Perfusion Imaging: Dynamic Contrast-Enhanced MRI

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UCLA Health System

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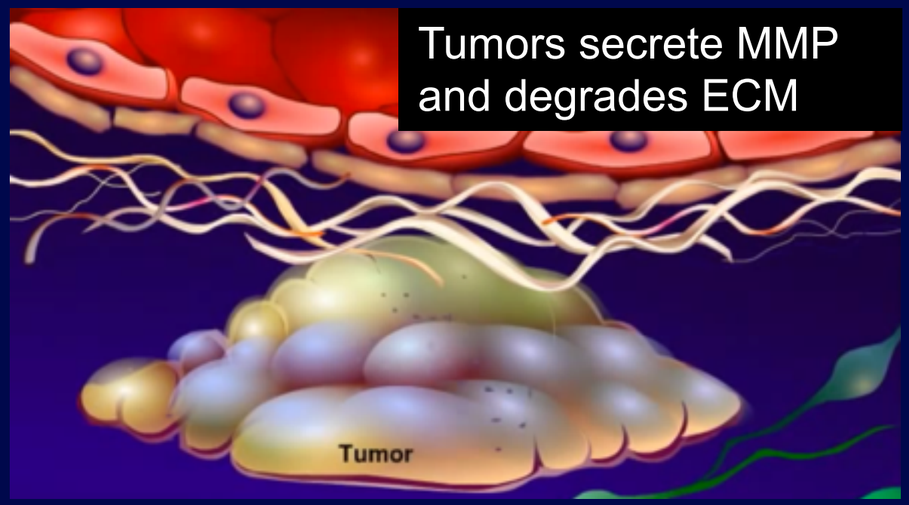
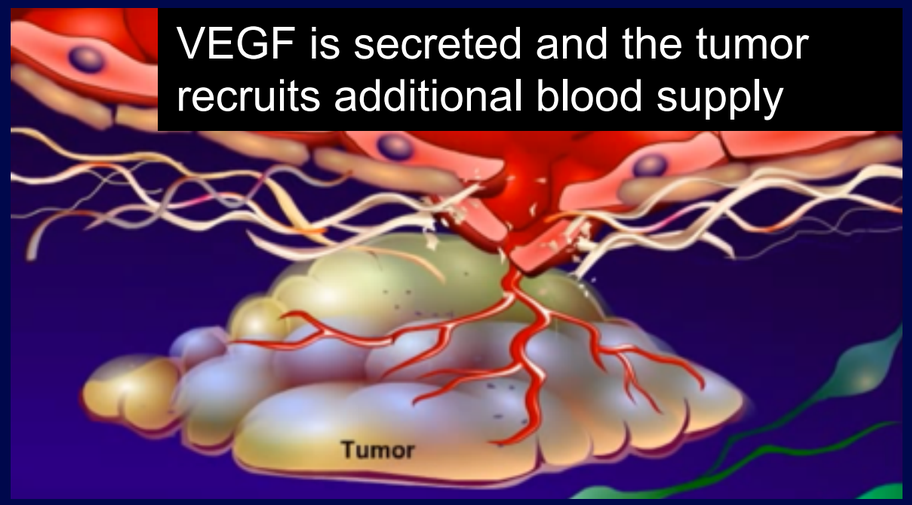
Tumor Angiogenesis

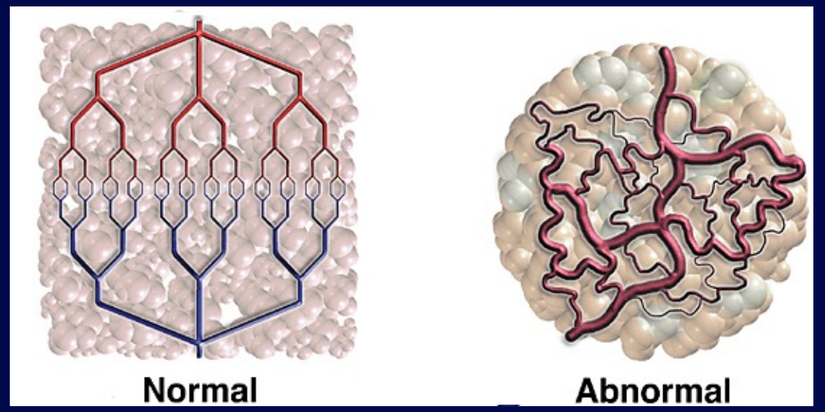




- Cancer cannot grow beyond a certain size without developing a vascular network to provide additional nutrients and oxygen for growth (angiogenesis)
- Recruited tumor vasculature is different from normal vasculature, measurable with contrast-enhanced MRI

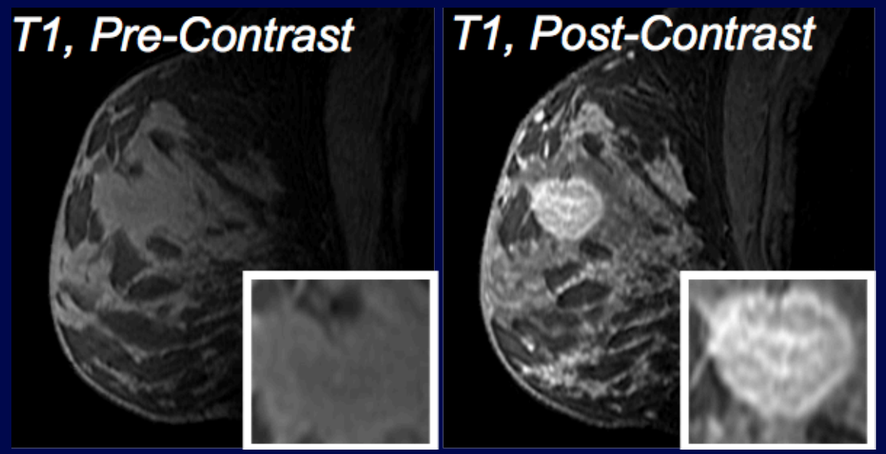
Tumor Vasculature and Enhancement

- Cancer has many traits different from surrounding tissue:
  - Unchecked cell proliferation
  - Cannot grow beyond a certain size without developing a vascular network



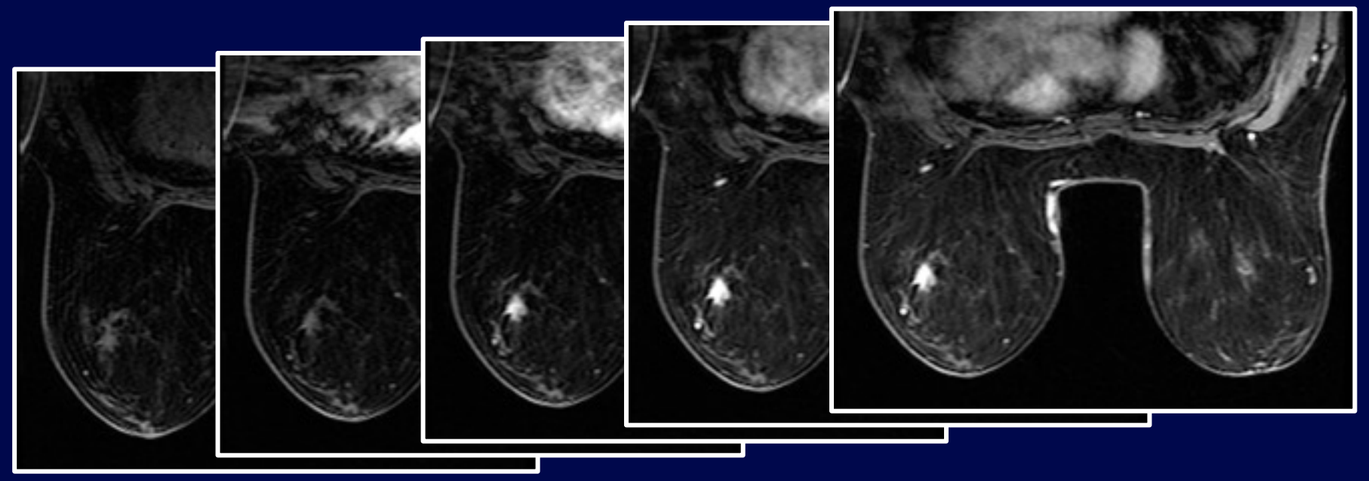
Jain R, Nat. Medicine 2001

- MRI has great potential to detect cancer and vascular abnormalities



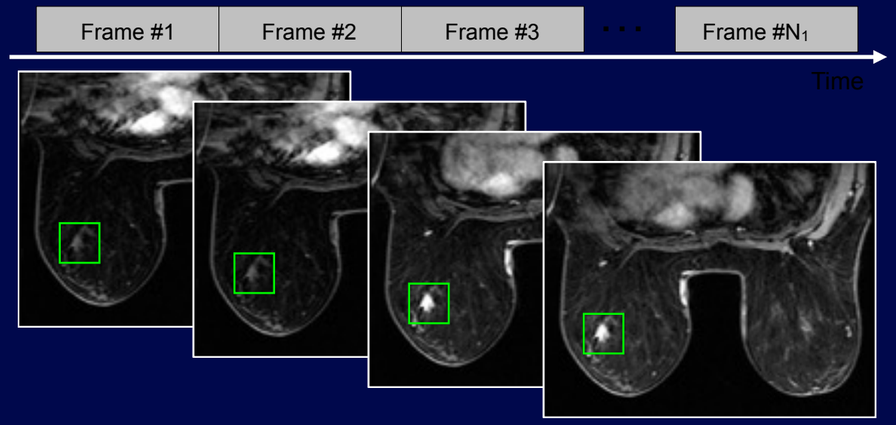
Contrast Enhanced MRI

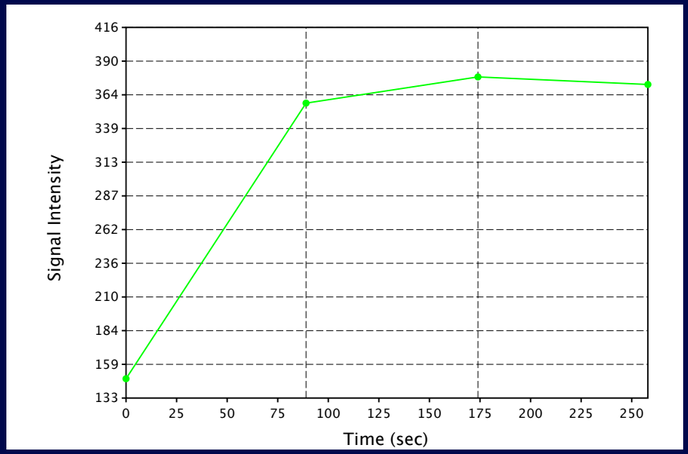
- One post-contrast image
- Pre- and post-contrast image
- “Slow” dynamic acquisition (~ minutes)
- “Fast” dynamic acquisition (~ seconds)



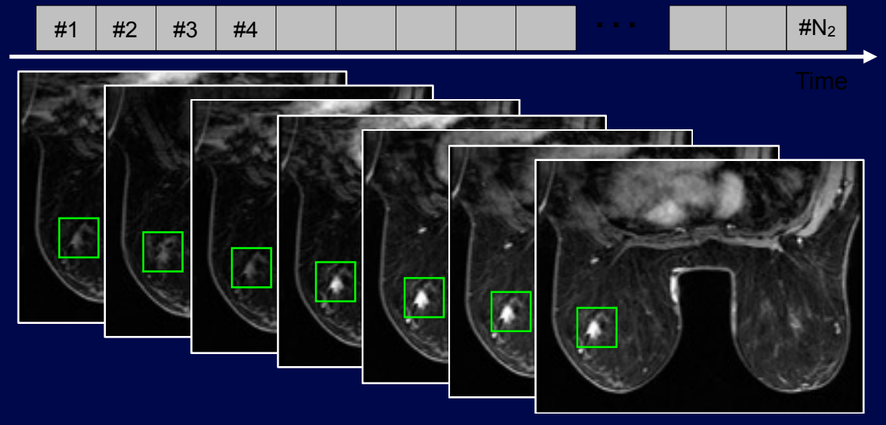
Dynamic Contrast-Enhanced (DCE) MRI

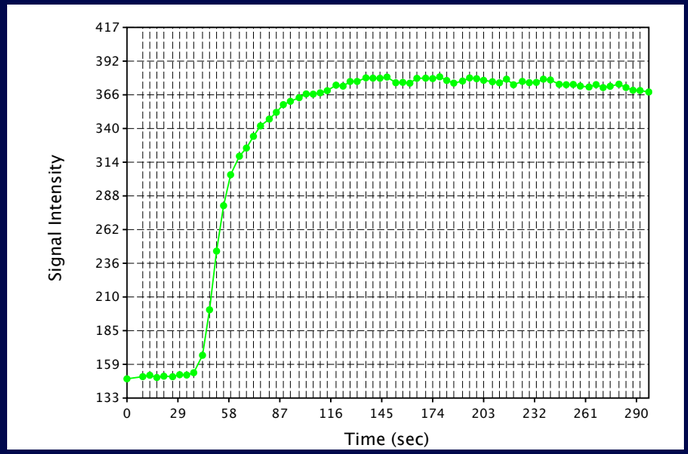
Conventional DCE-MRI





High Frame-Rate DCE-MRI





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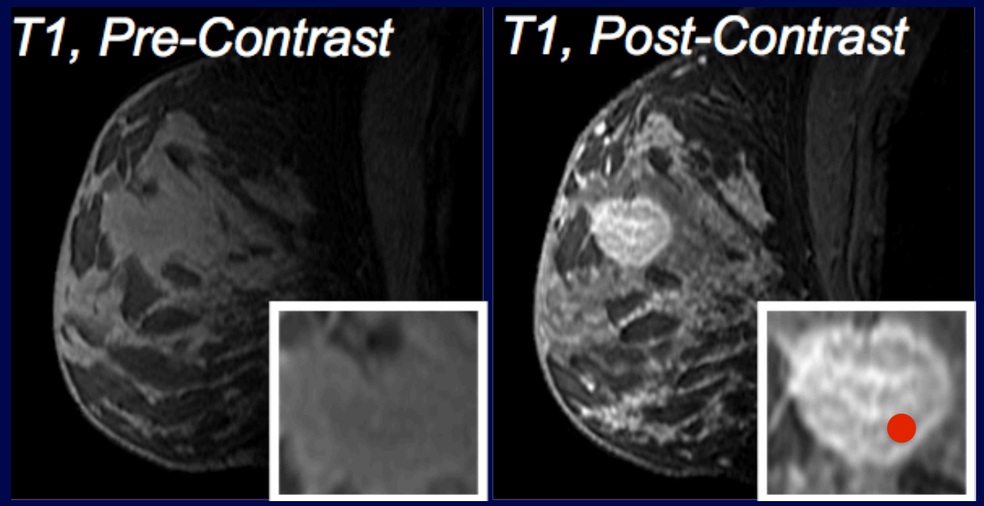
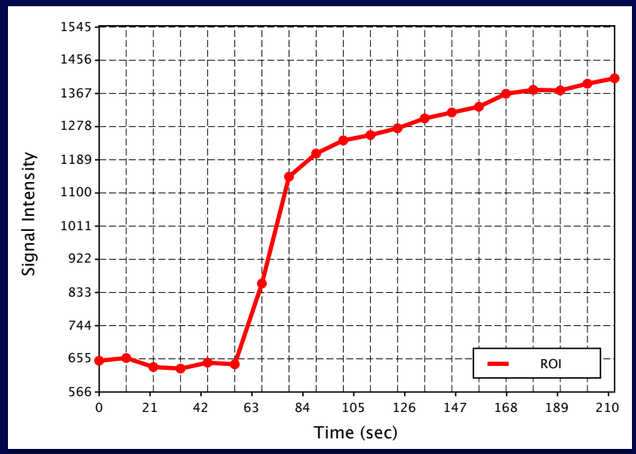
DCE-MRI: Temporal Resolution



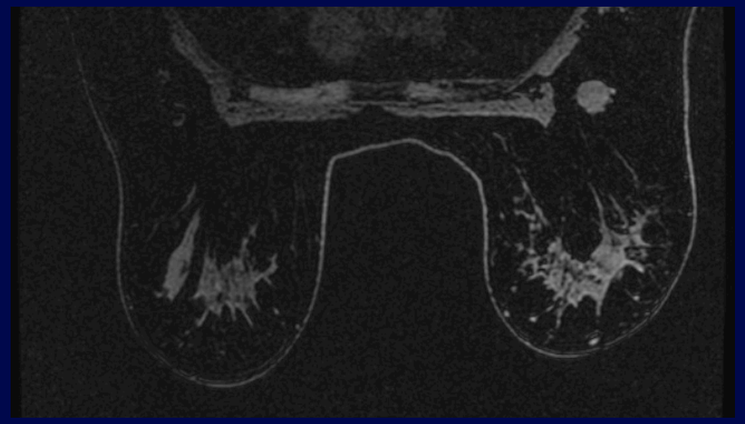


- High spatial and temporal resolution is desirable for DCE-MRI applications, especially for better quantitative analysis
- Many k-space data sharing schemes (e.g., TWIST and DISCO) become popular

