Quantitative Imaging Specialty Track
Quantitative Imaging: CT and MRI Session

Sources and Mitigation of MR Quantitative Imaging Measurement Errors

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Declaration of Financial Interests or Relationships

Speaker Name: Edward F. Jackson, PhD

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

Learning Objectives

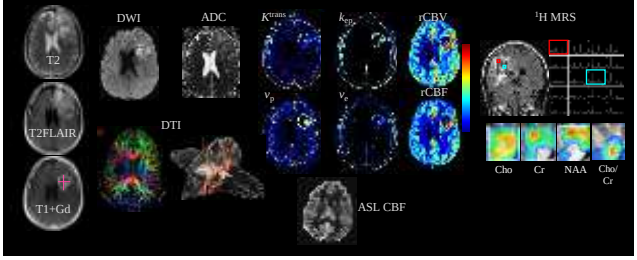
1. Understand the common sources of bias and variance in CT quantitative imaging applications and the options for mitigating such sources.
2. Understand the common sources of bias and variance in MR quantitative imaging applications and the options for mitigating such sources.
3. Appreciate some of the current applications of CT- and MR-based quantitative imaging biomarkers.

MR Quantitative Imaging Biomarkers

Opportunities

Current MR QIB Applications

Existing MR QIBs in Glioma: Morphological to Functional



MR QIBs in Glioma

Biological Process	MR Technique	MR QIB
Tumor Cellularity / Proliferation	^{1}H MRS, DTI/DWI	↑Cho, ↑Cho/NAA, ↓ADC
Necrosis	^{1}H MRS, Gd-enhanced, T2W	↑lipids, No Gd uptake, ↑T2W signal
Edema	T2FLAIR, DTI/DWI	↑FLAIR signal, ↑ADC, ↓FA
Gliosis	^{1}H MRS (short TE)	↑myo-inositol
Hypoxia	^{1}H MRS, BOLD	↑lactate, ↓ΔR2*
Angiogenesis / Permeability	DCE-MRI, DSC-MRI	↑K^{trans} & v_p, ↑rCBV & rCBF
Invasion	DTI, ^{1}H MRS	↓FA, ↑ADC, ↓NAA
Radiation Effects	SWI, DTI	Micro-hemorrhages (late), ↓FA

Modified version of Table 1 of Nelson, *NMR Biomed* 24:734-739, 2011

Current MR QIB Applications

Currently available MR QIBs:

- Cardiac Cine MR
  - Ejection fraction, wall thickness, *etc*.
  - Tagging – myocardial stress/strain
  - Delayed enhancement – myocardial perfusion
  - 4D flow

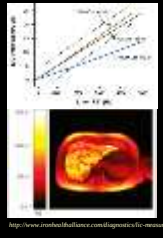
http://www.medandlife.ro/medandlife637.html

Markl *et al*., *JMRI* 36:1015, 2012

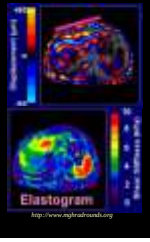
Current MR QIB Applications

Currently available MR QIBs:

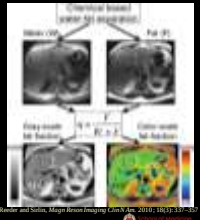
- Liver



http://www.ironhealthalliance.com/diagnostics/fic-measurement.jsp

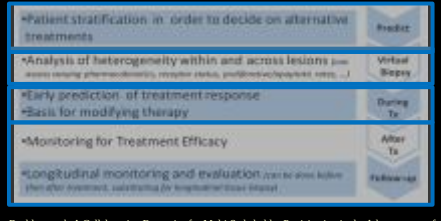


http://www.mphradrounds.org



Ruehm and Stolin, Magn Reson Imaging Clin N Am. 2010; 18(1):137–157

MR QIBs in Precision Medicine



Buckler, *et al*., A Collaborative Enterprise for Multi-Stakeholder Participation in the Advancement of Quantitative Imaging, *Radiology* 258:906-914, 2011

