# Design and Application of Models Pulmonary Function Preservation

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## Disclosures

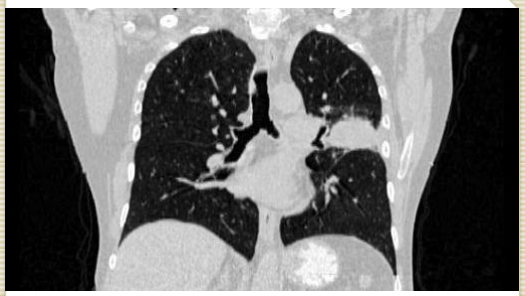
- Funding support for this work
  - NIH R01 CA166703



## Outline

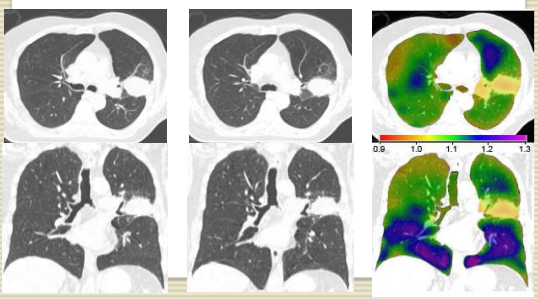
- Model Development
  - need for and approaches to improve repeatability
  - spatial-temporal nature of pulmonary ventilation
  - response maps
- Predictive Model Application
  - Clinical Trials

## Ventilation from 4DCT

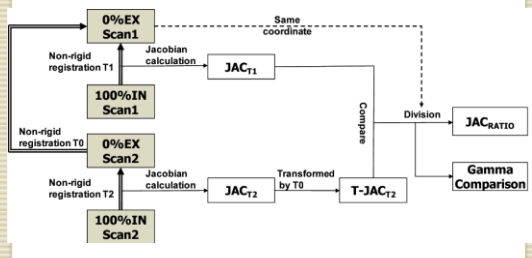


## Ventilation from 4DCT

End Exhale | End Inhale | Ventilation Map




## Repeatability




Du *et al.*: Reproducibility of lung tissue expansion measurements
Medical Physics, Vol. 39, No. 3, March 2012

## Repeatability Results good case

Du *et al.*: Reproducibility of lung tissue expansion measurements
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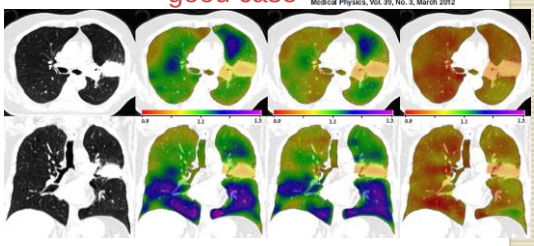


CT image Scan1 0EX | Ventilation image Scan1 | Ventilation image Scan2 | Ratio of 2 Ventilation images

## Repeatability Results bad case

Du *et al.*: Reproducibility of lung tissue expansion measurements
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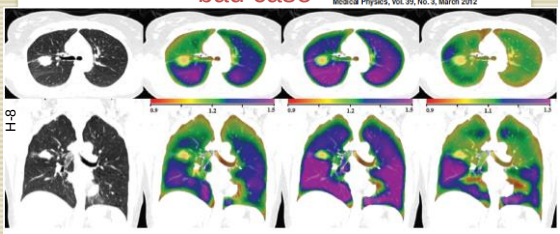
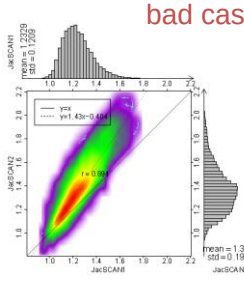



FIG. 6. Transverse (top) and coronal (bottom) views of (left to right) the original CT, $JAC_{T1}$, $JAC_{T2} \circ T0$, and $JAC_{RATIO}$ for human subject H-8. Note the color scales for $JAC_{T1}$ and $JAC_{T2} \circ T0$ are 0.9 to 1.5, and for $JAC_{RATIO}$ the scale is 0.9 to 1.3.