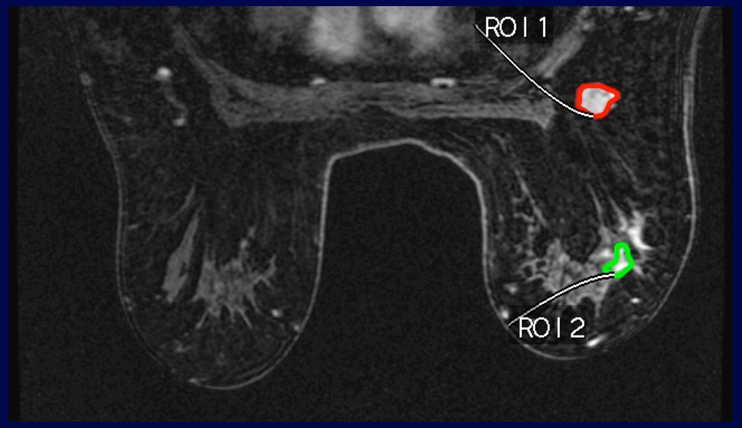
Madhuranthakam AJ, et al. MRM 2006
Herrmann KH, et al. JMRI 2011

Dynamic Contrast Enhanced (DCE) MRI

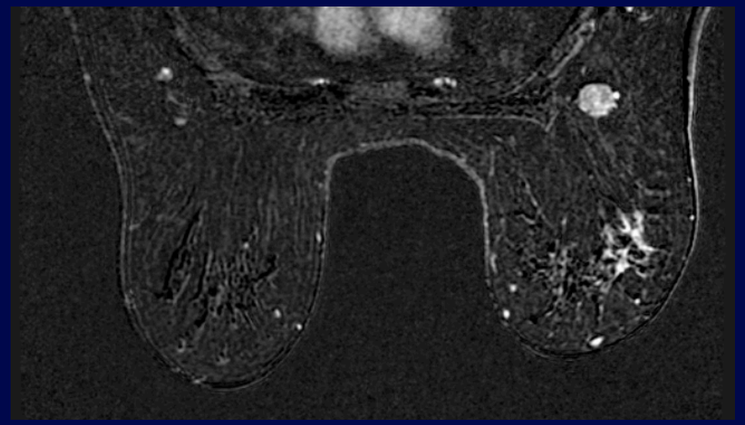
Pre-contrast

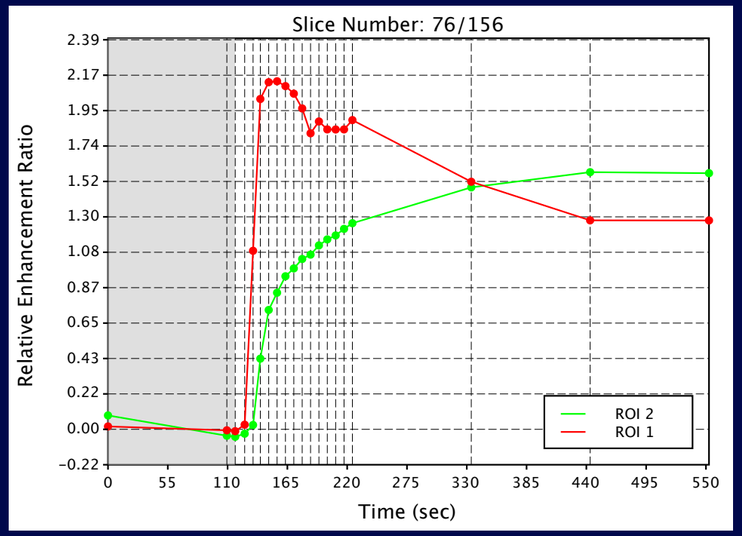


Peak-contrast



Subtraction





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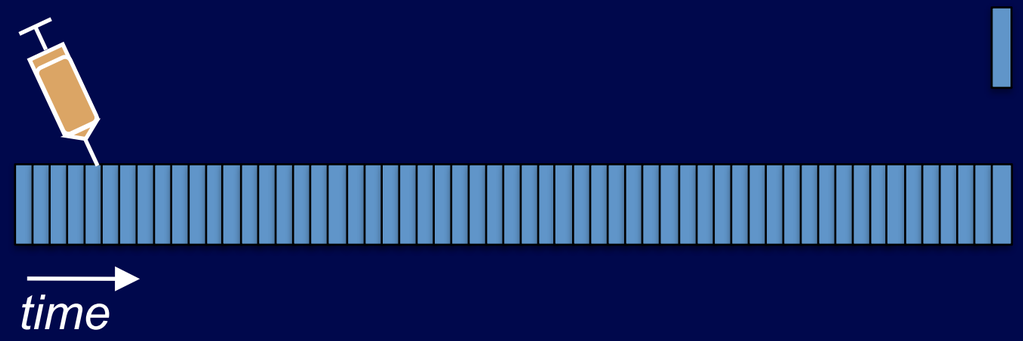
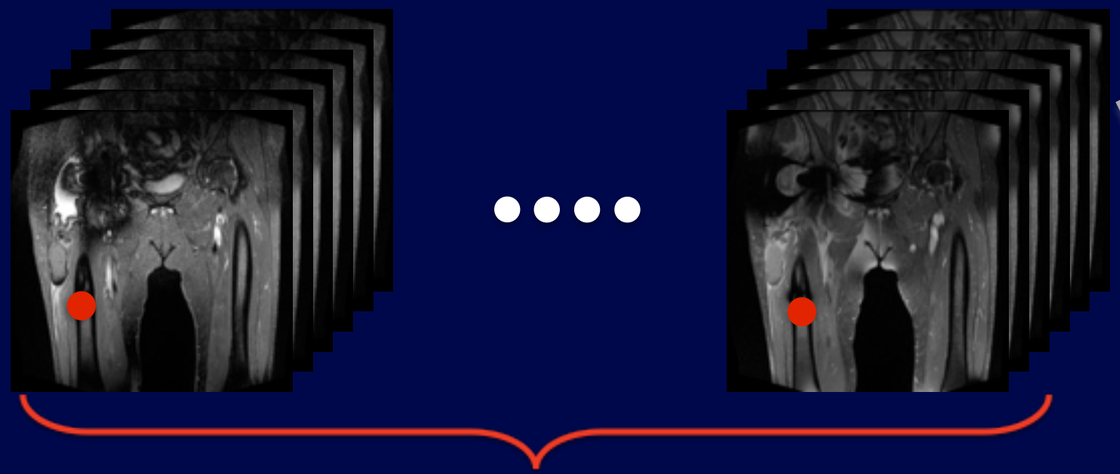
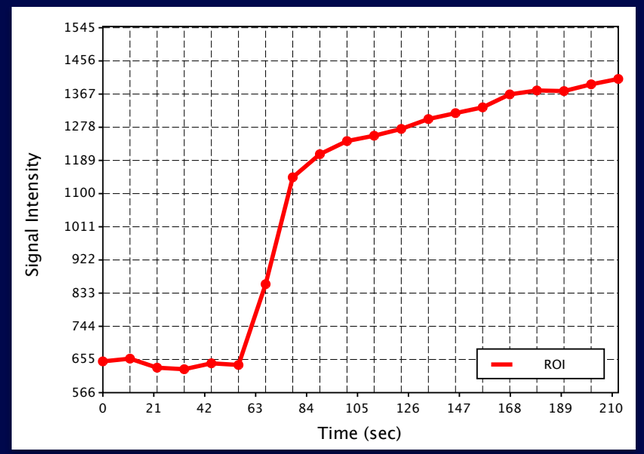
T1-weighed DCE-MRI

- DCE-MRI continuously monitors enhancement of tissue before and after injection of contrast agent



Dynamic 3D MR Imaging





Understanding Physiological Meaning

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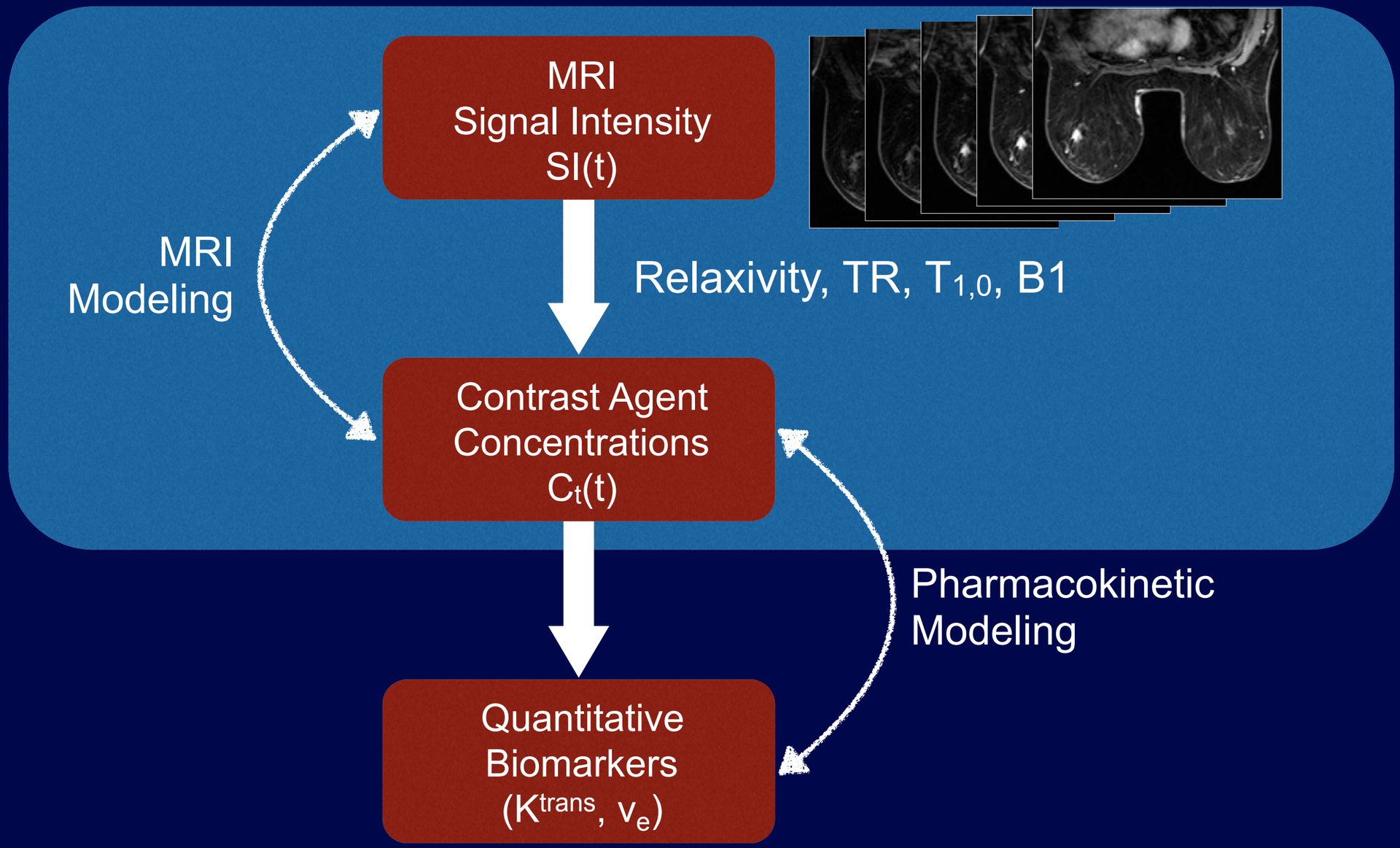
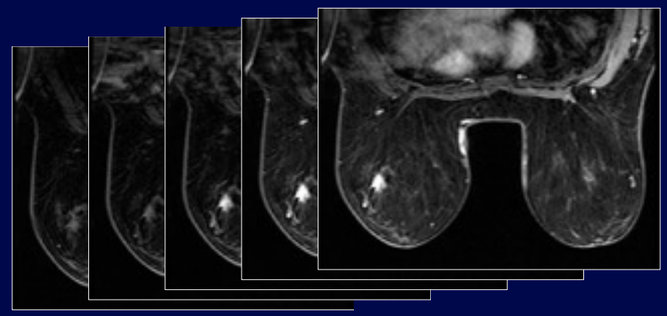
Quantitative DCE-MRI



Quantitative DCE-MRI



MRI
Signal Intensity
SI(t)

MRI
Modeling

Relaxivity, TR, $T_{1,0}$, B1

Contrast Agent
Concentrations
$C_t(t)$

Pharmacokinetic
Modeling

Quantitative
Biomarkers
(K^{trans}, v_e)

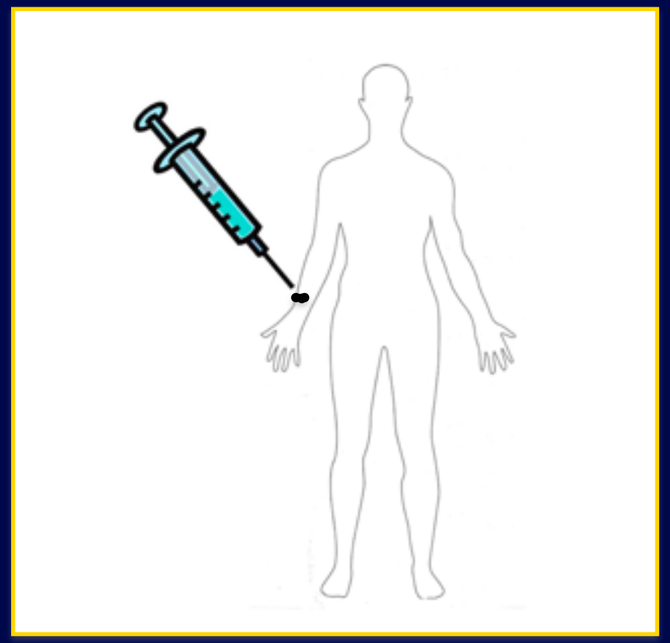
Outline of Topics

- Conversion from MR signal to concentration
  - T1 measurements
  - B1 inhomogeneity
- Conversion from concentration to quantitative biomarkers (pharmacokinetic modeling)
  - Standard Tofts (two-compartment) model
  - Arterial input function
  - Dispersion modeling
- DCE-MRI data analysis (post-processing option)

MRI Modeling:
MR Signal → Concentration

T1-weighed DCE-MRI

- DCE-MRI continuously monitors enhancement of tissue before and after injection of contrast agent