MR Quantitative Imaging Biomarkers

Challenges

MR QIB Challenges

MR Imaging System ≠ Measurement Device

- Measurement Device:
  - Specific measurand(s) with known bias and variance (confidence intervals)
  - Specific requirements for reproducible quantitative results
  - Example: a pulse oximeter
- MR Imaging Equipment:
  - Historically: best image quality in shortest time (*qualitative*)
  - No specific requirements for reproducible *quantitative* results (with few exceptions)

MR QIB Challenges

MR QIB challenges:

- Lack of detailed assessment of sources of bias and variance
- Lack of standards (acquisition and analysis)
- Highly variable quality control procedures
  - QC programs / phantoms, if any, typically not specific for *quantitative* imaging
- Little support (historically) from imaging equipment vendors
  - No documented competitive advantage of QIB (regulatory or payer)

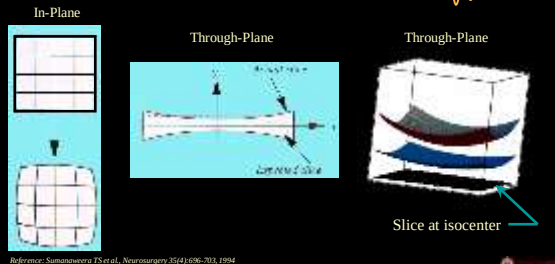
All lead to varying measurement results across vendors, centers, and/or time

General Challenges in MR Quantification

Arbitrary (and spatially- / temporally-dependent) signal intensity units

- Magnitude and homogeneity of B_o
- Magnetic field gradient nonlinearities, eddy currents, concomitant fields, *etc*.
- RF coil dependency: RF coil type, B_1 sensitivity profiles, subject positioning within the coil
- Slice profile variations (with RF pulse shape, flip angle, *etc*.)
- Off resonance effects
- Parallel imaging, compressed sensing, and other acceleration techniques
- System stability issues (B_0, RF & gradient subsystems, RF coils, *etc*.)

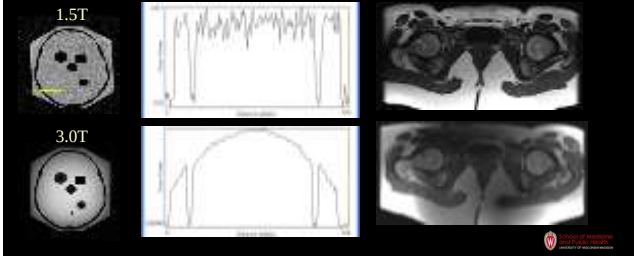
Gradient Field Nonlinearities



Reference: Sumanaweera TS et al., Neurosurgery 35(4):696–703, 1994

B_1 Non-Uniformity

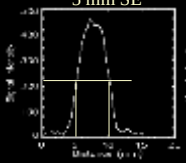
B_1 response non-uniformity & dielectric resonance effects



General Challenges in MR Quantification

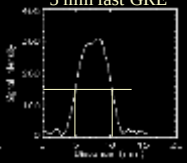
Slice profile variations (with RF pulse shape, flip angle, *etc*.)

5 mm SE



5.07 mm

5 mm fast GRE



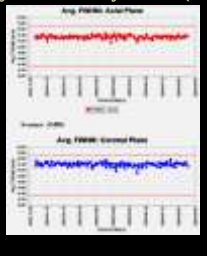
5.78 mm

Typically, faster imaging sequences use increasingly truncated RF pulses resulting in thicker slice profiles for a given prescribed slice thickness. This gives rise to increased partial volume effects.

Flip angle calibrations can also be negatively affected.

General Challenges in MR Quantification

System stability issues (RF & gradient subsystems, B_o, RF



For quantitative imaging, particularly in longitudinal studies, a rigorous quality control program is critical.