CT image Scan1 0EX | Ventilation image Scan1 | Ventilation image Scan2 | Ratio of 2 Ventilation images

## Repeatability Results bad case




Smoothed color density scatter plot

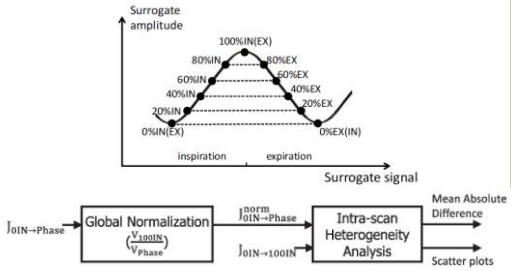
- Scatter points density from high to low: Red, Yellow, Green, Purple, White
- Dash line is the linear regression line, and solid line (y=x) is the reproducibility reference line
- The scatter distribution should converge at the solid line for perfect reproducibility
- Due to breath effort difference, there is an angle between dash line and solid line

Du

## Respiratory Effort Correction Strategies

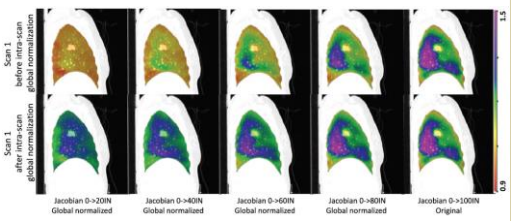
- None
- Global Normalization
- Image selection approaches
  - Equivalent Tidal Volume (ETV)
  - Equivalent Lung Volume (ELV)

## Global Normalization






## Global Normalization

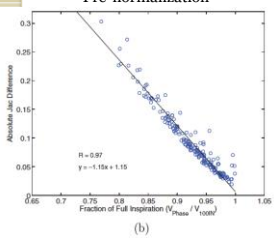



Intrascan lung expansion heterogeneity analysis after global normalization. Jacobian maps before (row 1) and after (row 2) intrascan global normalization for scan one of subject H-8.

Kaifang Du, Joseph M. Reinhardt, Gary E. Christensen, Kai Ding, John E. Bayouth. **Respirator effort correction strategies to improve the reproducibility of lung expansion measurements.** Medical Physics 43, 1259(2016);

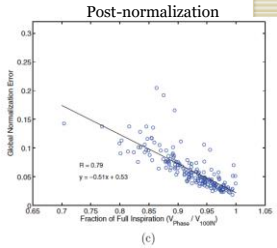
# Impact of Normalization

Pre-normalization




(b)

Post-normalization

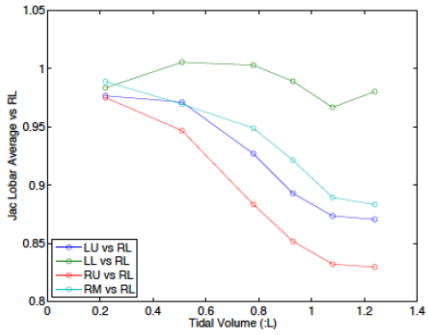



(c)

Kaifang Du, Joseph M. Reinhardt, Gary E. Christensen, Kai Ding, John E. Bayouth. **Respirator effort correction strategies to improve the reproducibility of lung expansion measurements.** Medical Physics 40, 123504 (2013)



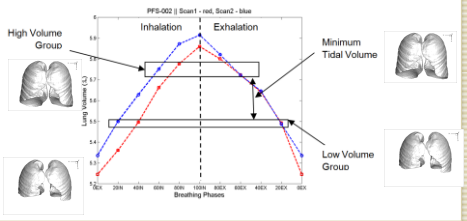
# Spatial Variation in Lung Expansion




Kaifang Du, Joseph M. Reinhardt, Gary E. Christensen, Kai Ding, John E. Bayouth. **Respirator effort correction strategies to improve the reproducibility of lung expansion measurements.** Medical Physics 40, 123504 (2013).

