(Technical aspects of) Breast DWI in Clinical Trials

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Disclosure: TLC is co-inventor of DWI-related IP assigned to and managed by the University of Michigan

NCI Clinical Imaging Steering Committee (CISC) July 19, 2022

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Breast DWI in Clinical Trials

Challenges:

- No clear consensus on where and how breast DWI should be applied
- Lack of prospectively validated ADC threshold supporting diagnostic decisions
- Lesion segmentation on distorted DWI/ADC is difficult (~15% interobserver variation [Tagliafico 2012] is comparable to ΔADC seen in ACRIN 6698)
- Current high variability in breast DWI quality owing to:
  - MRI system capabilities
  - Protocol variance and local skill level
  - Patient habitus & fat distribution
- Incorporation of new technologies vs standardization
  - Multi-shot EPI
  - Multi-band excitation
  - Gradient non-linearity correction
  - Within DWI registration
  - DWI to non-DWI registration
- Standardization of alternative biomarkers (non-Gaussian diffusion)

Breast DWI Standardization

Objective: Reduce Technical sources of ADC Variance that could otherwise mask biological differences in ADC

Organizations/Consortia Leading Standardization Efforts:

- Federal – FDA; NIH/NCI/Quantitative Imaging Network (QIN)
- Clinical trial cooperative groups IROC-/ECOG-ACRIN
- RSNA Quantitative Imaging Biomarker Alliance (QIBA)
- International Breast DWI working group within European Society of Breast Radiology (EUSOBI)

Diffusion-weighted imaging of the breast—a consensus and mission statement from the EUSOBI International Breast Diffusion-Weighted Imaging working group

Pascal Baltzer, Ritse M. Mann, Mami Iima, Eric E. Sigmund, Paola Clauser, Fiona J. Gilbert, Laura Martincich, Savannah C. Partridge, Andrew Patterson, Katja Pinker, Fabienne Thibault, Julia Camps-Herrero & Denis Le Bihan On behalf of the EUSOBI international Breast Diffusion-Weighted Imaging working group

European Radiology **30**, 1436–1450 (2020) | Cite this article

EUSOBI International Breast DWI WG Minimum Standards and QIBA Breast DWI Profile (ACRIN 6698)

Parameter	EUSOBI Int'l Breast DWI WG	QIBA Breast DWI (ACRIN 6698)
Field Strength	> 1.5T	1.5T or 3T
DWI Sequence	EPI-based	Single-shot EPI
Receiver coil	Breast > 4 channels	Breast > 4 channels
Orientation	Axial	Axial
In-plane resolution	$\leq$ 2 x 2 mm^2	(1.8 - 2.8) x (1.8 - 2.8) mm^2
Slice thickness	$\leq$ 4 mm	4 - 5 mm
Slice gap	NA	0 - 1 mm
Field-of-view	Bilateral Coverage	Bilateral Coverage
Number of b-values	2	2 - 4
Low b-value	0 - 50 s/mm^2	0 - 50 s/mm^2
High b-value	800 s/mm^2	600 - 800 s/mm^2
DWI directions	3 orthogonal	3 orthogonal
Parallel Imaging Factor	$\geq$ 2	$\geq$ 2
Fat saturation	SPAIR	SPAIR
TR	$\geq$ 3000 ms	$\geq$ 4000 ms
TE	Minimum	Minimum
Half-scan factor	NA	$\geq$ 0.65
Receiver bandwidth	Max to achieve min TE	Max to achieve min TE
Number of averages	Scan time < 5 min	2 - 5

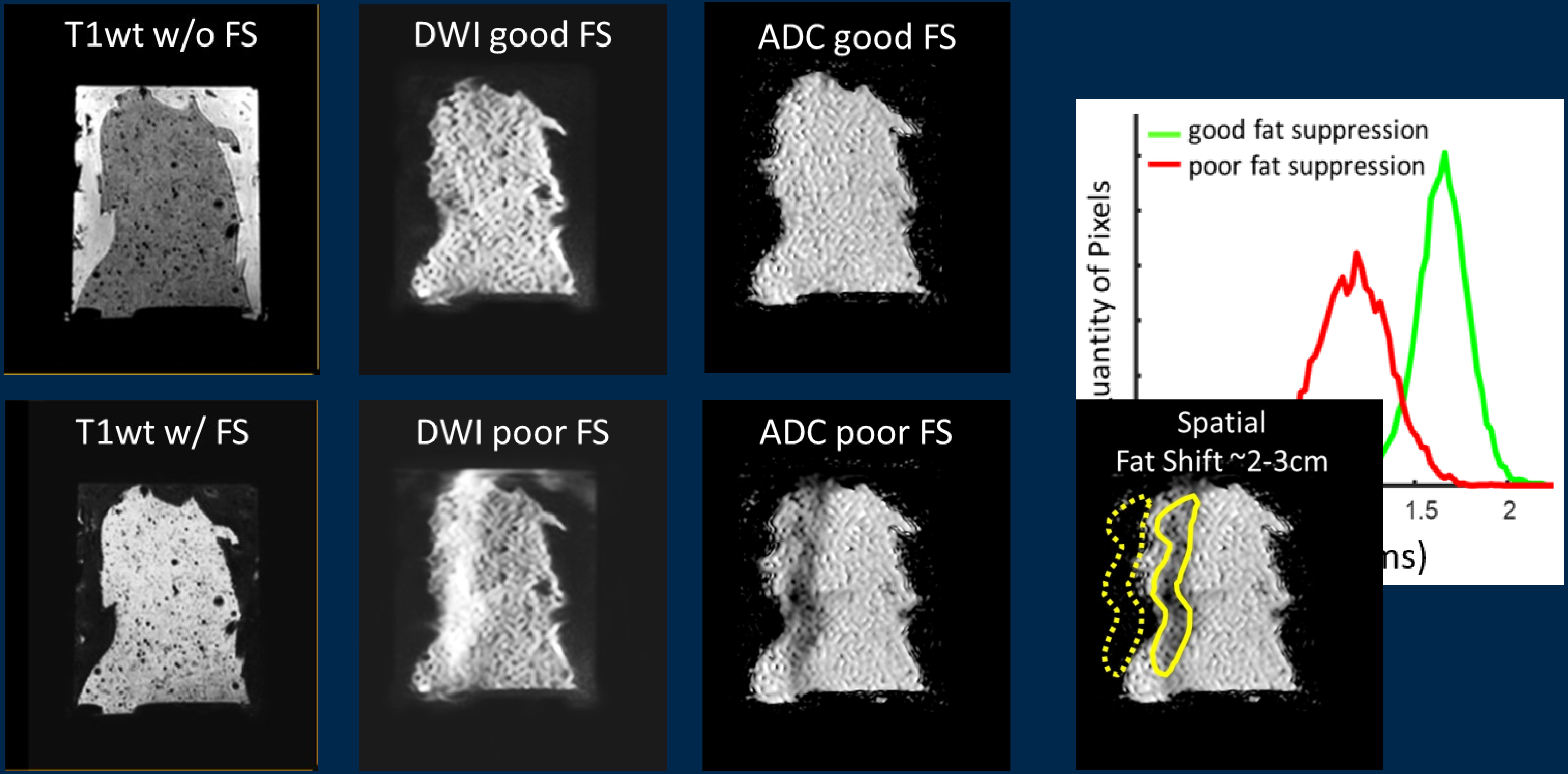
Critical Parameters / Methods Not (yet) Standardized

Allowed options & resultant image quality are platform-dependent

- DWI sequence class (single spin-echo, double spin-echo, bi-polar)
- Phase-encode direction (R/L vs A/P)
- Fat-shift direction (R vs L; A vs P)
- Magnetic field shim method
- b-value dependent averaging scheme
- Registration of directional DWI prior to creating trace DWI
- Registration of trace DWI to $DWI_{b=0}$ prior to creating ADC

