Lung Image Analysis of COVID19 and Cancer Patients:
CT Scan Alignment

Lecture by Margrit Betke, CS 585, April 14, 2020

BU Today, April 14, 2020: Life on the Front Lines – Stories of Doctors at BU Medical Center

Evan Berg, BMC ER physician:

"There is a lot of uncertainty about the [COVID-19] disease process. Even though the majority of people do exceedingly well, there is a minority of people who don't do well. Trying to understand why that is—and find some clinical markers and understand the risk factors—has been a learning process for all. [..]

Our understanding around the [..] best practices around treatment, and the outcomes for those needing hospitalization continue to evolve as we learn more and gain experience."
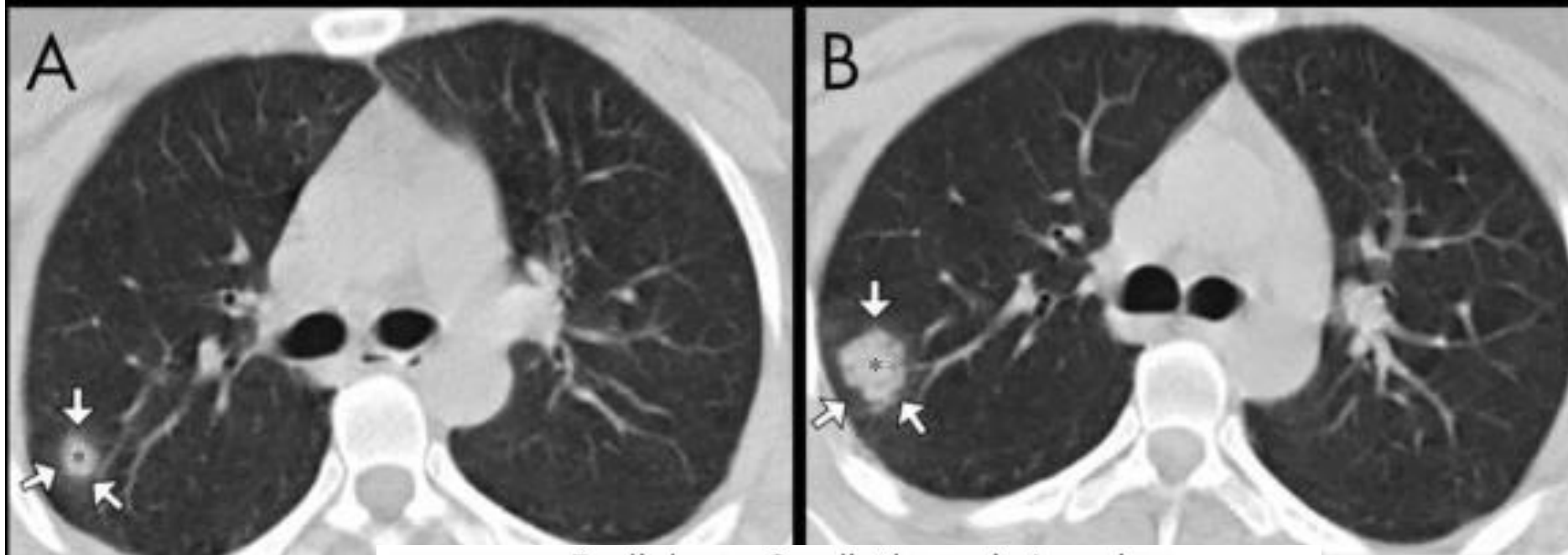
rsnagram Radiology: Cardiothoracic Imaging – COVID-19 Infection Presenting with CT Halo Sign

February 12, 2020

Nonenhanced axial chest CT images in a 27-year-old woman. A, Image shows a solid nodule (*) surrounded by a ground-glass halo in the posterior right upper lobe segment (arrows). B, Image at the same level as in A, obtained 4 days after, shows increase in size of the solid nodule (*), with development of small peripheral air bronchograms.

