PERFUSION IMAGING – PHARMACOKINETIC MODELING



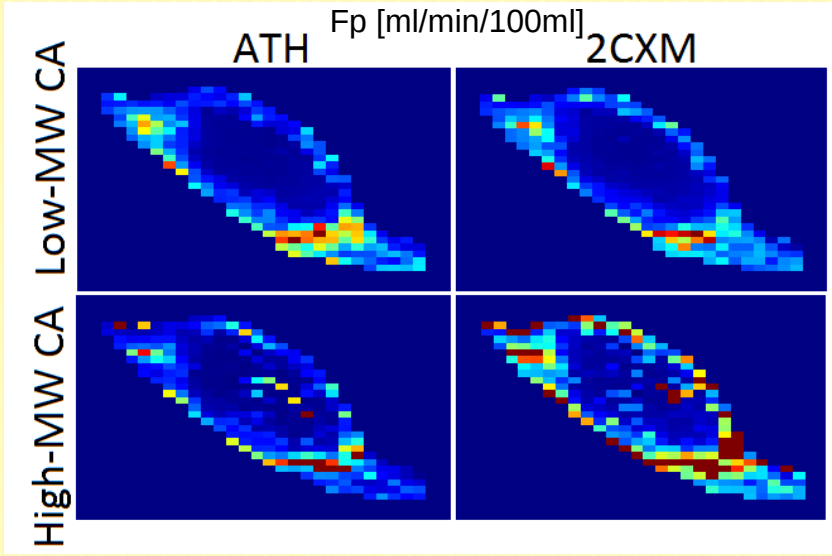


Scatter-plot parameters	AATH Mean	AATH SD	2CXM Mean	2CXM SD
Correlation coef. F_p	0.64	0.27	0.54	023
Correlation coef. v_p	0.72	0.16	0.49	0.32
Correlation coef. PS	0.75	0.12	0.25	0.17
Regression coef., F_p	1.20	0.35	1.15	0.16
Regression coef., v_p	0.98	0.27	0.43	0.30
Regression coef., PS	0.43	0.21	0.57	0.22

⇒ ATH better than 2CXM

- better optimization conditioning
- and/or more realistic (even though both are still simplistic)

difference not clear in visual assessment of perfusion maps:



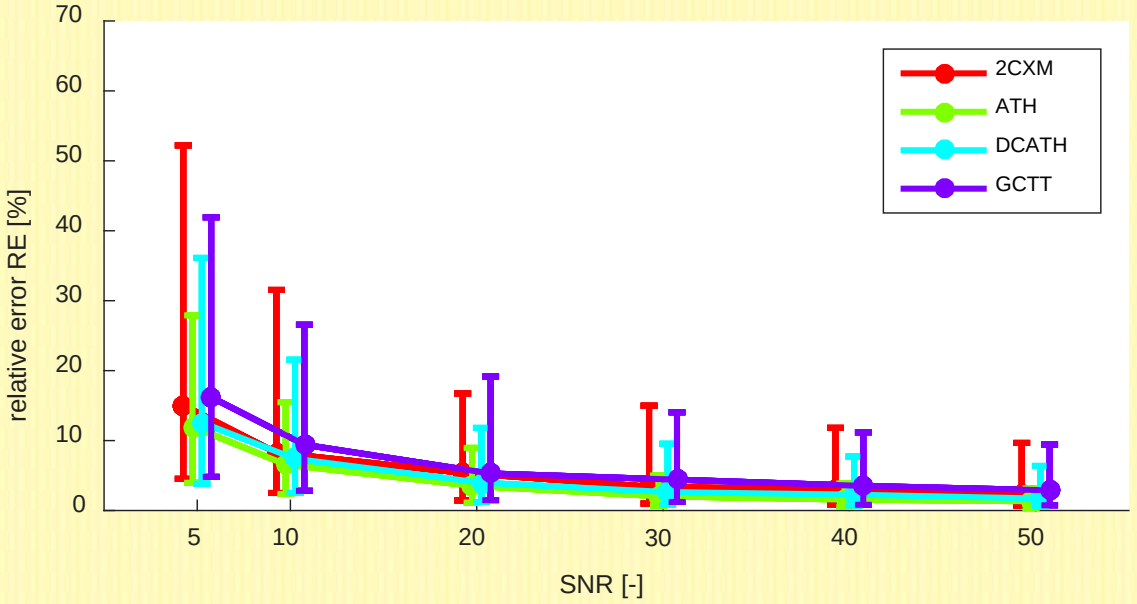
2. PERFUSION IMAGING – PHARMACOKINETIC MODELING

Comparison of
- 2CXM, ATH (aaTH) (4 parameters)
- DCATH, GCTT (5 parameters)

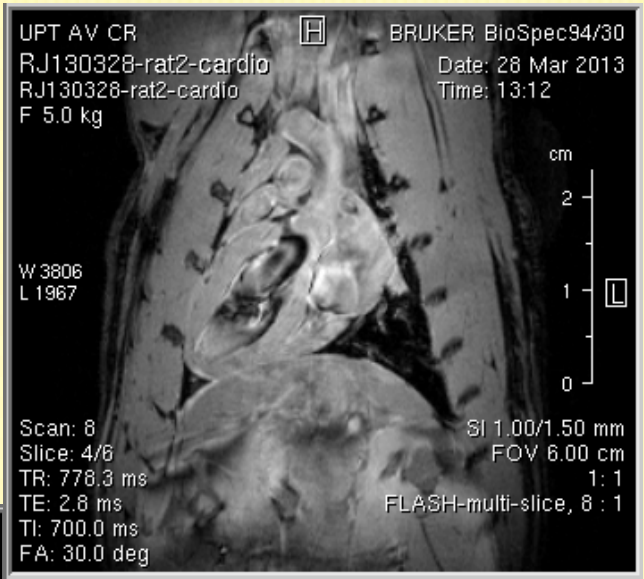
in terms of conditioning of the deconvolution problem