Components of frequent QC tests:

- Geometric accuracy
- Slice thickness
- Signal-to-noise ratio
- Uniformity
- High contrast spatial resolution
- Center frequency
- Transmit gain
- Contrast response

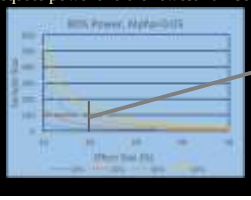
Adopting Metrology Principles in Imaging

- Sources of bias and variance in QIB measurands are identified and mitigated to the degree possible.
  - Bias* (accuracy):
    - Often difficult to assess due to absence of reference standard ("ground truth") measures
    - Potential role for application-specific phantoms
  - Precision* (variance):
    - Repeatability* – All conditions the same except short time separation ("test/retest")
      – Repeatability coefficient
    - Reproducibility* – Different operators, different days
      – Reproducibility coefficient

*Kessler, Barnhart, *et al*., *Stat Meth Med Res* 24:9-26, 2015; Sullivan, Obuchowski, *et al. Radiology* 277:813-825, 2016
available at www.rsna.org/qiba

Adopting Metrology Principles in Imaging

- Levels of bias and variance remaining after mitigation are characterized => confidence intervals.
- Knowing these levels translates to statistically valid study designs with adequate power and the fewest number of patients.



Number of patients:	
10%	12
20%	35
30%	78
40%	133

Bias / Variance Along the Imaging Chain

Boellaard, *J Nucl Med* 50(Suppl 1):11S-20S, 2009

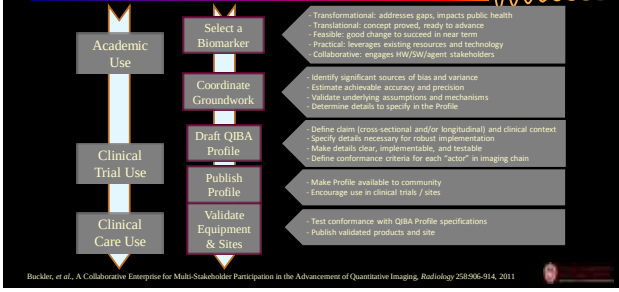
MR Quantitative Imaging Biomarkers

Initiatives

Selected MR QIB Initiatives

- RSNA: Quantitative Imaging Biomarkers Alliance (QIBA)
- ISMRM: *Ad Hoc* Committee on Standards for Quantitative MR
- NCI: Quantitative Imaging Network (QIN)
- NIST: Collaborations with all the above

RSNA QIBA Approach



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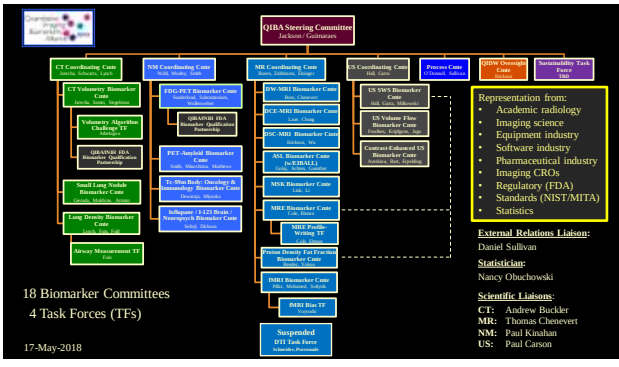


Current Profile Status *(As of 3/17/2018)*

- 20 Profiles (4 CT, 3 NM, 10 MR, 3 US)
- Technically Confirmed Stage*:
  - NM: *FDG-PET/CT SUV as an Imaging Biomarker for Measuring Response to Cancer Therapy**
- Consensus Stage*:
  - CT: *Tumor Volume Change* (v2.2) for tumor response (expected to be Technically Confirmed June 2018)*
  - CT: *Lung Nodule Volume Assessment & Monitoring in Low Dose CT Screening Quantification*
  - NM: *Quantifying Dopamine Transporters with ^{123}Iodine-labeled Ioflupane in Neurodegenerative Disease* (SPECT)
  - MR: *DCE-MRI Quantification* (v1.0) for tumor response
- In Public Comment Stage:
  - MR: DW-MRI for tumor response
  - MR: Elastography for liver fibrosis
  - MR: fMRI for pre-surgical planning
  - NM: F-18 PET amyloid for Alzheimer's Disease