CT Image of COV-19 Patient
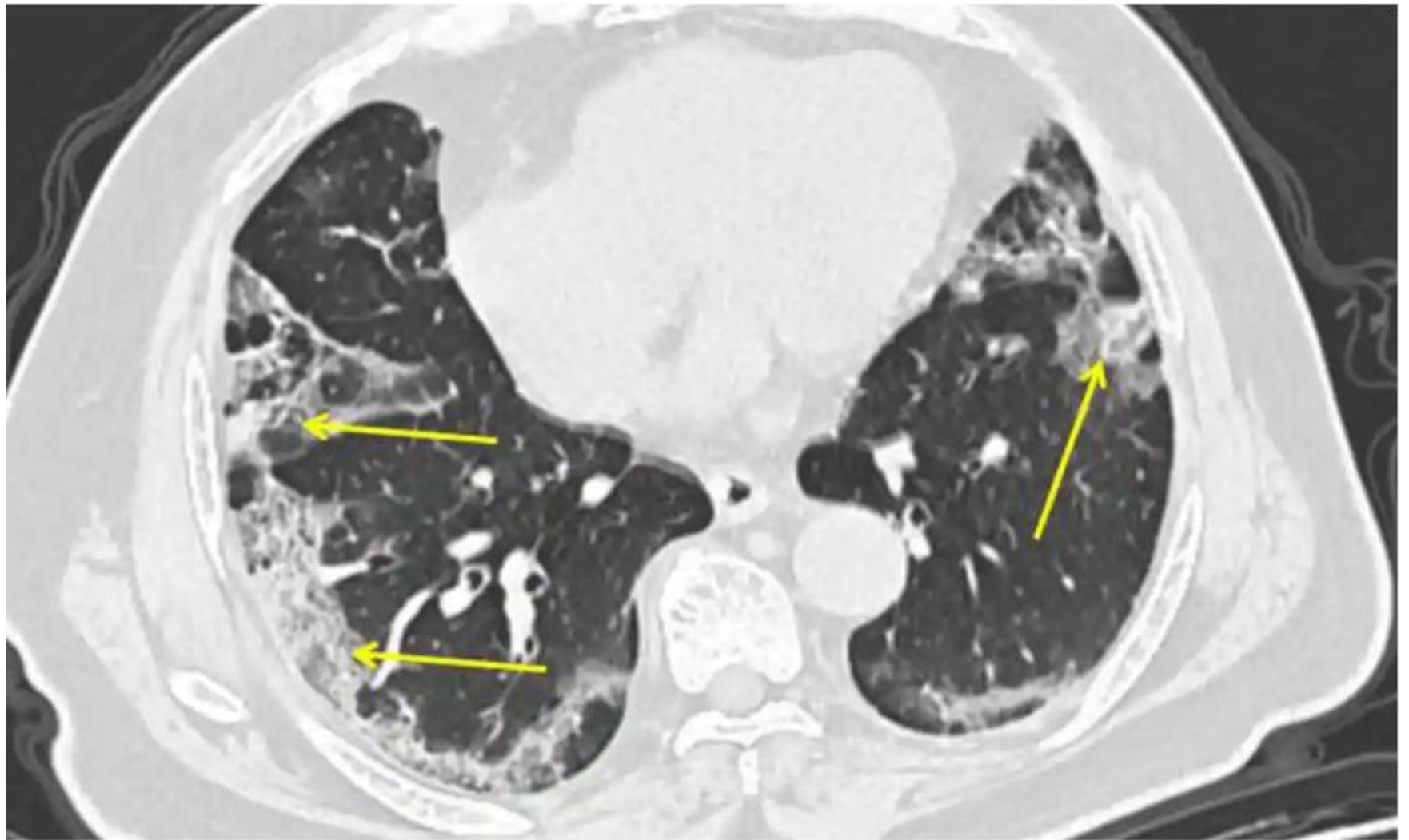
▲ Respiratory physician John Wilson explains the range of Covid-19 impacts. This image shows a CT scan from a man with Covid-19. Pneumonia caused by the new severe acute respiratory coronavirus 2 can show up as distinctive hazy patches on the outer edges of the lungs, indicated by arrows. Photograph: AP
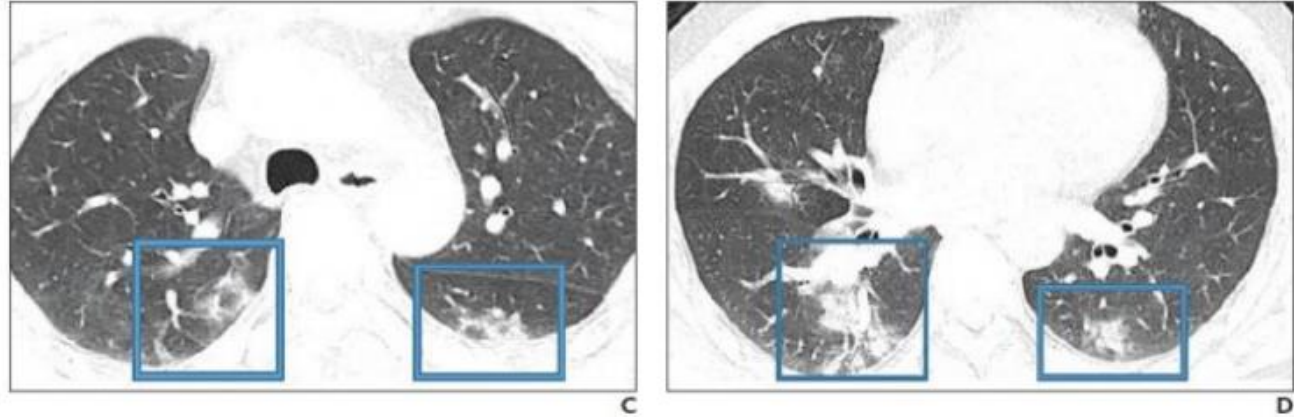
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COVID-19 disease progression visualized on consecutive CT scans