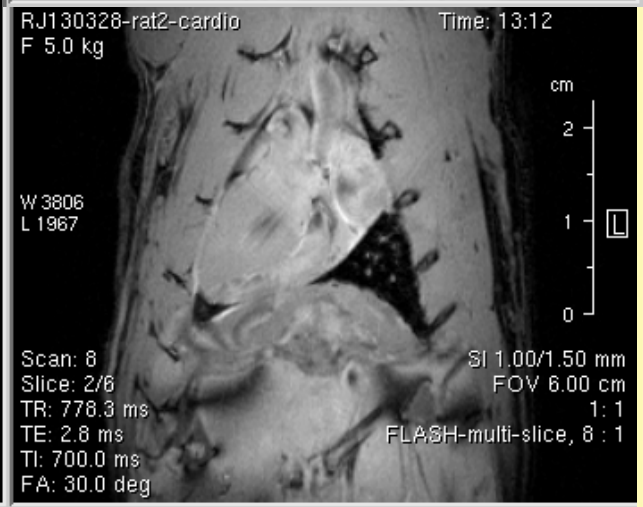
Synthetic data
- the same model used for data generation and deconvolution
- 3 tissues (glioblastoma, prostate and colorectal tumor)
- 100 noise realizations per tissue
- median and 25%, 75% percentiles of relative estim. error of F_p, Tc, E, v_e, BAT, α^{-1} , σ

