QIBA Perfusion, Diffusion, and Flow (PDF-MRI) Biomarker Committee: 2016 Overview

Michael A. Boss[1], John Kirsch[2], Mark A. Rosen[3], Thomas L. Chenevert[4], Dariya Malyarenko[4], Hendrik Laue[5], Caroline Chung[6], Krishna Nayak[7], James Provenzale[8], Walter Schneider[9], Ona Wu[10], Bradley Erickson[11], Alexander R. Guimaraes[12], Daniel Sullivan[8], and Edward F. Jackson[13]

[1]National Institute of Standards and Technology, [2]Siemens Healthcare, [3]University of Pennsylvania,, [4]University of Michigan, [5]Fraunhofer-MEVIS,
[6]MD Anderson Cancer Center, [7]University of Southern California, [8]Duke University, [9]University of Pittsburgh, [10]Massachussetts General Hospital, [11]Mayo Clinic, [12]Oregon Health & Science University, [13]University of Wisconsin

Quantitative Imaging Biomarkers Alliance — RSNA

SUMMARY AND GOALS OF THE PDF-MRI BIOMARKER COMMITTEE

The RSNA QIBA Perfusion, Diffusion, and Flow MRI Biomarker Committee (PDF-MRI BC) is composed of scientists representing imaging device manufacturers, image analysis laboratories, biopharmaceutical industry, academia, government research organizations, imaging core labs, and professional societies. The goal of the PDF-MRI BC is to define technical performance standards (QIBA Profiles) for data acquisition, data processing, and quality control procedures that enable consistent and reliable quantitative imaging biomarkers for assessment of physiologic measures related to perfusion, diffusion, and/or blood flow in normal and abnormal tissues.

The efforts of the PDF-MRI BC are motivated by the emergence of perfusion/diffusion/flow quantitative imaging biomarkers as a means of diagnosing pathologies, staging disease, and evaluating responsiveness to therapy. Despite variance in imaging techniques, parameter choices, vendor specifications, and analytic methods, the application of these physiologic measures in clinical medicine, translational research, and pharmaceutical studies continues to grow. Thus, there appears to be a promising future of these techniques for both clinical research and in routine clinical practice, particularly in the era of precision medicine. However, in order to fulfill this promise, it is essential that common quantitative endpoints are used and that results are reproducible and unbiased across imaging platforms, clinical sites, and time.

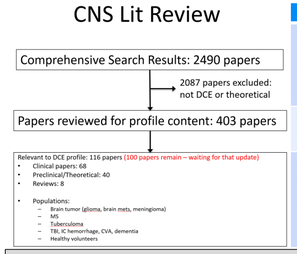
In the early development of the QIBA groups, the PDF-MRI BC (initially the DCE-MRI Technical Committee) began with a single focus on the use of Dynamic Contrast Enhanced (DCE) MRI for evaluating tumor response to certain vascular targeted therapies. However, in recent years, the PDF-MRI BC has expanded its scope to include other methods for tissue vascular assessment (*i.e.*, dynamic susceptibility contrast, or DSC), as well as diffusion methods including isotropic diffusion-weighted imaging (DWI, for apparent diffusion coefficient [ADC] measurement) and anisotropic diffusion tensor imaging (DTI) to determine the status of white matter tracts in the central nervous system.

Summary of PDF-MRI Biomarker Committee Goals

To develop consensus technical performance standards (QIBA Profiles), based on existing literature and and groundwork projects, regarding the appropriate data acquisition, data processing, and quality control procedures necessary to provide reproducible quantitative MR imaging biomarker measures of normal and diseased tissues.

TASK FORCES: DCE, DWI, DSC AND DTI

DCE Task Force, co-chairs Hendrik Laue and Caroline Chung: The DCE TF is preparing the DCE profile v2.0, covering 3 T and adding organ-specific information to the profile. 3 T requires B_1 correction: detailed information on sequences and requirements was provided by the QIBA vendor sub-committee (see Table at right). A Round 6 project for B_1 quantification began in 2016. An extensive literature search on DCE identifies organ-specific requirements and evaluates parameters and technologies used by researchers.



