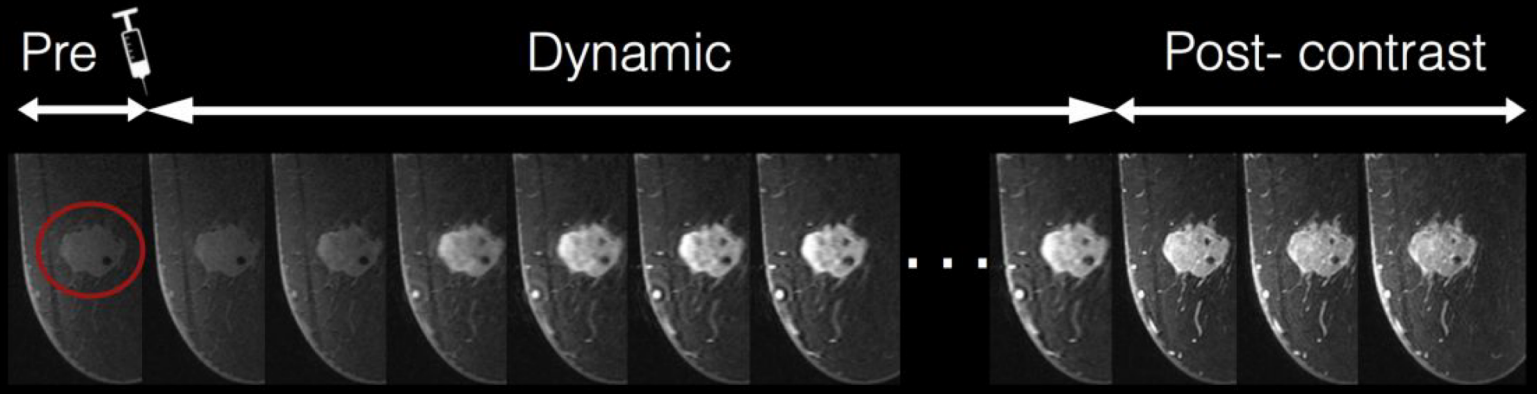
Breast dispersion imaging using undersampled DCE MRI

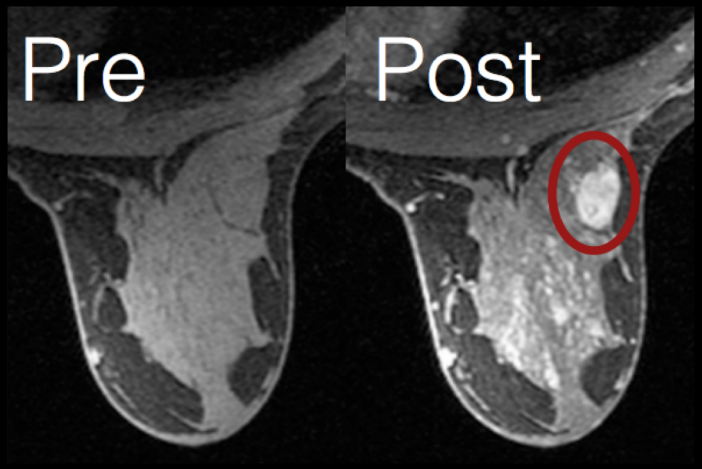
LINXI SHI, PH.D.
MENTOR: BRIAN HARGREAVES, BRUCE DANIEL
02/14/2019

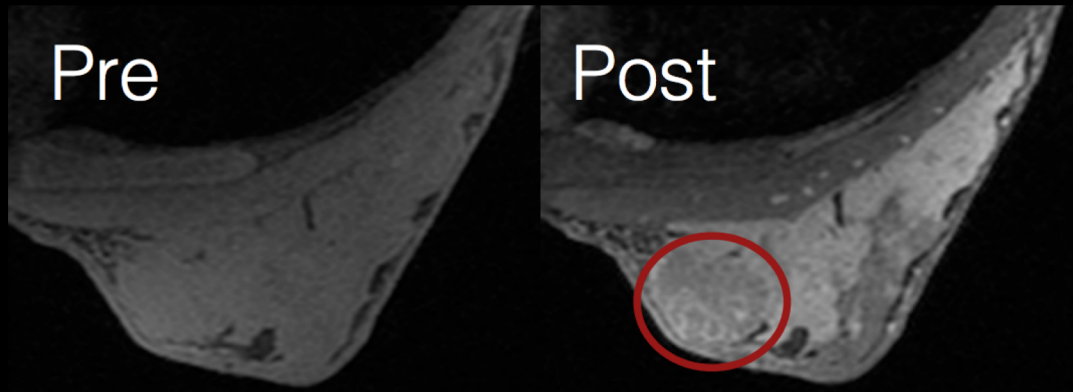
Stanford University

Introduction

Dynamic Contrast-enhanced (DCE) Breast MRI







The pattern of enhancement matters

Malignant tumors

- Signal intensity increased to 100% within the first 2 minutes[1].
- Aorta is enhanced within 11.5 seconds[2].
- Rapid uptake and washout of the contrast agent[3].

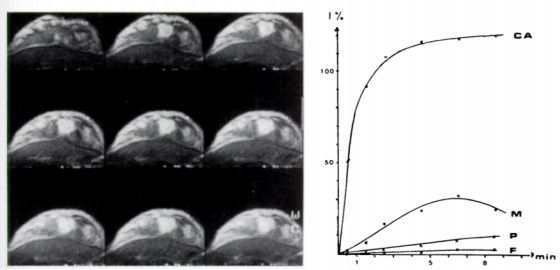
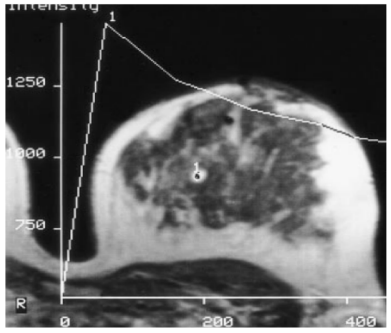


Figure 5. **(a)** Axial three-dimensional FLASH images before, 30 seconds after, and every minute after intravenous injection of 0.1 mmol/kg of Gd-DTPA (same section position). **(b)** Percentage increase in signal intensity (I) after injection of 0.1 mmol/kg Gd-DTPA in different breast tissues from those in **a**. *CA* = carcinoma, *M* = muscle, *P* = normal parenchyma, *F* = fat.



g.