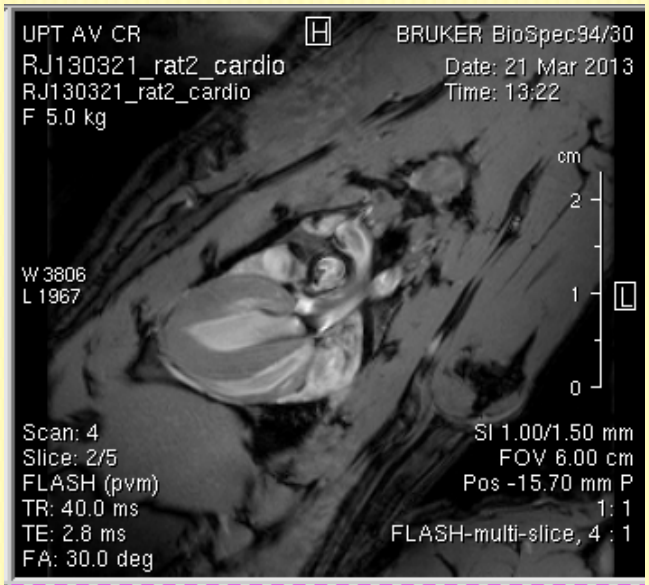
2CXM the worst
ATH the best

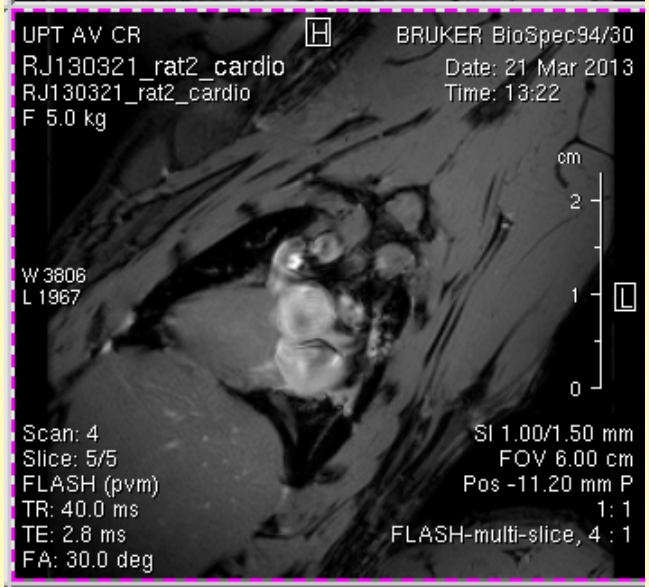


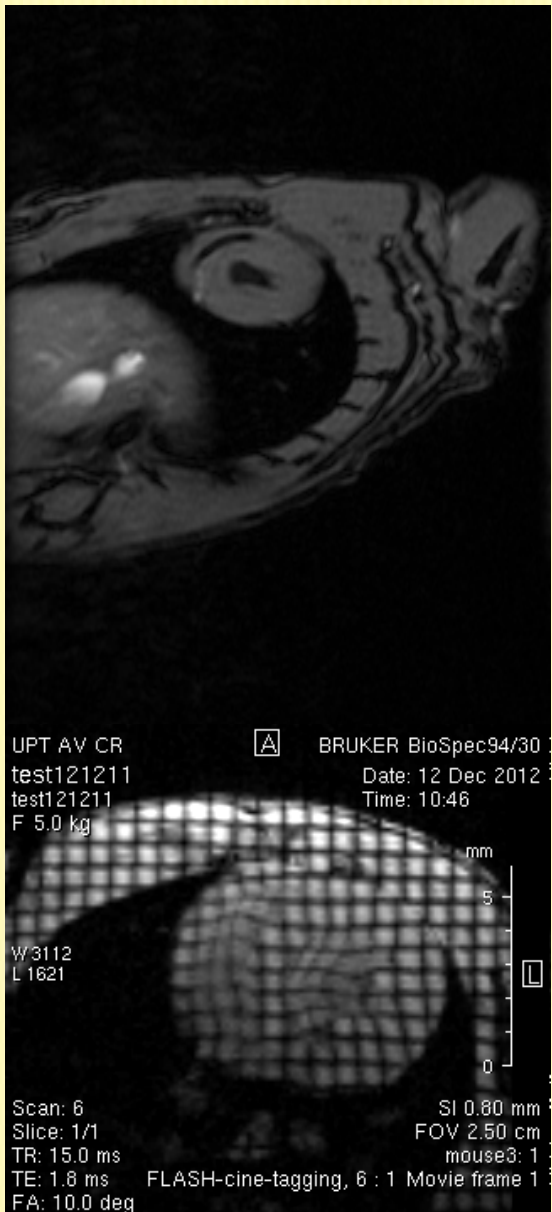
3. T1 QUANTIFICATION - MYOCARDIUM







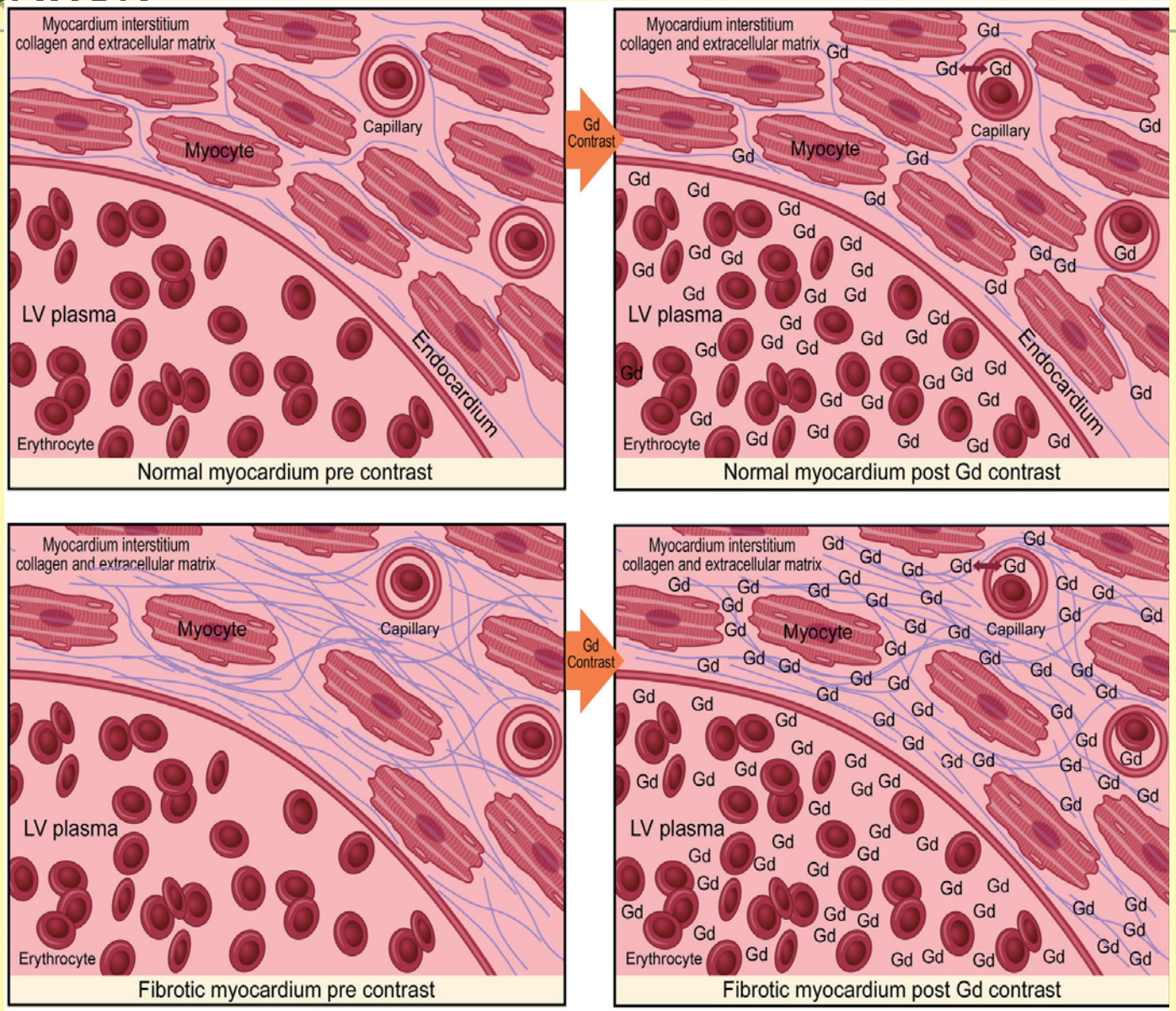




3. T1 QUANTIFICATION

Quantification of fibrosis

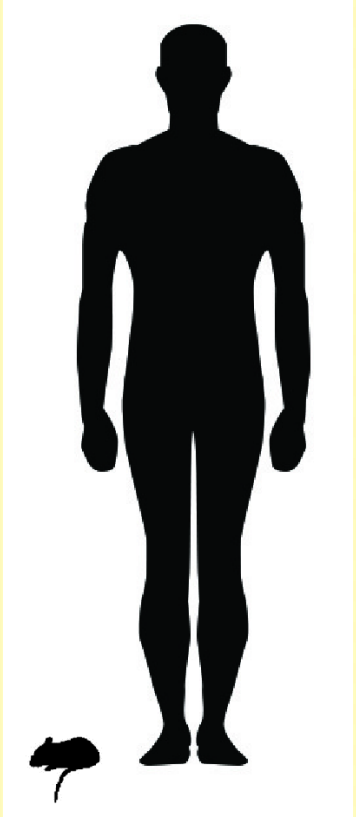
- Focal (myocardial infarction)