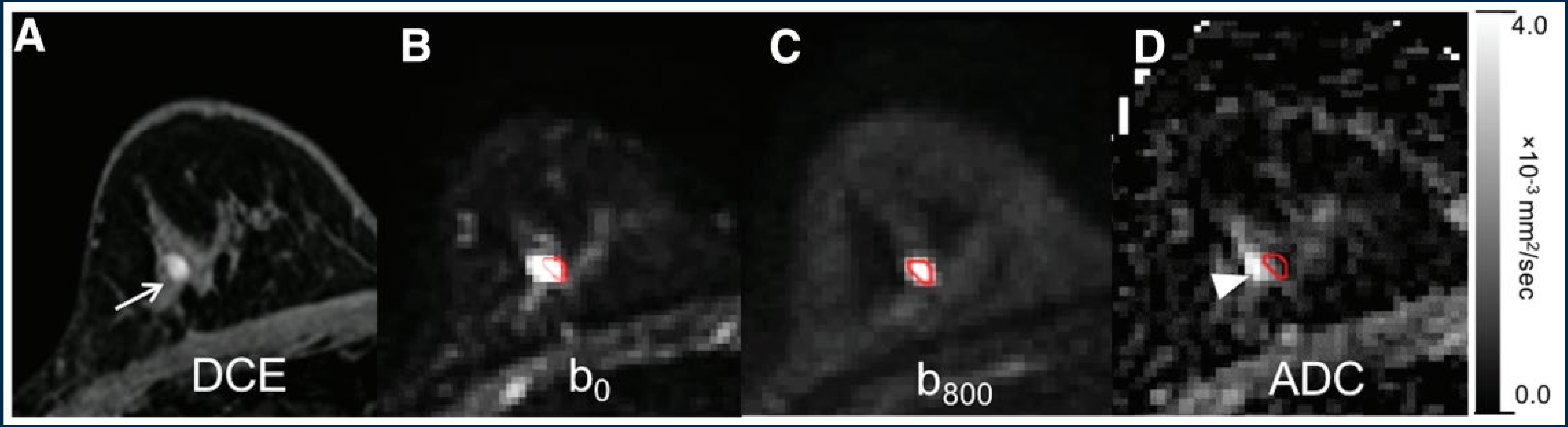
} Fat Suppression (Phase-encode direction, Fat-shift direction, Magnetic field shim method)

Fat Suppression is Crucial for Quantitative ADC in SS-EPI DWI



Spatial Mis-Match of SS-EPI DWI Across b-values

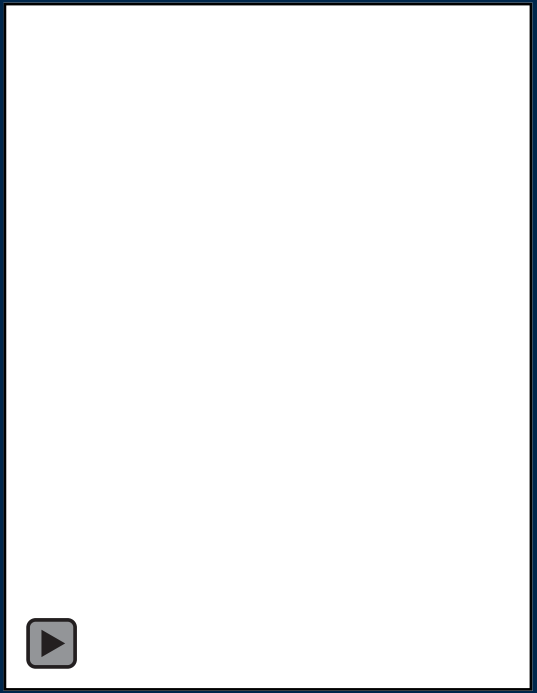
- Artifactual ADC
- Segmentation issues



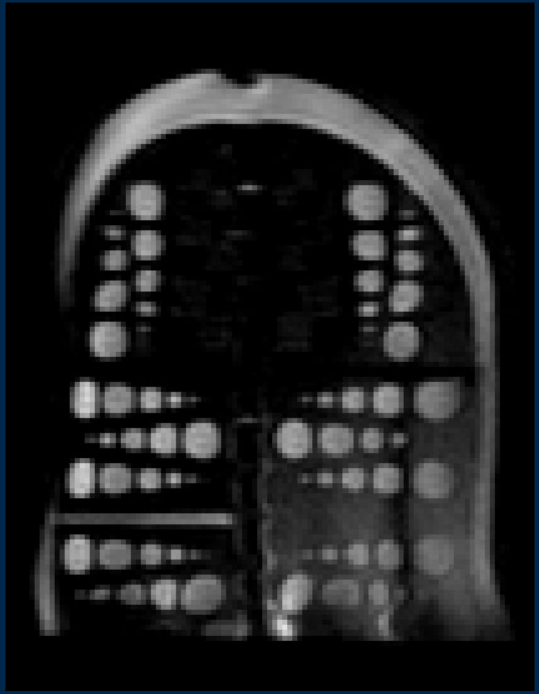
Whisenant, J.G., et al., Factors Affecting Image Quality and Lesion Evaluability in Breast Diffusion-weighted MRI: Observations from the ECOG-ACRIN Cancer Research Group Multisite Trial (A6702). J Breast Imaging, 2021. 3(1): p. 44-56.

Control of Eddy Currents in SS-EPI DWI
(post-acquisition DWI registration across b-value & directions)

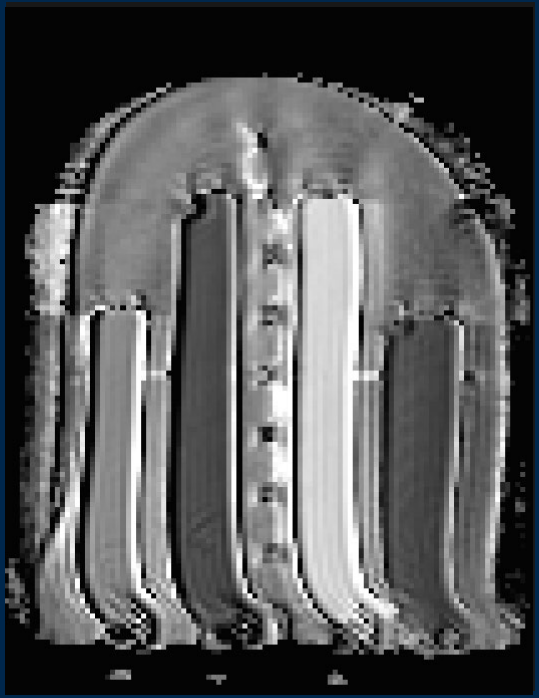
Allowed options & resultant image quality are platform-dependent