[1]*Kaiser WA, Zeitler E. Radiology 1989; 170:681-686.*

[2]*Boetes C, Barentsz JO, Mus RD, et al. Radiology 1994;193:777-781.*

[3]*Kuhl, C.K., et al., Radiology, 1999. 211(1): p. 101-10.*

Semi-quantitative analysis

- Compromises are made between spatial and temporal resolution.
- High spatial resolution imaging is increasingly being used.
- Three time-point acquisition
  - microvascular permeability (K)
  - extracellular fraction(v)
- ACR recommend
  - Spatial resolution: 1mm in-plane, 3 mm slice thickness
  - Temporal resolution: 120 s or less

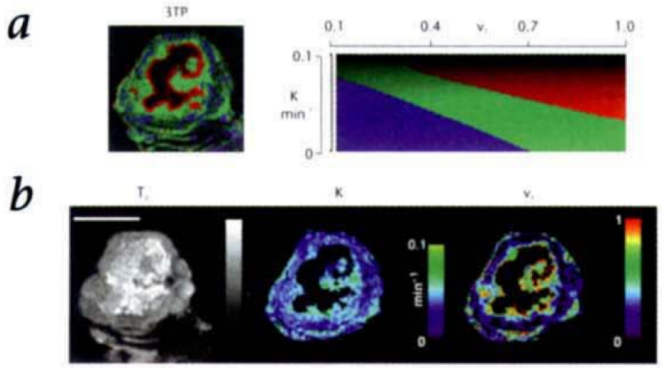
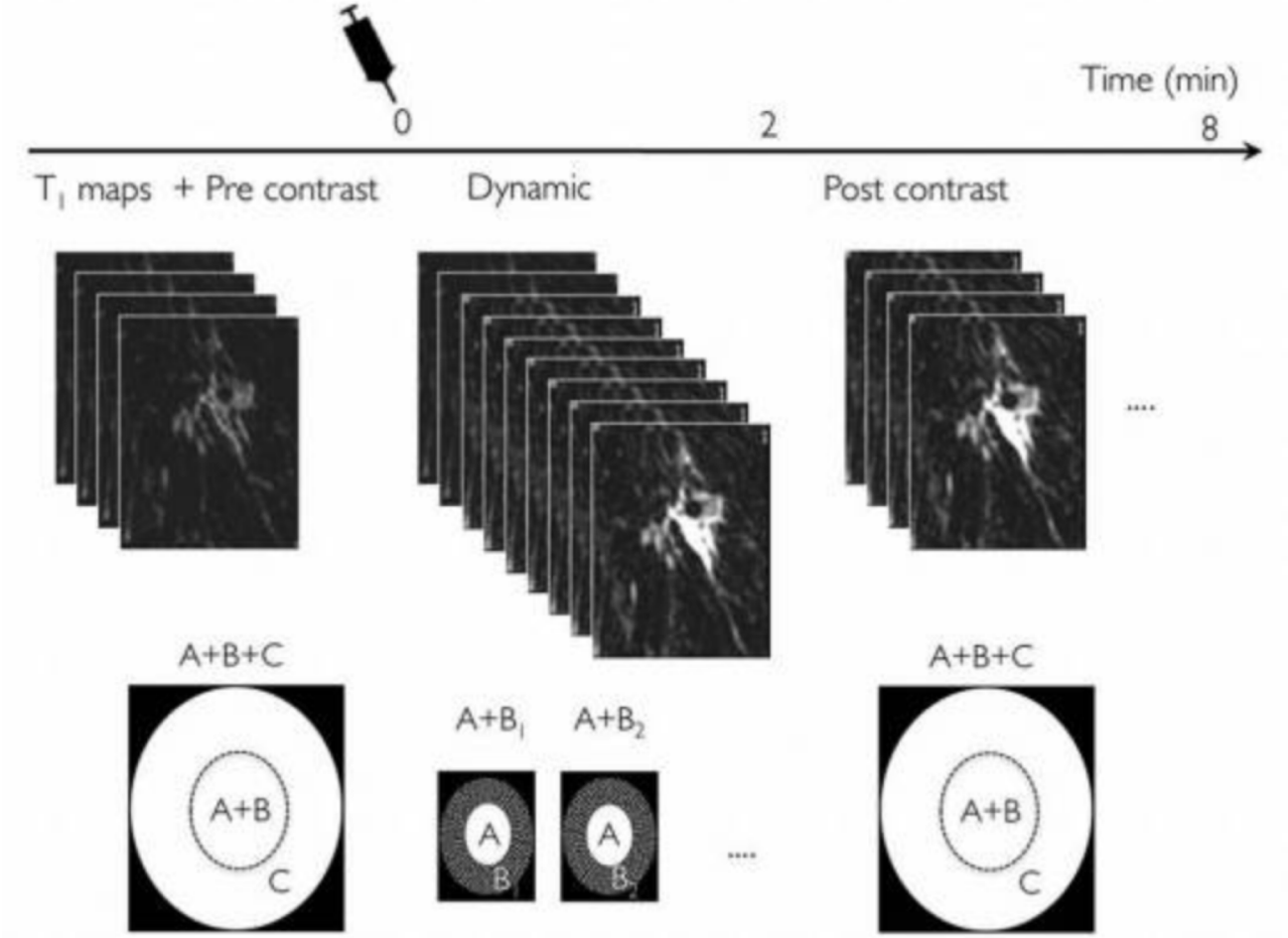


Fig. 1 A typical example of the performance of the 3TP method in MCF7 human breast tumor implanted in nude mice. *a*, Image obtained by the 3TP method and the corresponding calibration map for contrast enhancement in mice using the three time points: 0, 5 and 16 min and the parameters summarized in Table 1. *b*, T_2 weighted image and calculated images of microvascular permeability (*K*) and of fraction of extracellular volume (v_1) obtained by fitting enhancement data of 20 time points using kinetic image analysis[5].

Degani H, Gusis V, Weinstein D, Fields S, Strano S. Nature Medicine 1997;7:780-782.

