Declaration of Financial Interests or Relationships

Speaker Name: Peder Larson

I have the following financial interest or relationship(s) to disclose with regard to the subject matter of this presentation:

- Consultant: Human Longevity Inc
Outline

- Why Lung MRI?
- Challenges in Lung MRI
- Imaging Methods
  - $^1$H MRI
  - Inhaled Gasses ($O_2$, Hyperpolarized $^3$He, Hyperpolarized $^{129}$Xe, $^{19}$F)

Slides: [https://radiology.ucsf.edu/research/labs/larson/educational-materials](https://radiology.ucsf.edu/research/labs/larson/educational-materials)

*(Google: Peder Larson Group, Educational Materials link on sidebar)*
Pulmonary Imaging – X-ray

- Radiography (Xray)
  - Fast (~1 s)
  - Widespread
  - 2D projection (no volumetric information)
  - Ionizing radiation
Pulmonary Imaging – Computed Tomography (CT)

- High resolution CT is the gold standard for structural lung imaging
  - Exquisite structural information
  - High resolution (≤ 1 mm)
  - Fast (~1-10 s)
- “Indispensable in the monitoring of CF patients” (Radiopaedia.org)
  - Guide therapy and assess response
  - Evaluate a range of features, including tissue thickening, bronchiolitis, bronchiectasis, air trapping, mucus plugging
- Major drawback: Substantial Ionizing Radiation
  - Repeated examinations (often every 6-18 months)
  - Substantial exposure in childhood when sensitivity to radiation is much higher
  - Higher rate of radiation-induced malignancies with increases in life span
Pulmonary Imaging - MRI

- Magnetic Resonance Imaging (MRI): Currently not a major pulmonary imaging modality because
  - Slow (10s to minutes)
  - Spatial resolution not as good at CT
  - Prone to motion artifacts (respiration and cardiac)
  - Often use Breath-hold scanning, challenging for patients with compromised function and in pediatrics
  - Low proton density in lung tissue
  - Large susceptibility differences due to air in lungs leads to short T2*

Wielpütz et al; Am J Respir Crit Care Med 189, 956-965; 2014.

Why is Lung MRI so Challenging?

MR imaging of the lungs is difficult due to:

1) Cardiac and Respiratory Motion

2) Low Proton Density (0.15 g/ml)

3) Lung alveoli create local field inhomogeneities and susceptibility gradients \(\rightarrow\) very short T2* (~1ms)

†Fawcett/Gehr/Science Photo Library
If Pulmonary MRI is so hard, why should we do it?

- **MRI Advantages**
  - No ionizing radiation
  - Multiple image contrasts available reflecting ventilation, perfusion, cellularity, macromolecular content
  - Resolve lung motion to assess air trapping, motion defects, and tissue stiffness

- **Clinical Care**
  - Eliminate radiation exposure in routine imaging studies (especially important in pediatrics)
  - Allows more frequent imaging studies to monitor pulmonary structure & function

- **Understanding of disease and Development of therapeutics**
  - Perform research and longitudinal studies without limitations due to ionizing radiation exposure
  - Particularly valuable for pediatrics and for low acuity diseases such as asthma

- Many possible applications: bronchopulmonary dysplasia, asthma, pulmonary nodules, pulmonary embolism, Interstitial lung diseases, cystic fibrosis, obstructive airway disease, pulmonary infections
MR Imaging Methods

Generally, these fall into two classes

1. $^1$H MRI methods
   - Using endogenous water signal
   - Address key challenges of motion and short T2*

2. Inhaled gasses
   - Oxygen-enhanced MRI – $^1$H imaging when breathing 100% O$_2$
   - Hyperpolarized $^3$He (now uncommon due to $^3$He shortage)
   - Hyperpolarized $^{129}$Xe
   - $^{19}$F labeled gasses (non-hyperpolarized)
UTE and ZTE Lung Methods

- Ultrashort echo time (UTE) MRI
  - Specialized RF excitation, readout gradients, and image reconstruction
  - Capture rapid signal decay
  - Relatively robust to motion during scan
  - *Inherent information for motion estimation*

![Diagram showing RF, GZ, GX, GY, and DAQ signals with TE highlighted.]
Kevin Johnson’s “UWUTE”

- 3D radial UTE optimized for pulmonary imaging
- Variable density readout (improves SNR)
- Slab excitation (limits FOV to reduce aliasing and motion artifacts)

Motion correction

- Adaptive gating (e.g. bellows)
- Pseudo-random projection ordering (bit-reversed or golden-angle for retrospective data sorting)
- Center of k-space for data-driven motion estimation

UWUTE: Pulmonary Nodule Detection

- **Goal**: Detect clinically-relevant pulmonary nodules to enable metastatic disease screening in the lung
  - Routine detection with CT
  - Conventional MR sequences fail
- 5-minute Free breathing
- Adaptive bellows-based gating