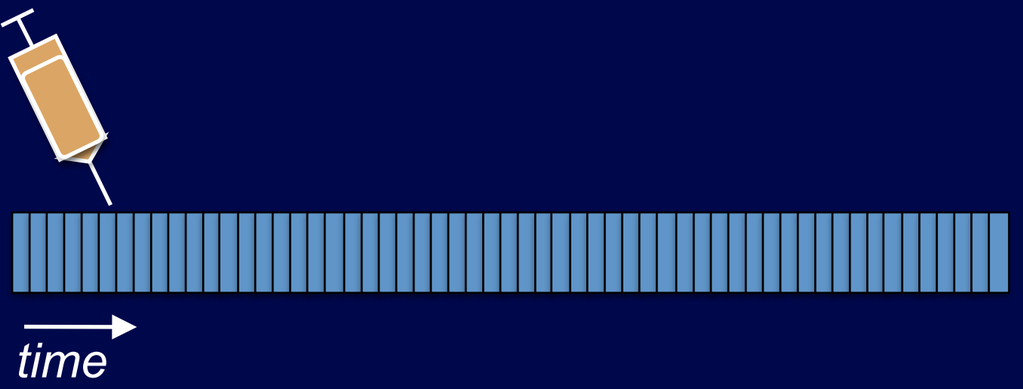
Concentrations

↓

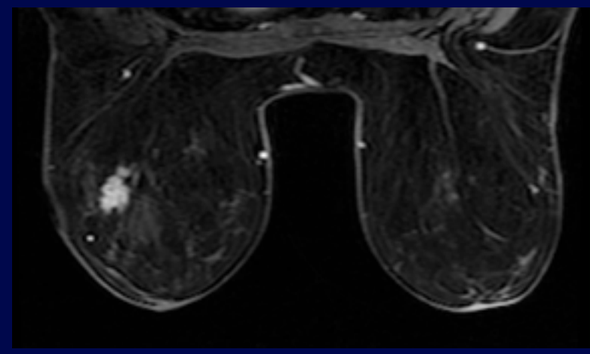
Relaxation Rates

↓

MR Signal Intensity



Dynamic 3D MR Imaging

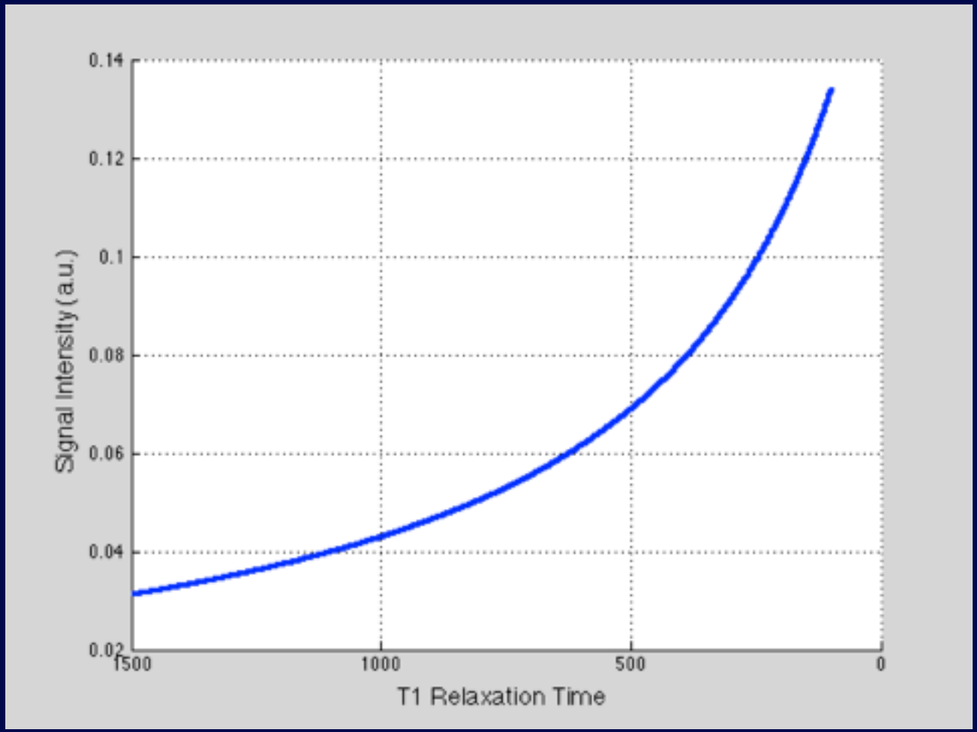


MR Signal Intensity

- Signal equation for RF-spoiled gradient echo (T1-weighted) sequence:

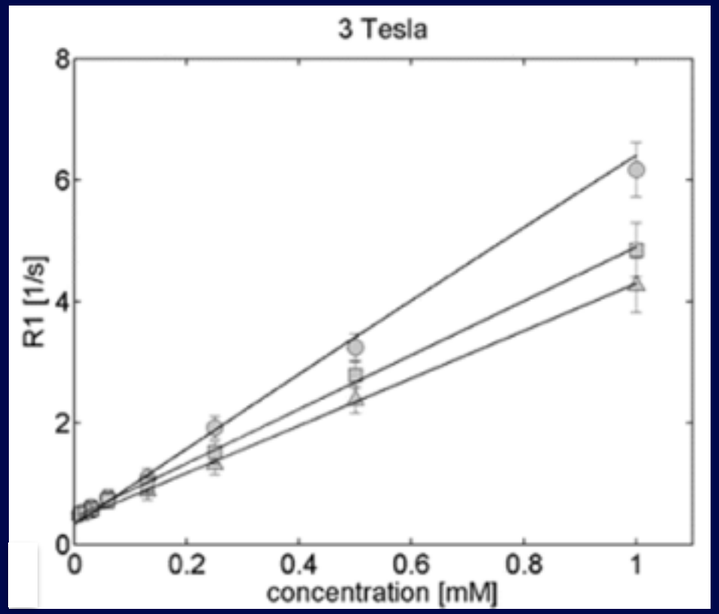
$$S \propto \frac{(1 - e^{-TR/T1}) \sin\theta}{1 - e^{-TR/T1} \cos\theta}$$

- MR signal intensity is not linearly proportional to T1 relaxation time



Relaxivity of Contrast Agent

- 1/T1 (R1) is linearly proportional to concentration
  - Relaxivities (r1) of the contrast agent determine the slopes



Gadolinium Chelate	r1 relaxivities at 3T ($L\ mmol^{-1}\ s^{-1}$)
Magnevist (Gd-DTPA)	3.3
Gadovist (Gd-BT-DO3A)	3.6
MultiHance (Gd-BOPTA)	6.3

Pintaske J. Investigative Radiology 2006

Quantitative DCE MRI

- Measurement of baseline relaxation time ($T_{1,0}$) is required to monitor concentration C(t) from MR signal intensity

$$\frac{1}{T_1(t)} = \frac{1}{T_{1,0}} + \gamma \cdot C_t(t)$$

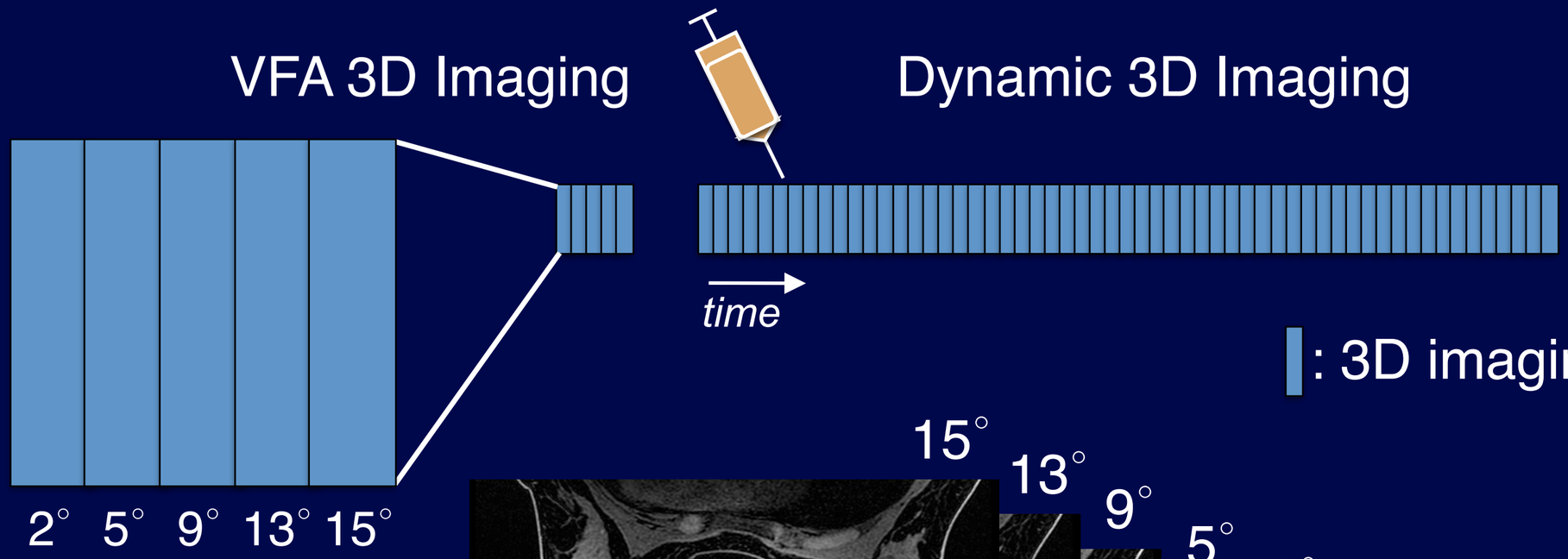
Relaxation time

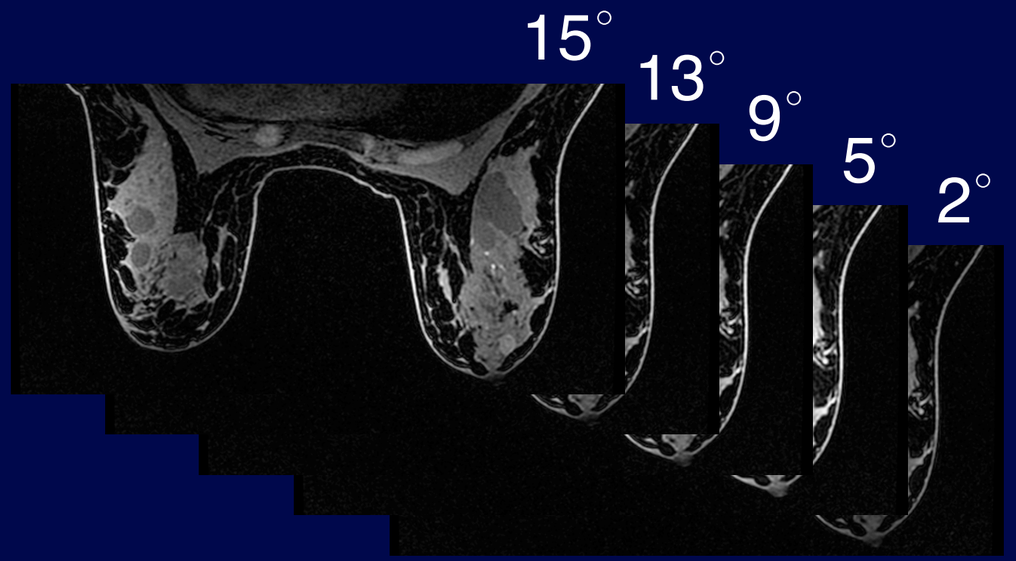
Baseline relaxation time

Contrast agent concentration

- Assume $T_{1,0}$ vs. Measure $T_{1,0}$
- Variable flip angle (VFA) approach, often called DESPOT1, is a common choice for fast 3D volumetric $T_{1,0}$ mapping

VFA $T_{1,0}$ Measurements

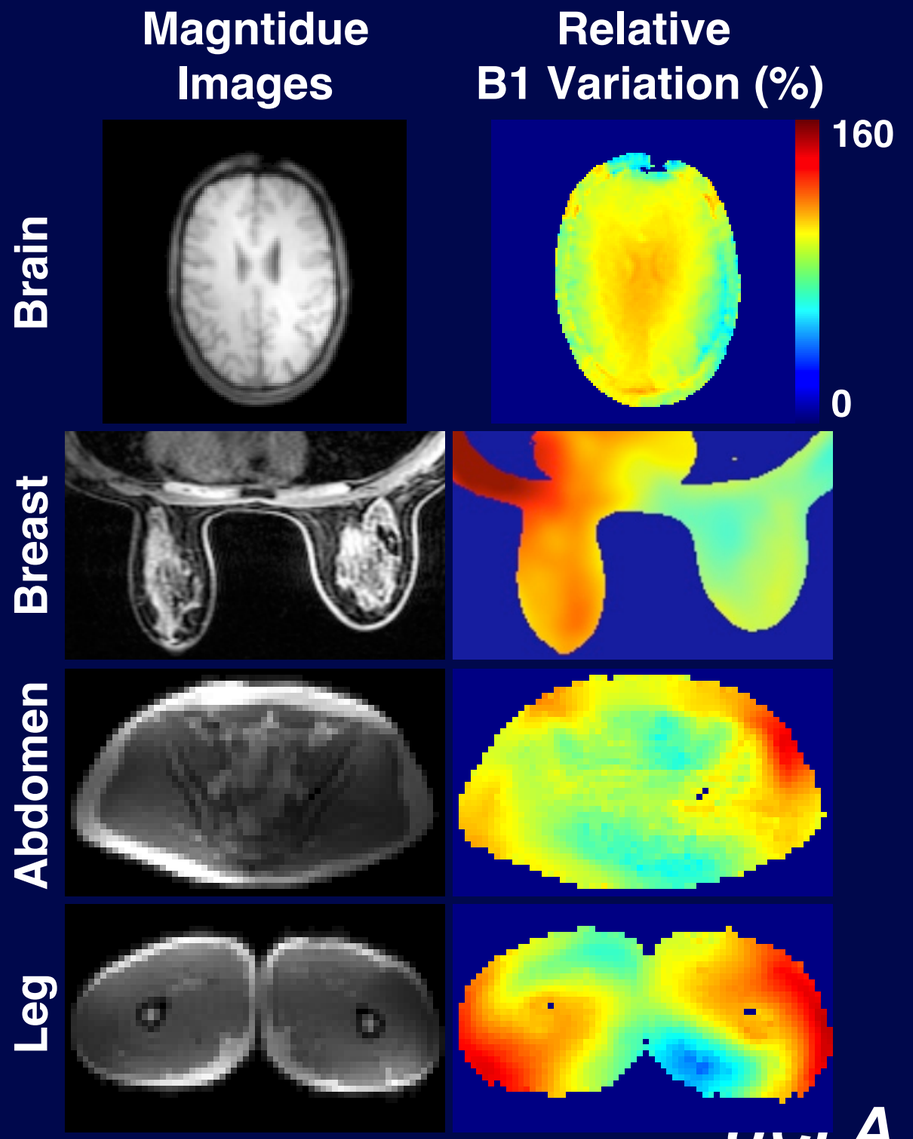




B1 inhomogeneity at 3T

- VFA $T_{1,0}$ mapping is sensitive to B1 inhomogeneity

- Transmit RF (B1) field inhomogeneity can create 30 – 50 % flip angle variation across the body at 3T

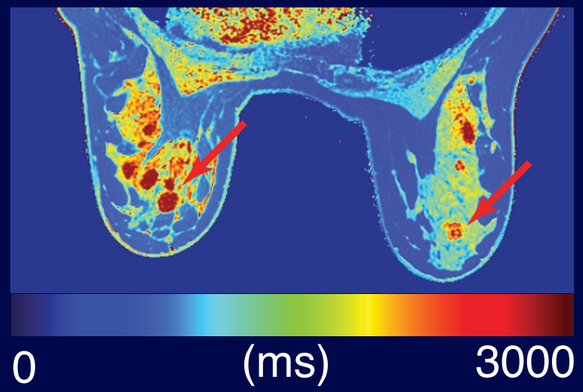


Sung K, et al. JMRI 2008
Azlan C, et al. JMRI 2010
Hancu I, et al. ISMRM 2010 p.2470
Sung K, et al. JMRI 2013

Compensating for B1 inhomogeneity

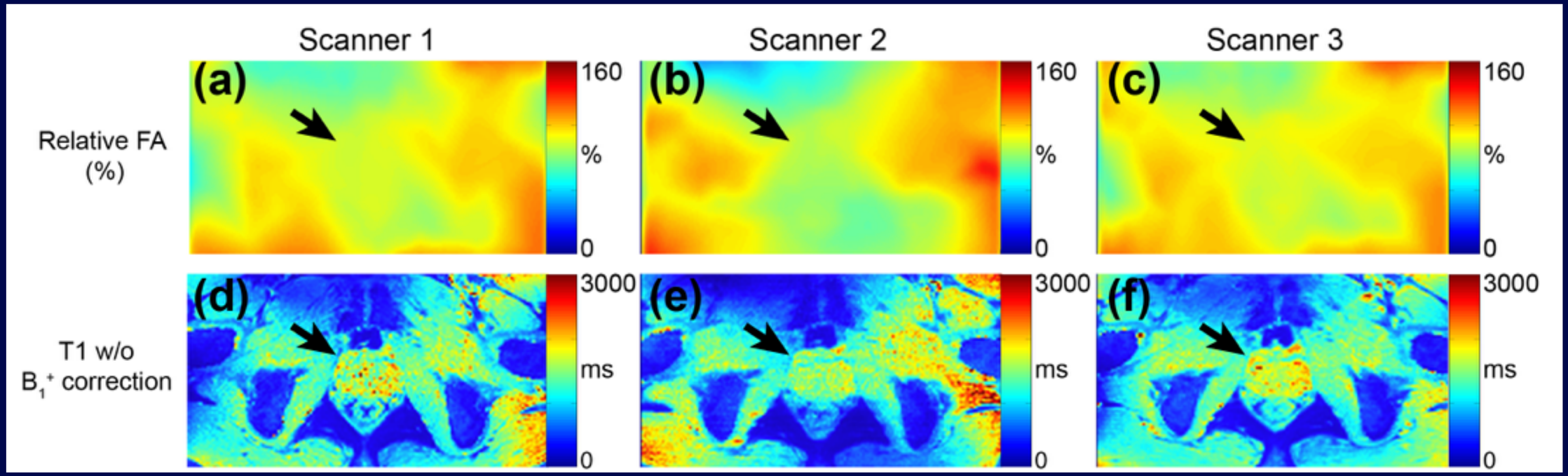
- Additional B1 measurements / B1 shimming may be needed to compensate for B1 inhomogeneity
- There exist other ways to compensate for B1 inhomogeneity

T_1 map using VFA



Sung K, MRM 2013

Challenges: Inter- and Intra-scanner Variability



K Sung, et. al., MRM 2013

N Rangwala, et. al., JMRI 2016

Summary

- Pre-contrast T1 ($T_{1,0}$) information is needed for conversion from MR signal to concentration
  - Assume $T_{1,0}$ from literature
  - Measure $T_{1,0}$ using VFA