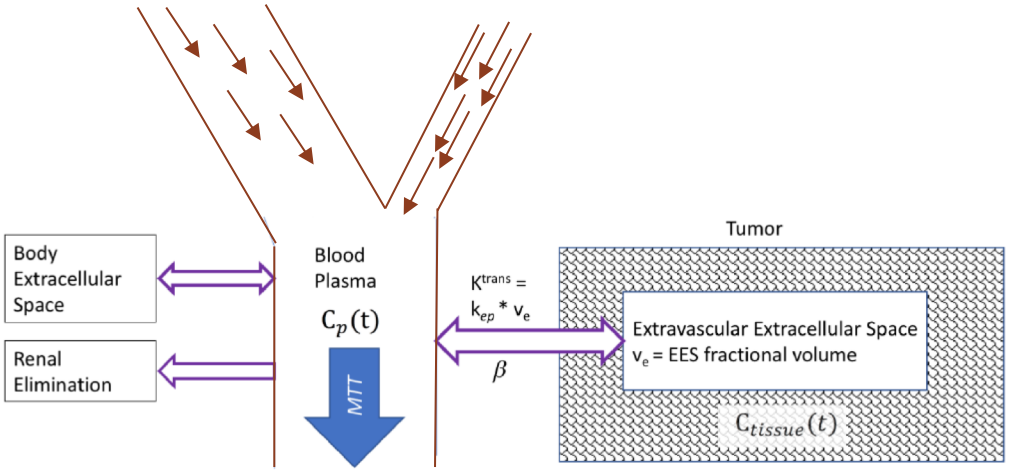
Image Acquisition for quantitative analysis

Differential subsampling with Cartesian ordering (DISCO) DCE-MRI



M. Saranathan, et. al., *J. Magn. Reson. Imaging*, 2014. 40(6): p. 1392-1402

Quantitative Analysis: Pharmacokinetic model



- $C_t\ (t)$: Tissue Concentration(mMol/l)
- $C_p\ (t)$: Plasma Concentration(mMol/l)

- K^{trans}: Transfer Constant(min^{-1})
- k_{ep} : Flux rate (min^{-1})
- v_e : Fractional volume of EES
- v_p : Fractional volume of plasma

Standard Tofts Model:

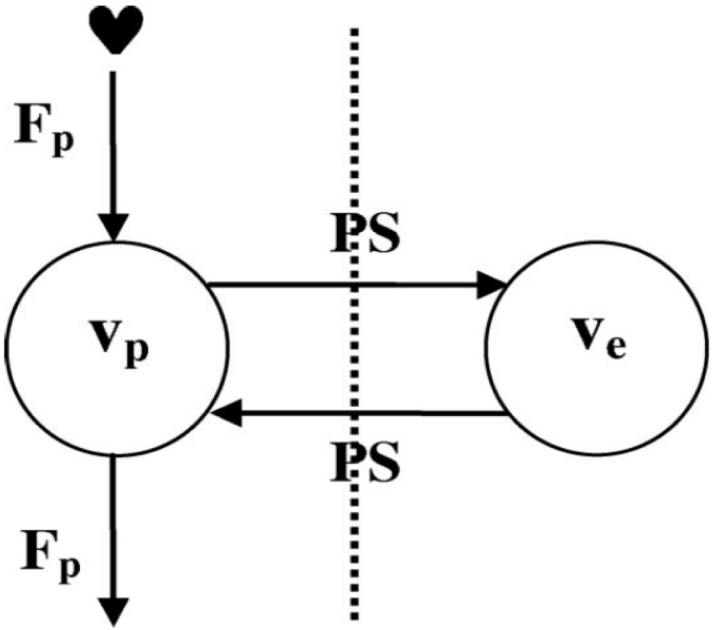
Extended Tofts Model (2CXM):

$$C_t(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(\tau) e^{-k_{ep}(t-\tau)} d\tau$$

$$C_t(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(\tau) e^{-\frac{K^{trans}}{v_e}(t-\tau)} d\tau \; ; k_{ep} = \frac{K^{trans}}{v_e}$$

Tofts et al., JMRI 1999

Comprehensive 2CXM



AN TRANSIT TIME (MTT) IS CONSIDERED

$$C_t(t) = F_p C_p(t) * \left[Ae^{-\alpha t} + (1-A)e^{-\beta t}\right];$$

$$k_{01} = A \cdot (\alpha - \beta) + \beta; k_{12} = \frac{\alpha\beta}{k_{01}}; k_{21} = \alpha + \beta - k_{12}; v_p = F_p / k_{01}$$

$$PS = k_{21} \cdot v_p$$

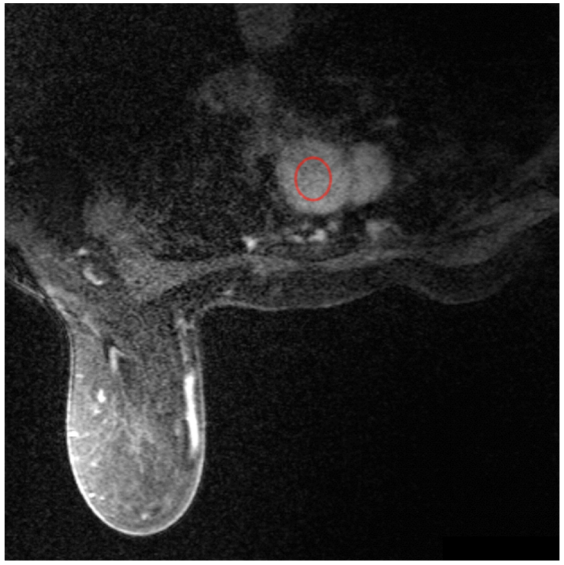
$$MTT = v_p / (PS + F_p)$$

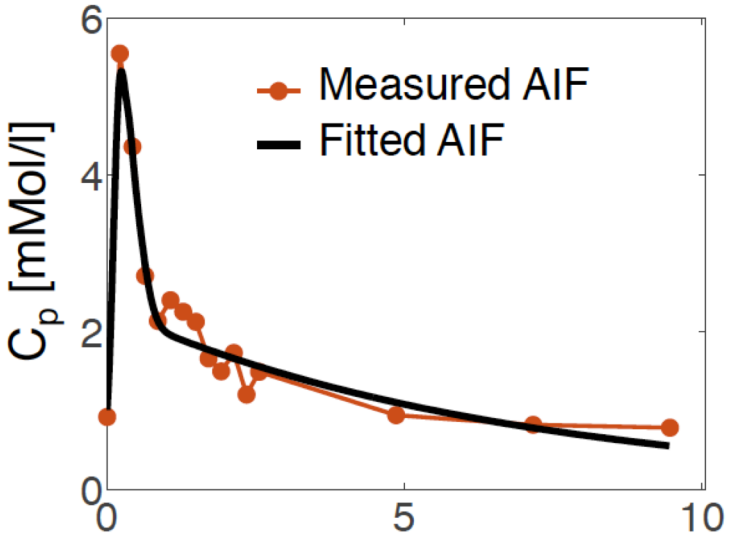
- F_p : plasma perfusion
- PS : permeability and surface area of the capillary walls
- MTT : the ratio of the volume of distribution in the plasma space (v_p) to the total plasma inflow ($PS + F_p$).