Burris, Larson, Johnson, Hope et al; *Radiology* 2015.
Neonatal Pulmonary MRI

- Cincinnati Children’s Hospital
- Dedicated Neonatal 1.5 T MRI
- 3D UTE (UWUTE)
- Self navigation

May 16, 2019

UTE Cones: Pulmonary Nodules in Pediatrics

(a) 12 year-old with Bilateral nodules

(b) 6 year-old with partially calcified nodule

(c) 11 year-old with lung base nodule

(d) 3 year-old with lung base nodule

Acquired with UTE Cones sequence, fat suppression, no motion correction, in sedated subjects
MRI Sequence comparison

- Sedated 5 year-old
- Only UTE shows signal from the lung parenchyma, and has the most clear visualization of the pulmonary vasculature without motion artifacts.

Other UTE Trajectories

- Twisted Projection Imaging (Boada MRM 1997 doi:10.1002/mrm.1910380624)
- Cones (Gurney et al. MRM 2006 doi: 10.1002/mrm.20796)
- FLORET (Robison et al MRM 2018 doi: 10.1002/mrm.26500)
- Stack of Spirals
- Stack of Stars

Madelin JMRI 2013 doi: 10.1002/jmri.24168

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Major Challenge: Motion

Image quality substantially compromised in up to 30% of patients due to uncorrected motion (Irregular breathing, Coughing, Bulk motion)

Particularly problematic for children and patients with compromised pulmonary function
Motion Compensation and Reconstruction

- With UTE and ZTE, center of k-space or low-resolution images for motion estimation
- Motion Estimation can be used for hard-gating (binning), soft-gating or XD motion-resolved reconstructions


Motion Estimation: Dynamic 3D Navigator with Local Low-Rank


- Create Image-based navigator \([1]\) from low-frequency portion of k-space data
- Challenge: high-frame rate (>2Hz) and spatial resolution (<1cm) -> ~200-fold undersampling!
- Solution: Enforce a local low-rank constraint across time

\[
\text{argmin}_{M_k} \frac{1}{2} \|DSM_k - y_k\|^2 + \lambda \sum_{i \in \Omega} \|L_i M_k\|_*,
\]

Dynamic 3D Navigator with Local Low-Rank Recon

Motion Estimation: Dynamic 3D Self-navigator

Use only center of space for dynamic reconstruction with local low-rank constraint and parallel imaging (>200-fold undersampled)

6mm isotropic resolution

300ms temporal resolution

Cystic Fibrosis (CF) patients
“Extreme MRI”

- Super-high-resolution dynamic reconstruction
  - 1.25mm isotropic
  - 515 ms temporal resolution across 4 minute scan

- Extreme undersampling, extreme computational and memory cost
  - Use multi-scale low-rank factorization
  - Stochastic optimization

Ong, Zhu, Larson, Lustig, et al. ISMRM 2019 #1176 (Thursday 1:57pm 710B)
“Extreme MRI”

- 1.6mm isotropic
- 560 ms temporal resolution across 5 minute scan

Scan time: 4 m 40 s
TR: 2.8 ms
TE: 80 μs
Temporal Res: 560 ms
Matrix Size: 320 x 185 x 189
Spatial Res: 1.6 x 1.6 x 1.6 mm³

Ong, Zhu, Larson, Lustig, et al. ISMRM 2019 #1176 (Thursday 1:57pm 710B)
Motion Compensation Strategies

1. Data organization
   • Bin data
   • Reject bulk motion periods

2. Image Reconstruction
   • Single phase with hard or soft-gating (SG)
   • Motion-resolved reconstruction with EXtra Dimensional (XD) methods
Motion-corrected Image Reconstruction

- Motion-resolved (MR)
- Soft-gating (SG)
- Motion-Correction (MoCo)
- Iterative Motion-Correction (I-MoCo)

5 year-old, unsedated, 5-minute scan with bulk motion

Zhu, Lustig, Larson et al. Proc ISMRM 2019 #4492
Thursday 8:15am Computer #120
Pediatric Lung Pathologies Observed with UTE MRI and Motion Compensation

Pneumatoceles (8 yo)  

Bronchiolitis Obliterans (11 yo)  

CT  

CT

To UTE or not to UTE: other $^1$H approaches

- Ultrafast SSFP (Bieri MRM 2013 DOI: 10.1002/mrm.24858)
  - Short TE (< 1ms) with partial Fourier readout
  - Signal gain from T2* refocusing from SSFP
  - With very short TR (< 2ms), can achieve no banding artifacts at 1.5T
  - Derive ventilation and perfusion via Fourier Decomposition (more in later slides)
Quantitative Lung Physiology with GRE MRI (Hopkins, Prisk et al UCSD)