*rsna.org/qiba

For details: qibawiki.rsna.org

Current Profile Status *(As of 3/17/2018)*

- In Final Stage of Development for Public Comment Release:
  - CT: Lung densitometry for COPD
  - US: Ultrasound shear wave speed for liver fibrosis
  - MR: Proton density fat fraction (PDFF) for liver disease
- In Earlier Stages of Development:
  - CT: Tumor volume change for liver lesions
  - MR: Dynamic susceptibility contrast (DSC)-MRI for perfusion assessment in brain
  - MR: Diffusion tensor imaging (DTI) for traumatic brain injury – on hold
  - MR: Revised DCE-MRI to address 3T and parallel imaging
  - MR: T_2 and $T_{1\rho}$ MSK MR for degenerative joint disease
  - US: Contrast-enhanced ultrasound (CEUS) for perfusion studies
  - US: Ultrasound volume flow for perfusion studies – *collaboration with AIUM*
  - MR: Arterial spin labeling (ASL) MR – *collaboration with ESR EIBALL*

For details: qibawiki.rsna.org

QIBA Groundwork Projects

QIB Implementation and Qualification

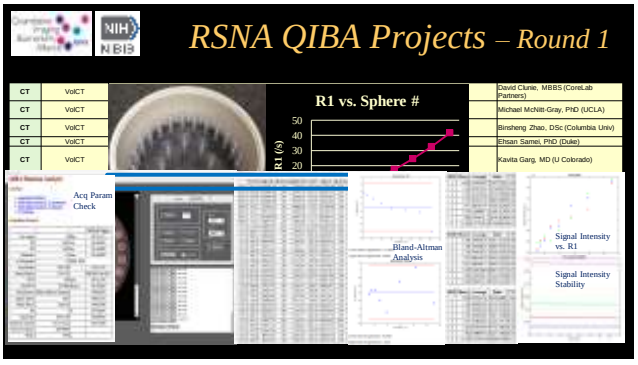
- Data acquisition => Physical phantoms & datasets
  - Application specific phantoms

- Data analysis => Synthetic phantoms & datasets
  - Application specific "digital reference objects" or DROs
  - Clinical trial datasets

- Qualification=> "Fit for purpose" <= clinical trials

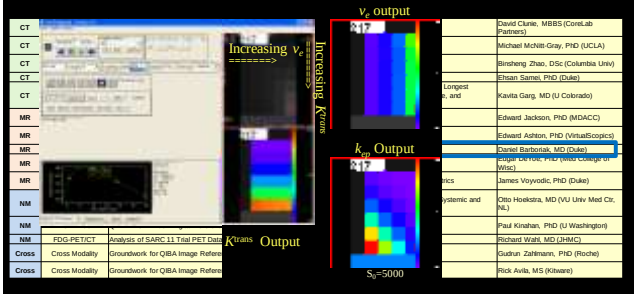
QIBA groundwork projects funded by 3 contracts from NIH National Institute of Biomedical Imaging and Bioengineering

RSNA QIBA Projects – Round 1



CT	VolCT		David Clunie, MBBS (CoreLab Partners)
CT	VolCT		Michael McNitt-Gray, PhD (UCLA)
CT	VolCT		Binsheng Zhao, DSc (Columbia Univ)
CT	VolCT		Ehsan Samei, PhD (Duke)
CT	VolCT		Kavita Garg, MD (U Colorado)