Determination of $C_p\ (t)$

- $C_p\ (t)$: Arterial Input Function (AIF)
  - Subject-specific AIF (sAIF)
  - Gaussian and exponential model

$$C_p(t) = \sum_{n=1}^{N} \frac{A_n}{\sigma_n \sqrt{2\pi}} \exp\left(\frac{-(t - T_n)^2}{2\sigma_n^2}\right) + \frac{\alpha \exp(-\beta t)}{(1 + \exp(-s(t - \tau)))}$$

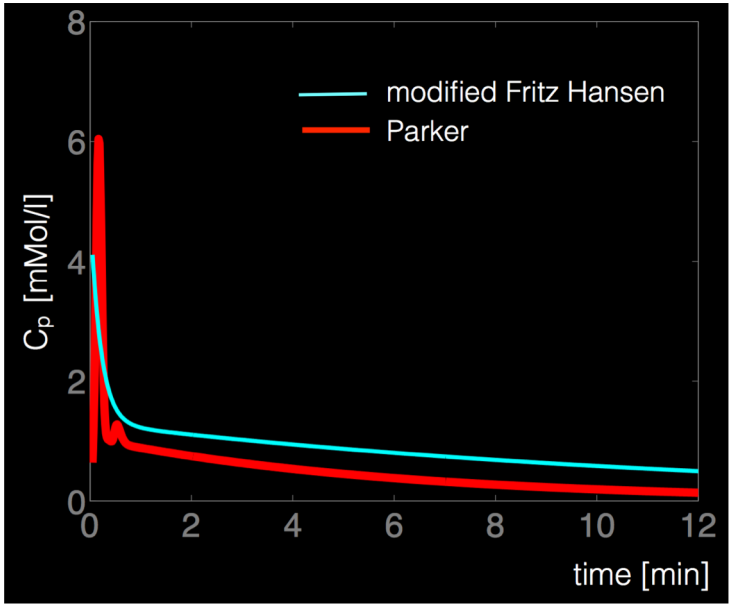




Parker et al., MRM, 2006

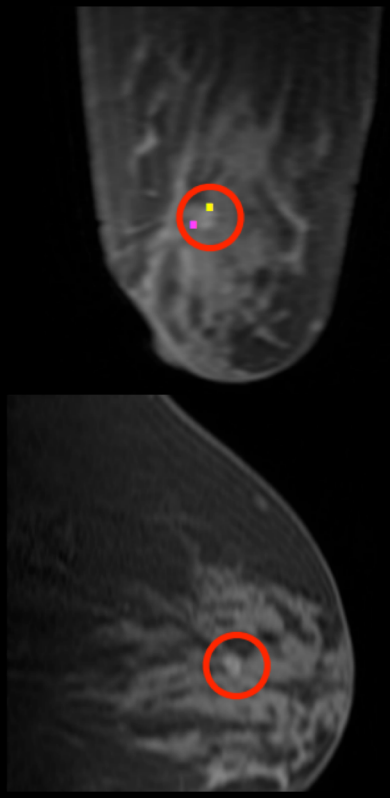
Determination of $C_p\ (t)$

- $C_p\ (t)$: Arterial Input Function (AIF)
  - Population AIF (pAIF):
  - Modified Fritz Hansen bi-exponential model $C_p(t) = D(a_1\, e^{-m_1 t} + a_2\, e^{-m_2 t})$