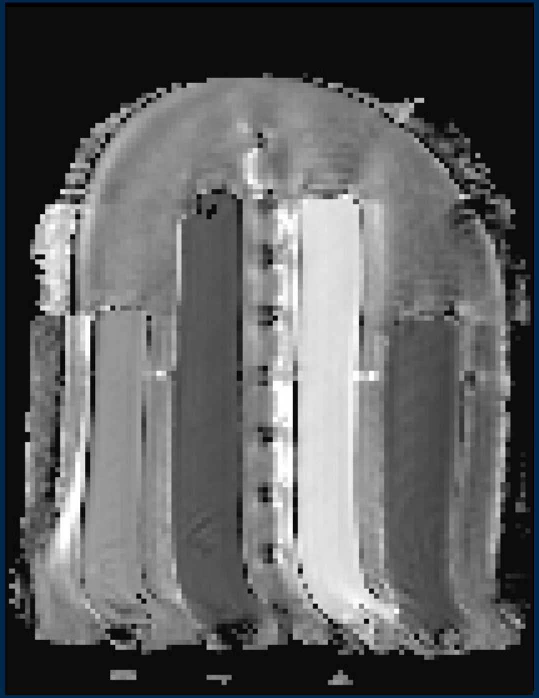
3-ortho axis
directional DWI



Trace DWI



ADC w/o registration

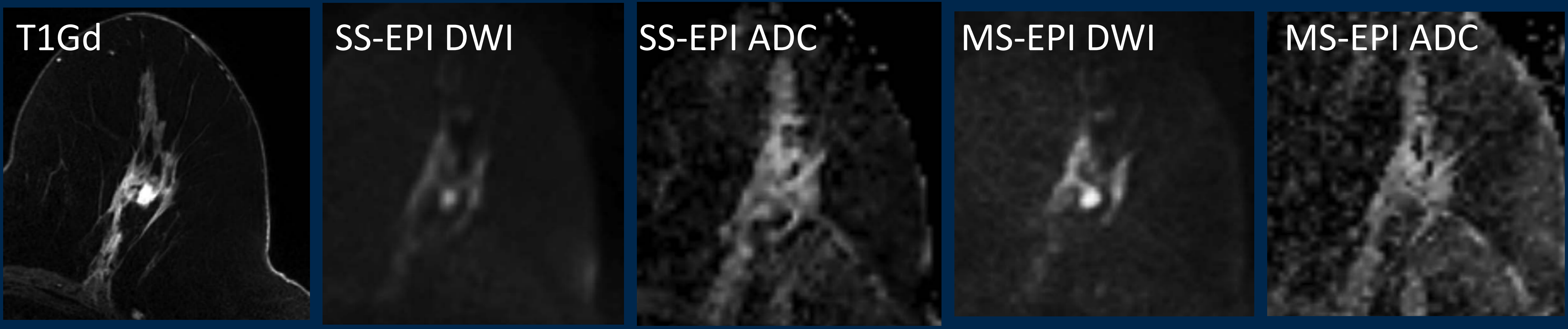


ADC w/ registration *

** Many ways to implement image registration*

Multi-shot EPI Breast DWI

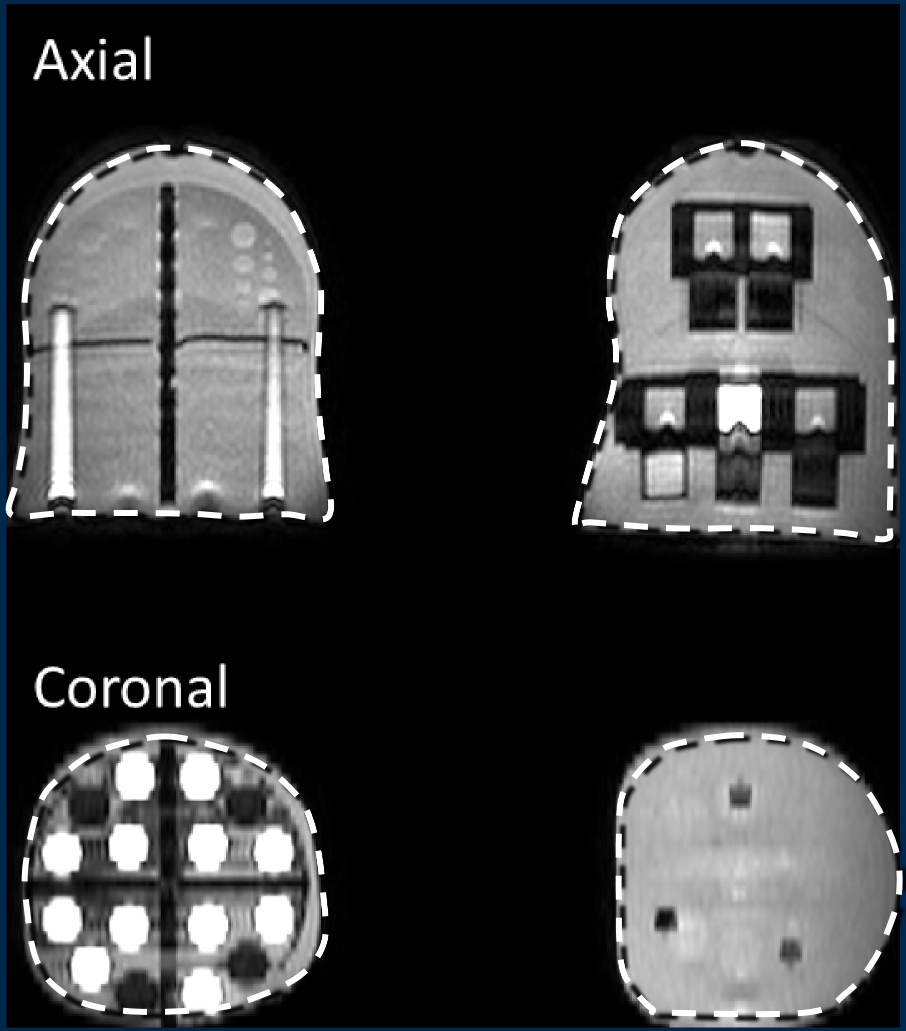
- Subset of EPI echos acquired in each read-out segment
- Multiple segments acquired over multiple shots to collect full dataset
- Additional acquisition/reconstruction steps to combine data to control motion artifact
- *Increased spatial resolution & reduced geometric distortion on DWI*
- Can increased scan time for full coverage
- MRI vendor-dependent; not yet standardized or universally available

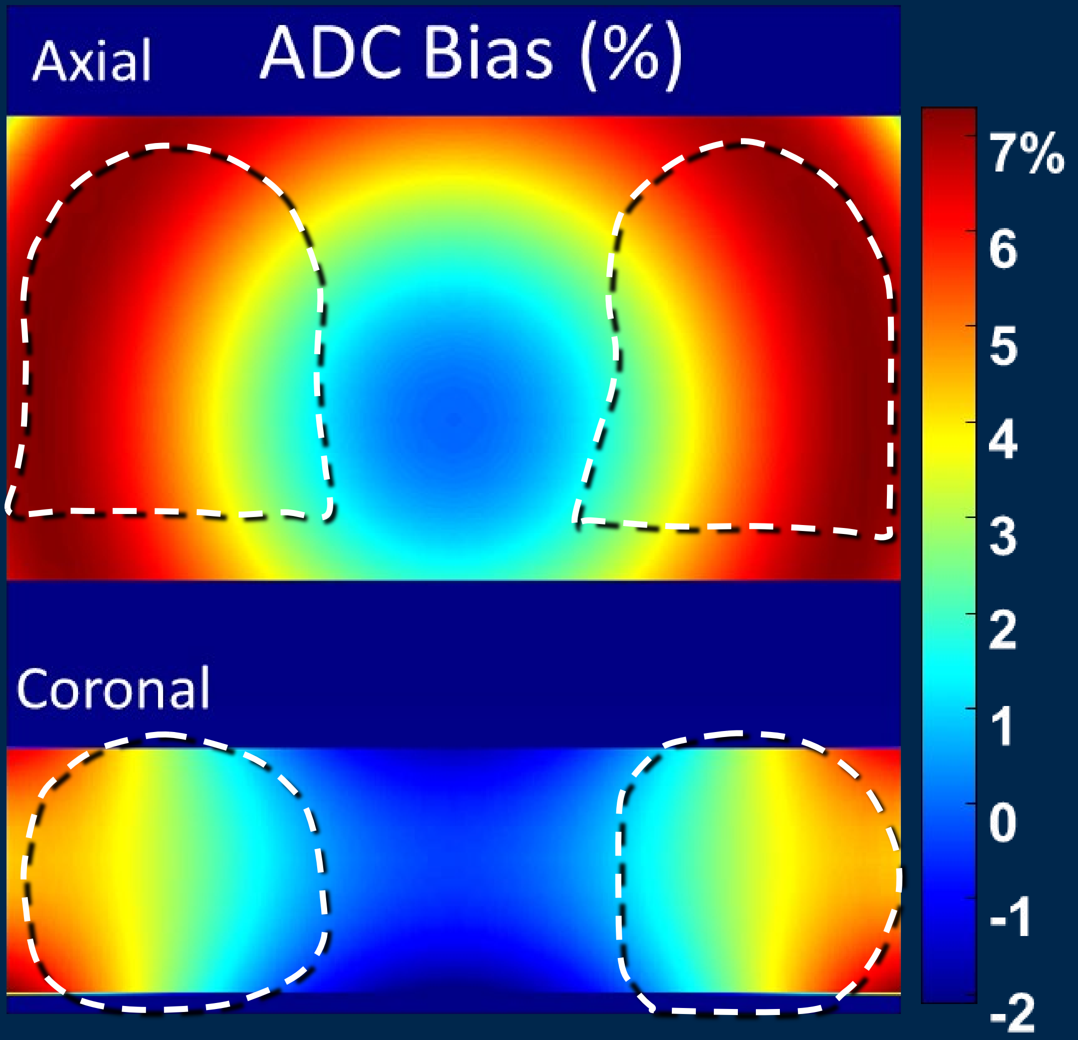


Wisner, D.J., et al., High-resolution diffusion-weighted imaging for the separation of benign from malignant BI-RADS 4/5 lesions found on breast MRI at 3T. J Magn Reson Imaging, 2014. 40(3): p. 674-81