Fields	Results
Outcome measures reported	Ktrans Ve, Vp > Vb Kep, Ki AUGC, AUC rCBV, CBV, CBF MTT, Max SI, max SI rate/slope
Field strength	0.5T: 2 papers on multiple sclerosis 1.5T: 29 3T: 21
Acquisition parameters for brain tumors	TR: 3.8-11.9ms (majority between 3.8-6ms) TE: 1-4.2 ms FA: 6-30 deg Temporal resolution: 1-60s (majority 1.25-6.5s) Slice thickness: 2.5-6 mm Overall scan time: 1.5 – 12 min (majority 2.8-6.5min) Coil: 'head coil' (not usually specified)

Vendor Name	GE	Philips	Siemens	Toshiba
Usable Models	MR750, MR750w	Achieva, Ingenia	Skyra, Prisma	Vantage Titan
Required Software	DV23.0 or newer	DREAM: R5.2, DAM: RS 3.2; AFI: 2.5	VD13, VE11	MPower 2.5 and above
Sequence Name	FastB1Map	DREAM, Dual TR, Dual FA	tfl_B1Map	RSDE FASE2D (enable Pulse->Mapping)
Sequence type	Bloch-Siegert shift; 2D	DAM, AFI, DREAM, 2D + 3D	Pre-SAT-TFL, 2D	K-space spatial domain filtering, 2D
Reference/Patent	MRM 63:1315, (2010)	MRM 57:192 (2007); 55:1326 (2006); 68,1517 (2012)	MRM 64:439.(2010)	US Patent: US 8,077,955 B2

Left: Flow chart for literature review of the CNS.
Middlet: Summary of CNS literature review
Right: Important information from different vendors on required soft- and hardware, sequence names, B_1 mapping method used and related publications, coming out of DCE TF and vendor sub-committee collaboration.

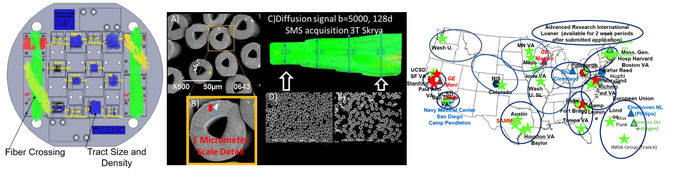
DWI Task Force, co-chairs Thomas Chenevert and Michael Boss: The DWI Profile v1.0 is being drafted to address technical performance standards for the acquisition of apparent diffusion coefficient (ADC) measurements in brain and liver (claims at right). ADC phantom scanning and analysis has occurred at multiple sites, informing the Profile, slated for release for public comment in coming months. A Round 5 project to develop a DWI DRO was completed.

Claim 1a: A measured change in the ADC of a brain lesion of 11 % or larger indicates that a true change has occurred with 95 % confidence.

Claim 2a: A measured change in the ADC of a liver lesion of 26 % or larger indicates that a true change has occurred with 95 % confidence.

DSC Task Force, co-chairs Ona Wu and Brad Erickson: The DSC TF generated a working draft of its Profile v1.0, including claim language, while simultaneously performing a literature search and conducting a Round 5 phantom project to inform profile claims. The profile address the technical performance standards for tissue-normalized first-pass area-under-the gadolinium concentration curve (AUC-TN) and the transfer constant (K2), which is often used as a biomarker of disease progression or response to treatment. A Round 6 project to develop a web-accessible DSC-DRO is underway.

DTI Task Force, co-chairs James Provenzale and Walter Schneider: The DTI TF has developed a working draft of their Profile v1.0. Regularly scheduled task force meetings are being held, while an existing effort to generate a ground-truth DTI phantom is leveraged to inform the Profile claims. Initial results of the DTI phantom using research scanners has been promising, and plans are being developed for a larger scale distribution of phantom copies. A Round 6 project to examine the phantom using in-product pulse sequences will also inform the Profile.



Left: Layout of DTI phantom neuronal mimics. **Middle**: Illustration of (A and B) taxon size, (C) various arrays of taxons to simulate white matter fibers of known differing thickness as imaged using 128 directions and a b value of 5,000, and (D and E) differing densities and distances of taxons, simulating varying degrees of vasogenic edema. **Right**: Proposed distribution network of phantom

OTHER ACCOMPLISHMENTS

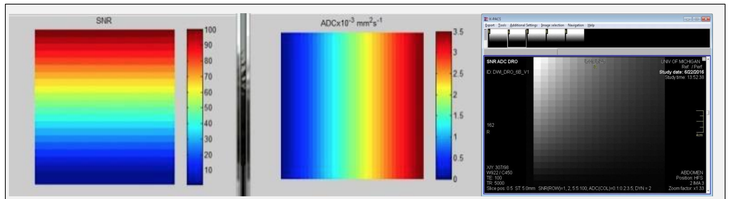
To date, the PDF-MRI BC has achieved a number of accomplishments in the course of both Profile development and technical groundwork projects. These include:

- Completion of the v1.0 DCE-MRI Profile, including incorporation of public comments
- Successful completion of all Round 1-4 groundwork projects with deliverables including:
  - Completion of the RSNA QIBA DCE-MRI phantoms and testing in a multi-site, multi-vendor environment.
  - Completion of the DCE-MRI digital reference object (DRO), with testing of more than 15 distinct software platforms, and reporting metrics of software performance.
  - Initiation of the ACRIN 6701 clinical trial, which incorporated key aspects of the v1.0 DCE-MRI Profile.
  - Completion of groundwork projects needed to generalize the v1.0 DCE-MRI Profile to include 3.0 T field strengths and parallel imaging.
  - Development and distribution of software for analysis of DCE-MRI DRO data.
  - Development and distribution of a DWI ADC Phantom and associated data analysis software (QIBAPhan). Results provided reproducibility metrics for ADC as a function of *b*-value.
  - Development and distribution of an automated software analysis package for use with the RSNA QIBA DCE-MRI phantom.
  - Development and distribution of an extended DCE-MRI DRO addressing additional variables, including 3.0 T, variable cardiac output, *etc*.

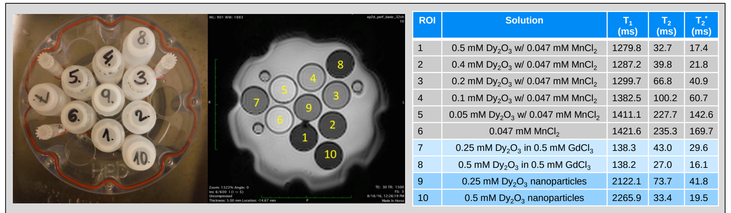
GROUNDWORK PROJECTS

Groundwork projects are specific investigational activities, funded by the National Institute of Biomedical Imaging and Bioengineering (NIBIB), to aid in the implementation of PDF-MRI BC areas of investigation. Groundwork projects seek to provide material resources (*e.g.*, phantoms, digital reference objects, software) to aid investigators seeking to obtain reproducible quantitative imaging biomarkers, or to provide data from field testing of the robustness of quantitative imaging biomarkers when applied to data acquisition (phantom or human data) in a multi-institutional framework. Groundwork projects are not themselves designed to test specific aspects of biological or pharmaceutical phenomena reflected by the quantitative imaging biomarkers. Rather, they enable development of tangible products to aid in Profile development or revision, to allow demonstration of conformance with such Profiles, and to demonstrate robustness of the quantitative imaging biomarkers(s) in practice. Recently completed and upcoming groundwork projects in PDF include:

Round 5 Projects



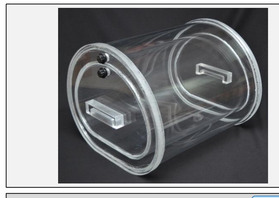
DWI-DRO development for ADC analysis, PI Dariya Malyarenko
The final DWI DRO DICOM was validated against DWI DICOM standard, tested with select commercial and public SW, and uploaded to QIDW (under "DWI phantom community"). The delivered DRO consists of five single-frame DWI DICOM series (with six images for six *b*-values) that differ by generated random noise samples and number of pseudo-averages per *b*-value. Each DRO image in a series contains 16x20 pixel blocks of magnitude DWI intensities for input SNR (22-horizontal) and ADC (18-vertical) parameter pairs simulated using mono-exponential decay model with a specific *b*-value. For each DWI image, Rician noise is modeled by (pseudo) quadrature acquisition with independent random noise samples using geometric mean of three-direction magnitude DWI images. In addition to providing means to evaluate performance of quantitative DWI analysis SW against ground truth (input SNR and ADC), the adopted multi-pass DRO format, similar to QIBA DWI phantom protocol, allows optional testing the SW capabilities to estimate true (input) random noise and quantify Rician noise bias.