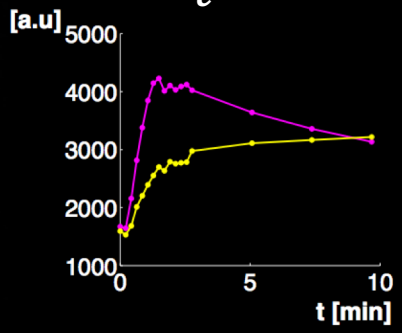


Walker-Samuel et al., PMB, 2006
Parker et al., MRM, 2006

Pharmacokinetic Mapping

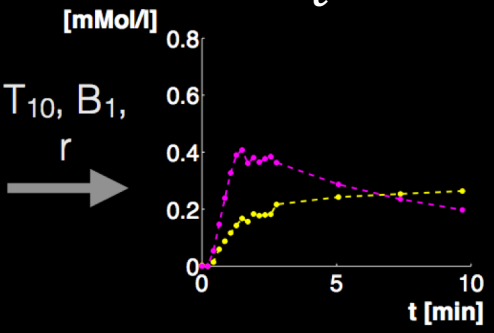


S_t



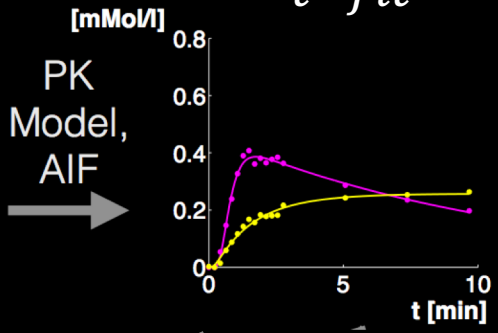
T_{10}, B_1, r

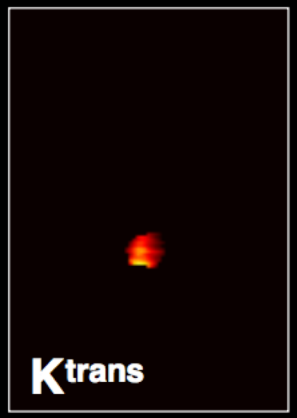
C_t

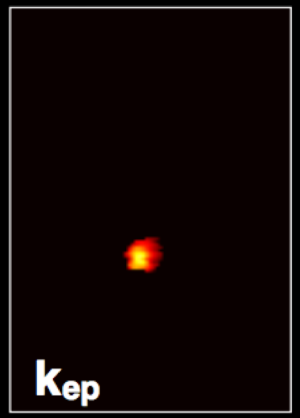


PK Model, AIF

C_{t-fit}

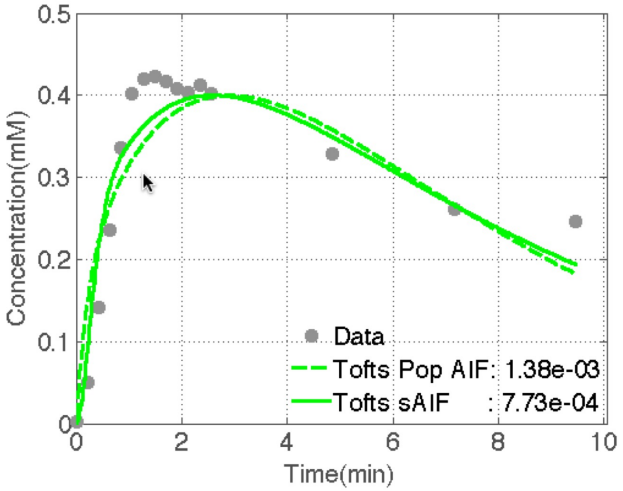


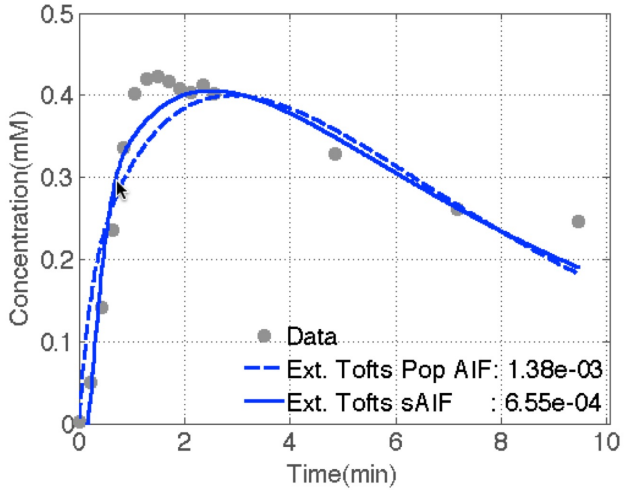


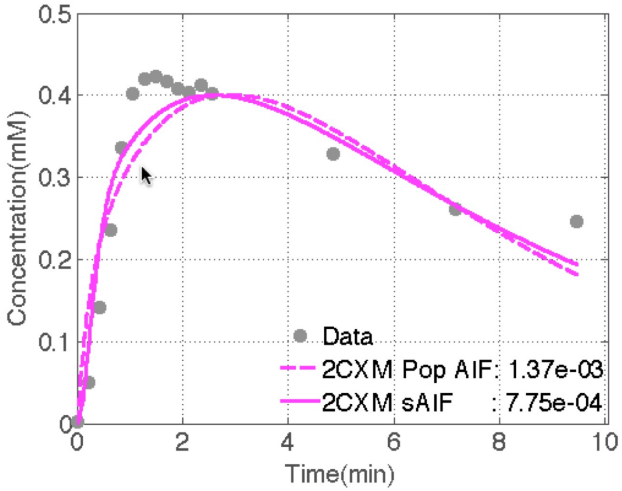


Courtesy: Dr. Subashini Vedanthm

Limitations







Fitting with 2CXMs with global uniform $C_p\ (t)$

- Improved fitting with sAIF in the first 2-3 very early enhancement time points
- All models have limited accuracy in catching up the rapid enhancement
- Hard to obtain correct AIF
- A uniform AIF might not be ideal

Objective

- Inspired by the intravascular dispersion concept, we replace the global AIF with a local AIF in order to account for local variations in contrast delivery.
- Compare the goodness-of-fit of the dispersion and non-dispersion models
- Compare diagnostic performance of the dispersion and non-dispersion models

Methods

Dispersion model : mLDRW model

- The intravascular transport of a bolus of contrast agent is driven by a combination of dispersion and convection effects

$$\frac{\partial}{\partial t} C_p\,(x,t) = D\frac{\partial^2}{\partial^2 x} C_p\,(x,t) - v\frac{\partial}{\partial x} C_p\,(x,t)$$

- Assuming a Gaussian distribution of the traveling contrast bolus $C_p\,(t)$, it can be solved using a modified local density random walk (mLDRW) model

$$\boldsymbol{C_p\,(t) = \alpha\sqrt{\frac{\kappa}{2\pi t}}\, e^{-\frac{\kappa(t-MTT)^2}{2t}}\; ;\kappa = v^2/D}$$

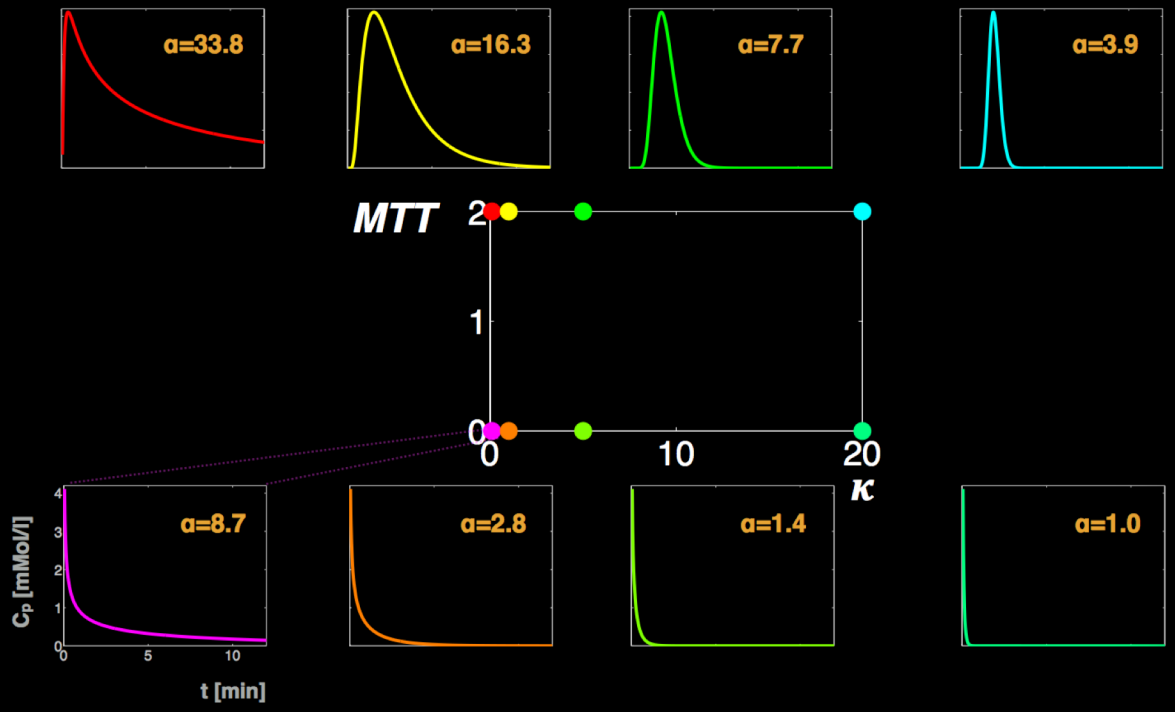
- mLDRW model:

$$C_t\,(t) = \alpha\sqrt{\frac{\kappa}{2\pi t}}\, e^{-\frac{\kappa(t-MTT)^2}{2t}} * K^{trans} e^{-k_{ep}\ t}$$

mLDRW model

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

κ dispersion term [min^{-1}]
MTT mean transit time [min]
κ ∝ (1/Dispersion coefficient)



Courtesy: Dr. Subashini Vedanthm
Mischi et al., IEEE EMBS 2013, Carr et al., ISMRM 2014

Comparison

- The standard Tofts model

$$C_t\,(t) = C_p\,(t) * K^{trans} e^{-K^{trans}\,t/v_e} = C_p\,(t) * K^{trans} e^{-k_{ep}\,t}$$

- The extended Tofts model

$$C_t\,(t) = v_p C_p\,(t) + C_p\,(t) * K^{trans} e^{-k_{ep}\,t}$$

- The comprehensive 2CXM

$$C_t\,(t) = F_p C_p\,(t) * [Ae^{-\alpha t} + (1 - A)e^{-\beta t}]$$

- mLDRW model

$$C_t\,(t) = \alpha\sqrt{\frac{\kappa}{2\pi t}}\, e^{-\frac{\kappa(t-MTT)^2}{2t}} * K^{trans} e^{-k_{ep}\,t}$$

Data Acquisition

- 37 patients (24 to 73 yrs) with 60 known masses
  - 43 malignant tumors (32 IDC, 3 ILC, 2 Mucinous Carcinoma, 6 DCIS)
  - 17 benign lesions

- A 0.1 mmol/kg dose of Gadobutrol (Gadovist) was injected at the rate of 2 ml/sec followed by a 20ml saline flush

- Imaging acquisition
  - Differential subsampling with Cartesian ordering (DISCO) DCE-MRI
  - 3D RF-spoiled gradient recalled echo (SPGR) sequence with Dixon fat-water separation

Evaluation

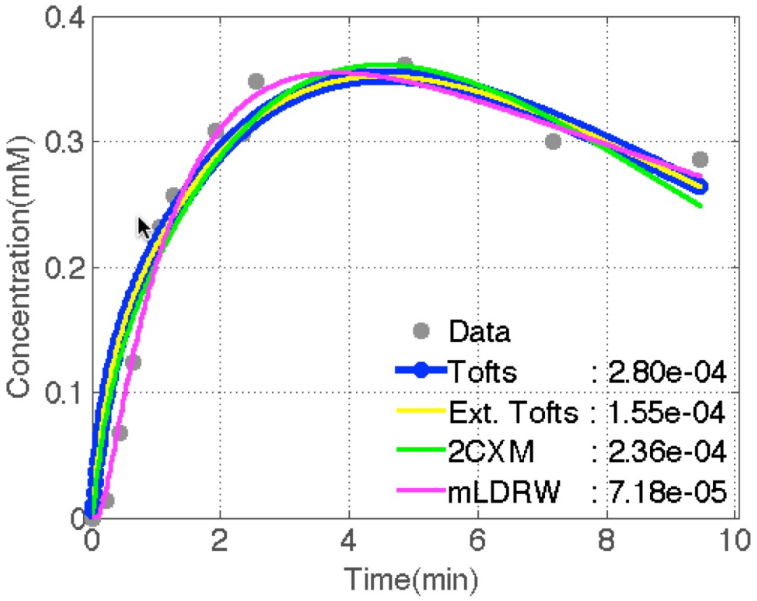
- Goodness-of-fit:
  - $MSE = \frac{SSE}{n-m}$
  - F test: evaluate if the mLDRW model generates a significant better fitting to other models

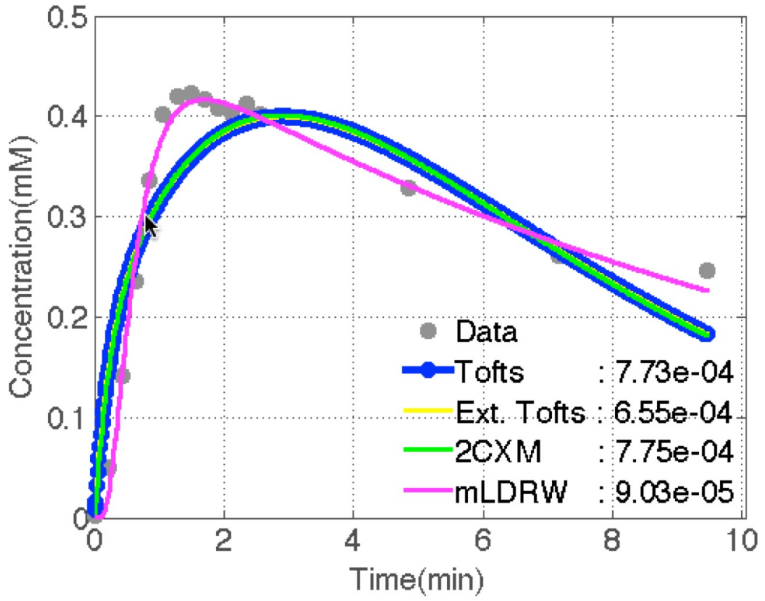
- Diagnostic performance
  - ROC curve is built over the ROI voxels representing the class of malignant and benign tissue for each model
  - The ROC generation is performed via a 5-fold cross validation process on 60 tumors.