Scan 1:
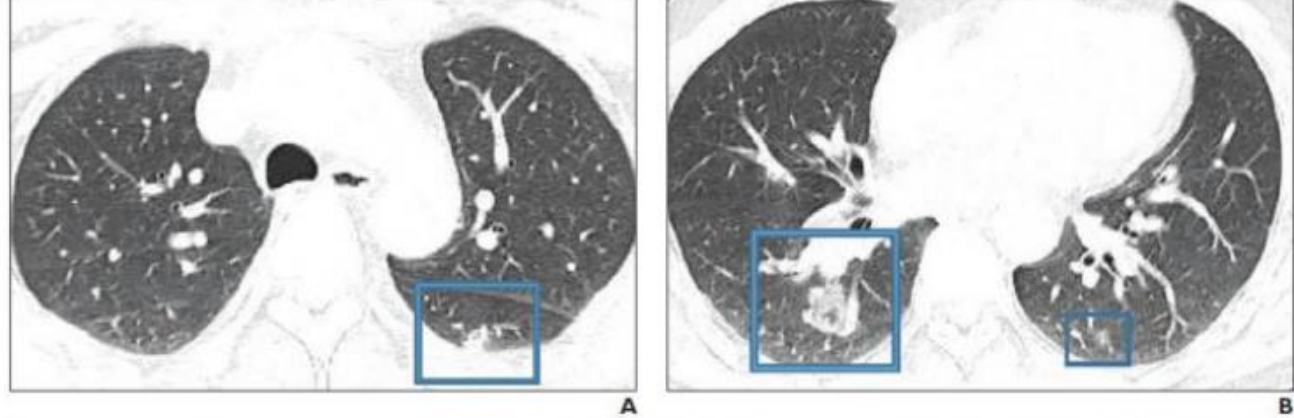
Scan 2:

CAPTION

A and B, Initial CT images obtained show small round areas of mixed ground-glass opacity and consolidation (rectangles) at level of aortic arch (A) and ventricles (B) in right and left lower lobe posterior zones. C and D, Follow-up CT images obtained 2 days later show progression of abnormalities (rectangles) at level of aortic arch (C) and ventricles (D), which now involve right upper and right and left lower lobe posterior zones.
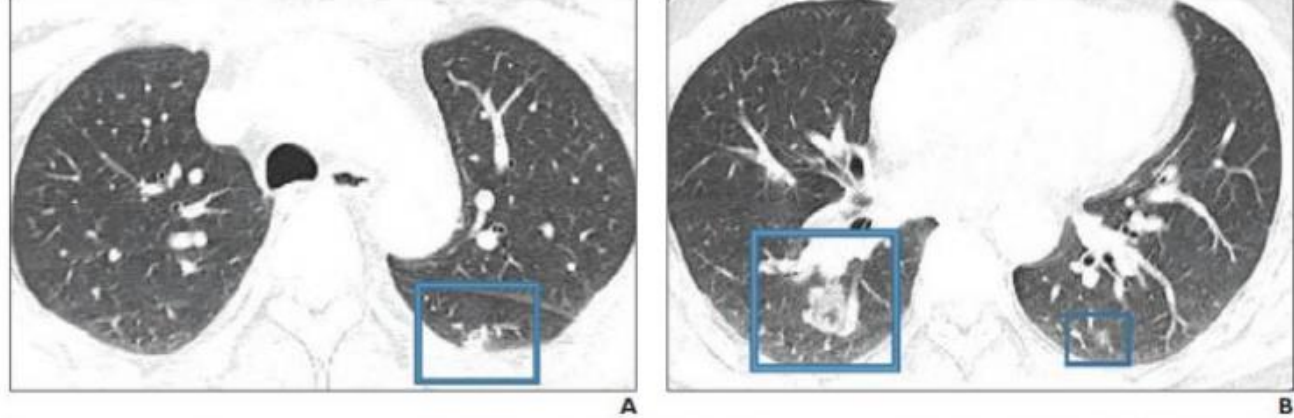
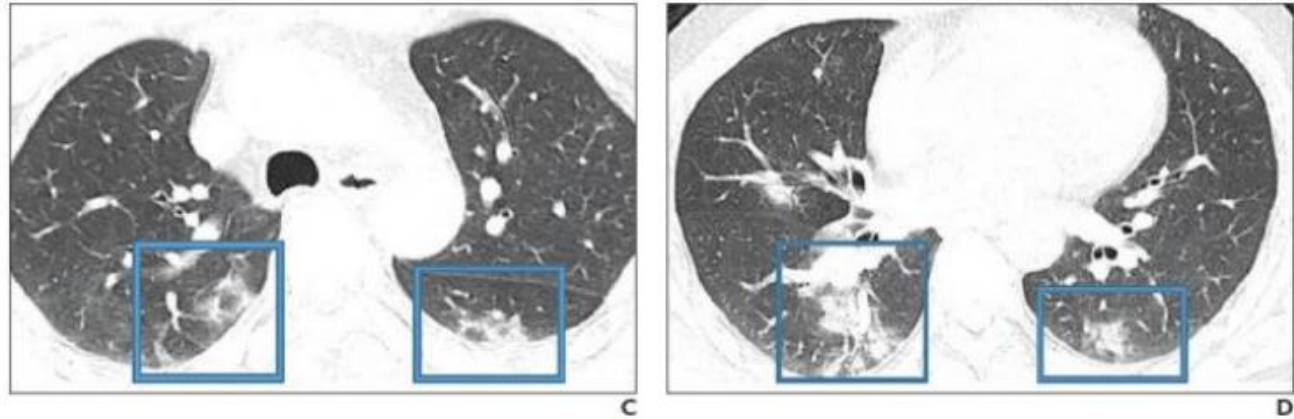**CREDIT**

American Journal of Roentgenology (AJR)

Definition:

A pulmonary consolidation is a region of lung tissue that has filled with liquid instead of air.

Normally soft tissue found in the aerated lung has hardened (white regions in images).

Scan 1:

Scan 2:

CAPTION

A and B, Initial CT images obtained show small round areas of mixed ground-glass opacity and consolidation (rectangles) at level of aortic arch (A) and ventricles (B) in right and left lower lobe posterior zones. C and D, Follow-up CT images obtained 2 days later show progression of abnormalities (rectangles) at level of aortic arch (C) and ventricles (D), which now involve right upper and right and left lower lobe posterior zones.
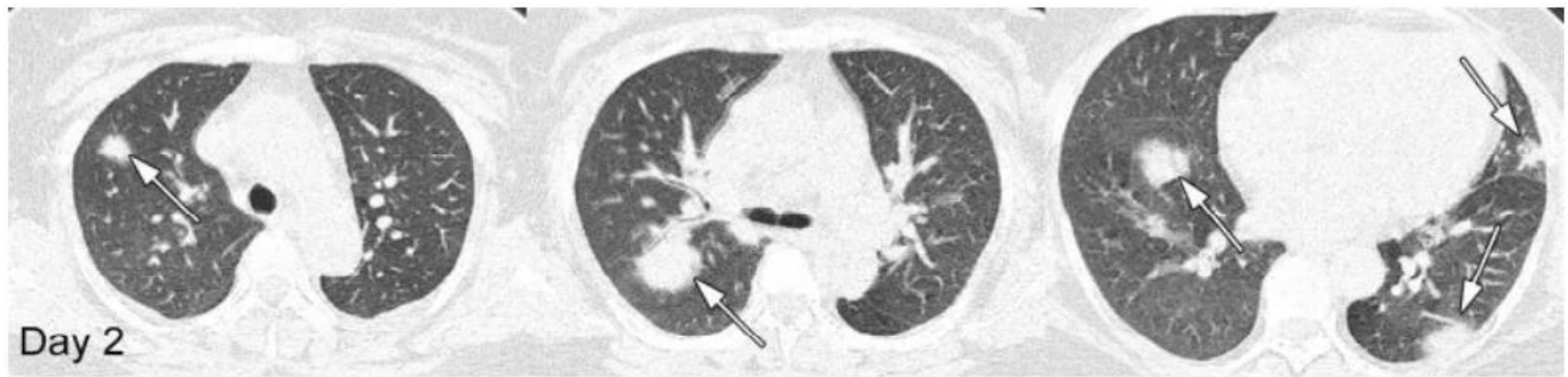
CREDIT
American Journal of Roentgenology (AJR)