# Respiratory Effort Correction Strategies

Equivalent Lung Volume (ELV) criteria

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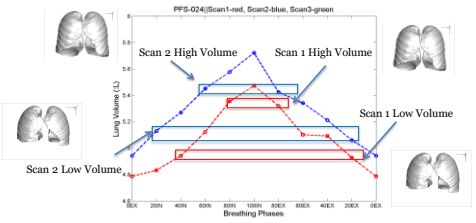
Equivalent Tidal Volume (ETV) criteria

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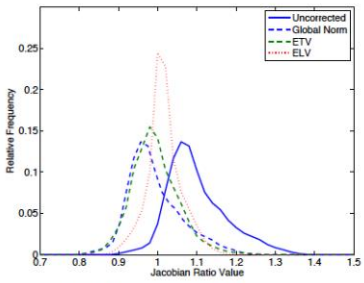
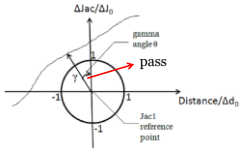
# Respiratory Effort Correction




(a) Histograms of $JAC_{RATIO}$

Kaifang Du, Joseph M. Reinhardt, Gary E. Christensen, Kai Ding, John E. Bayouth. **Respirator effort correction strategies to improve the reproducibility of lung expansion measurements.** Medical Physics 40, 123504 (2013).

# Calculating Repeatability Gamma Index




Gamma comparison considers both spatial distance difference and Jacobian difference.

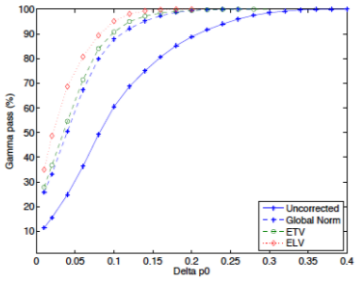
Pass% = Pass voxel counts / total lung voxels x 100%

$$\gamma(\vec{r_2}, \vec{r_1}) = \min_{\vec{r_2}} \{\Gamma(\vec{r_2}, \vec{r_1})\} = \min_{\vec{r_2}} \{\sqrt{(\frac{\vec{r_2} - \vec{r_1}}{\Delta d_0})^2 + (\frac{\frac{J_2(\vec{r_2})}{J_1(\vec{r_1})} - 1}{\Delta_* J_0})^2}\}$$

In this experiment, we use: $\Delta d_0 = 4mm$ and $\Delta J_0 = 5\%$

Daniel, Low, James F. Dempsey. "Evaluation of the gamma dose distribution comparison method" Medical Physics, 30:2455-2464,2003).

# Respiratory Effort Correction




(b) Gamma pass rate curves

Kaifang Du, Joseph M. Reinhardt, Gary E. Christensen, Kai Ding, John E. Bayouth, **Respirator effort correction strategies to improve the reproducibility of lung expansion measurements.** Medical Physics 40, 123504 (2013)

# Respiratory Effort Correction Impact

TABLE I. Summary of mean and CV of $JAC_{RATIO}$, MSE, and gamma pass rate for reproducibility before effort correction, after global normalization, after ETV, and after ELV in subjects with tidal volume difference less than 100 cc, greater than or equal to 100 cc, and all subjects (shown as cohort mean ± standard deviation).