Result

Goodness-of-fit

- Population AIF used in non-dispersion models



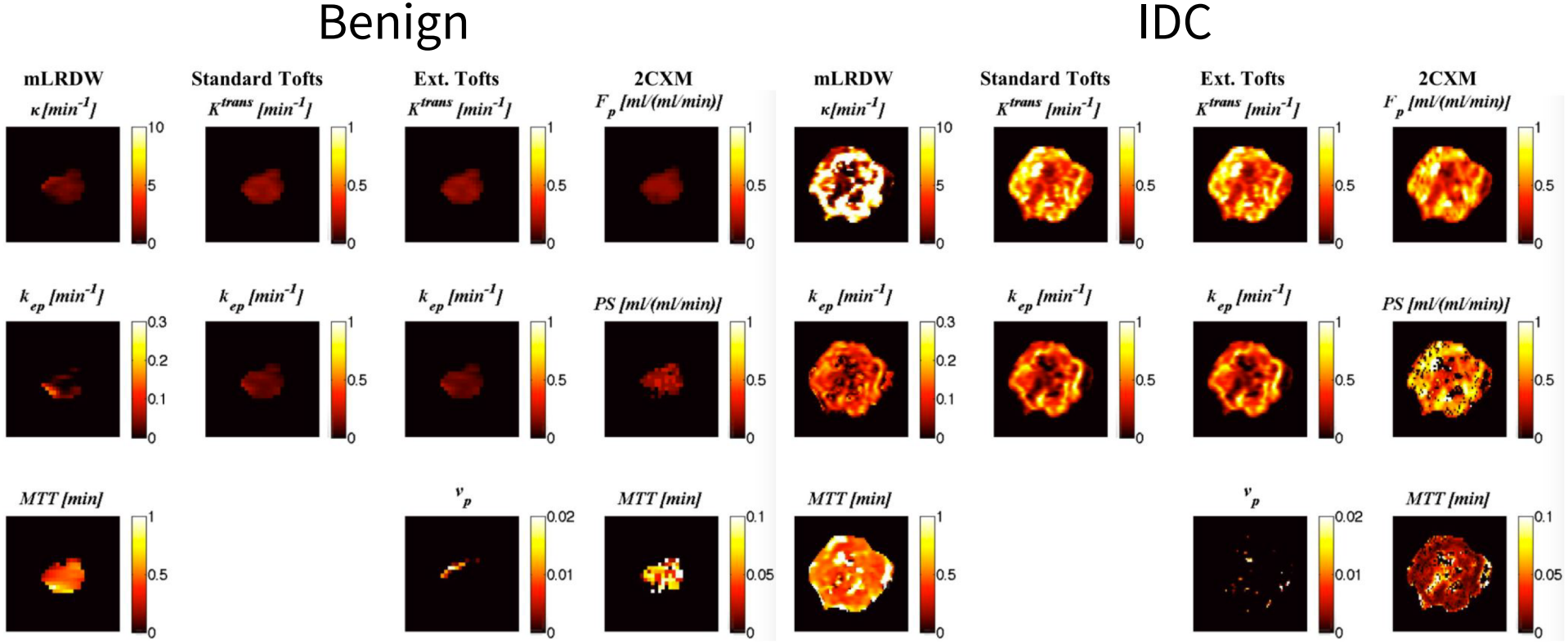


Goodness-of-fit

- Fitting errors over the entire dataset

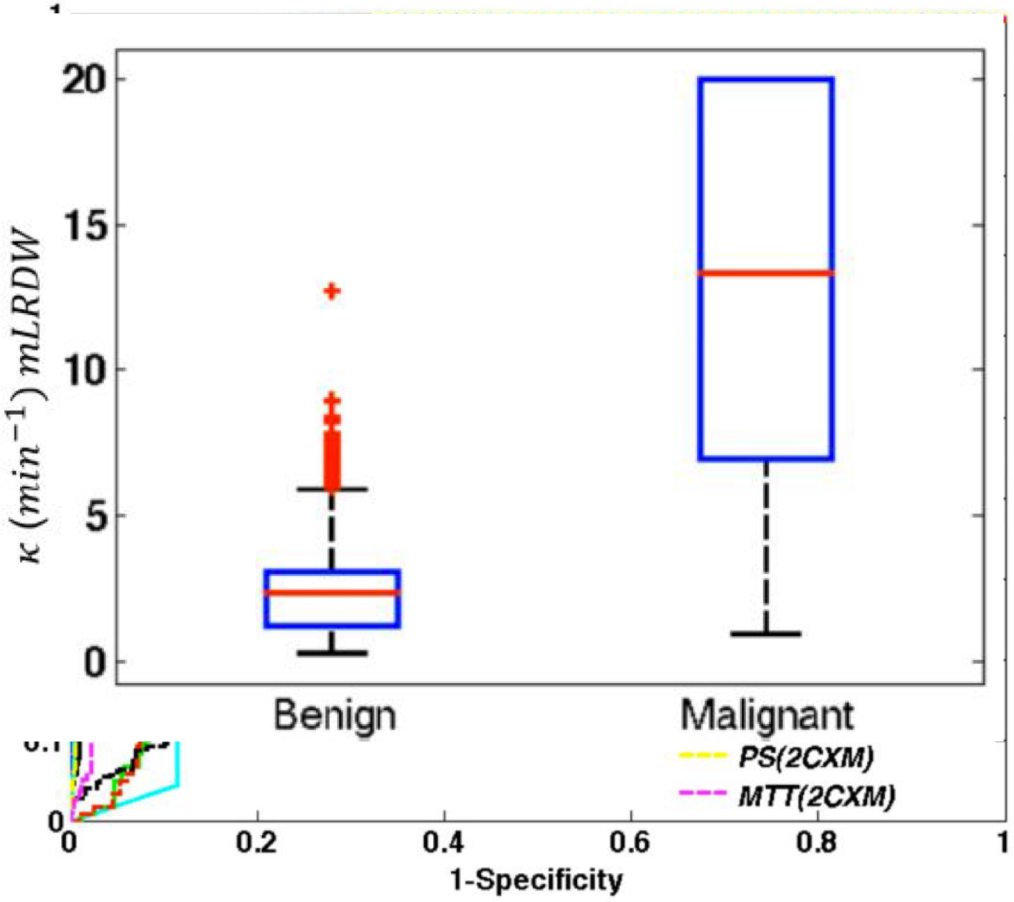
		MSE	p (F-test)
Population AIF (pAIF, 60 tumors)	Tofts	0.0058±0.0106	<<0.01
	Ext. Tofts	0.0057±0.0105	<<0.01
	2CXM	0.0035±0.0066	<<0.01
	mLDRW	0.0013±0.0026	
Patient-Specific AIF (sAIF, 18 tumors)	Tofts	0.0051±0.0079	0.0095
	Ext. Tofts	0.0045±0.0067	0.0245
	2CXM	0.0037±0.0064	0.0254
	mLDRW	0.0023±0.0041	