COV-19 Patient improves on follow-up CT scan:

Ground-glass opacities

Lungs of a 54-year-old woman who presented with fever on day 2 of symptoms.

WU Y, XIE Y-I, WANG X. LONGITUDINAL CT FINDINGS IN COVID-19 PNEUMONIA: CASE PRESENTING ORGANIZING PNEUMONIA PATTERN. RADIOLOGY: CARDIOTHORACIC IMAGING DOI: 10.1148/RYCT.20202000031. PUBLISHED ONLINE FEBRUARY 1, 2020. © RADIOLOGICAL SOCIETY OF NORTH AMERICA.

A follow-up CT on day 11, three days after initiation of antiviral treatment, showed significant improvement of the ground-glass opacities.

WU Y, XIE Y-I, WANG X. LONGITUDINAL CT FINDINGS IN COVID-19 PNEUMONIA: CASE PRESENTING ORGANIZING PNEUMONIA PATTERN. RADIOLOGY: CARDIOTHORACIC IMAGING DOI: 10.1148/RYCT.20202000031. PUBLISHED ONLINE FEBRUARY 1, 2020. © RADIOLOGICAL SOCIETY OF NORTH AMERICA.

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CS 585: Image and Video Computing

Ground-glass opacities on CT are hazy regions that do not obscure the underlying bronchial structures or pulmonary vessels.
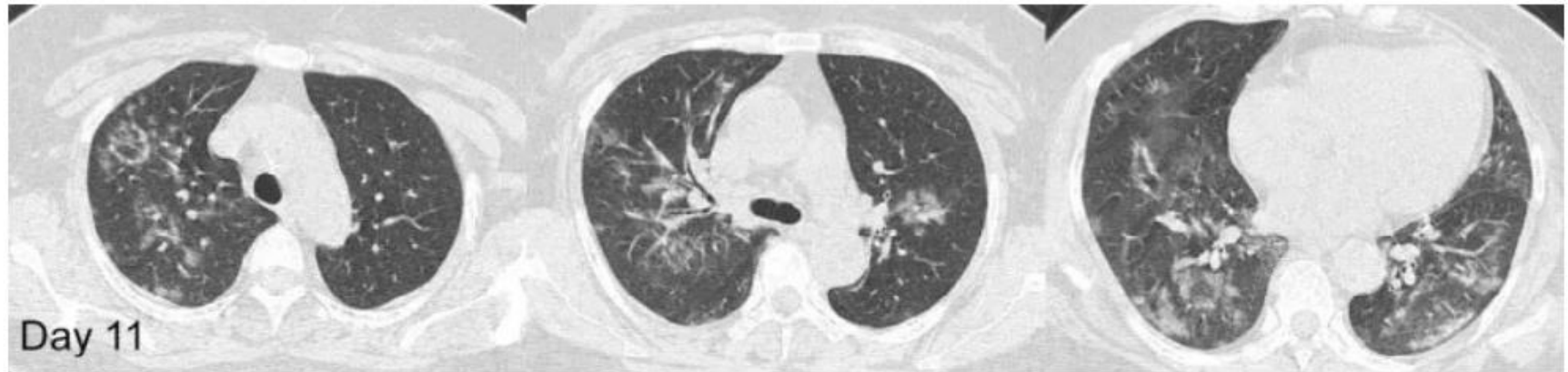
A ground-glass opacity indicates a partial filling of air spaces in the lungs by **exudate** (seeped out fluid) or **transudate** (pushed out fluid), as well as interstitial thickening or partial collapse of lung **alveoli** (tiny air sacs of the lungs which allow for rapid gaseous exchange).