Gradient Non-Linearity (GNL) in DWI

Spatially-dependent b-value → Spatially-dependent ADC bias

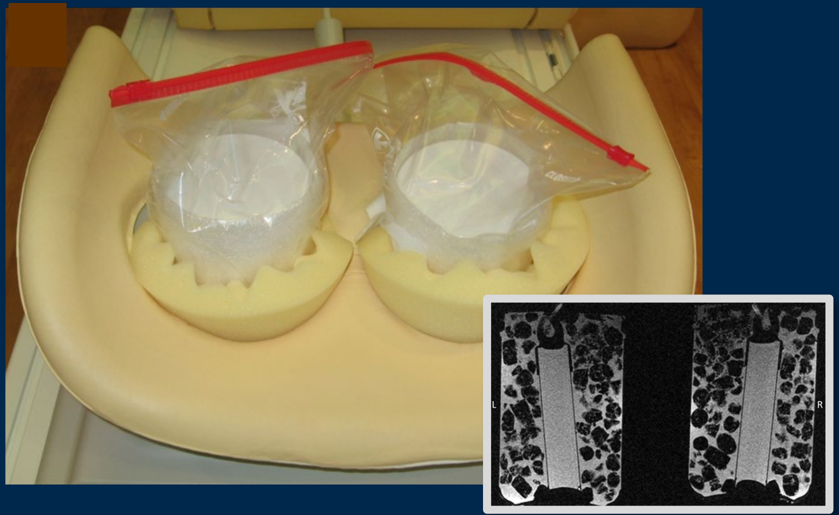


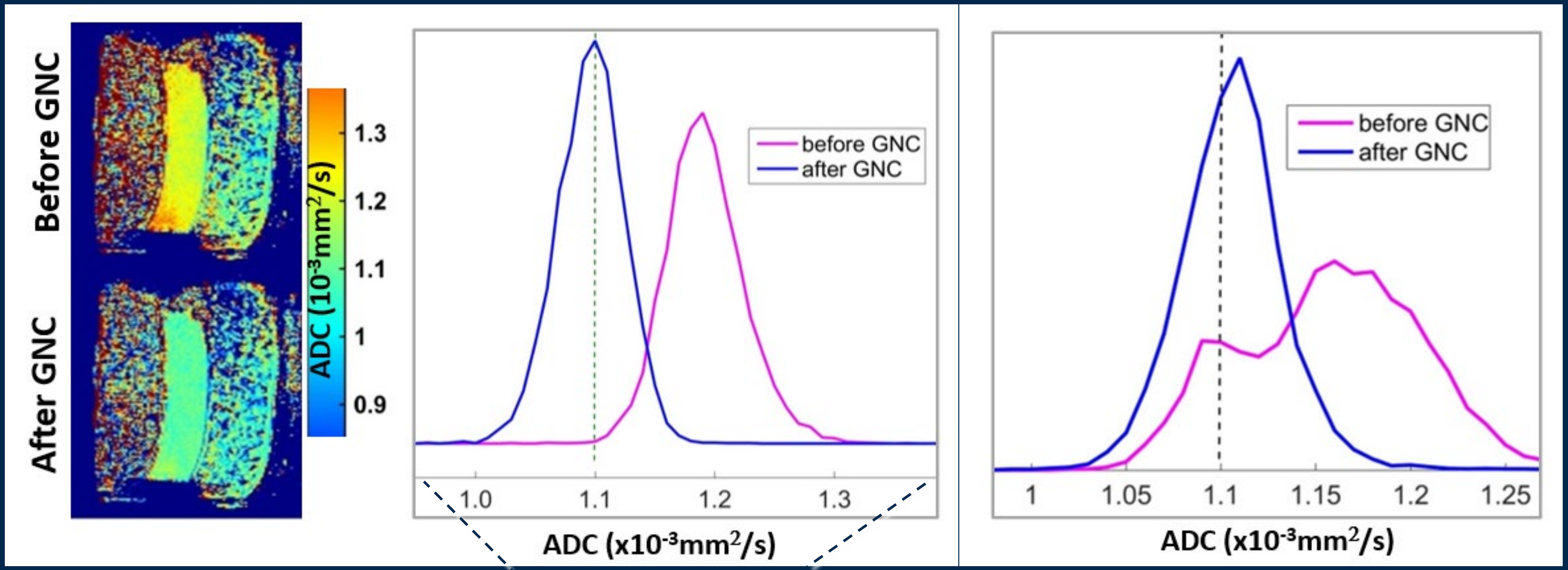


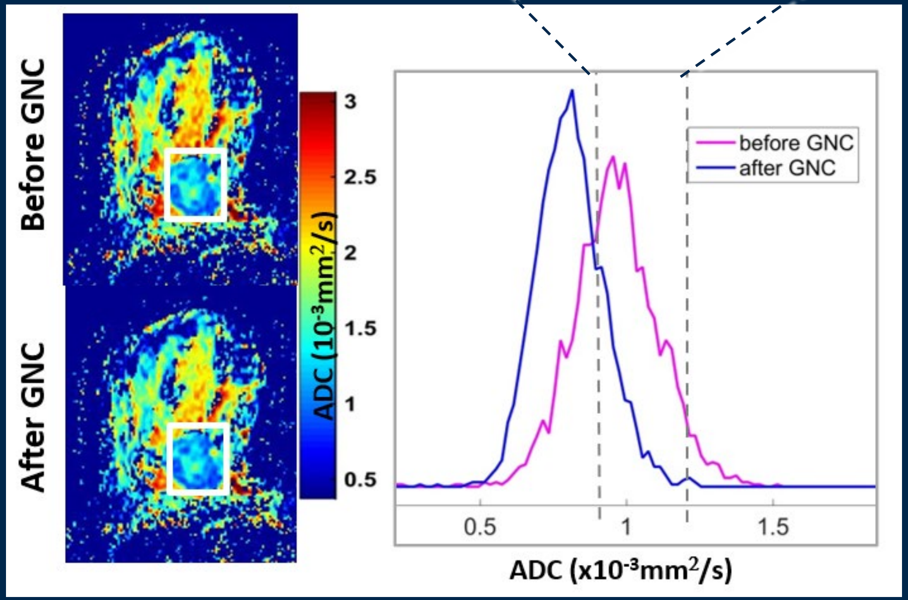
CaliberPhan_bMap_di2508251355s706_ph2bval800ddirTr.mhd

Gradient Non-Linearity (GNL) in DWI
(Spatially-dependent b-value)

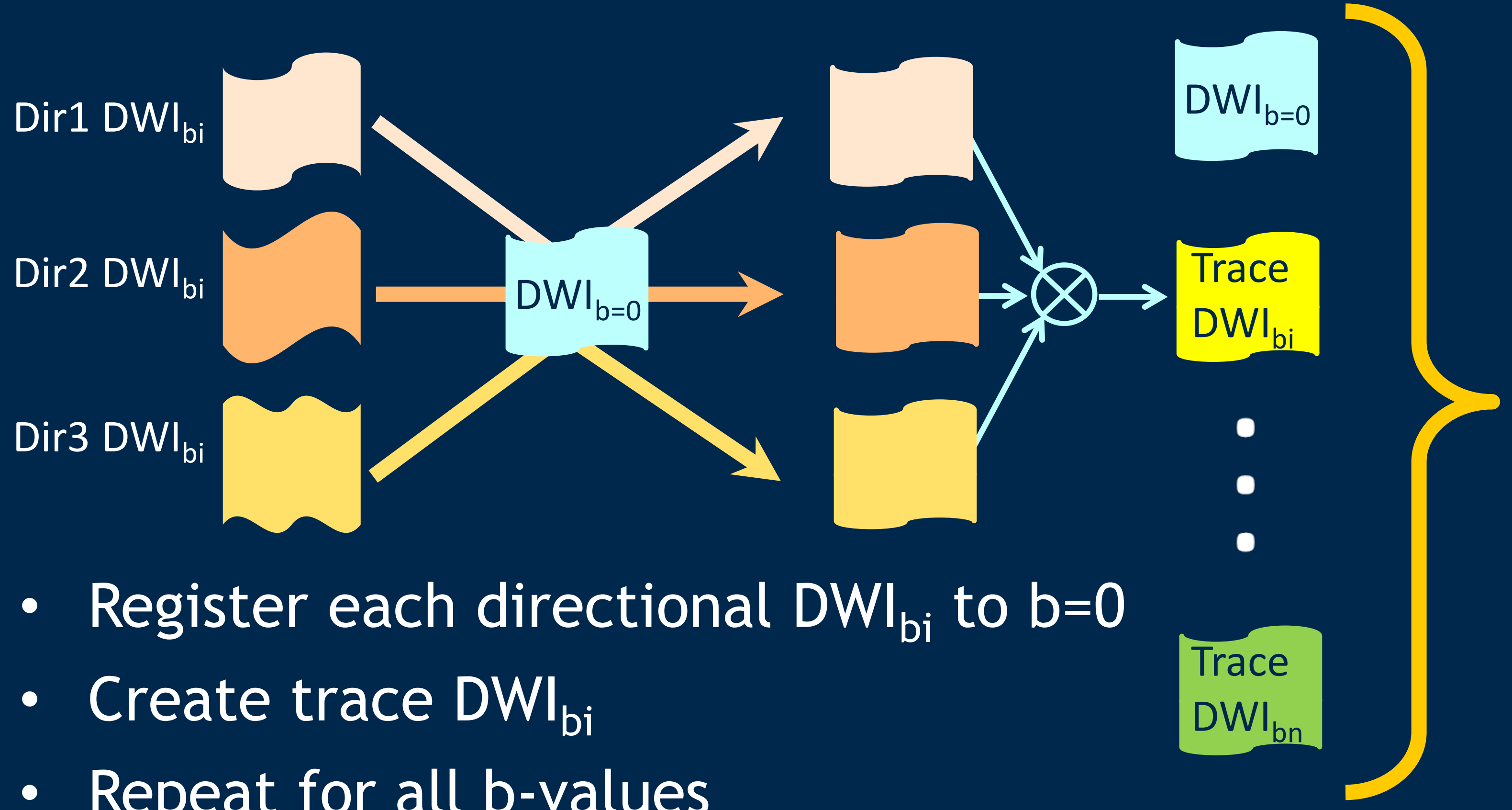
Ice-water phantom ACRIN 6698:
Target left vs right bias < 5%