- Diffusive (dilated cardiomyopathy)

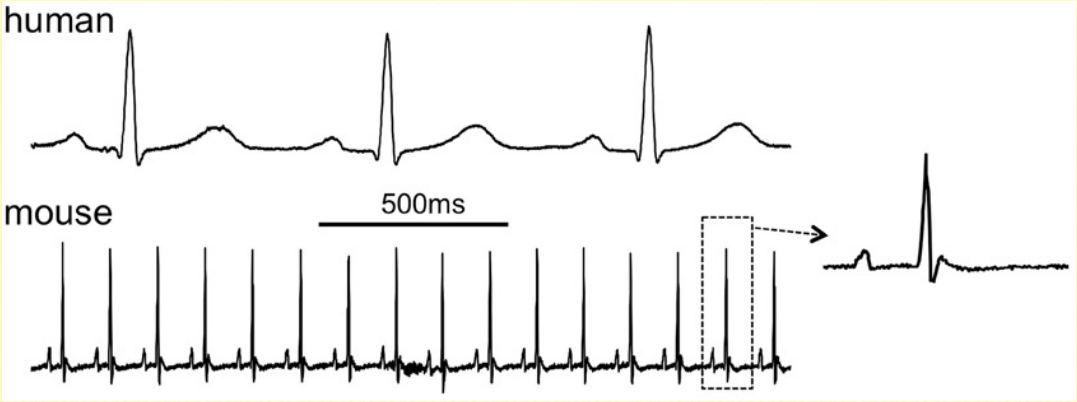


Jellis, Kwon, Cardiovascular Imaging, 2013

3. T1 QUANTIFICATION

- Small animal model
  - Smaller size of the heart
  - Faster ECG and respiration rates
  - rat: 350 BPM, 40-60 1/min
  - (mouse: 450 BMP, 50-80 1/min)
  - in anesthesia
  - no breathhold acquisition possible