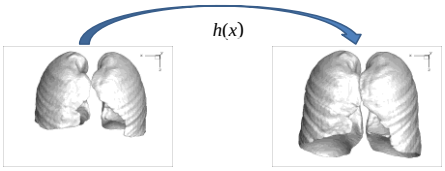
| Subjects | Parameter | Before correction | After global | After ETV | After ELV |
|---|---|---|---|---|---|
| <100cc | Mean | 1.00 ± 0.01 | 1.01 ± 0.01 | 1.01 ± 0.01 | 1.00 ± 0.01 |
| | CV (× $10^{-2}$) | 6.95 ± 2.28 | 6.95 ± 2.28 | 8.26 ± 3.53 | 6.54 ± 2.54 |
| | MSE (× $10^{-2}$) | 0.74 ± 0.45 | 0.73 ± 0.45 | 0.95 ± 0.76 | 0.65 ± 0.62 |
| | Gamma (%) | 75.4 ± 10.5 | 75.0 ± 10.8 | 75.7 ± 8.0 | 75.6 ± 10.8 |
| ≥100cc | Mean | 1.02 ± 0.05 | 1.00 ± 0.02 | 1.00 ± 0.02 | 1.00 ± 0.01 |
| | CV (× $10^{-2}$) | 7.20 ± 2.02 | 7.20 ± 2.02 | 6.30 ± 2.14 | 5.81 ± 2.26 |
| | MSE (× $10^{-2}$) | 1.23 ± 0.73 | 0.71 ± 0.44 | 0.62 ± 0.43 | 0.51 ± 0.40 |
| p ≥ 0.01 | Gamma (%) | 57.1 ± 14.5 | 68.4 ± 9.6 | 72.1 ± 12.6 | 76.3 ± 12.7 |
| All | Mean | 1.01 ± 0.04 | 1.00 ± 0.02 | 1.00 ± 0.01 | 1.00 ± 0.01 |
| | CV (× $10^{-2}$) | 7.11 ± 2.08 | 7.11 ± 2.08 | 6.74 ± 2.53 | 6.10 ± 2.34 |
| | MSE (× $10^{-2}$) | 1.05 ± 0.68 | 0.72 ± 0.44 | 0.69 ± 0.51 | 0.57 ± 0.49 |
| p < 0.01 | Gamma (%) | 64.0 ± 15.8 | 70.9 ± 10.3 | 72.9 ± 11.6 | 76.1 ± 11.7 |

Kaifang Du, Joseph M. Reinhardt, Gary E. Christensen, Kai Ding, John E. Bayouth, **Respirator effort correction strategies to improve the reproducibility of lung expansion measurements.** Medical Physics 40, 123504 (2013)



# Measurement of Lung Ventilation

- Regional volume change reflects lung function (Reinhardt et al.)
  - Transformation ***h(x)*** from image registration
  - Calculate Jacobian determinant of the transformation




0%EX
(End of Expiration)

100%IN
(End of Inspiration)

J. M. Reinhardt, K. Ding, K. Cao, G. E. Christensen, E. A. Hoffman, and S. V. Bodas. Registration-based estimates of local lung tissue expansion compared to xenon-CT measures of specific ventilation. Medical Image Analysis, (12)6 2008

## Cost Function for Image Registration

$$C_{\text{TOTAL}} = C_{\text{SSTVD}} + \rho_1 C_{\text{SSVMD}} + \rho_2 C_{\text{LAP}}$$

Cost Minimization

- $C_{\text{SSTVD}}$ - sum of squared tissue volume difference
- $C_{\text{SSVMD}}$ – sum of squared vesselness measure difference
- $C_{\text{LAP}}$ - Laplacian regularization constraint

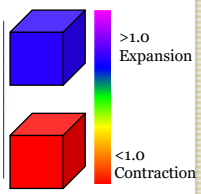
$$\begin{aligned} C_{\text{SSTVD}} &= \int_{\Omega} [V_2(\mathbf{x}) - V_1(\mathbf{h}(\mathbf{x}))]^2 \, d\mathbf{x} \\ &= \int_{\Omega} \left[ v_2(\mathbf{x}) \frac{I_2(\mathbf{x}) + 1000}{1055} - v_1(\mathbf{h}(\mathbf{x})) \frac{I_1(\mathbf{h}(\mathbf{x})) + 1000}{1055} \right]^2 d\mathbf{x} \end{aligned}$$

## Measurement of Lung Ventilation

- Regional volume change reflects lung function (Reinhardt et al.)
  - Transformation ***h(x)*** from image registration
  - Calculate Jacobian determinant of the transformation

Jacobian

$$J(h(x)) = \begin{vmatrix} \frac{\partial h_1(x)}{\partial x_1} & \frac{\partial h_2(x)}{\partial x_1} & \frac{\partial h_3(x)}{\partial x_1} \\ \frac{\partial h_1(x)}{\partial x_2} & \frac{\partial h_2(x)}{\partial x_2} & \frac{\partial h_3(x)}{\partial x_2} \\ \frac{\partial h_1(x)}{\partial x_3} & \frac{\partial h_2(x)}{\partial x_3} & \frac{\partial h_3(x)}{\partial x_3} \end{vmatrix}$$