Pharmacokinetic mapping (voxel-by-voxel)



Diagnostic Performance

- AUC for κ is 0.96, the highest among all the compared parameters.
  - Sensitivity of $87.1\% \pm 3.9\%$
  - Specificity of $93.1\% \pm 2.8\%$



Discussion and Limitations

- The malignant tissue is highly correlated with the 'hot spots' in the dispersion map κ (i.e., $\kappa = v^2/D$)
  - Vascular endothelial growth factor (VEGF)
  - Vascular tortuosity mechanism has a counter effect on dispersion

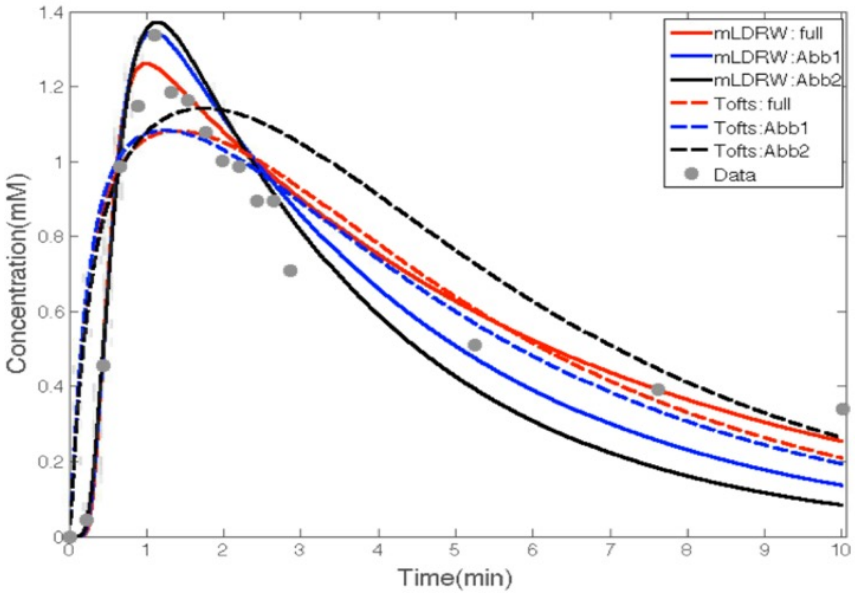
- A constant T_{10} value to convert the DCE signal-time curves to tissue concentration-time curves without acquiring the T_{10} maps and B_1 maps that account for the spatially varying signal changes

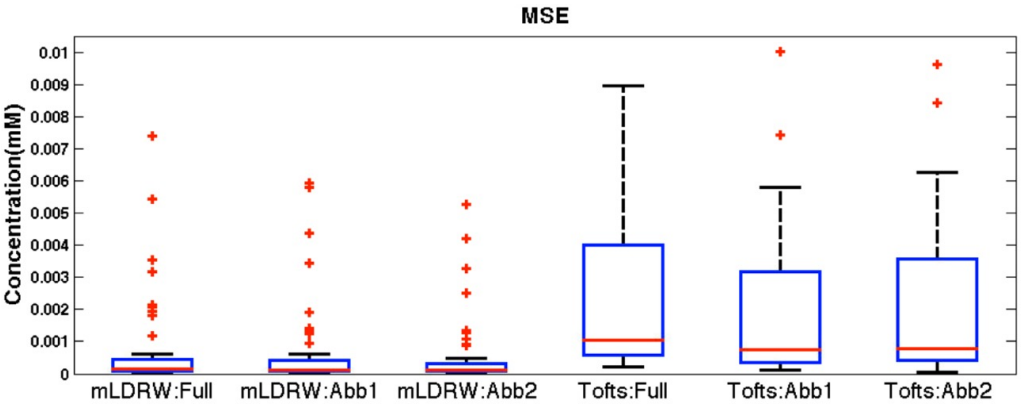
Conclusion

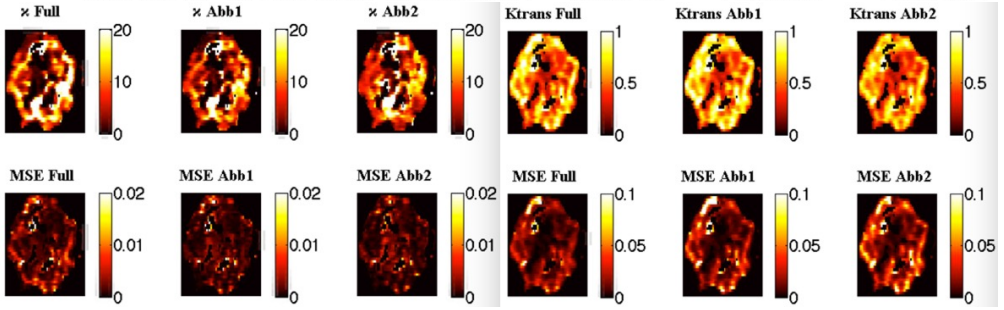
- A new window is proposed to investigate the physiology of breast tumor microcirculation through the estimation of an intravascular dispersion property
- The mLDRW dispersion no longer requires the measurement of AIF
- The goodness-of-fit is greatly improved with mLDRW model
- The dispersion related parameter, κ, demonstrates superior performance in discriminating benign and malignant tumor.

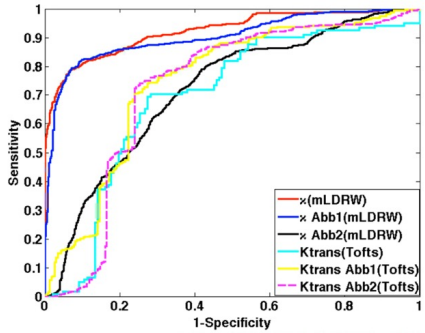
Future work: Abbreviated DCE

ABBREVIATED DCE









Power Pitch, Breast Pharmacokinetic Mapping using an Abbreviated Dynamic Contrast Enhanced (DCE) MRI Protocol. Joint Annual Meeting ISMRM / ESMRMB, May 11-16, 2019, Montreal, CA

Acknowledgement

- Bruce Daniel
- Brian Hargreaves
- Subashini Srinivasan
- Jianmin Yuan
- Catherine Moran
- Steffi Perkins

Thank you