ROI	Solution	T_2 (ms)	T_2 (ms)	T_2^* (ms)
1	0.5 mM Dy_2O_3 w/ 0.047 mM $MnCl_2$	1279.8	32.7	17.4
2	0.4 mM Dy_2O_3 w/ 0.047 mM $MnCl_2$	1287.2	39.8	21.8
3	0.2 mM Dy_2O_3 w/ 0.047 mM $MnCl_2$	1299.7	66.8	40.9
4	0.1 mM Dy_2O_3 w/ 0.047 mM $MnCl_2$	1382.5	100.2	60.7
5	0.05 mM Dy_2O_3 w/ 0.047 mM $MnCl_2$	1411.1	227.7	142.6
6	0.047 mM $MnCl_2$	1421.6	235.3	169.7
7	0.25 mM Dy_2O_3 in 0.5 mM $GdCl_3$	138.3	43.0	29.6
8	0.5 mM Dy_2O_3 in 0.5 mM $GdCl_3$	138.2	27.0	16.1
9	0.25 mM Dy_2O_3 nanoparticles	2122.1	73.7	41.8
10	0.5 mM Dy_2O_3 nanoparticles	2265.9	33.4	19.5

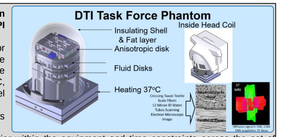
Dynamic susceptibility contrast MRI phantom, PI Ona Wu
The DSC phantom effort coordinates resources and personnel from MGH, NIST, Leiden University, and the Mayo Clinic. The goal of the project is to generate a test object that can be easily shipped between sites, allowing for evaluation of the measurement of T_2*, while maintaining physiologically-relevant ratios of T_2* to T_1. Novel nanoparticles systems have been evaluated, with current efforts focused on relaxation time ratios, stability, and analysis routines. The prototype phantom repurposes the NIST-QIBA diffusion phantom shell for multi-vendor compatibility (left); images acquired using standardized acquisitions (middle) have generated promising results (right).

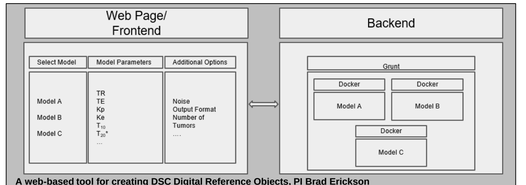
Round 6 Projects



RF Transmit Calibration for DCE-MRI, PI Krishna Nayak:
This project will create two phantoms and will (1) measure and compare the spatial RF transmit inhomogeneity across different scanners, vendors, and sites, and will (2) compare methods for RF transmit measurement that can be used to correct data prior to quantitative DCE-MRI analysis. This will inform the claims and protocol guidance in the next DCE-MRI profile. The phantom at left will hold a T_1-tuned fluid in the center chamber, which will be surrounded by a fat mimic.

Measurements of Reproducibility of DTI Metrics on Clinical MR scanners using a DTI Phantom, PI James Provenzale:
1. Determine precision, variability, cross device/vendor match, and longitudinal stability of measurements. The measurements will include at least three measurements to assess the variability of FA, ADC, RD, AD and NODDI-based compartment model metrics.
2. Determine sensitivity and contrast-to-noise ratios (CNR) for key tissues, including grey/white CNR.
3. Determine the optimal imaging performance frontier within the equipment and time constraints across the set of measurement options (e.g. how should voxel size and directions change with magnet strength and what is the detection sensitivity of the resulting protocol).
4. Monitor within Duke and Durham VA scanner metrics across time with covariates of scanner strength, scanner vendor and scanner model.
5. Take into account differences in head coils (if any) as well as the effects of software and hardware upgrades (if any) during the course of the study.





A web-based tool for creating DSC Digital Reference Objects, PI Brad Erickson
The figure above depicts a schematic diagram of the proposed web-based system. The user selects one of the available models for simulating DSC signal. Once the selection is made, a second tab will enable selection of the available model parameters. A third tab will then enable selection of additional parameters like the addition of noise, format output, and number of simulated tumors.
The User Interface will issue calls to modules implementing the various DSC models via REST. We use Grunt to map the REST parameters to those required by a particular model and to hand back to DRO that is created. Grunt is an open source tool (https://github.com/Mayo-QIN/grunt) that enables deployment of code developed as a RESTful API service. Each model is implemented as a Docker module.

PUBLICATIONS AND PRESENTATIONS

1. Newitt D, Fedorov A and Malyarenko D. "MRI subgroup: ADC mapping and ADC DICOM challenges". NCI QIN-2016 annual Face-to-Face Meeting, Rockville, MD, April 2016.
2. Boss M, Keenan K, Stupic K, Russek S. "*In Vivo* Map Making with Magnetic Resonance: Standards for Quantitative Imaging". NCSL International Annual Conference, St. Paul, MN, July 2016.

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