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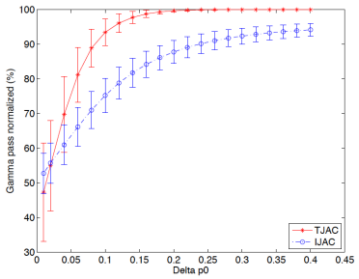
## Technical Details Matter

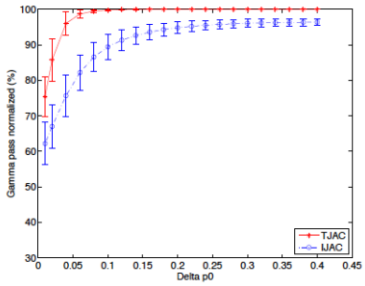
(avg of 10 human subjects)




Du et al., Med. Phys. 40 (2013)

## Ventilator Controlled Respiration

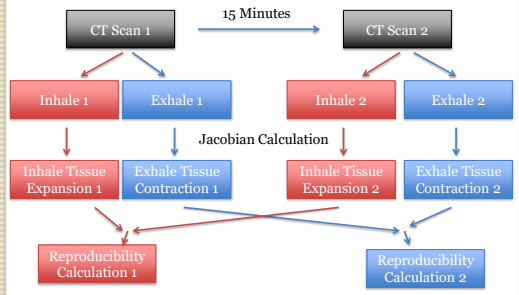
(sheep subjects)





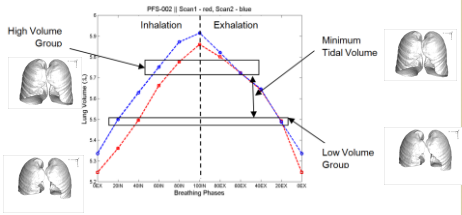

Du et al., Med. Phys. 40 (2013)

## Inhale or Exhale???




## Respiratory Effort Correction Strategies

Equivalent Lung Volume (ELV) criteria

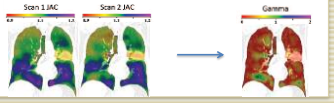



Kaifang Du, Joseph M. Reinhardt, Gary E. Christensen, Kai Ding, John E. Bayouth. **Respirator effort correction strategies to improve the reproducibility of lung expansion measurements.** Medical Physics 40, 123504 (2013).

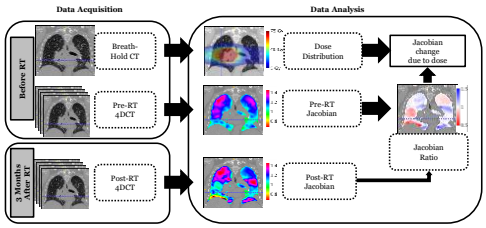
## Inhale Wins!

- Inhalation Jacobian maps were more repeatable
- 2mm distance-to-agreement
- 5% ventilation difference

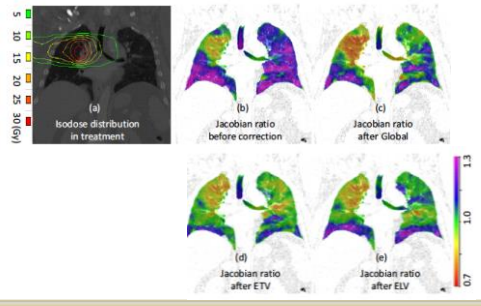
| | Subject | Inhale Gamma Pass Rate | Exhale Gamma Pass Rate | |
|---|---|---|---|---|
| ELV Subjects | PFS-002 | 88.9 | 80.5 | |
| | PFS-004 | 84.7 | 72.4 | |
| | PFS-010 | 70.7 | 67.4 | |
| | PFS-011 | 80.6 | 68.0 | |
| | PFS-012 | 67.6 | 66.0 | |
| | **Average** | **78.5** | **70.9** | **p = .027*** |
| ETV Subjects | PFS-009 | 74.6 | 81.1 | |
| | PFS-024 | 65.4 | 62.9 | |
| | PFS-047 | 68.8 | 64.2 | |
| All Subjects | **Average** | **75.2** | **70.3** | **p = .064** |