- VFA $T_{1,0}$ mapping requires
  - Careful selection of a set of flip angles
  - Sufficient SNR (e.g., multiple measurements)
  - Compensation for B1 inhomogeneity (for ≥ 3T applications)

Pharmacokinetic Modeling: Concentration → Quantitative Biomarkers

Pharmacokinetics

- Pharmacokinetics
  - What the body does to the drug (or contrast agent)
  - Related “doses of drug” to “concentrations of drug at various locations in the body”
- Although pharmacokinetics is a leap from the molecular and cellular analyses,
  - We are interested in kinetic phenomena that occur at the level of the whole body

Compartment Models

- The body is divided into compartments
  - Vascular plasma space
  - Extracellular extravascular space (EES) or interstitial space
  - Intracellular space
- Each compartment is assumed to be well-mixed
  - Uniform concentration in each compartment
  - Want to know how the average concentration of the drug varies with time in the compartment
  - Mass can be transferred between different compartments
  - Inputs for drug entering the body / Outputs for drug clearance

Compartment Models

- Each compartment has:
  - Volume
  - Average concentration of drug
- Principles
  - Mass conservation
  - Rate constants for transfer between compartments
- Compartment models are not mechanistic
  - Several processes are lumped in black boxes

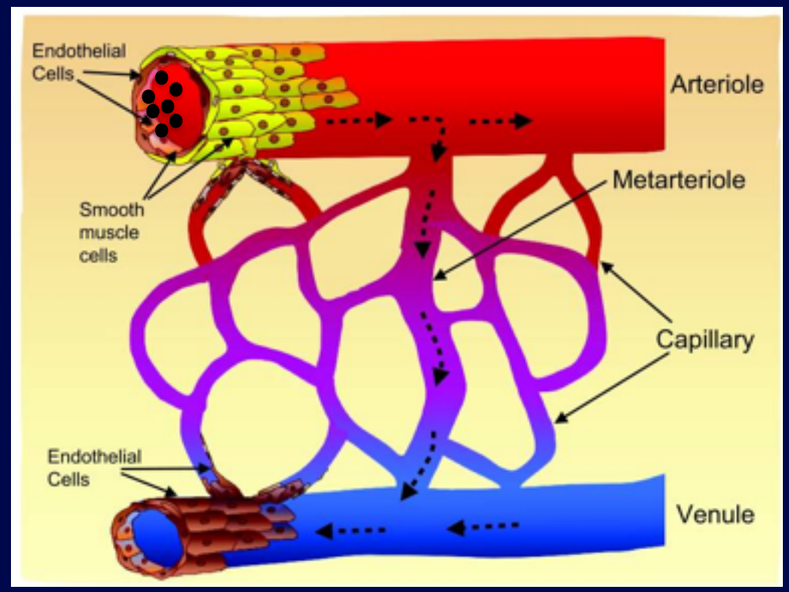
Drug Administration and Clearance

- Drug administration
  - Controlled release from devices
  - Intravenous injection

- Drug Clearance
  - Renal excretion
  - Renal and liver excretion

Pharmacokinetic Modeling

- Three tissue compartments
  - Vascular plasma space
  - Extracellular extravascular space (EES)
  - Intracellular space



Pharmacokinetic Modeling

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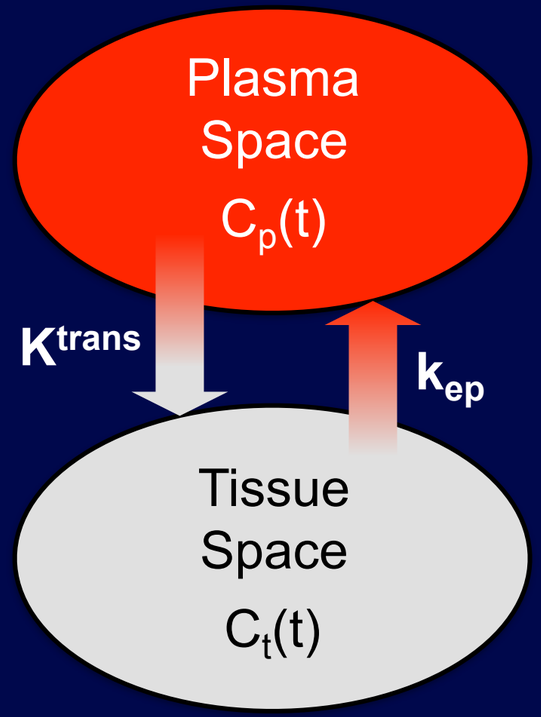
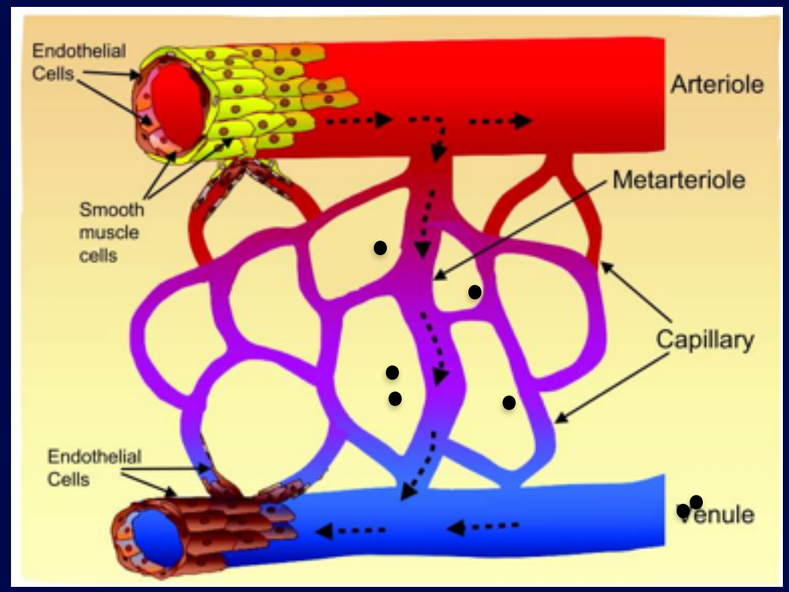
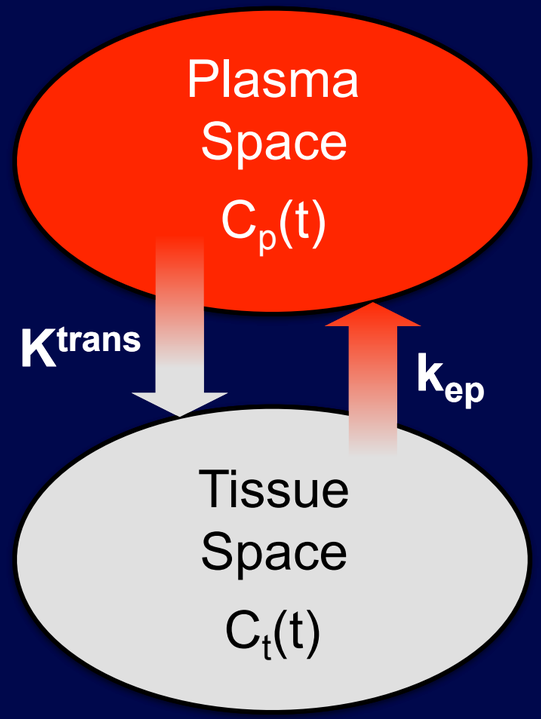




Fick's First Law of Diffusion



- Fick's first law relates **diffusive flux** to the concentration field (flux from high to low concentration) with magnitude that is **proportional to the concentration gradient**

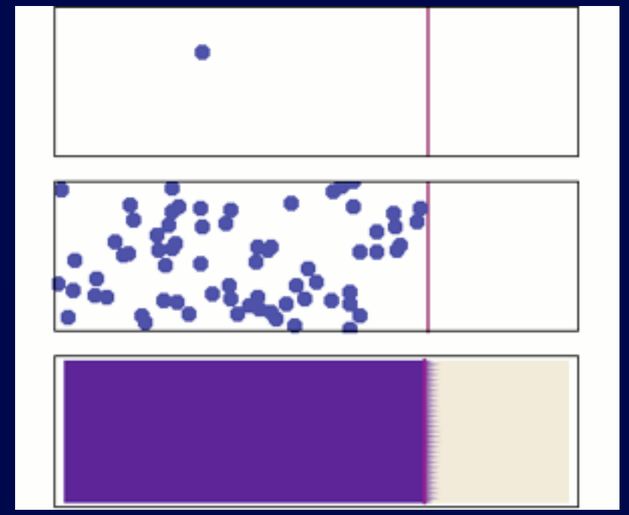
- Fick's first law gives:

$$\Phi_d = \mathrm{PA}(\mathrm{C}_1 - \mathrm{C}_2)$$

Diffusive flux

Transfer constant

Concentrations on each side of membrane



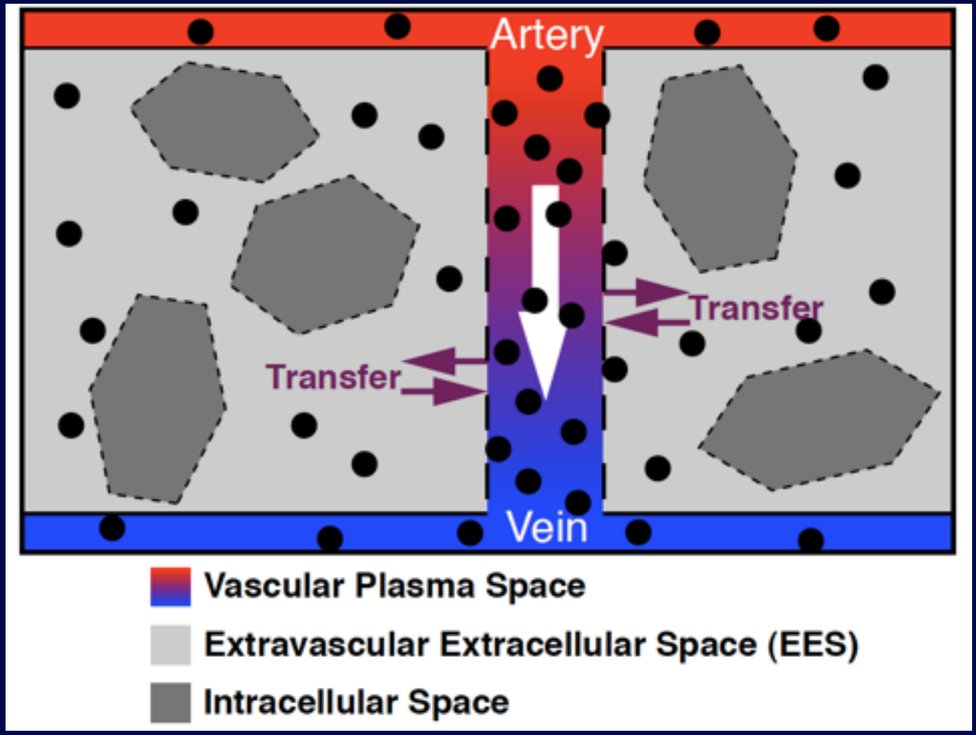
$$\frac{d\mathrm{C}_t}{dt} = \mathrm{K}^{trans}(\mathrm{C}_p - \mathrm{C}_t / v_e)$$

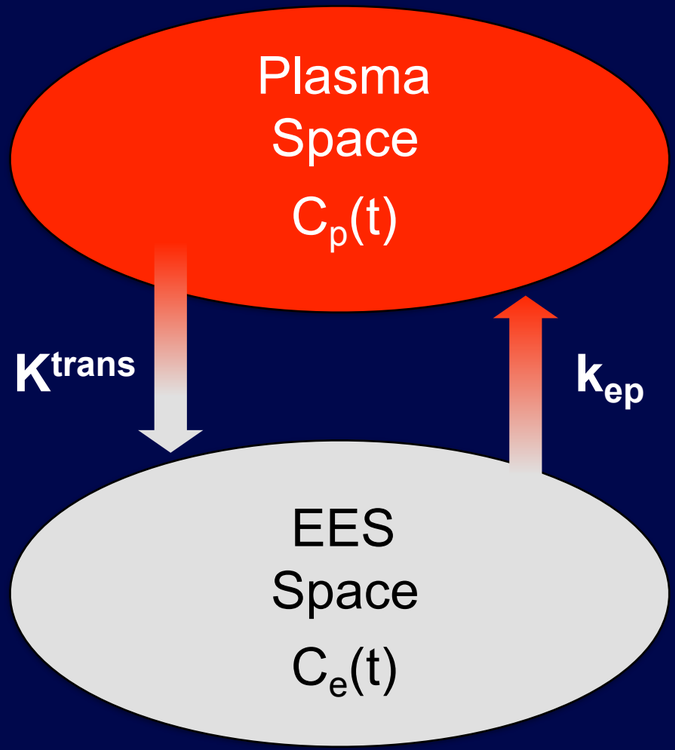
Volume of EES per unit volume of tissue

Kety SS, Pharmacol Rev 1951

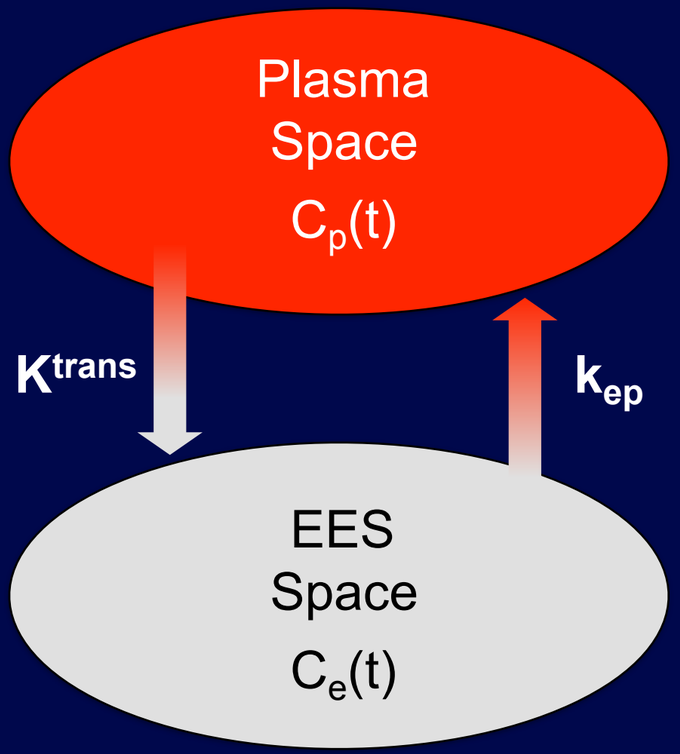
Pharmacokinetic Modeling

- Two tissue compartments
  - Vascular plasma space
  - Extracellular extravascular space (EES)





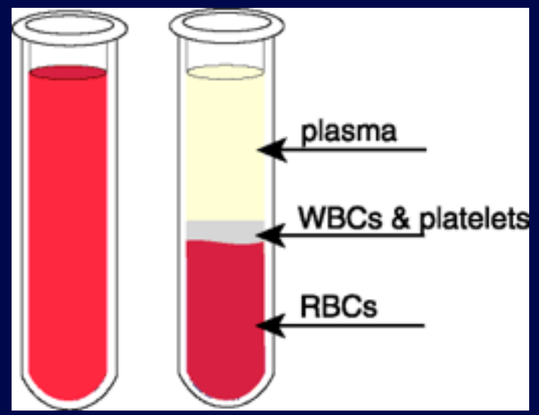
Standard Tofts Model



$$\frac{dC_t}{dt} = K^{trans}(C_p - C_t/v_e)$$

- Tissue concentration ≠ EES concentration
  - $C_t = v_e \cdot C_e$
- Plasma concentration ≠ Blood concentration
  - $C_p = C_b/(1\text{-}Hct)$