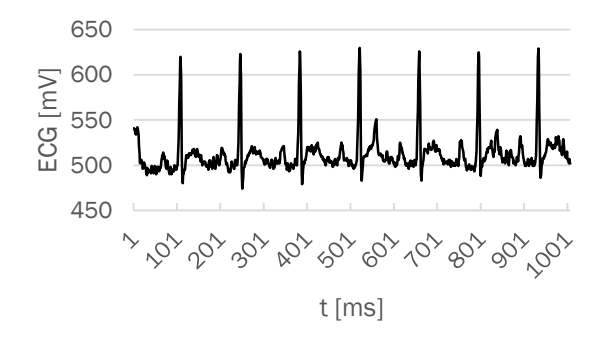


Kease, Front. Physiol, 2012

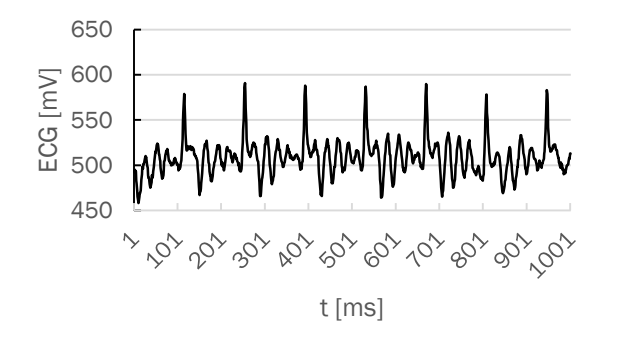
3. T1 QUANTIFICATION

ECG triggering

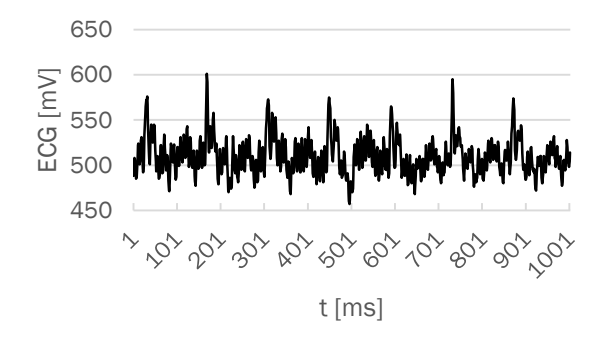
- needle subcutaneous ECG elecrodes



ECG of rat, outside the magnetic field



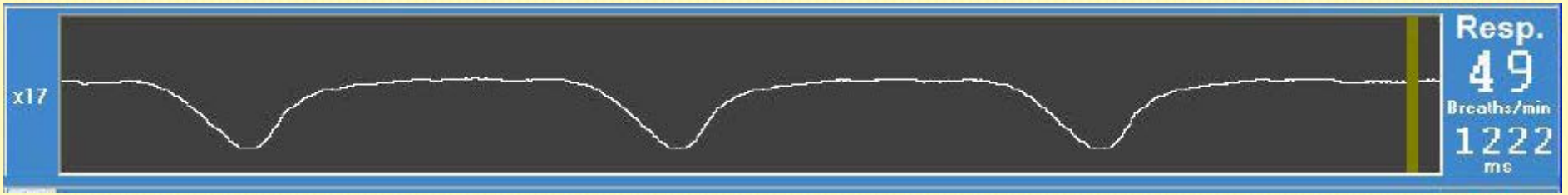
ECG of rat, inside the magnetic field



ECG of rat, during the data acquisition

Respiration triggering

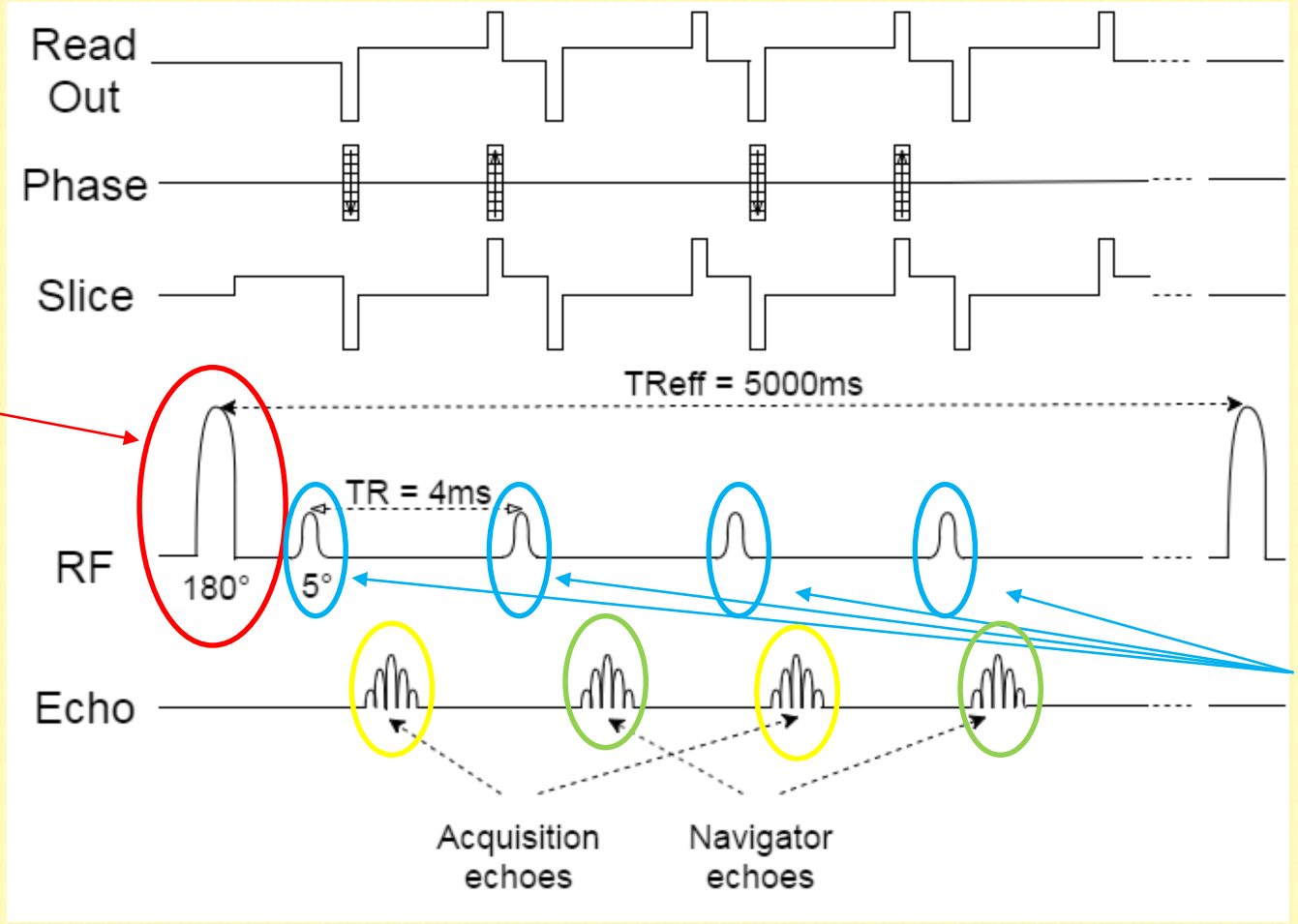
- respiration pillow



3. T1 QUANTIFICATION