## Measuring Ventilation Change Following RT

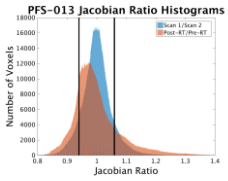



## Impact of effort correction on response assessment



## Establishing a Change post RT

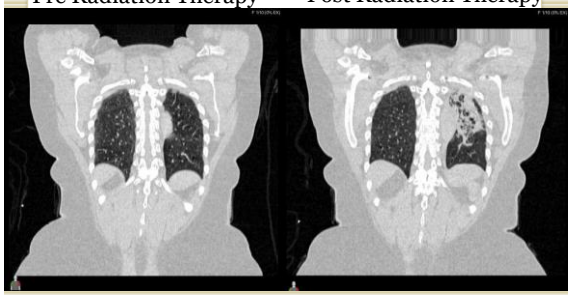
- Need a control
- Used repeat pre-RT scans
- Compare magnitude of changes between repeat scans and pre-RT and post-RT
- Used voxel-wise Jacobian ratios



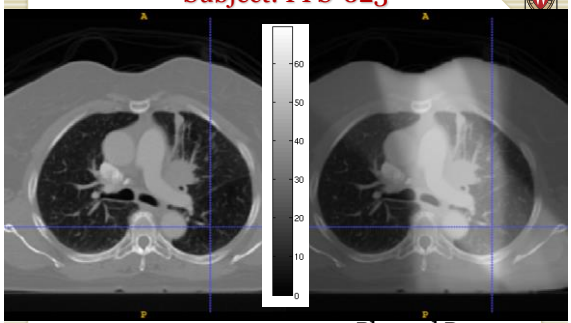

WE-AB-202-3 Quantifying Ventilation Changes Due to Radiation Therapy Using 4DCT Jacobian Calculations - Patton