Day 2

Lungs of a 54-year-old woman who presented with fever on day 2 of symptoms.

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Day 11

A follow-up CT on day 11, three days after initiation of antiviral treatment, showed significant improvement of the ground-glass opacities.

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CS 585: Image and Video Computing

Chest CT scan of COVID 19 patient
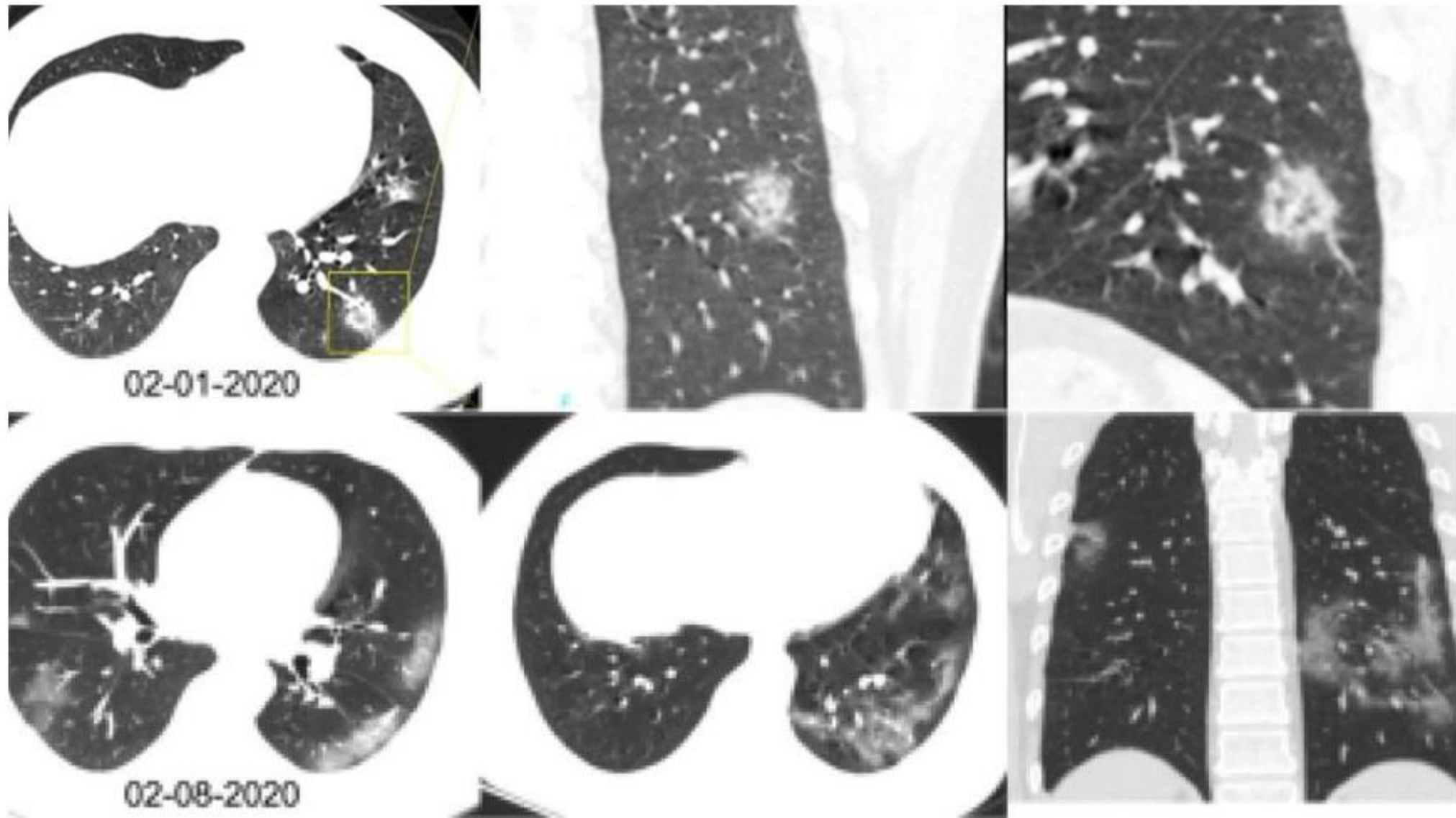
Chest CT scans of a 34-year-old man with coronavirus in China. (Mount Sinai Medical System)