Retrospective gating

- no measuring of ECG and respiration, navigators

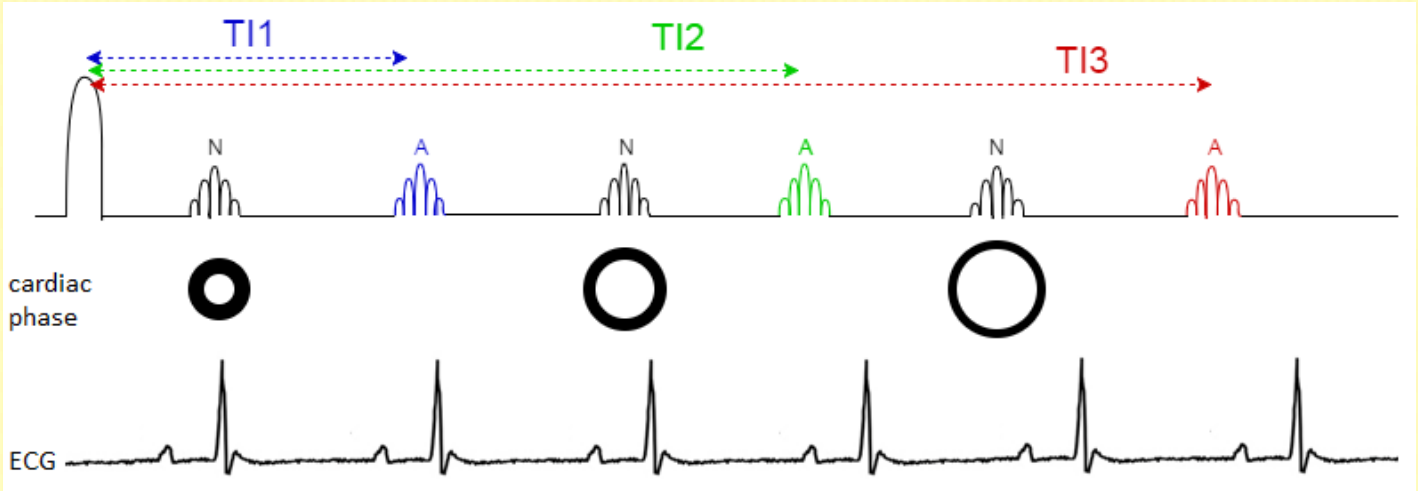


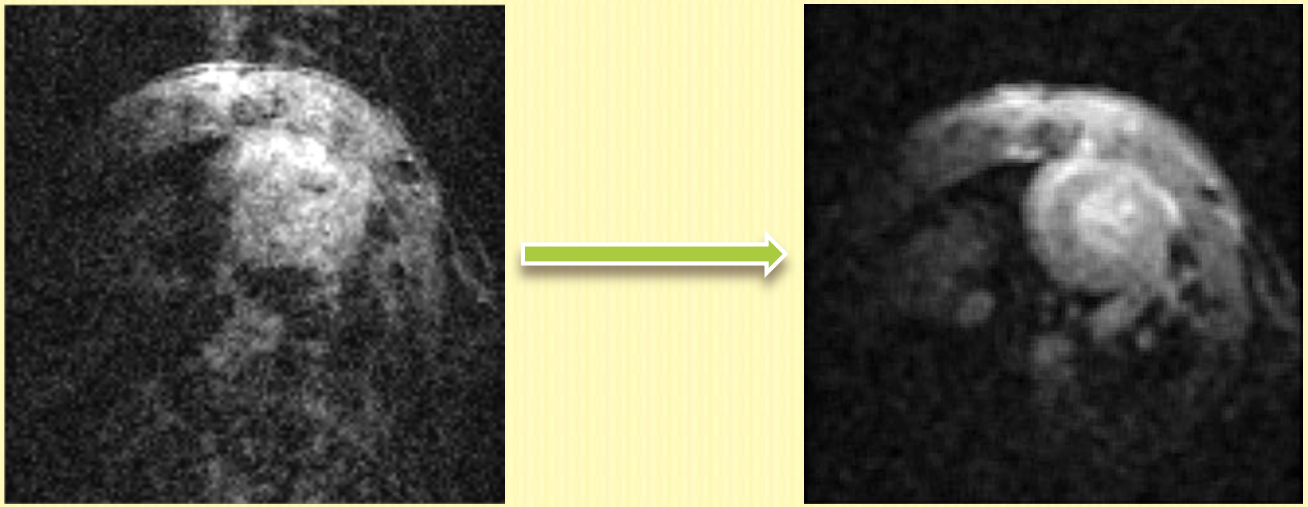
Nonselective inversion pulse

1000 FLASH excitation pulses

3. T1 QUANTIFICATION

Image reconstruction

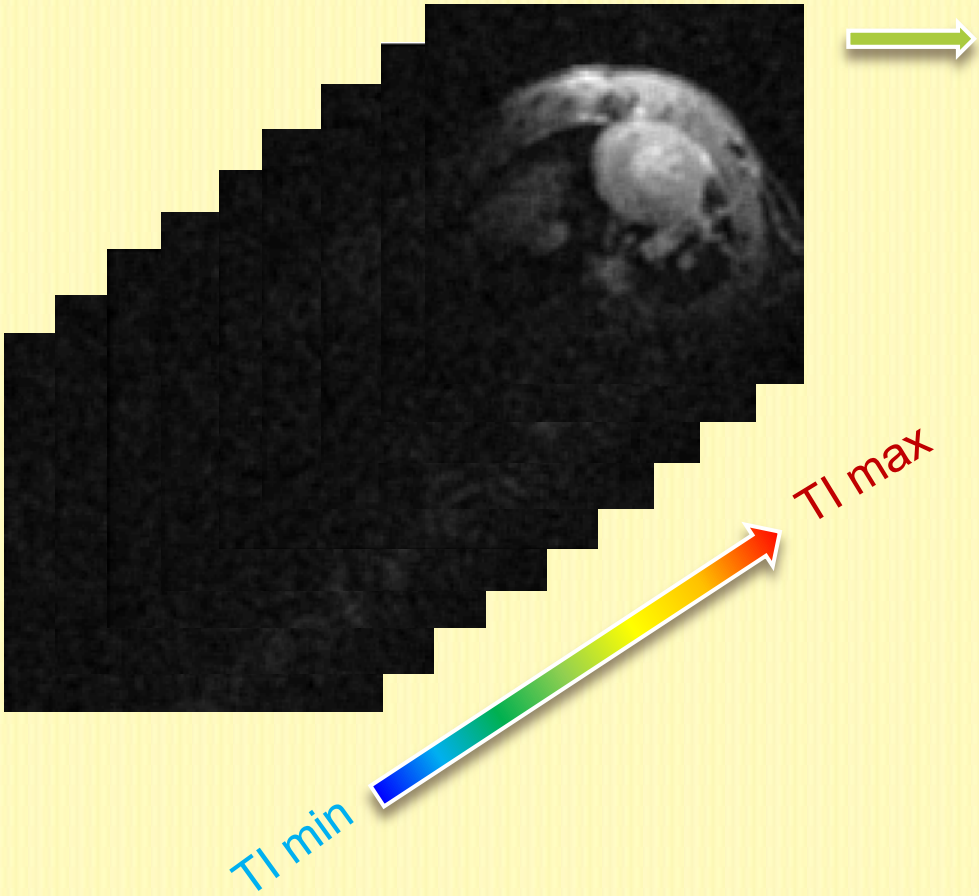


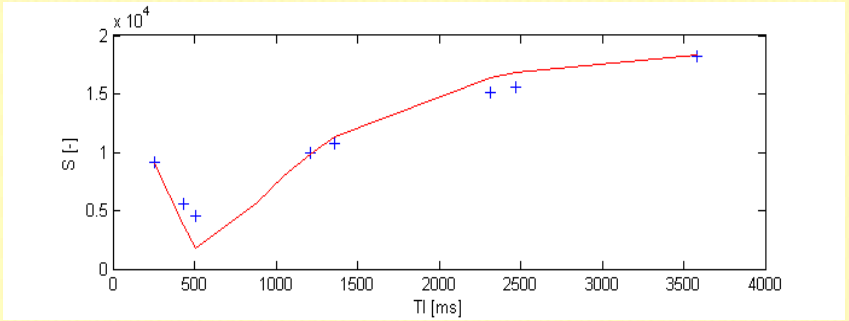


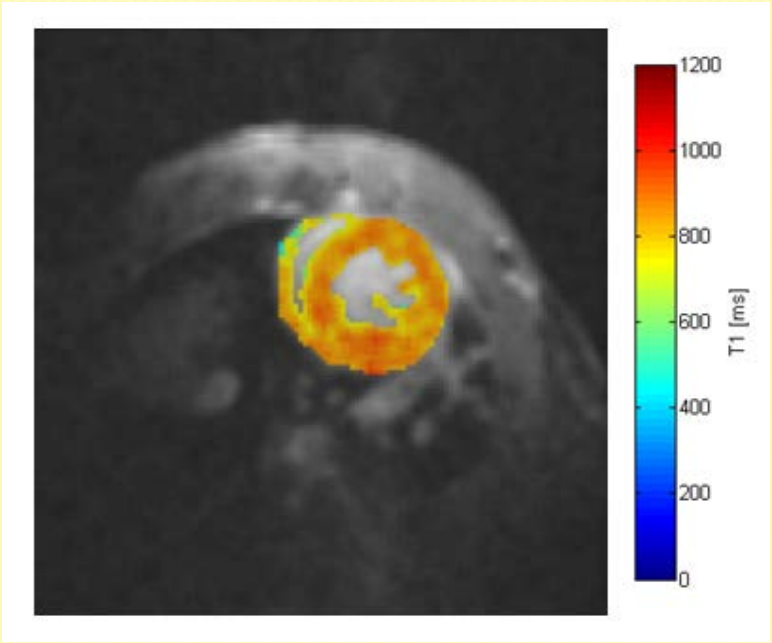
3. T1 QUANTIFICATION

$$S = |S_0(1 - 2e^{-\frac{TI}{T_1}})|$$

Image reconstruction







3. T1 QUANTIFICATION

Doxorubicin