## Changes after RT

Pre Radiation Therapy Post Radiation Therapy

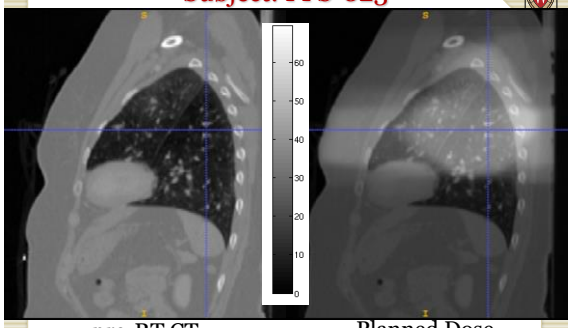


## Subject: PFS-023



pre-RT CT Planned Dose

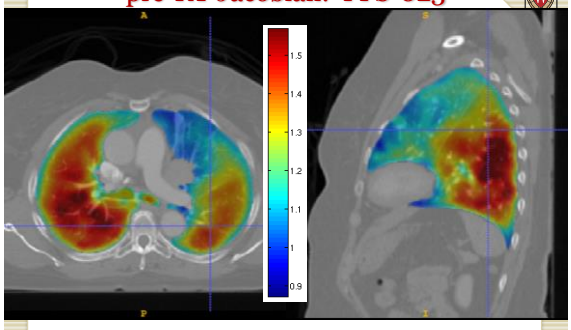
## Subject: PFS-023




pre-RT CT Planned Dose

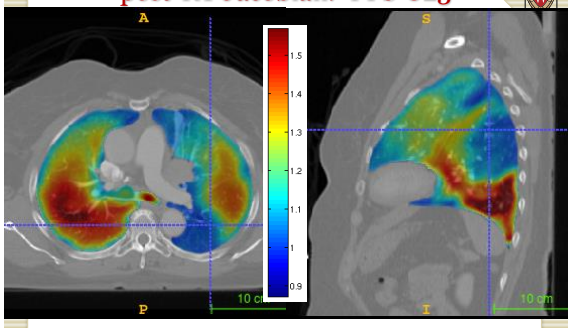


## pre-RT Jacobian: PFS-023

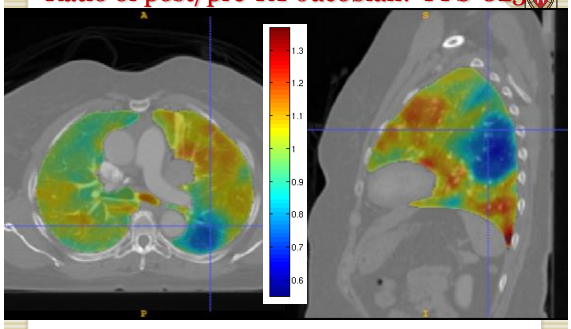





## post-RT Jacobian: PFS-023

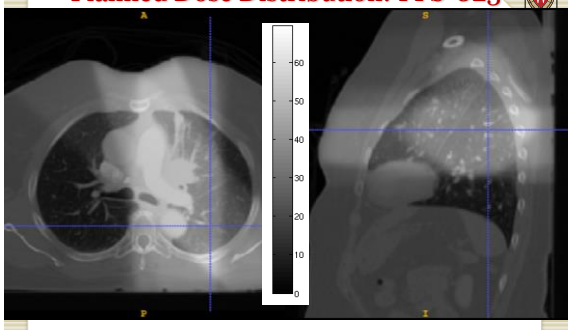


## Ratio of post/pre-RT Jacobian: PFS-023



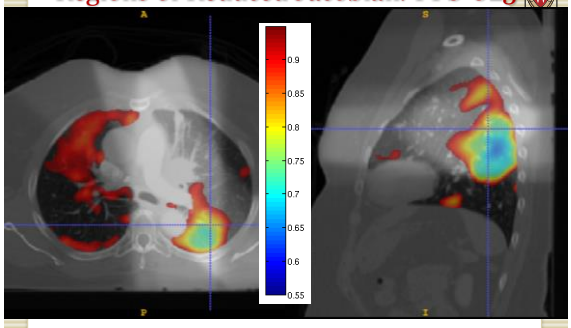


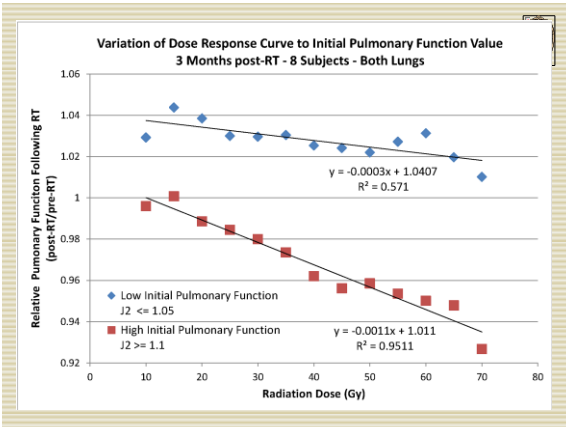

## Planned Dose Distribution: PFS-023

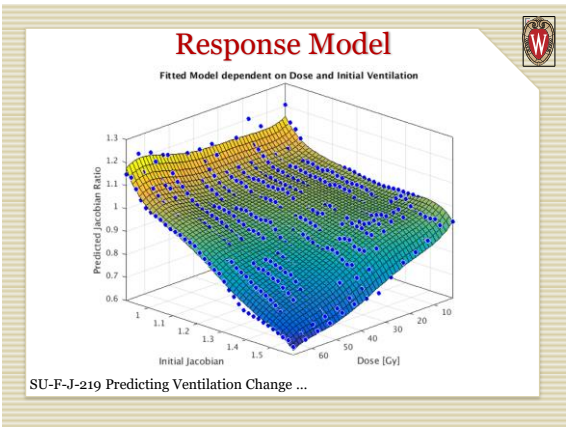


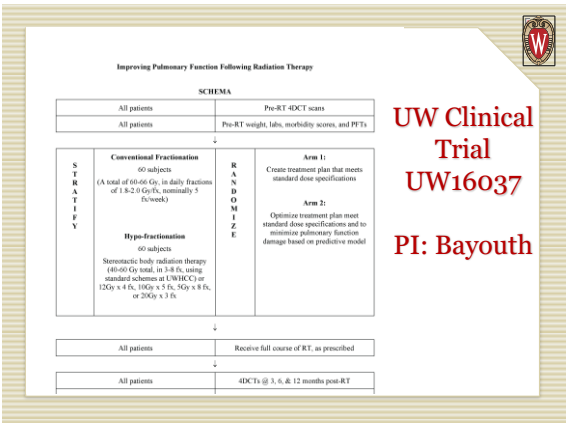


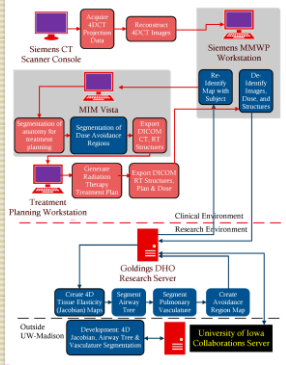

## Regions of Reduced Jacobian: PFS-023




Variation of Dose Response Curve to Initial Pulmonary Function Value
3 Months post-RT - 8 Subjects - Both Lungs
Relative Pumonary Funciton Following RT (post-RT/pre-RT)
1.06
1.04
1.02
1
0.98
0.96
0.94
0.92
0
10
20
30
40
50
60
70
80
Radiation Dose (Gy)
y = -0.0003x + 1.0407
R² = 0.571
Low Initial Pulmonary Function
J2 <= 1.05
High Initial Pulmonary Function
J2 >= 1.1
y = -0.0011x + 1.011
R² = 0.9511


Response Model
Fitted Model dependent on Dose and Initial Ventilation
Predicted Jacobian Ratio
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
Initial Jacobian
1
1.1
1.2
1.3
1.4
1.5
Dose [Gy]
10
20
30
40
50
60
SU-F-J-219 Predicting Ventilation Change …


Improving Pulmonary Function Following Radiation Therapy
SCHEMA
All patients
Pre-RT 4DCT scans
All patients