RSNA QIBA Projects – Round 1



CT			David Clunie, MBBS (CoreLab Partners)
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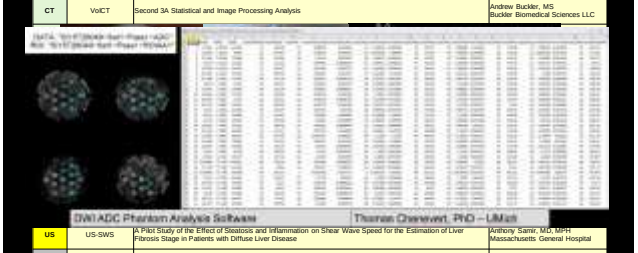
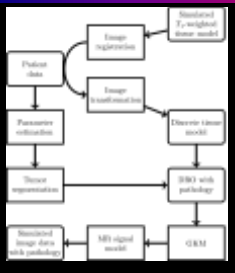
CT			Binsheng Zhao, DSc (Columbia Univ)
CT			Ehsan Samei, PhD (Duke)
CT		Longest	Kavita Garg, MD (U Colorado)
MR			Edward Jackson, PhD (MDACC)
MR			Edward Ashton, PhD (VirtualScopics)
MR			Daniel Barboriak, MD (Duke)
MR			Jaygar DeYoe, PhD (Med College of Wisc)
MR		rics	James Voyvodic, PhD (Duke)
NM		ystemic and	Otto Hoekstra, MD (VU Univ Med Ctr, NL)
NM			Paul Kinahan, PhD (U Washington)
NM	FDG-PET/CT	Analysis of SARC 11 Trial PET Data	Richard Wahl, MD (JHMC)
Cross	Cross Modality	Groundwork for QIBA Image Refere	Gudrun Zahlmann, PhD (Roche)
Cross	Cross Modality	Groundwork for QIBA Image Refere	Rick Avila, MS (Kitware)

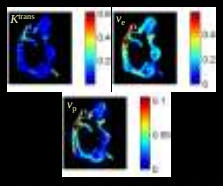
RSNA QIBA Projects – Round 3



CT	VolCT	Second 3A Statistical and Image Processing Analysis	Andrew Buckler, MS Buckler Biomedical Sciences LLC
US	US-SWS	A Pilot Study of the Effect of Steatosis and Inflammation on Shear Wave Speed for the Estimation of Liver Fibrosis Stage in Patients with Diffuse Liver Disease	Anthony Samir, MD, MPH Massachusetts General Hospital
Cross	Cross	Design and Statistical Analysis of Studies of Compliancy with QIBA Claims	Nancy Obuchowski, PhD Cleveland Clinic Foundation

Anthropomorphic DCE-MRI DRO





R Bosca, E Jackson. *Phys Med Biol* 61(2):974-982, 2016

QIBA Phantoms & Datasets

- Physical Phantoms
  - Volumetric CT Liver Phantom (arterial/portal venous phase)
  - DCE-MRI Phantom and analysis software
  - DWI ADC Phantom and analysis software
  - DSC-MRI Phantom
  - Shear Wave Speed Phantoms (varying viscoelastic properties) – for both US SWS and MRE
- Digital Reference Objects (Synthetic Phantoms)
  - Volumetric CT DRO (Liver, Lung, Kidney)
  - DCE-MRI DRO (T_1 mapping and K^{trans}, v_e) and analysis software
  - DWI ADC DRO
  - DSC-MRI DRO
  - fMRI DROs (motor and language mapping)
  - PET SUV DRO
  - SPECT DRO (^{123}I dopamine transporter, DaTscan/Ioflupane; in development)
- Datasets & Data Analysis Applications on QIDW

Quantitative Imaging Network (QIN)

- NCI-funded (CIP)
  - PAR-18-248 (UG3/UH3) and PAR-18-249 (U01)
- 34 technical teams since 2008
- Three working groups:
  - Clinical Trial Design and Development
  - Bioinformatics/IT and Data Sharing
  - Image Analysis and Performance Metrics

- Involved in a variety of algorithm comparison "challenges" in addition to individual investigator research projects. Translation of QI tools to clinical research and, ultimately, to patient care.