Matsuzawa T. Comp Haematol Int 1996



Standard Tofts Model

$$C_t(t) = K^{trans} \int_0^t C_p(t') e^{-k_{ep}(t-t')} dt'$$

Tissue Concentration

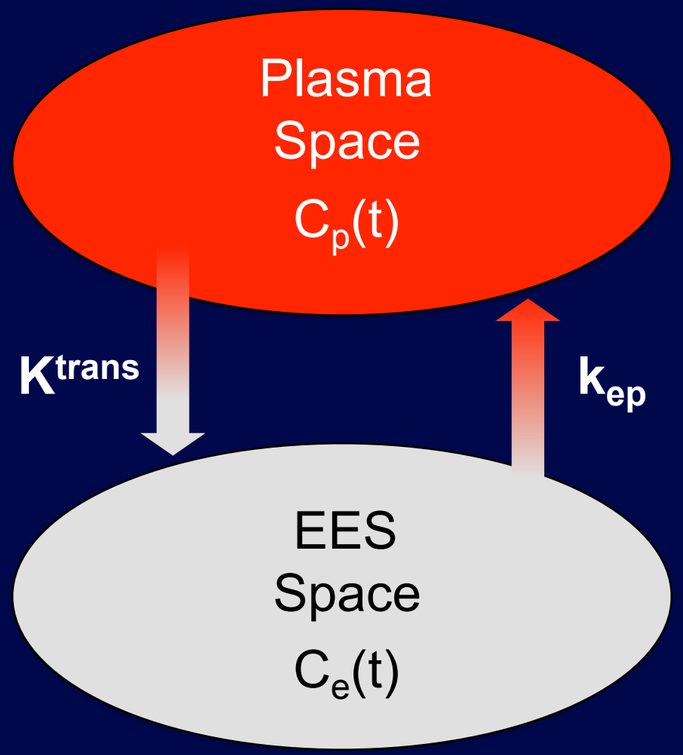
Arterial Input Function

Standard Tofts

Symbol	Preferred short name	Units	Full name
K^{trans}	Transfer constant[a]	min^{-1}	Volume transfer constant between blood plasma and EES
k_{ep}	Rate constant	min^{-1}	Rate constant between EES and blood plasma
v_e	EES[d]	None	Volume of extravascular extracellular space per unit volume of tissue[e]

Tofts P, JMRI 1991

Arterial Input Function (AIF)



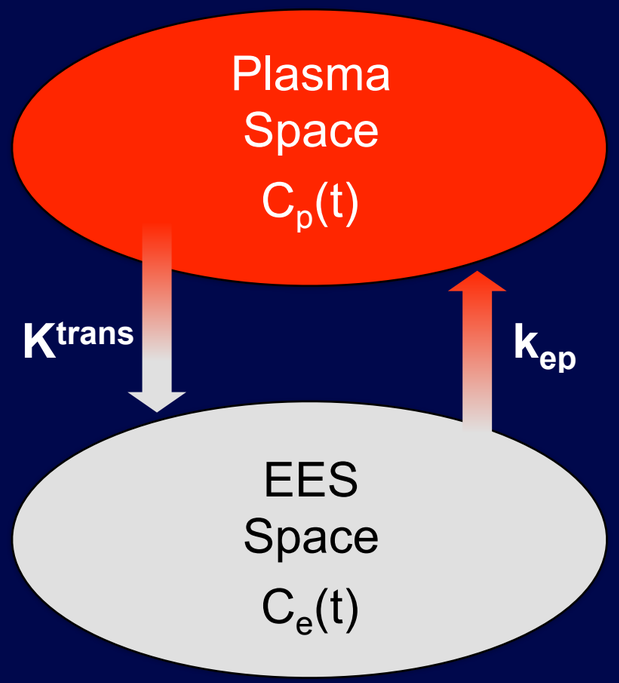
- Population-averaged AIF:
  - Bi-exponential model
  - Bi-exponential + linear upslope model
  - Single Gaussian + exponential model
  - Dual Gaussian + exponential model

McGrath DM, MRM 2009

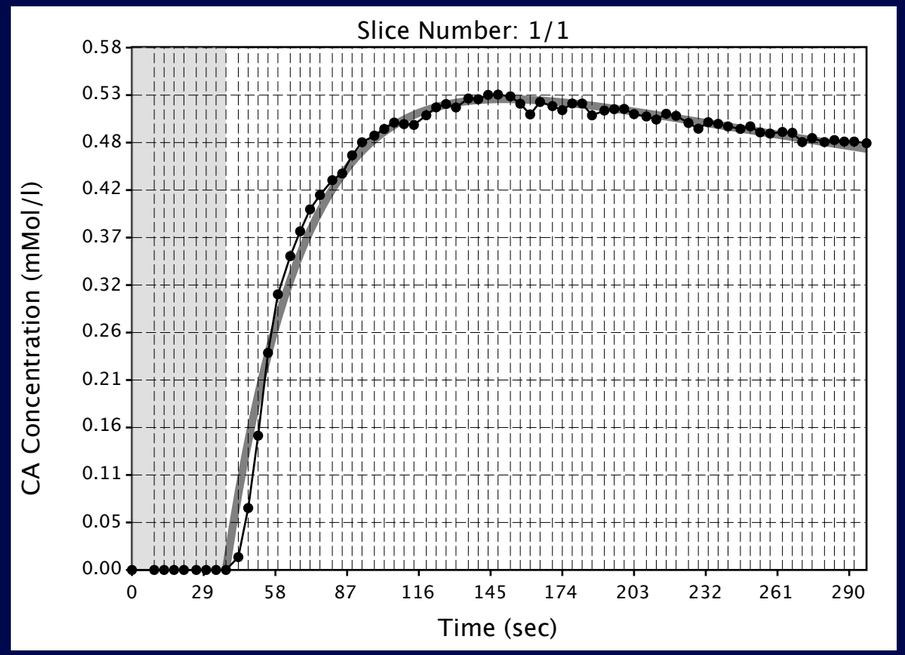
- Subject-based AIF requires
  - High temporal and spatial resolution
  - Compensation for flow-enhancement

Bi-exponential Model: Weimann AIF

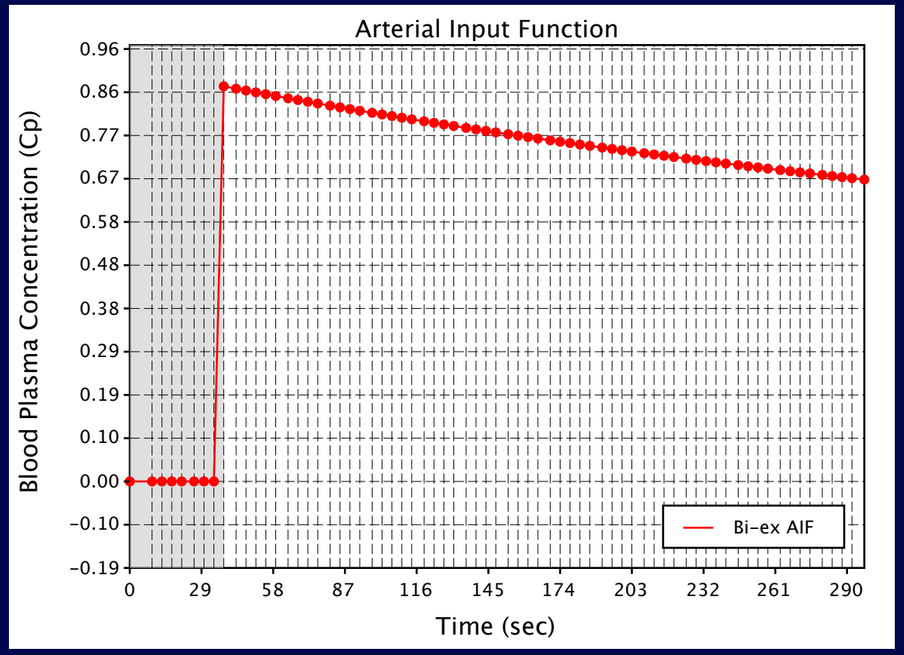
$$C_t(t) = K^{trans} \int_0^t C_p(t') exp\left(\frac{-K^{trans}(t-t')}{v_e}\right) dt'$$



$C_t(t)$



$C_p(t)$



K^{trans} = 1.32 min^{-1} **k_{ep} = 1.91 min^{-1}**

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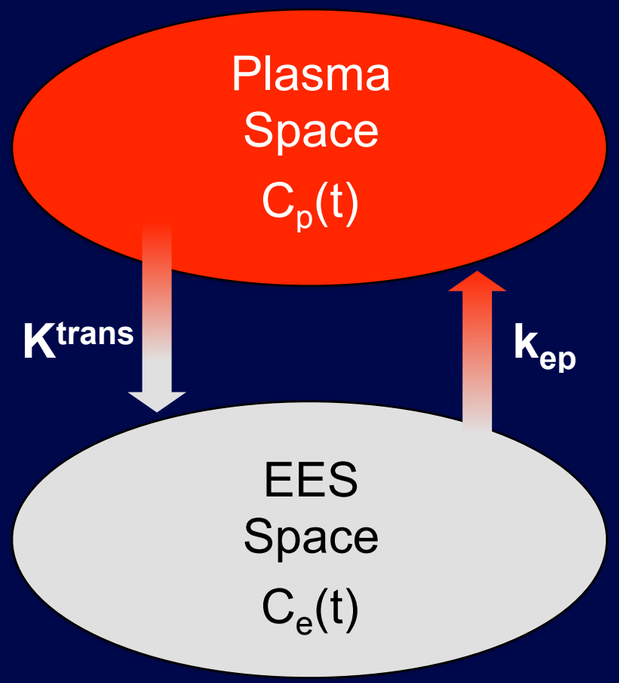
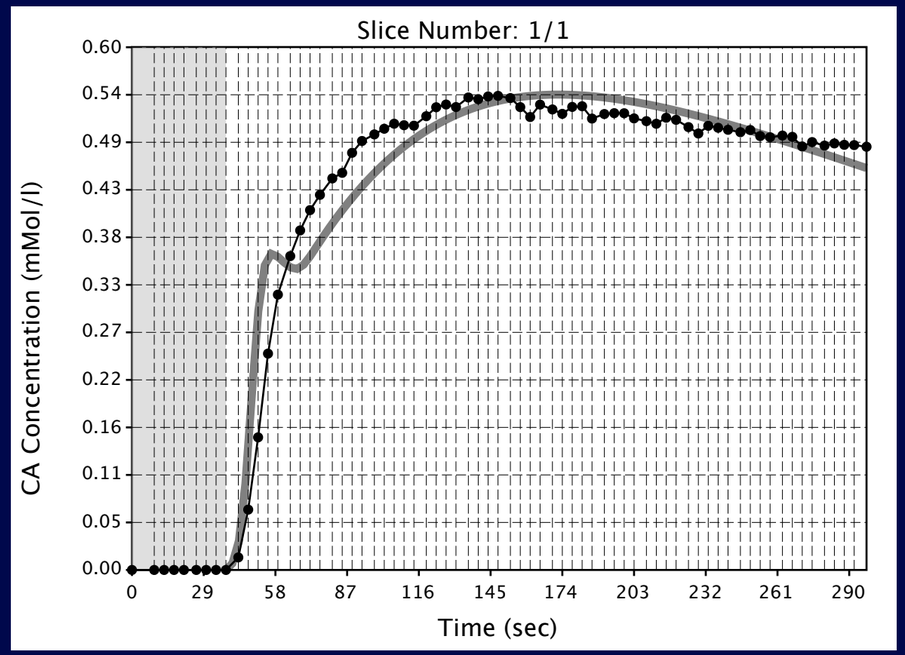
Dual-Gaussian+Exponential Model: Parker AIF

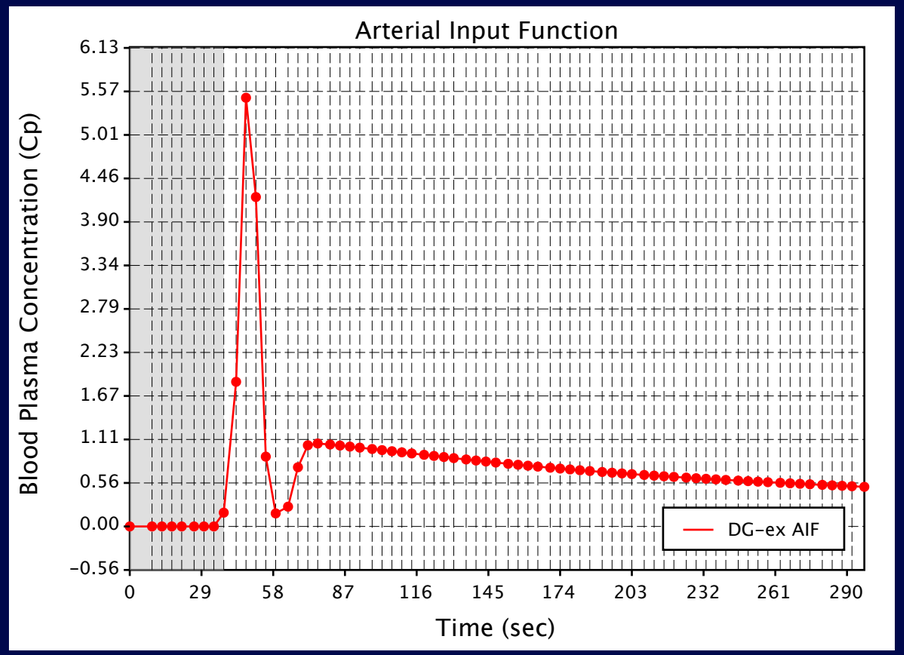
$$C_t(t) = K^{trans} \int_0^t C_p(t') exp\left(\frac{-K^{trans}(t-t')}{v_e}\right) dt'$$



$C_t(t)$



$C_p(t)$



K^{trans} = 0.47 min^{-1}

k_{ep} = 0.65 min^{-1}

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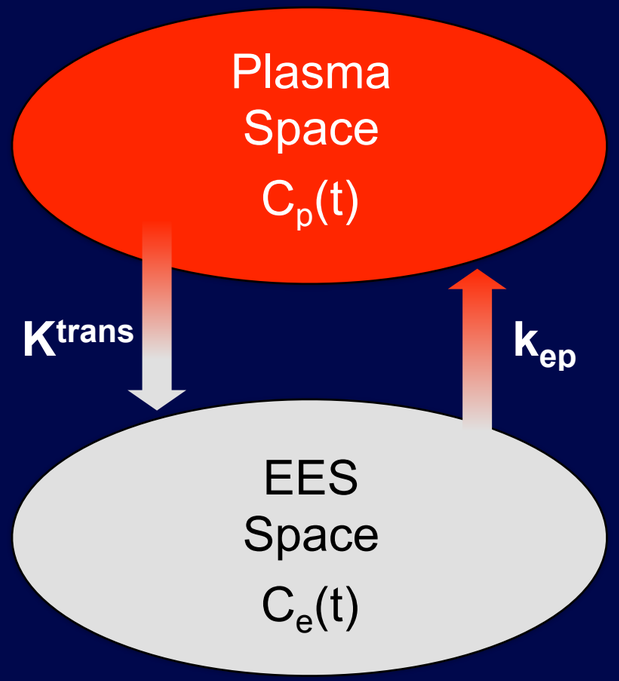
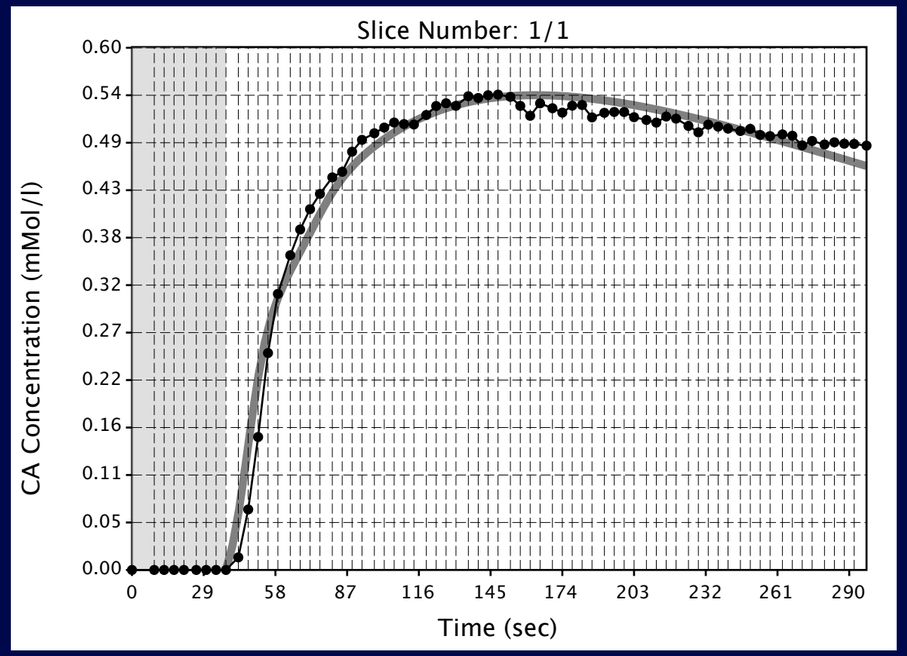
Subject-based AIF