Pre-RT weight, labs, morbidity scores, and PFTs
STRATIFY
Conventional Fractionation
60 subjects
(A total of 60-66 Gy, in daily fractions of 1.8-2.0 Gy/fx, nominally 5 fx/week)
Hypo-fractionation
60 subjects
Stereotactic body radiation therapy (40-60 Gy total, in 3-8 fx, using standard schemes at UWHCC) or 12Gy x 4 fx, 10Gy x 5 fx, 5Gy x 8 fx, or 20Gy x 3 fx
RANDOMIZE
Arm 1:
Create treatment plan that meets standard dose specifications
Arm 2:
Optimize treatment plan meet standard dose specifications and to minimize pulmonary function damage based on predictive model
All patients
Receive full course of RT, as prescribed
All patients
4DCTs @ 3, 6, & 12 months post-RT
UW Clinical Trial UW16037
PI: Bayouth




## Data Management / Workflow

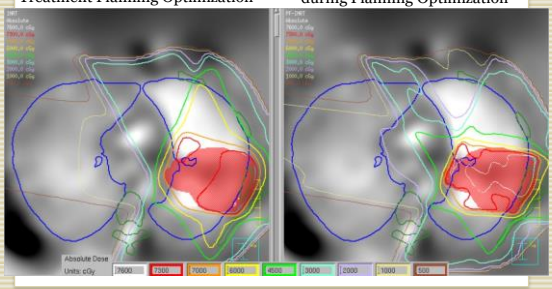
Clinical workflow for 120 subjects

- use quantitative 4DCT imaging to characterize pulmonary biomechanics
- build a model that predicts how these parameters change following RT
- use the model to improve therapy outcomes.

## Functional Treatment Planning

Pulmonary Function ignored during Treatment Planning Optimization

Pulmonary Function considered during Planning Optimization




## Conclusions

- Repeatability scans are a useful metric to assess ventilation measures in absence of ground truth
- Ventilation computations vary with calculation technique, phase of breathing cycle, and respiratory effort
- Models of ventilation (lung tissue compliance) changes following RT should include radiation dose and initial ventilation

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