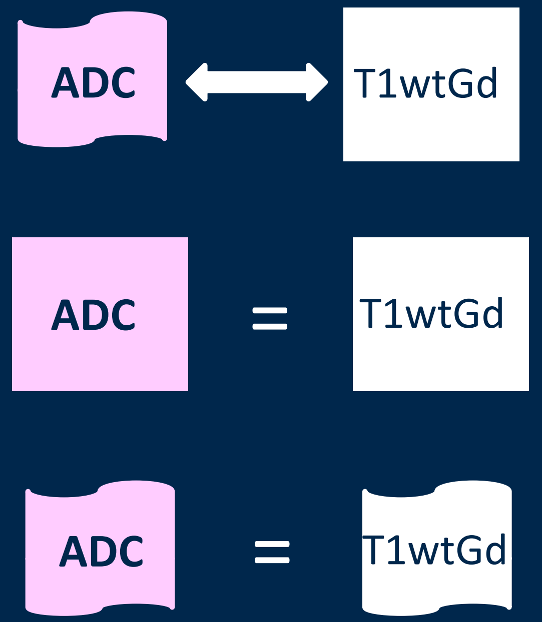






Preferred SS-EPI DWI Correction Workflow





- Register each directional DWI$_{bi}$ to b=0
- Create trace DWI$_{bi}$
- Repeat for all b-values
- Perform mono-exponential fit on trace DWI
- Perform GNL correction
- Co-Register T1wtGd and DWI$_{b=0}$ to aid segmentation

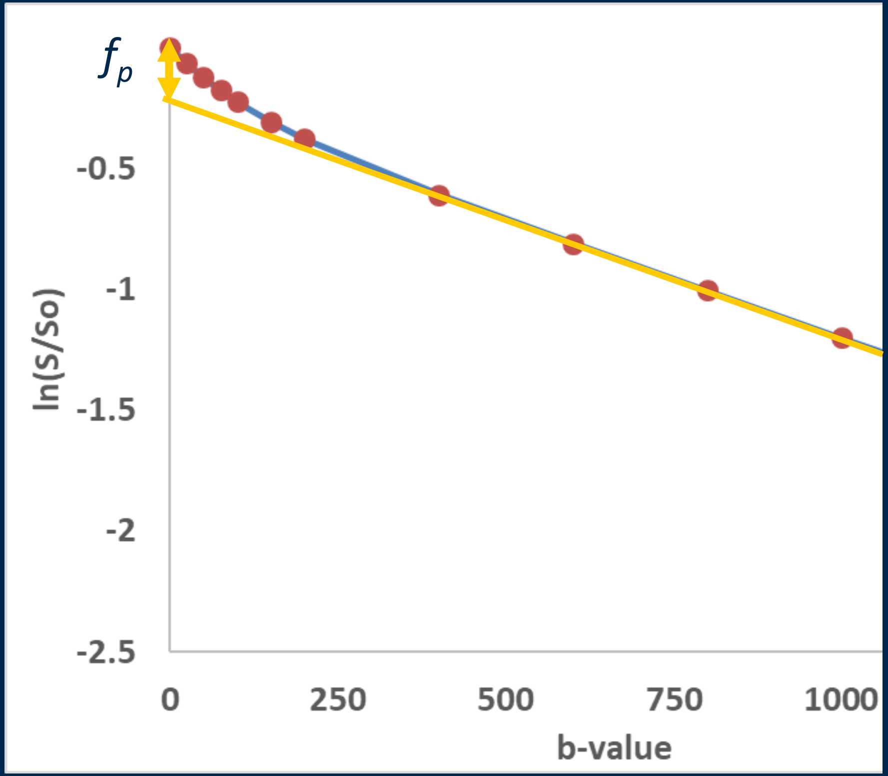
Caution:
Image registration routines are another source of variation

Beyond ADC: Non mono-exponential diffusion biomarkers

- Intra Voxel Incoherent Motion (IVIM)

$$\frac{S(b)}{S_o} = f_p \cdot e^{-b \cdot D^*} + (1 - f_p) \cdot e^{-b \cdot D_{tiss}}$$

  - perfusion fraction f_p
  - blood pseudo-diffusion D^*
  - tissue diffusion D_{tiss}



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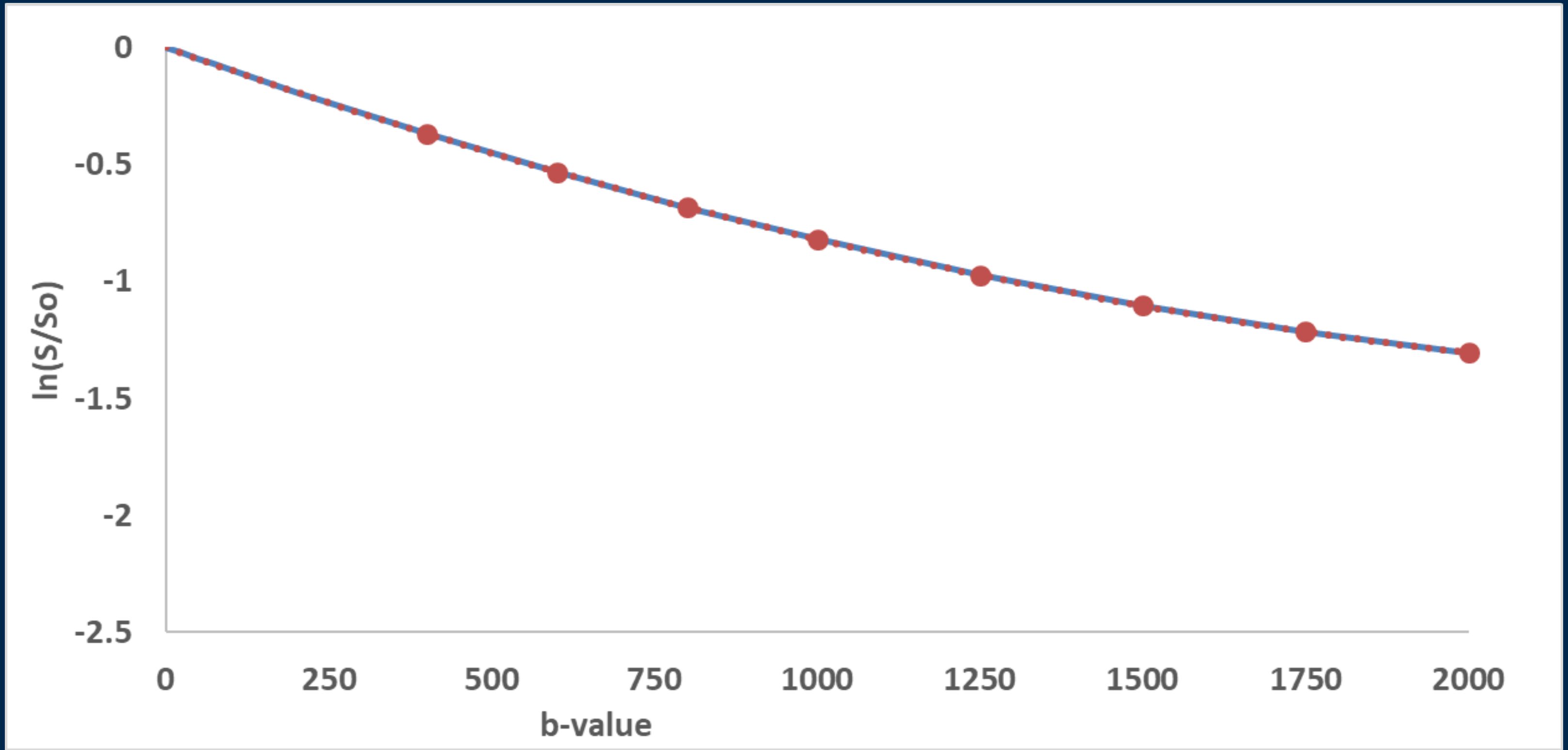
- Kurtosis

$$\frac{S(b)}{S_o} = e^{\left[-b \cdot D_k + \frac{K}{6}(b \cdot D_k)^2\right]}$$