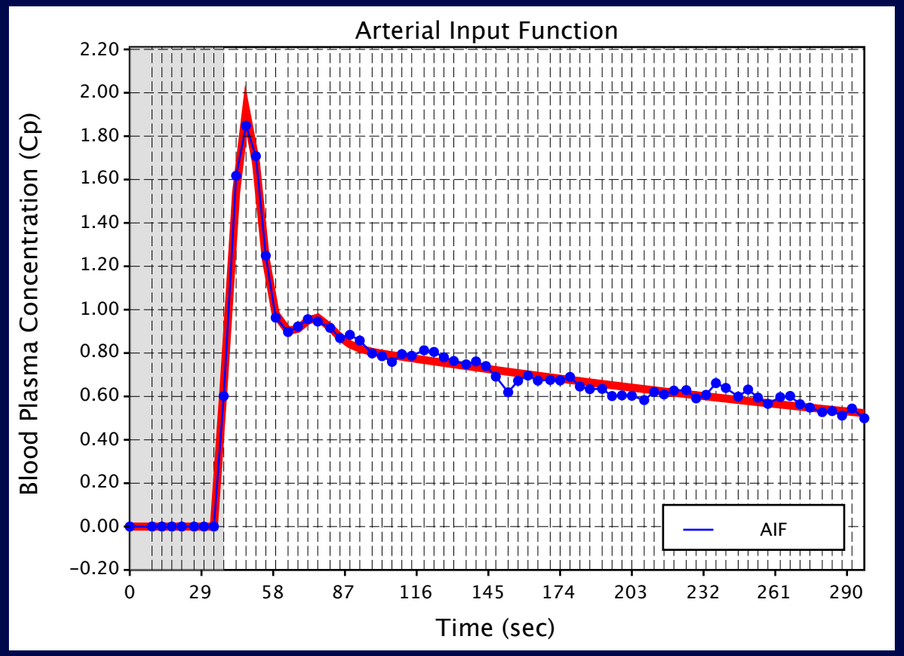
$$C_t(t) = K^{trans} \int_0^t C_p(t') exp\left(\frac{-K^{trans}(t-t')}{v_e}\right) dt'$$



$C_t(t)$



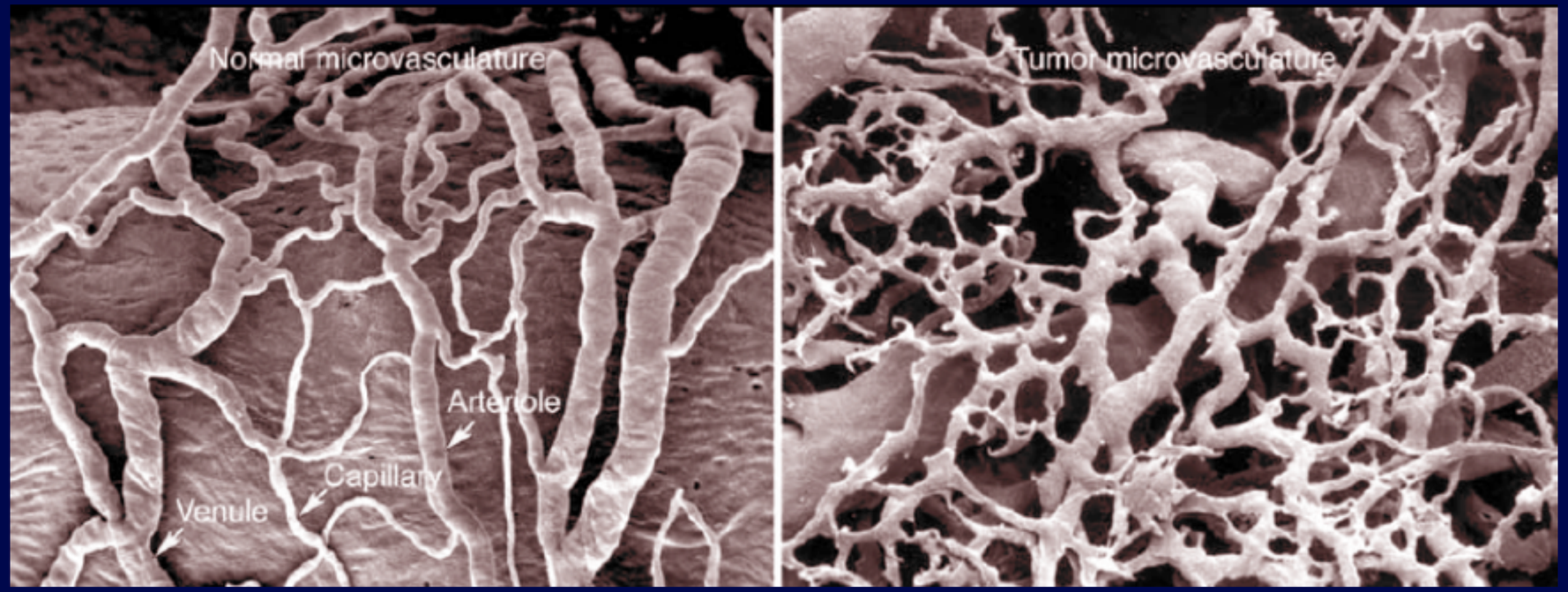
$C_p(t)$



K^{trans} = 0.35 min^{-1}

k_{ep} = 0.87 min^{-1}

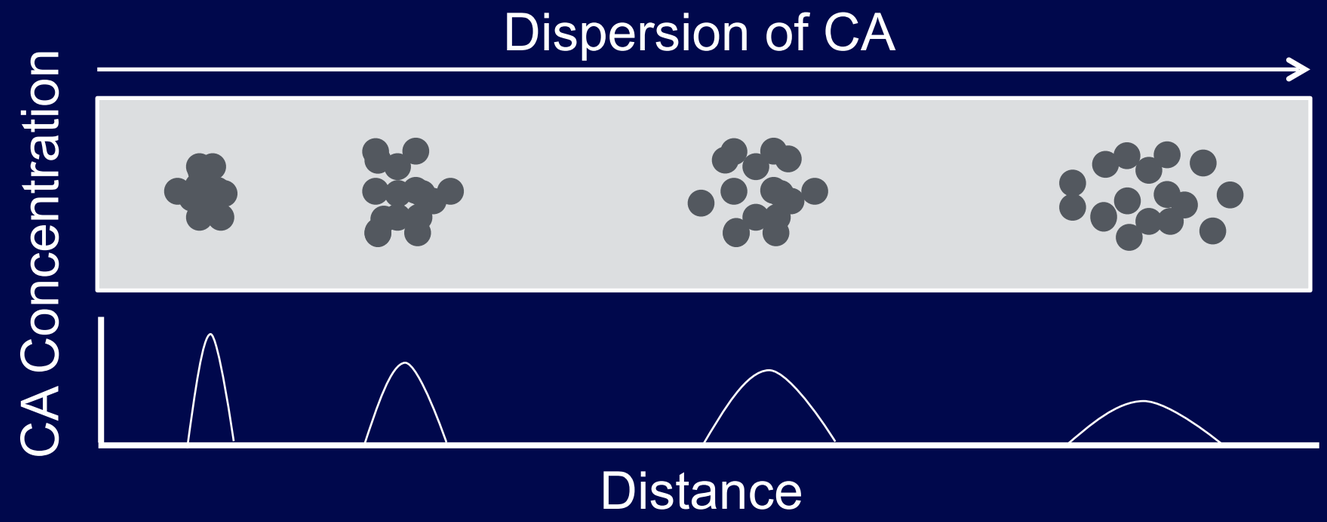
Delay and Dispersion Model



- Recruited vasculature is characterized by irregular vessels with increased permeability
- Delay and dispersion model offers another quantitative measure of vasculature

Delay and Dispersion Model

- Contrast agent will disperse as it travels through the vasculature



Dispersion Model History

Magnetic Resonance in Medicine 44:466–473 (2000)

Delay and Dispersion Effects in Dynamic Susceptibility Contrast MRI: Simulations Using Singular Value Decomposition

Fernando Calamante,* David G. Gadian, and Alan Connelly

Contrast-ultrasound diffusion imaging for localization of prostate cancer.

Authors: M. Kuenen, M. Mischi, H. Wijkstra

View research catalog entry for this paper

Journal: *IEEE transactions on medical imagi...*
Year: 2011
Volume: 30
Issue:
Pages: 1493-1502

CONTRAST DISPERSION MAPPING IN DCE MRI: A NEW OPTION FOR PROSTATE CANCER DETECTION

Massimo Mischi[1], Kyveli Kompatsiari[1], Tamerlan Saidov[1], Marc Engelbrecht[2], Hessel Wijkstra[1,2], and Marcel Breeuwer[1,3]
[1]*Eindhoven University of Technology, Eindhoven, Netherlands,* [2]*Academic Medical Center, Amsterdam, Netherlands,* [3]*Philips Healthcare, Best, Netherlands*

ISMRM 2013 p.95

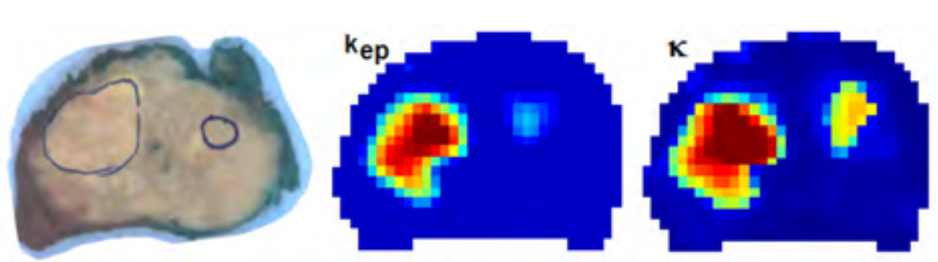


Fig. 1: Histology results with corresponding parametric maps of k_{ep} and dispersion κ.

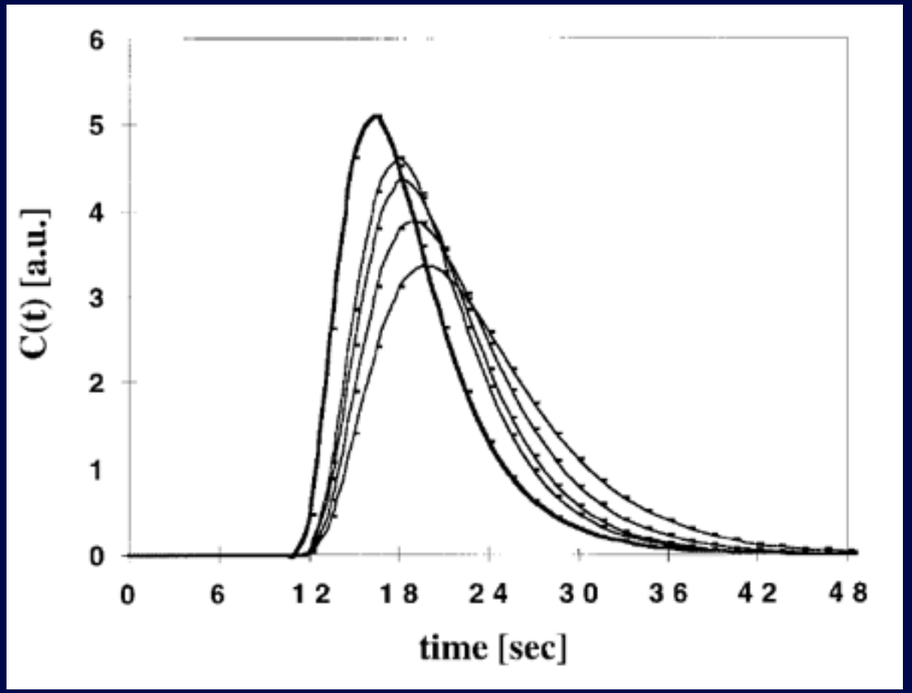
Magnetic Resonance in Medicine 44:466–473 (2000)

Delay and Dispersion Effects in Dynamic Susceptibility Contrast MRI: Simulations Using Singular Value Decomposition

Fernando Calamante,* David G. Gadian, and Alan Connelly

$$C_a(t) = C_a^{(est)}(t) \otimes h^*(t)$$

$$h^*(t) = -\frac{dR^*(t)}{dt} = \beta \cdot e^{-\beta t}$$



Standard Tofts

$$C_t(t) = K^{trans} \int_0^t C_p(t') e^{-k_{ep}(t-t')} dt'$$

Population Averaged AIFs ($C_p(t)$):
Weimann, Fritz-Hans, Parker

Standard Tofts

$$C_t(t) = K^{trans} \int_0^t C_p(t') e^{-k_{ep}(t-t')} dt'$$

Population Averaged AIFs ($C_p(t)$):
Weimann, Fritz-Hans, Parker

Dispersion

$$C_p(t) = \alpha \sqrt{\frac{\kappa}{2\pi t}} \cdot e^{\frac{-\kappa(t-\mu)^2}{2t}}$$

$$C_t(t) = \beta \int_0^t \sqrt{\frac{\kappa}{2\pi t}} \cdot e^{\frac{-\kappa(t-\mu)^2}{2t}} \cdot e^{-k_{ep}(t-t')} dt'$$

Standard Tofts

$$C_t(t) = K^{trans} \int_0^t C_p(t') e^{-k_{ep}(t-t')} dt'$$

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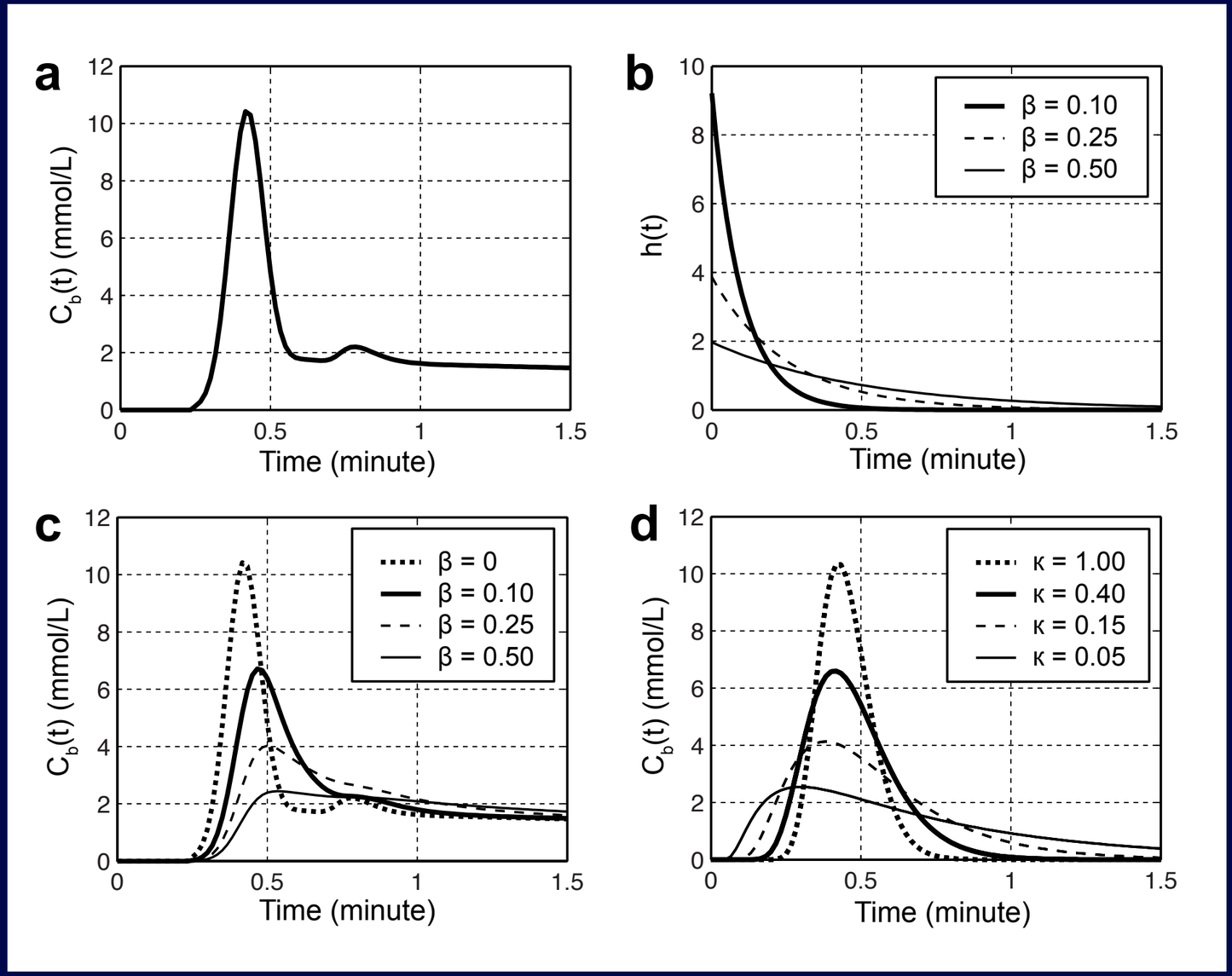
$$C_t(t) = \beta \int_0^t \sqrt{\frac{\kappa}{2\pi t}} \cdot e^{\frac{-\kappa(t-\mu)^2}{2t}} \cdot e^{-k_{ep}(t-t')} dt'$$