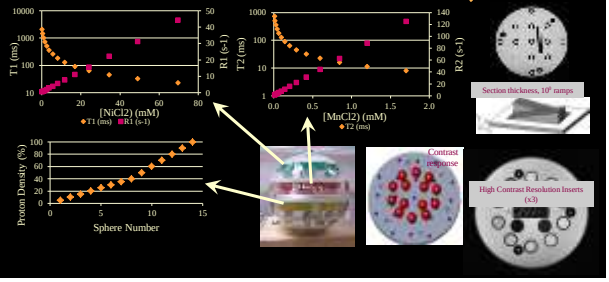
https://imaging.cancer.gov/programs_resources/specialized_initiatives/qin Accessed 7/29/2018

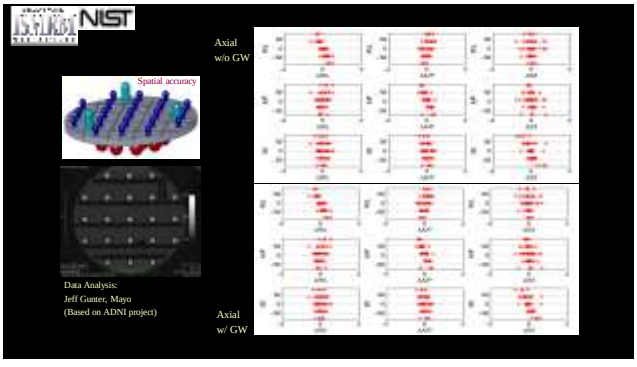
ISMRM MR QIB Efforts

Ad Hoc Committee on Standards for Quantitative MR

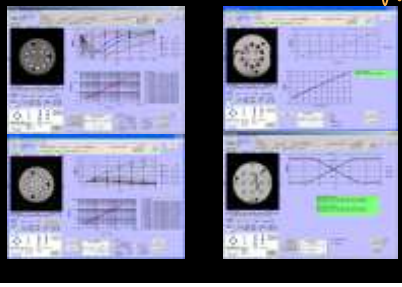
- Membership has included MR physicists, technologists, radiologists, NIST representatives, NIH representatives, vendors, pharma. Expertise in research trials using quantitative MR.
- Current status:
  - White paper on quantitative MR
  - Defined the specifications for and development of a MR System Phantom (collaboration with and funding by NIST)
  - Multicenter/multivendor phantom pilot studies

NIST/ISMRM MR System Phantom

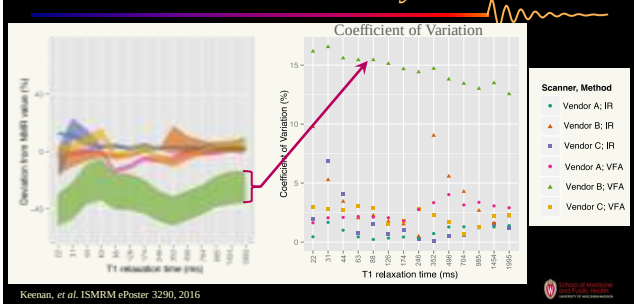




NIST/ISMRM MR System Phantom



NIST/ISMRM MR System Phantom



Keenan, *et al.* ISMRM ePoster 3290, 2016

Acknowledgments

- RSNA and QIBA Biomarker Committee & Task Force Co-Chairs & Members
- Daniel Barboriak, MD & Ryan Bosca, PhD - DCE Digital Reference Objects
- Stephen Russek, PhD, Kathryn Keenan, PhD, Michael Boss, PhD, Karl Stupic, PhD - NIST: MR System Phantom & ADC Phantom
- Thomas Chenevert, PhD - DWI Phantom Analysis Software
- Robert Nordstrom, PhD - NCI Cancer Imaging Program
- NIBIB Contracts HHSN268201000050C, HHSN268201300071C, HHSN268201500021C