- Stretched Exponential

$$\frac{S(b)}{S_o} = e^{-(b \cdot DDC_\alpha)^\alpha}$$



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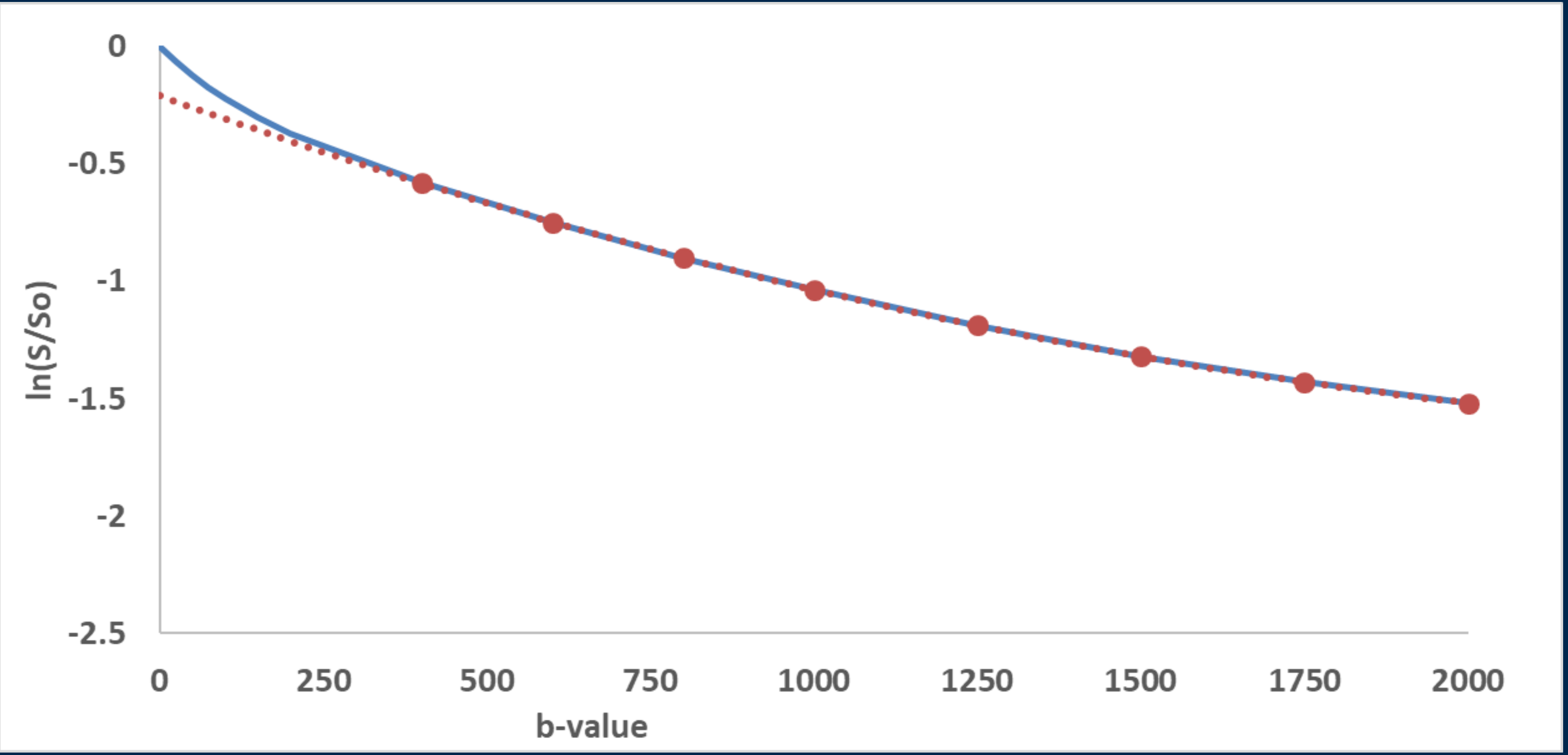

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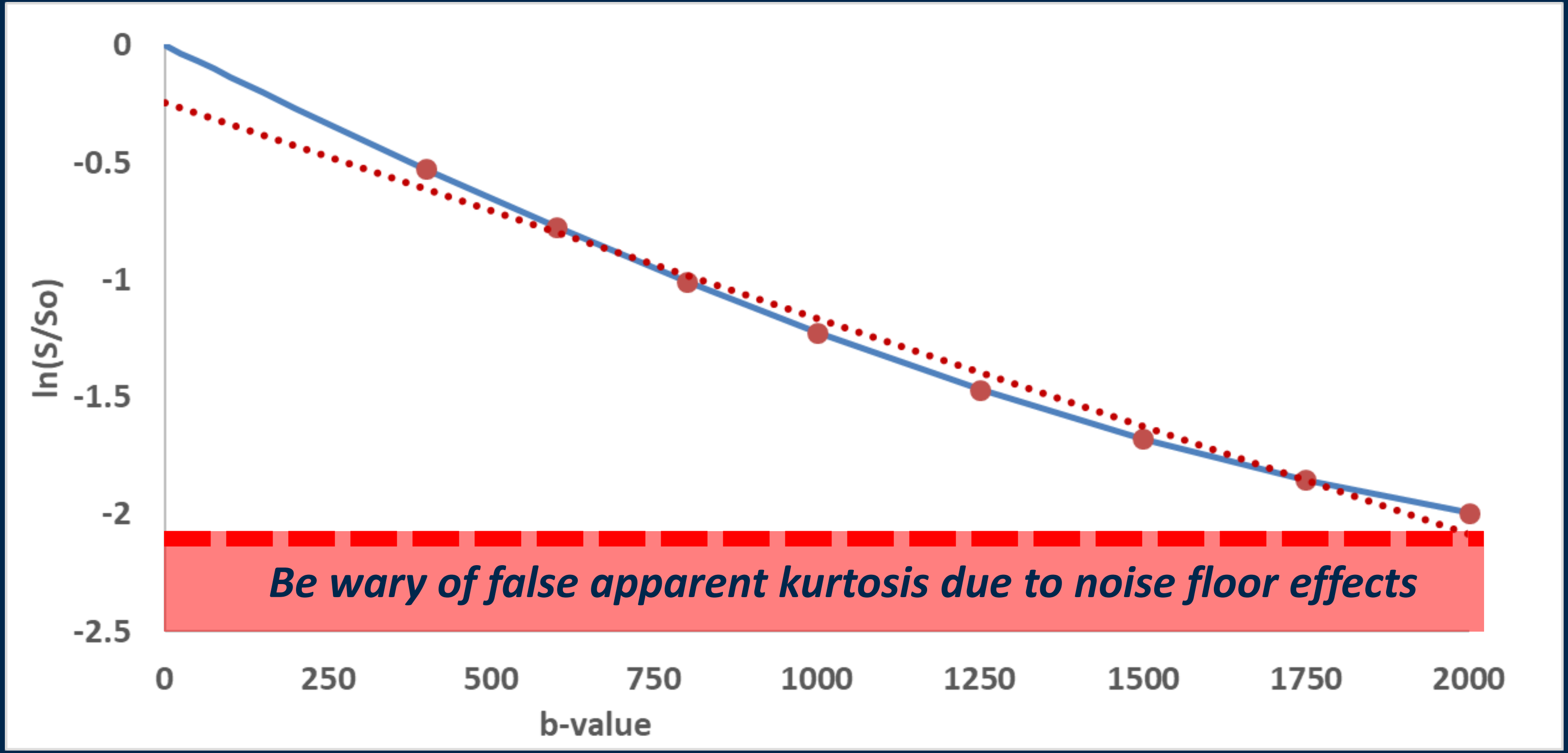


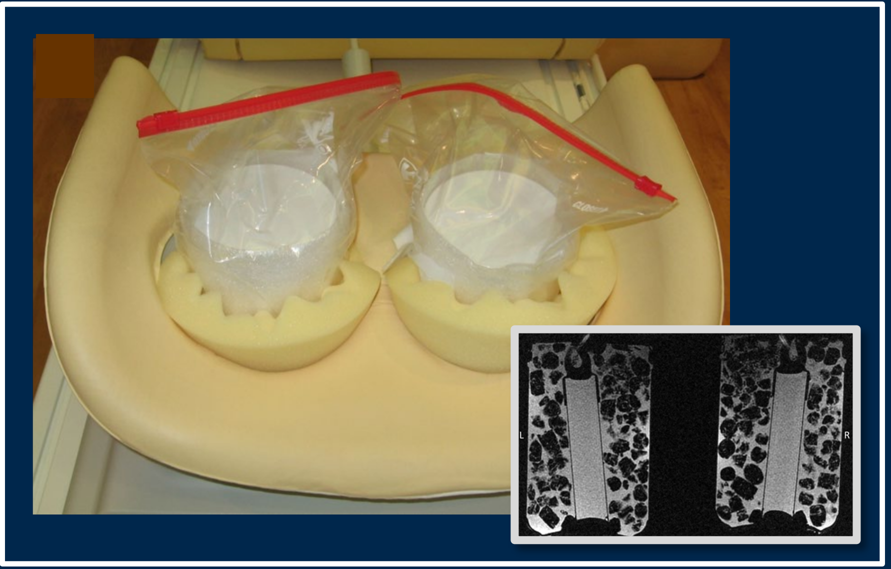
Repeatability of Breast ADC and Advanced Metrics

				wCV (%)					
	N subjects	# b-values	bmax	ADC	fp	D*	Dslow	α	DDC
Newitt (2018)	71	4	800	4.8%					
Partridge (2022)	71	4	800		12.4%		6.0%		
Jerome (2021)	21	13	700	9.4%	97%	29%	4.7%	12%	9.4%