Modified Dispersion

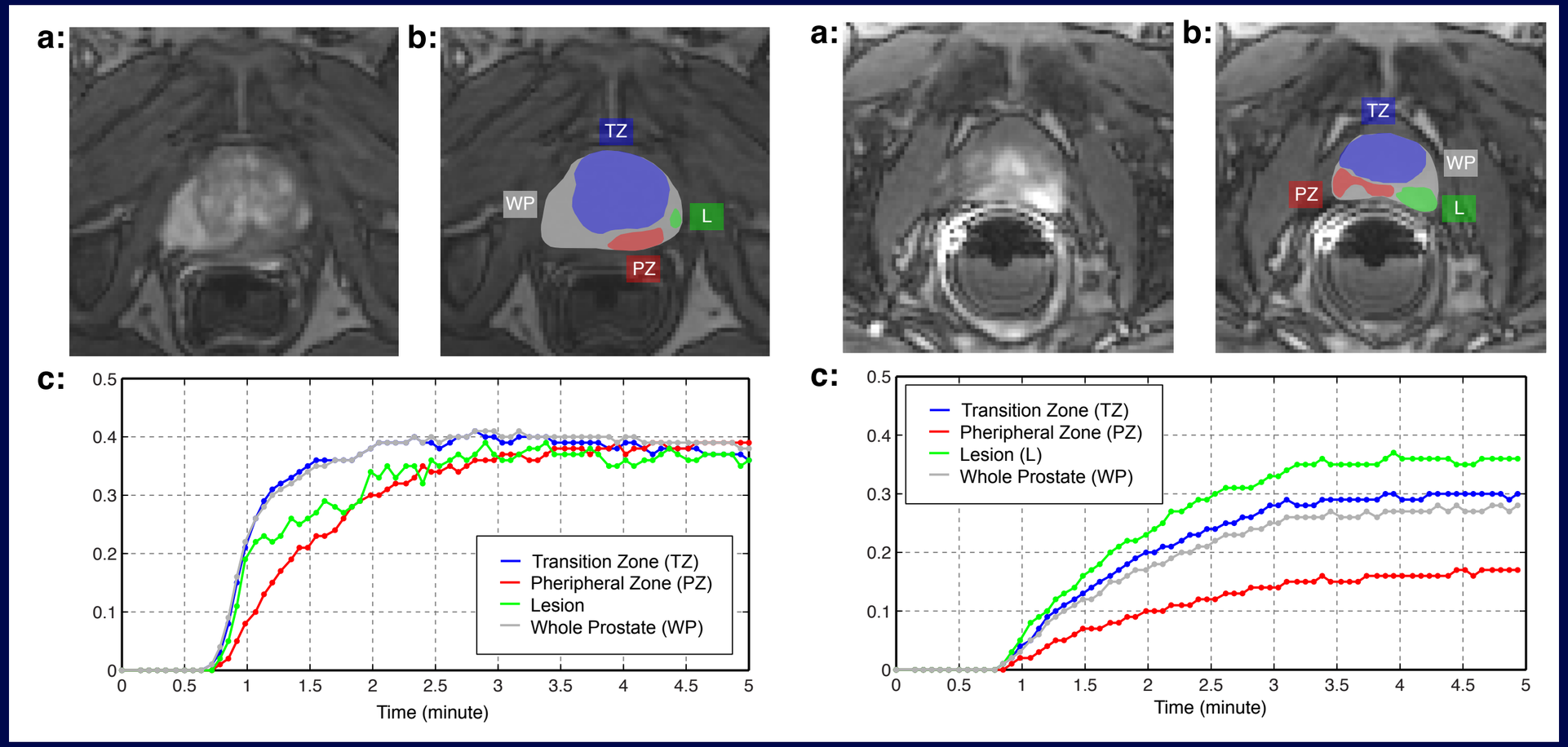
$$C_t(t) = K^{trans} \int_0^t C_p(t') e^{-k_{ep}(t-t')} dt'$$

$$C_p^{dispersed} = C_p(t) \star h(t) \qquad h(r) = \frac{1}{\beta} e^{-t/\beta}$$

Dispersion vs. Modified Dispersion



GS 4+4 vs. GS 3+4 (PZ)



Low Dispersion

High Dispersion

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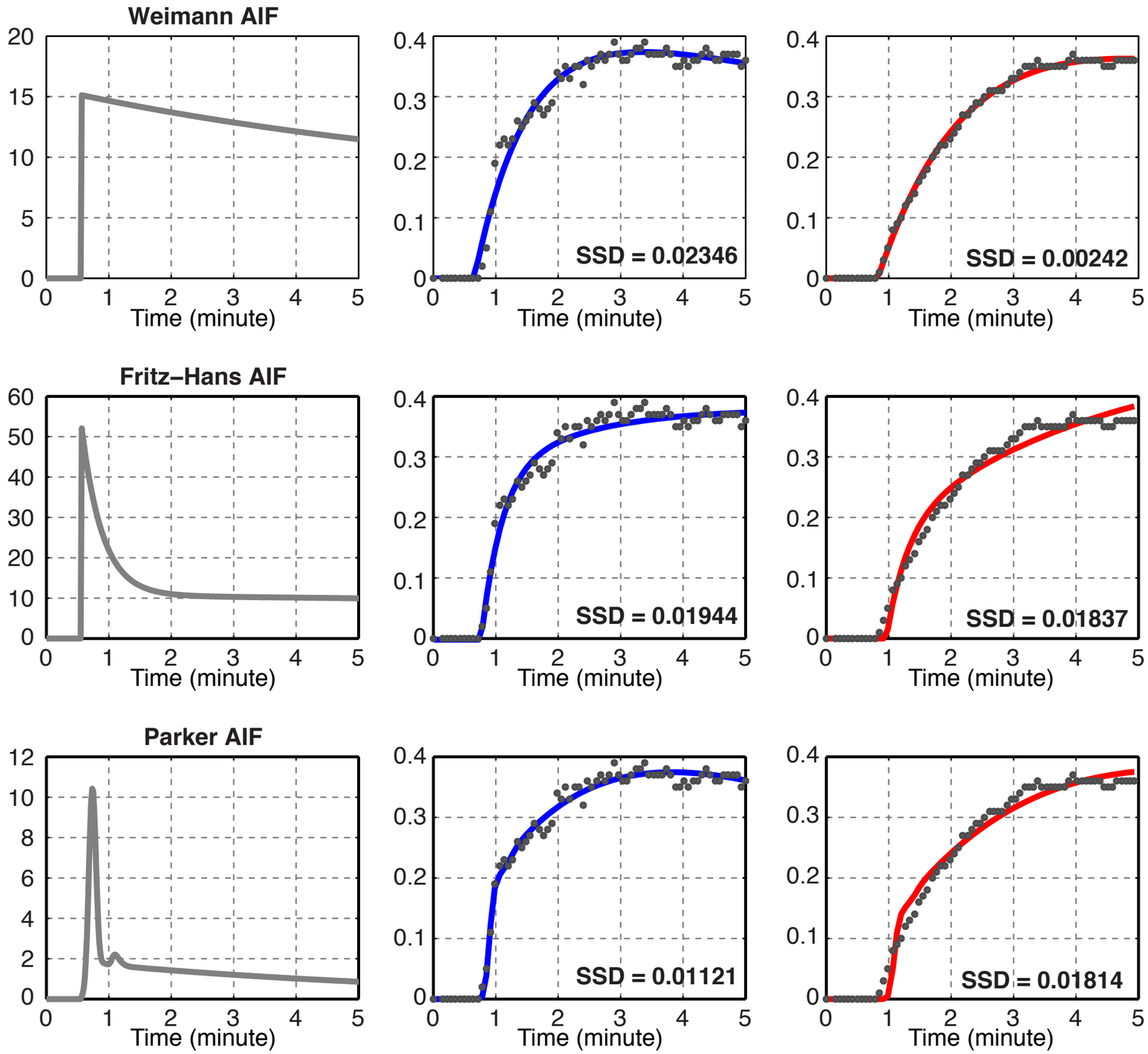
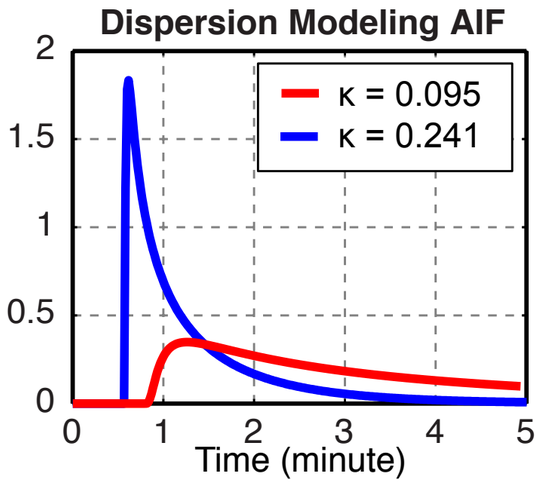

Weimann AIF
Time (minute)
SSD = 0.02346
SSD = 0.00242
Fritz–Hans AIF
SSD = 0.01944
SSD = 0.01837
Parker AIF
SSD = 0.01121
SSD = 0.01814

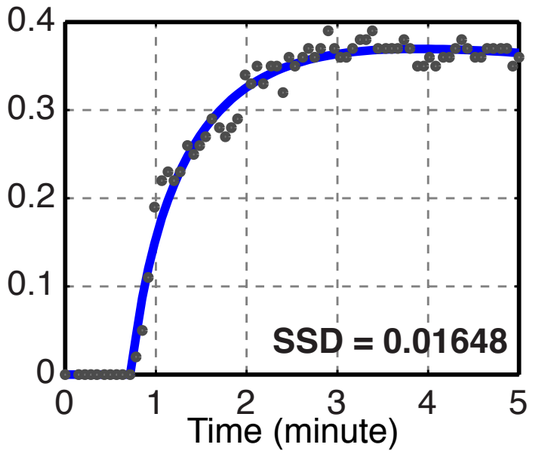
Dispersion Modeling

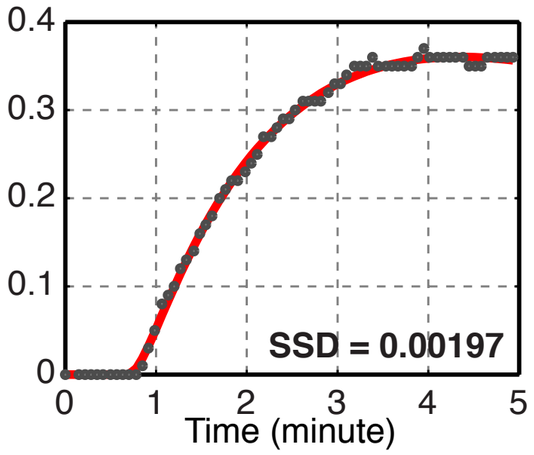
$$C_p(t) = \alpha\sqrt{\frac{\kappa}{2\pi t}} \cdot e^{\frac{-\kappa(t-\mu)^2}{2t}}$$

Dispersion

$$C_t(t) = \beta\int_0^t \sqrt{\frac{\kappa}{2\pi t}} \cdot e^{\frac{-\kappa(t-\mu)^2}{2t}} \cdot e^{-k_{ep}(t-t')}dt'$$





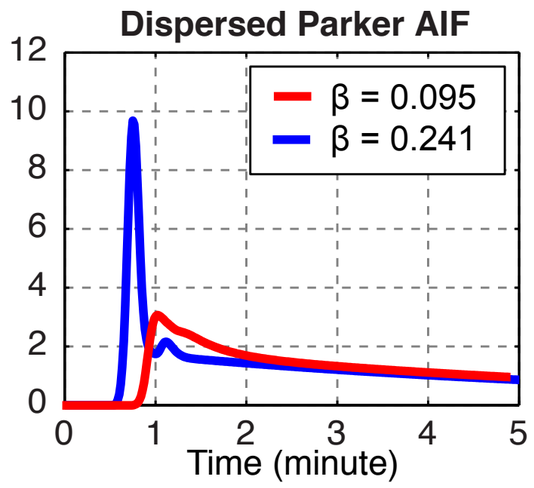


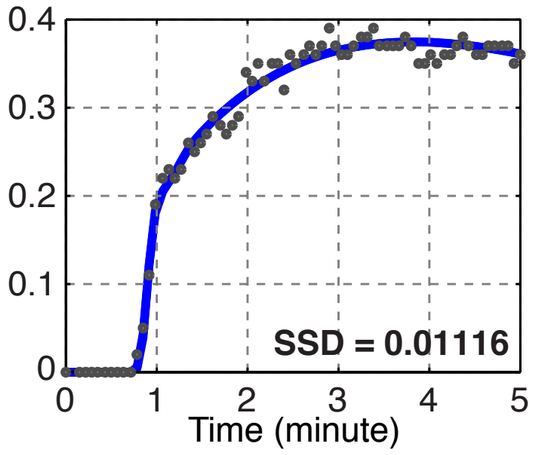
Modified Dispersion Modeling

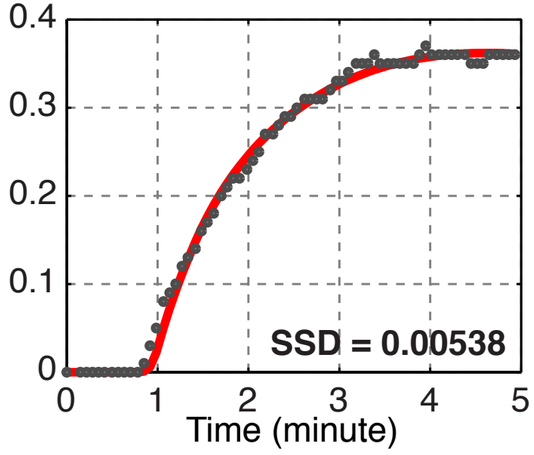
$$C_t(t) = K^{trans} \int_0^t C_p(t')e^{-k_{ep}(t-t')}dt'$$

Modified Dispersion

$$C_p^{dispersed} = C_p(t) \star h(t) \qquad h(r) = \frac{1}{\beta} e^{-t/\beta}$$

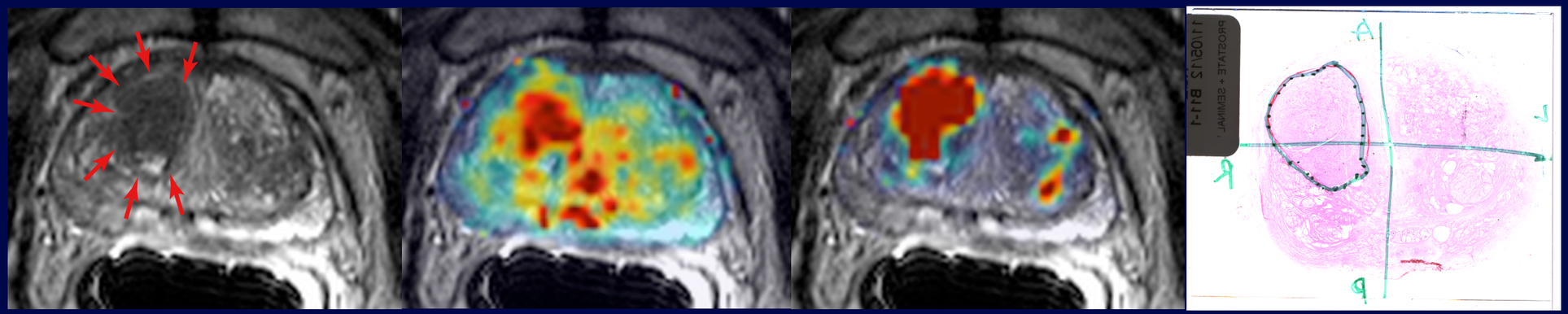






Dispersion vs. Tofts model

T2-weighted Image | **Standard Tofts Model** | **Dispersion Model** | **Histopahtology**