- 2D sagittal dynamic imaging with BODY coil; 1.5cm slice, ~1.5mm in-plane

- Fast 2D gradient-echo sequence
  - Use partial k-space for short TE (~1ms) and short TR (<5 ms)
  - Fast 2D scanning with parallel imaging
  - Can freeze respiratory motion

- Estimate proton density based on 2 TEs and external phantom
- Derive Ventilation and Perfusion
- Combine with Pulmonary ASL methods and oxygen-enhanced imaging

Fourier Decomposition MRI

- Fourier Decomposition (FD) methods derive ventilation (V) and perfusion (Q) in the lung without contrast agents.
  - Variations: Matrix pencil (MP), and Phase-resolved functional lung (PREFUL) methods.
    - Based on fast 2D dynamic scanning (e.g. FLASH or, for 1.5T, ultrafast-SSFP), \(~0.5\) s temporal resolution.
    - Register dynamic images and analyze temporal frequency amplitudes.
    - Ventilation changes with amplitude of respiration frequency due to tissue density changes.
    - Perfusion changes with amplitude of cardiac frequency due to in-flow/time-of-flight effects.

Variations:

- Matrix Pencil (MP)
- Phase-Resolved Functional Lung (PREFUL)
Perfusion changes with amplitude of cardiac frequency due to time-of-flight effects.

Ventilation changes with amplitude of respiration frequency due to tissue density changes.
Oxygen enhanced MRI

- $O_2$ shortens $T1$ and $T2^*$ (See ISMRM 2019 #1889 for details)
  - T1w MRI sensitive to oxygen uptake & ventilation
  - UTE beneficial to remove confounding $T2^*$ losses
- Compare images with room air and breathing 100% $O_2$
- Signal Changes reflect ventilation

Oxygen enhanced MRI Relaxation

Triphan et al. JMRI 2014. doi:10.1002/jmri.24692
Hypermolarized Gasses

- Noble gases (e.g. $^3$He, $^{129}$Xe) can be hyperpolarized via Spin Exchange Optical Pumping

- $^{129}$Xe is most common ($^3$He is in global shortage)
  - 10-40% polarization!
  - Anesthetic
  - Tissue solubility

- Subjects breathe in hyperpolarized gas, and image

- Phase 3 Clinical Trial of Hyperpolarized $^{129}$Xe

- Clinical trial consortium (lead: Jason Woods, Cincinnati Children’s Hospital)

Hyperpolarized $^{129}$Xe Ventilation

- Image gas distribution to measure ventilation
- Fast imaging (breath-hold, T1 ~ 20s after inhalation)

Hyperpolarized $^{129}$Xe Diffusion-weighted Imaging

- Diffusion-weighted imaging to estimate alveolar sizes
- Image enlarged airways as in emphysema

Hyperpolarized $^{129}$Xe Dissolved Phase Imaging

- Large chemical shift ~200 ppm between gas and dissolved phases of $^{129}$Xe
- Allows for imaging of gas exchange within the lung
19F Gasses

- Inhale inert fluorinated gasses e.g. tetrafluoromethane (CF₄), sulfur hexafluoride (SF₆), hexafluoroethane (C₂F₆) and perfluoropropane (C₃F₈ or PFP)
- Ventilation imaging
- Flourine-19 has a similar frequency to ¹H so no additional hardware needed
- 100% natural abundance, No background signal
- Non-toxic, inexpensive, and no hyperpolarization required
- Short T2* ~1-2ms, use UTE
Summary

- Lung MRI is challenging due to motion, short-T2*, and low signal, but there are many advances in imaging methods and inhaled contrasts.

- \(^1\)H Imaging Methods
  - UTE and ZTE MRI – Offer ability to capture rapid signal decay and motion. Provides arguably highest resolution anatomical information.
  - Fast 2D gradient-echo methods – Derive functional measurements (ventilation and perfusion) without the need for custom sequences or hardware.

- Inhaled gasses
  - Oxygen-enhanced MRI – Assess ventilation and perfusion as a result of relaxation effects.
  - Hyperpolarized \(^{129}\)Xe – multiple functional measurements of ventilation, perfusion, and gas exchange.
  - \(^{19}\)F – alternative to hyperpolarized gas for background-free ventilation imaging.
Software Resources

https://github.com/PulmonaryMRI/pulmonary-MRI-reconstruction

- Motion management methods for 3D center-out acquisitions (e.g. UTE radial, cones)

ANTs https://github.com/ANTsX/ANTs


https://github.com/fumguo/Pulmonary-MRI-and-CT-biomarker-framework

https://github.com/UCSDPulmonaryImaging/Deforminator

PREFUL processing – contact Jens Vogel-Claussen, Hannover Medical School
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