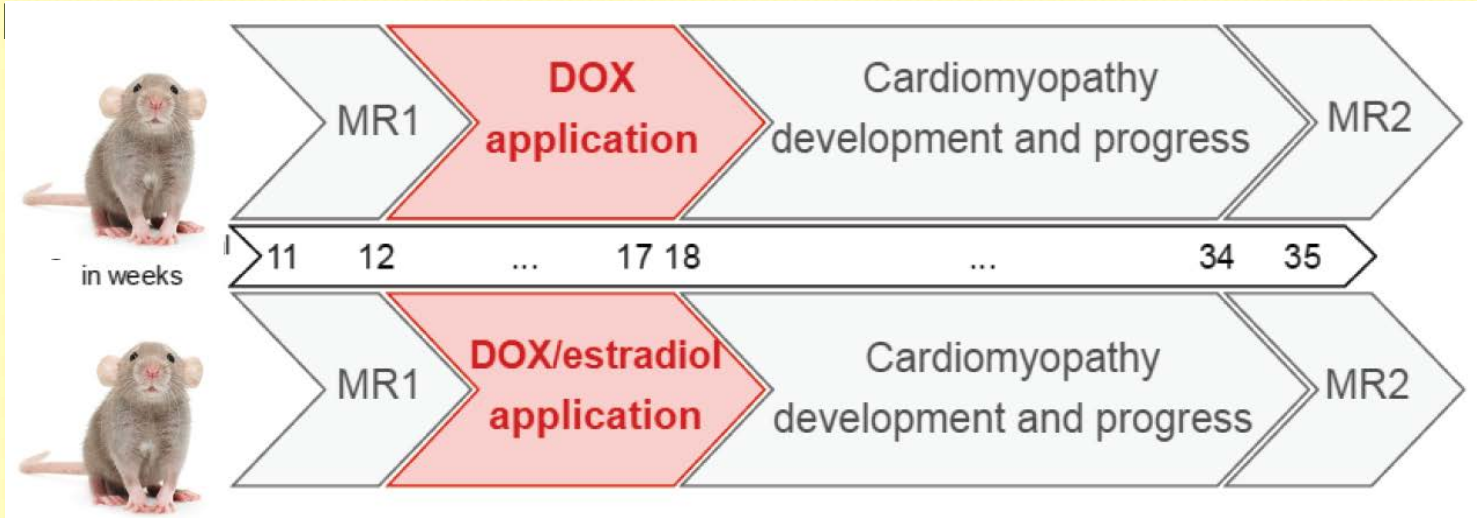
chemotherapy

model of dilated cardiomyopathy

3. T1 QUANTIFICATION

Doxorubicin study

- 18 rats (9 rats survived)
  - 9 doxorubicin treatment (5 survived)
  - 9 doxorubicin + estradiol (hormone-probably increases doxorubicin cardiotoxicity) treatment (4 survived)
- 2 examinations
  - Baseline
  - 18 weeks after treatment
- Anatomical imaging (ejection fraction)
-

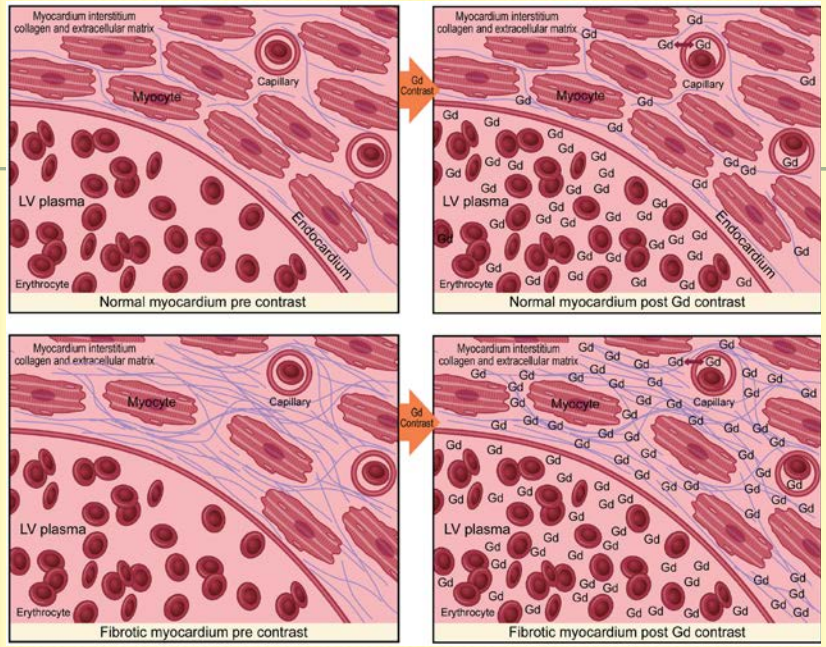


3. T1 QUANTIFICATION

Dilated cardiomyopathy

Fibrosis:

- Higher pre-contrast T1
- Lower post-contrast T1
- Lower ejection fraction

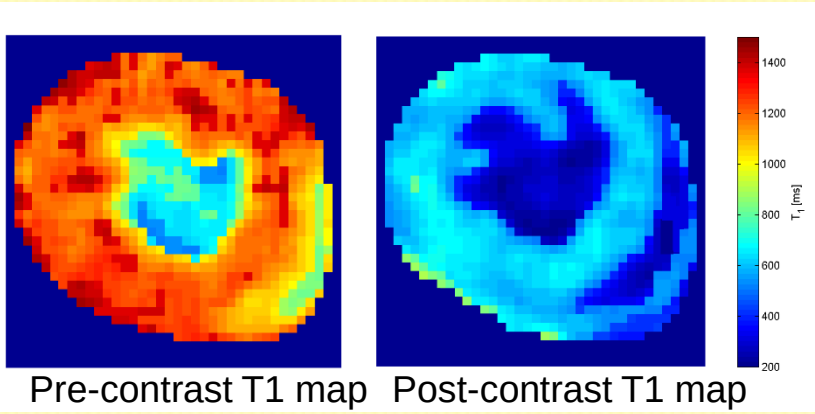


Jellis, Kwon, Cardiovascular Imaging, 2013

Results

Results of statistical analysis for measurements pre versus post treatment

	DOX/ estradiol	DOX	
native T1	↑	↑*	⟹ fibrotic tissue in myocardium
post-contrast T1	↓*	↑	⟹ fibrotic tissue in myocardium (in DOX/estradiol group)
LVEF	↓*	↓*	⟹ cardiotoxicity of both DOX and estradiol confirmed



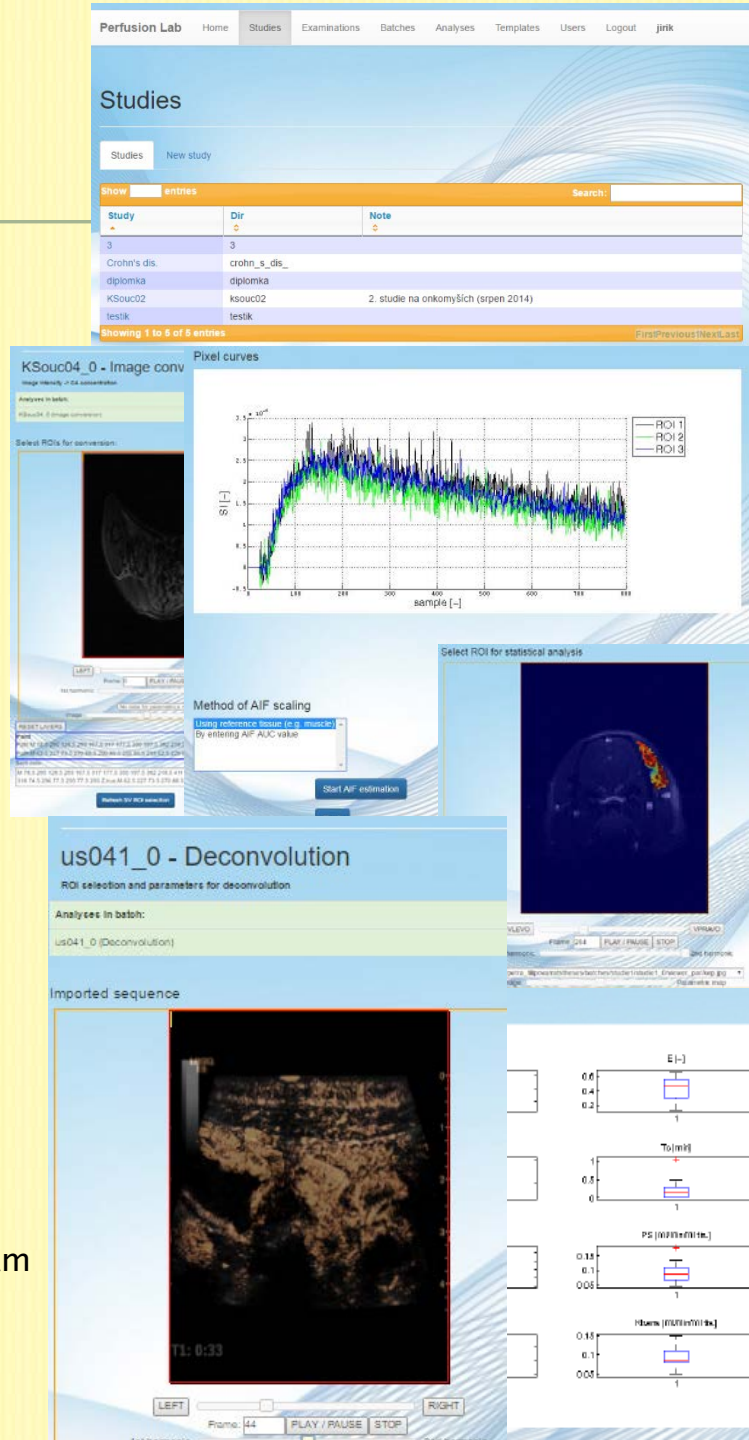
Pre-contrast T1 map Post-contrast T1 map

** indicates a statistical signicant result*

CONCLUSIONS

qMRI

- comparability of the data generated at different sites and time points and using different scanners
- assumptions of models
- underlying models have to be realistic and lead to well-posed and well-conditioned approximation
- animal studies – alternative ways of validation

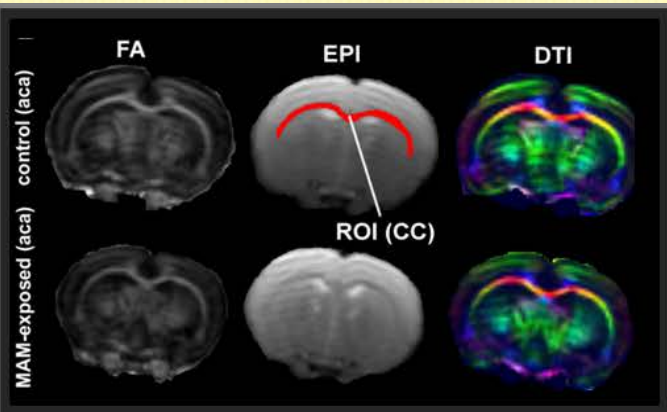


http://perflab.cerit-sc.cz/

DCE-MRI
- Blind deconvolution (so far preclinical AIF)
- ATH, 2CXM, Tofts, ext. Tofts pharmacokinetic models
- …more will come soon

DCE-US
- Bolus&burst
- AIF models: 2gam, 3gam
- Automatic image registration
- So far – single regions
- …more will come soon

THANK YOU FOR YOUR ATTENTION!



ISI ASCR