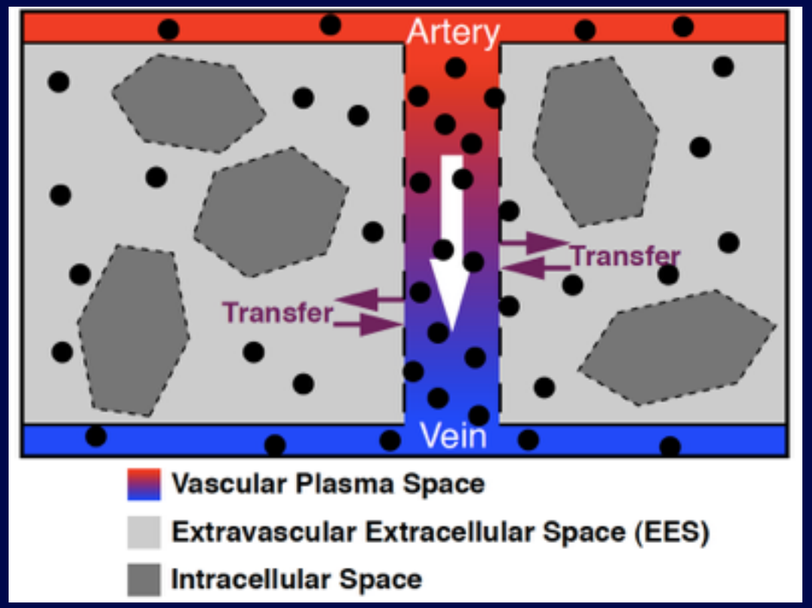
Gleason 3+4

Dispersion model shows the clearest delineation between tumor and normal tissue

Physiological Understanding

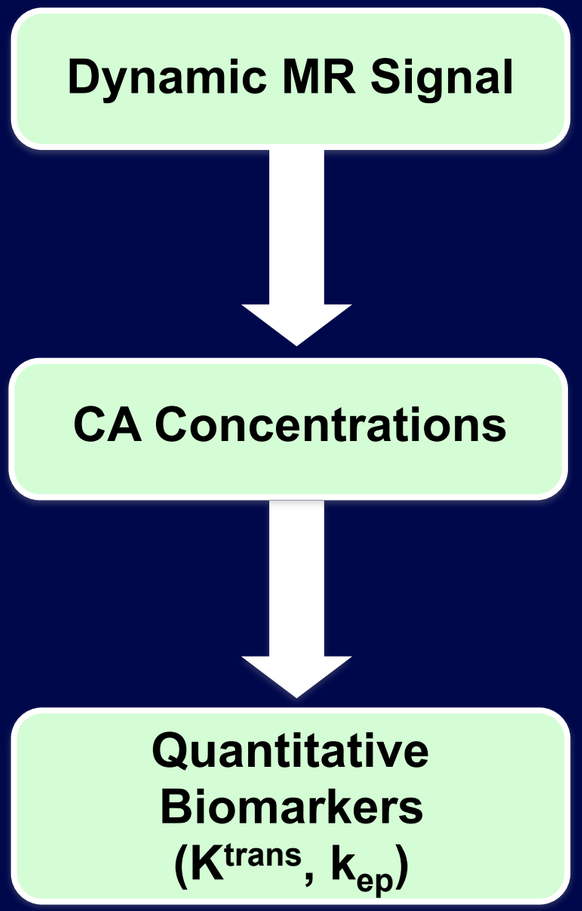
- PK parameters are sensitive to a choice of the AIF model
- PK parameters can have different physiological meaning
  - High-permeability case
  - Low-permeability case
  - Mixed case
- Extended Tofts model

$$\mathrm{C}_t(t) = v_p \mathrm{C}_p + \mathrm{K}^{trans} \int_0^t \mathrm{C}_p(t') exp\left(\frac{-\mathrm{K}^{trans}(t-t')}{v_e}\right) dt'$$



Post-processing Option: DCE-MRI Data Analysis

Quantitative Data Analysis



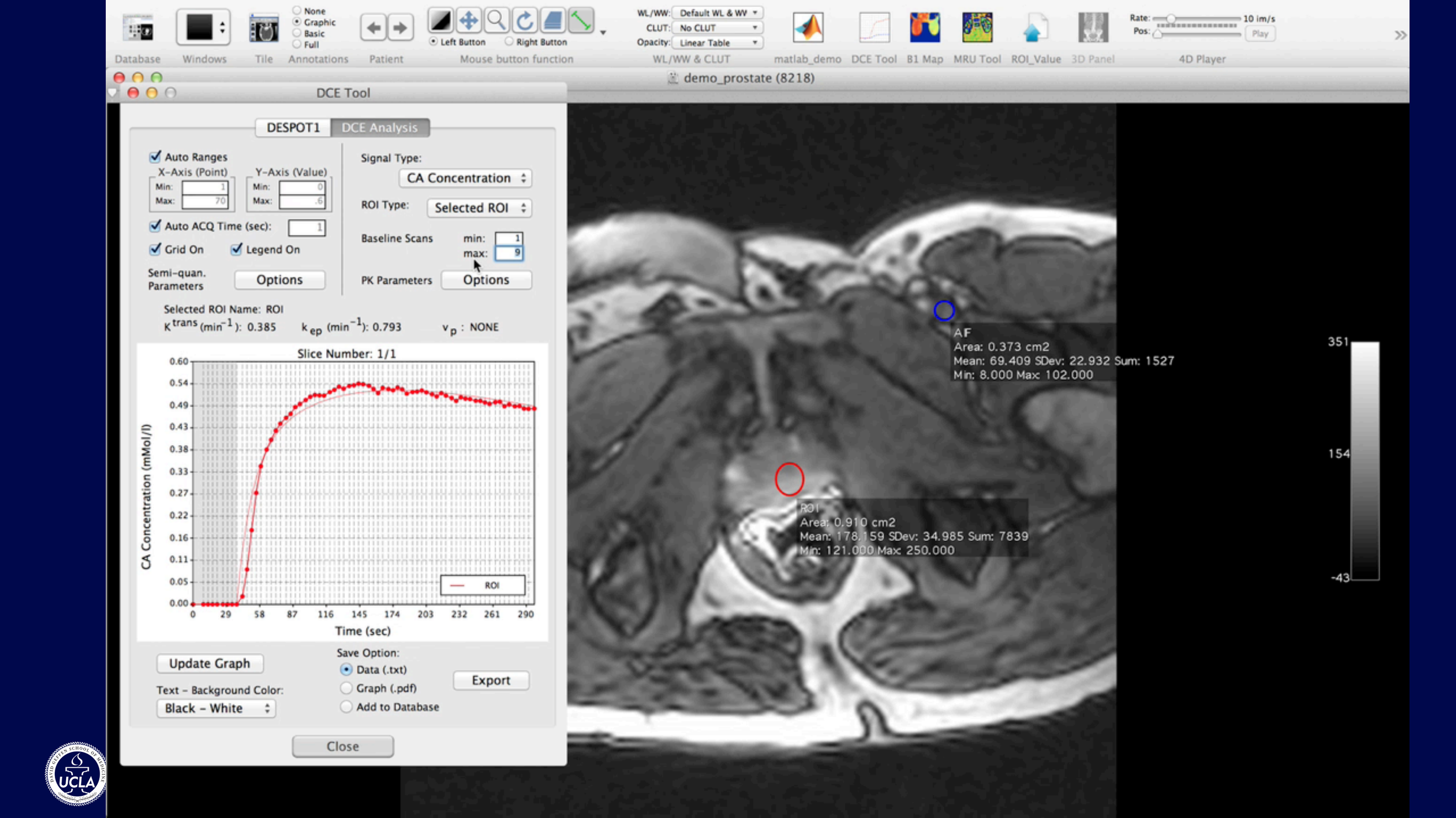
- Software tools should facilitate:
  - $T_{1,0}$ map generation
  - Conversion from MR signal to CA concentration
  - Regions of interest (ROIs) plots
  - PK parameter calculation
- Software tools should also be able to:
  - Handle large 4D (3D + time) data
  - Manage DICOM databases
  - Locate regions of interests
  - Export back to DICOM databases

OsiriX Plug-in: DCE Tool

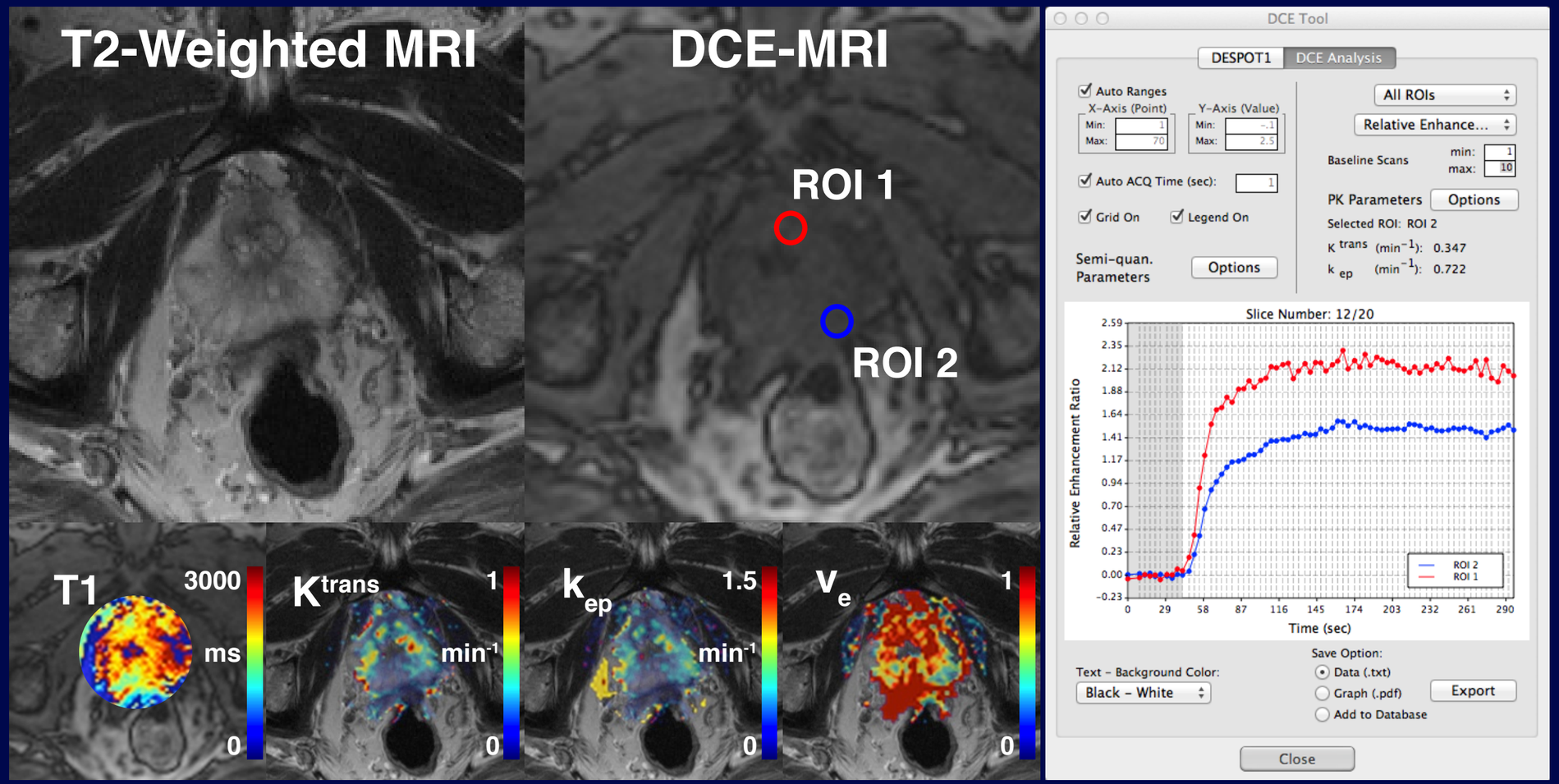
- DCE-MRI analysis software (DCE Tool)
  - Plug-in to OsiriX (open-source medical image processing software)

A Rosset et al, J of Digital Imaging 2004

- Selected features for DCE Tool:
  - $T_{1,0}$ map calculation (with an option for B1 compensation)
  - Supports for several AIF functions
    - PK parameter calculation (standard Tofts / extended Tofts models)
    - Semi-quantitative parameter calculation (initial slope, area under the curve, etc)


Database
Windows
Tile
None
Graphic
Basic
Full
Annotations
Patient
Left Button
Right Button
Mouse button function
WL/WW: Default WL & WW
CLUT: No CLUT
Opacity: Linear Table
WL/WW & CLUT
matlab_demo
DCE Tool
B1 Map
MRU Tool
ROI_Value
3D Panel
Rate: 10 im/s
Pos:
Play
4D Player
demo_prostate (8218)
DCE Tool
DESPOT1
DCE Analysis
Auto Ranges
X-Axis (Point)
Min: 1
Max: 70
Y-Axis (Value)
Min: 0
Max: .6
Auto ACQ Time (sec): 1
Grid On
Legend On
Semi-quan. Parameters
Options
Signal Type:
CA Concentration
ROI Type:
Selected ROI
Baseline Scans
min: 1
max: 9
PK Parameters
Options
Selected ROI Name: ROI
K trans (min-1): 0.385
k ep (min-1): 0.793
v p : NONE
Slice Number: 1/1
CA Concentration (mMol/l)
Time (sec)
ROI
Update Graph
Text - Background Color:
Black - White
Save Option:
Data (.txt)
Graph (.pdf)
Add to Database
Export
Close
AF
Area: 0.373 cm2
Mean: 69.409 SDev: 22.932 Sum: 1527
Min: 8.000 Max 102.000
ROI
Area: 0.910 cm2
Mean: 178.159 SDev: 34.985 Sum: 7839
Min: 121.000 Max: 250.000
351
154
-43

Quantitative DCE-MRI Software



Sung K, RSNA 2011

http://kyungs.bol.ucla.edu/software/DCE_tool/DCE_tool.html

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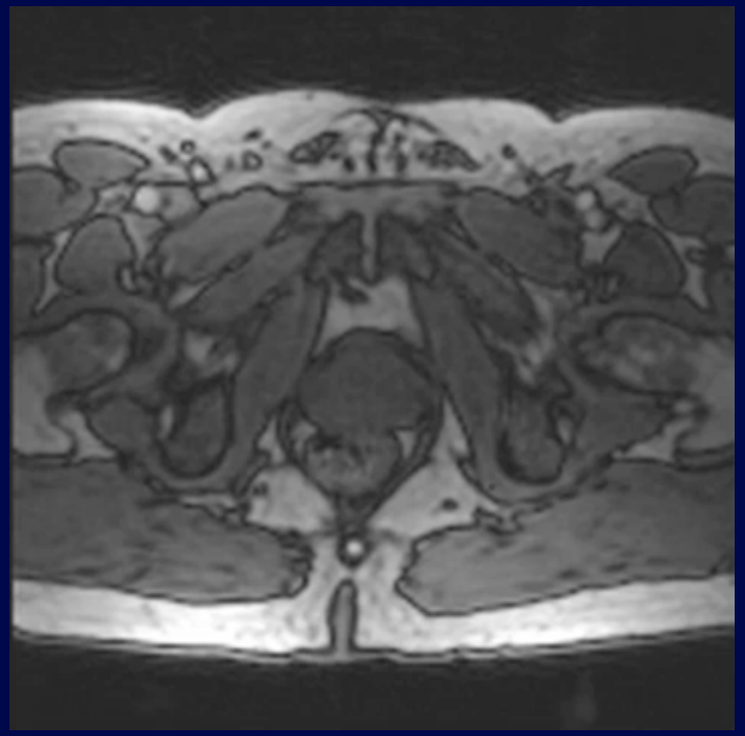
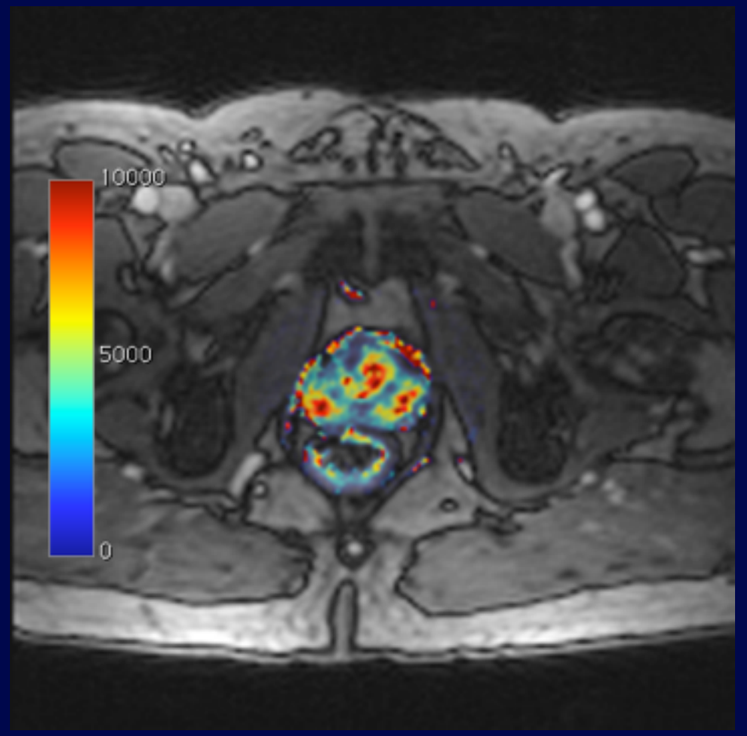
Prostate DCE-MRI

- Prostate DCE-MRI



K^{trans} (min^{-1} X 10000)



Temporal resolution ~ 4sec
Spatial resolution = 1.6 X 1.6 X 3.6 mm

Overall Summary

- DCE-MRI has great potential to accurately produce quantitative biomarkers for cancer imaging
- PK parameters can represent different meanings depending on various assumptions
- Understanding possible sources of errors is critical for accuracy and precision
- Standard imaging protocol and image analysis are important for reproducible results

Thank You!

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