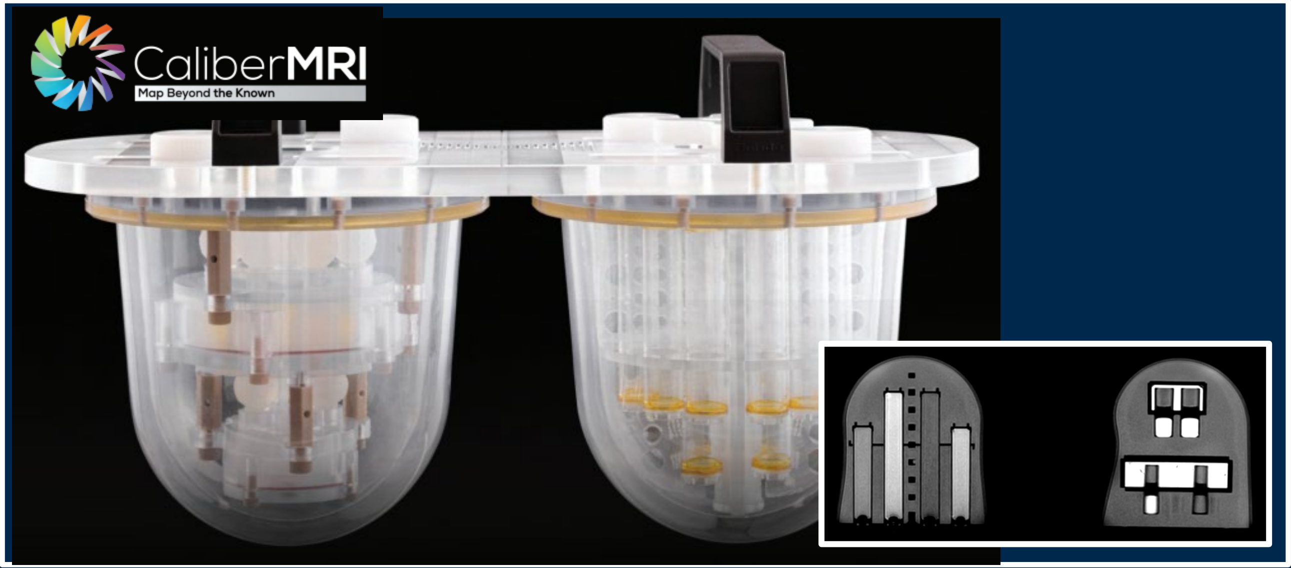
- Relative uniformity in mono-exponential ADC fit algorithms
- Greater variability in options to derive non-Gaussian metrics
  - Constrained vs unconstrained non-linear least squares
  - Segmented methods
  - Bayesian methods
- Lacking standardization in advanced metric fitting
- Unlike ADC, advanced metric generation not available on MRIs

Physical Phantoms for Breast DWI / ADC QC

- Ice water-based (used in ACRIN 6698 & 6702)
  - \+ Inexpensive
  - \+ Provides an absolute ADC reference
  - \- Inconvenient preparation for each use
  - \- Only single ADC value



- Polyvinylpyrrolidone (PVP)-based (ISPY2)
  - \+ Convenient setup
  - \+ Multiple PVP materials
  - \+ Geometric and T1 targets
  - \+ On-board LCD thermometer
  - \- Cost

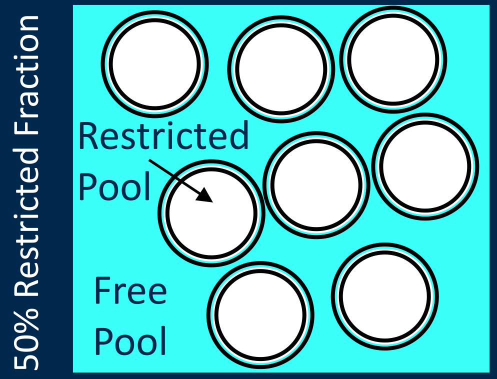


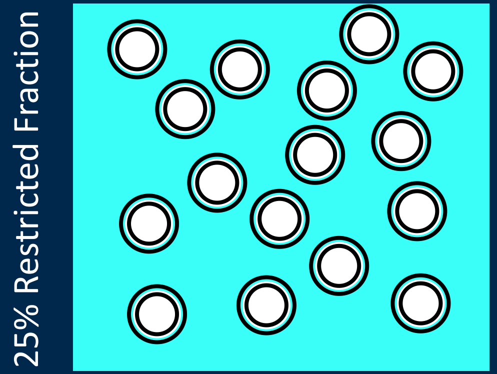
Physical Kurtosis Phantoms

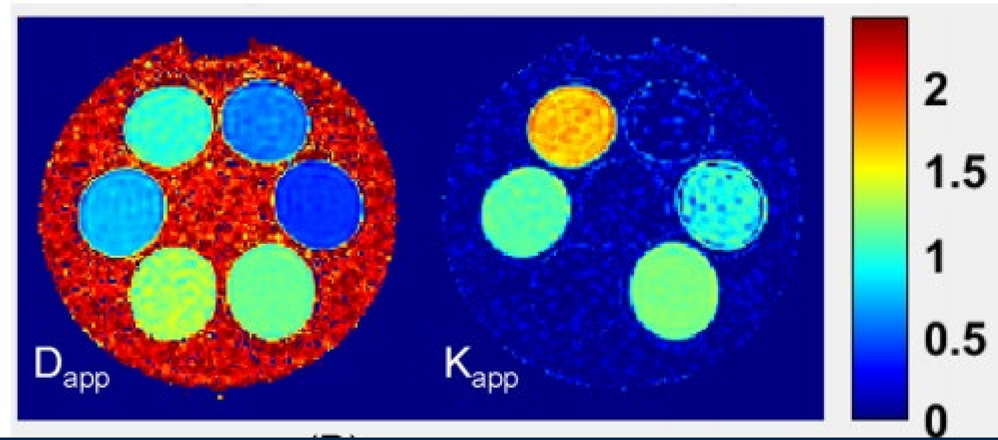
Scott D. Swanson
ISMRM 2019 and 2020

Malyarenko, D.I., et al., Multicenter Repeatability Study of a Novel Quantitative Diffusion Kurtosis Imaging Phantom. Tomography, 2019. 5(1): p. 36-43.

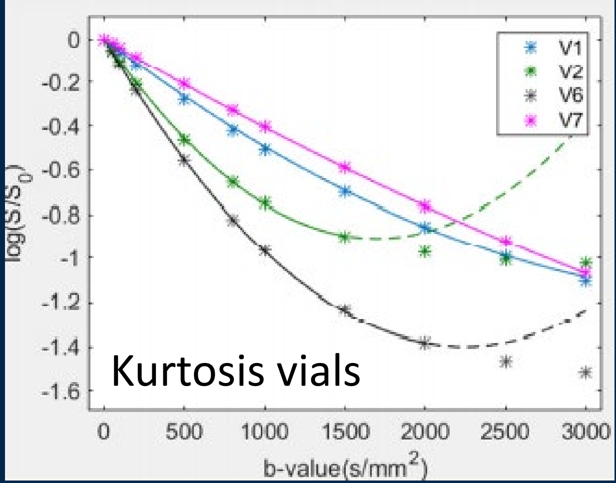
- Chemical composition of lamellar vesicles determines particle size, hence restricted diffusion compartment size
- Vesicles created by combining surfactant with cetearyl alcohol
- Low concentration (~1% w/w) with varying molar ratios used to create tunable apparent diffusion and kurtosis values, D_{app} and Kapp:

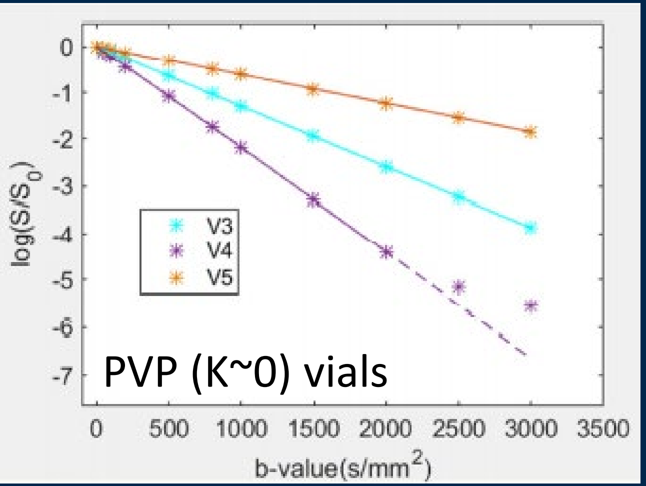






Vial#	Sample	D_{app} ± 95% CI	K_{app} ± 95% CI
V1	DEC-CTAB	0.71 ± 0.014	1.11 ± 0.017
V2	CA-BTAC	1.02 ± 0.022	1.69 ± 0.013
V3	PVP20%	1.27 ± 0.017	0.04 ± 0.013
V4	Water	2.16 ± 0.034	0.06 ± 0.021
V5	PVP40%	0.60 ± 0.012	0.08 ± 0.022
V6	PL161	1.11 ± 0.014	1.29 ± 0.009
V7	CA-CTAB	0.39 ± 0.013	0.84 ± 0.076

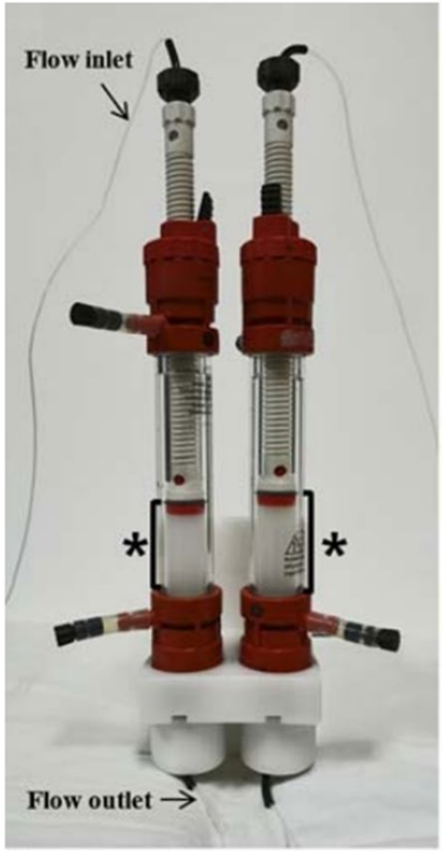


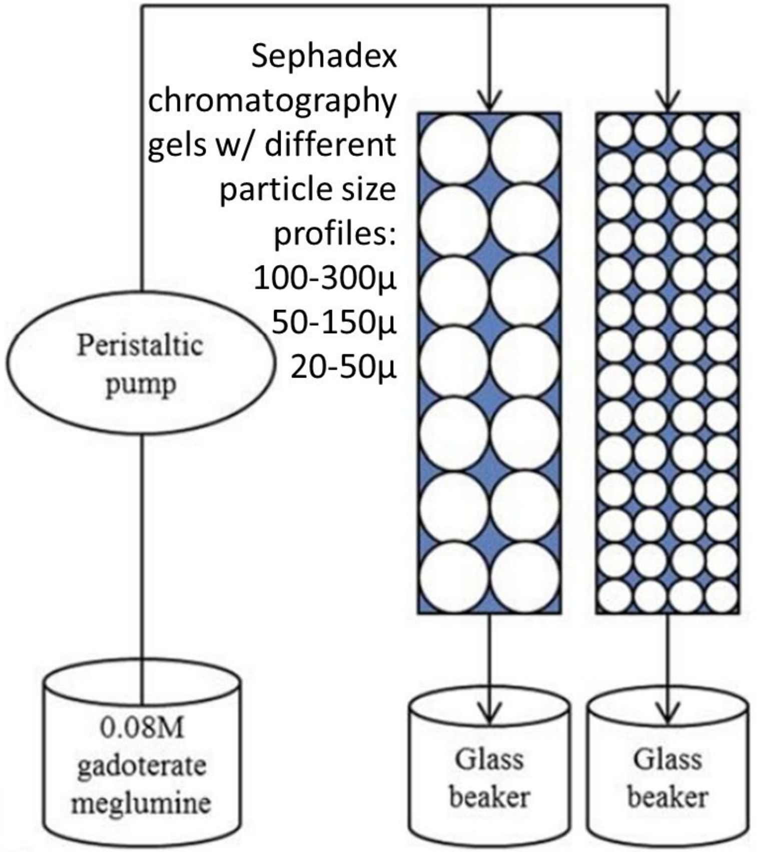


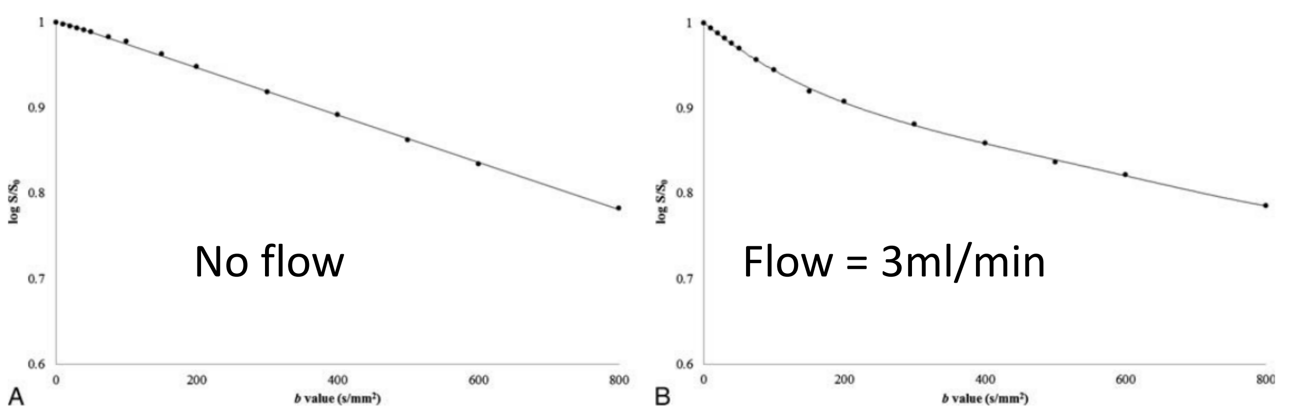
Physical IVIM Phantoms

Cho, G.Y., et al., A versatile flow phantom for intravoxel incoherent motion MRI. Magn Reson Med, 2012. 67(6): p. 1710-20.

Lee, J.H., et al., Perfusion Assessment Using Intravoxel Incoherent Motion-Based Analysis of Diffusion-Weighted Magnetic Resonance Imaging: Validation Through Phantom Experiments. Invest Radiol, 2016. 51(8): p. 520-8.







	Free Fitting	Segmented Fitting
ADC		4.97%
D_{slow}	4.57%	4.36%
f	7.78%	8.99%
D_{fast}	112.31%	6.59%
$f \cdot D_{fast}$	40.92%	11.68%

CV indicates coefficient of variation; ADC, apparent diffusion coefficient; IVIM, intravoxel incoherent motion; D_{slow}, slow diffusion coefficient; f, perfusion fraction; D_{fast}, fast diffusion coefficient; $f \cdot D_{fast}$, product of f and D_{fast}.

Summary: To Advance Breast DWI in Clinical Trials

Greater manufacturer involvement

- Standardization / harmonization of acquisition protocols at deeper level
- Incorporation of new technologies (eg. multi-shot methods)

Greater core-lab involvement

- Site / system qualification in performing DWI
- Ongoing quality control
- Site Training
- Standardization of analysis workflow including advanced off-line processing

Thank You!

U Michigan
Dariya Malyarenko
Brian Ross
Yuxi Pang
Scott Swanson

U Washington
Savannah Partridge
Debosmita Biswas

UCSF
David Newitt
Nola Hylton
Lisa Wilmes
Jiachao Liang

MSKCC
Amita Dave
Ramesh Paudyal
Amaresha Konar Shridhar

Philips
Ajit Devaraj
Johannes Peeters

General Electric
Luca Marinelli

Siemens
Axel vom Endt
Jin Ning

NIH / NCI
P01 CA85878
P30 CA046592
U01 CA166104
R01 CA190299
U01 CA211205 MSKCC

QIBA - RSNA
NIH 895800

Breast DWI in Clinical Trials

Advantages / Strengths:

- Sensitive to relevant biophysical qualities of breast disease
- Independent of magnetic field strength
- Standard breast DWI technique is widely available & moderately fast
- Non contrast study – allows repeatability study
- Complimentary to highly-sensitive DCE; DWI improves lesion characterization
- Primary biomarker, ADC
  - Is quantitative
  - ADC map generation algorithm standardized & built into all MRIs
  - Phantom reference materials exist and are absolute