02-01-2020

02-08-2020

CS 585: Image and Video Computing
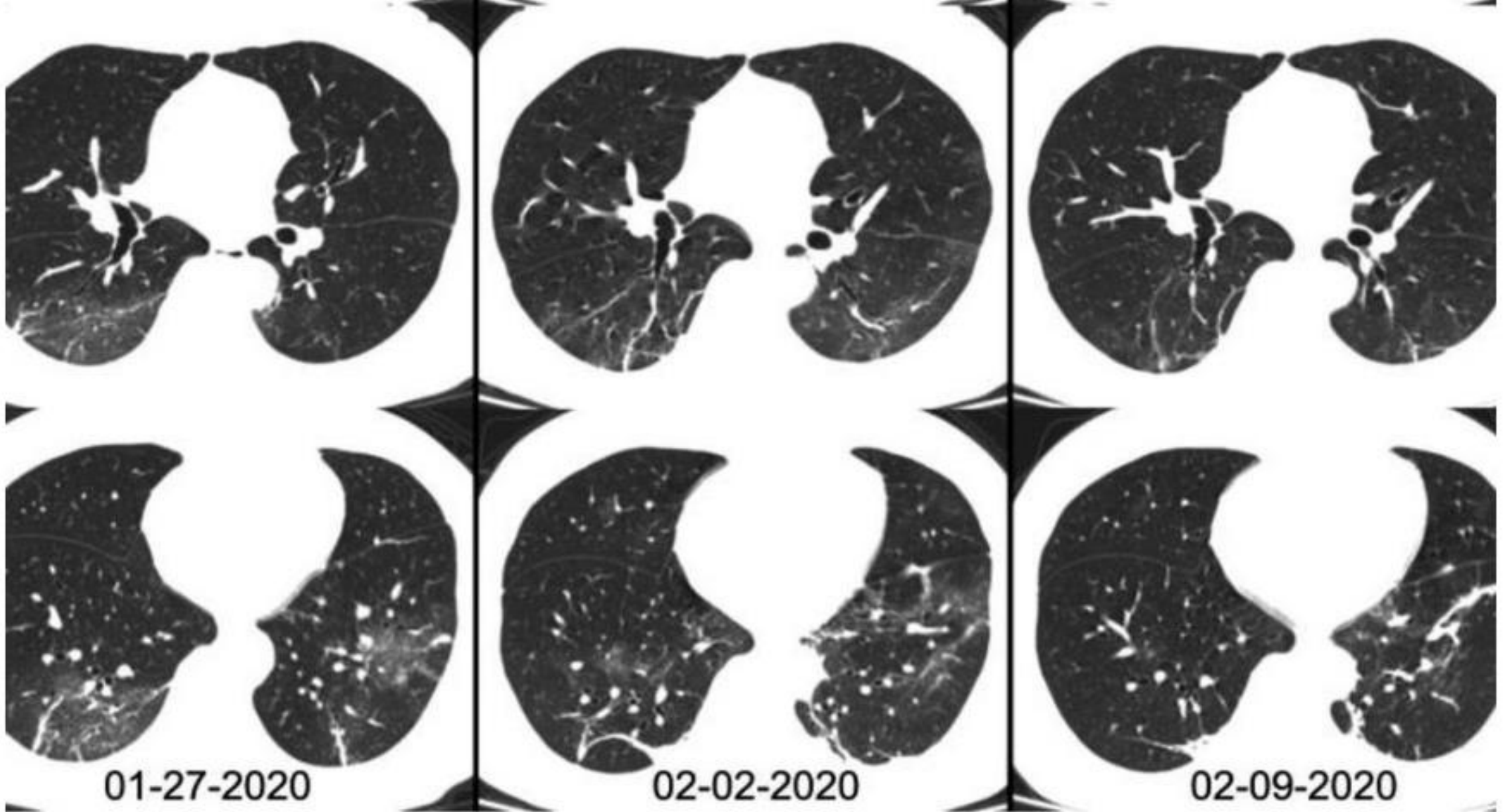
Chest CT images of a 46-year-old with coronavirus in China. (Mount Sinai Medical System)

CS 585: Image and Video Computing

AI-supported Evaluation of Consecutive CT Scans requires

- 2D Absolute Orientation = Image Registration = Image Alignment

- 3D Absolute Orientation = 3D Registration = 3D Scan Alignment

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COVID-19 CT Scan Evaluation Process that I am Proposing:
Given a pair of corresponding images:
Compute Alignment

Semi-automatic Evaluation:
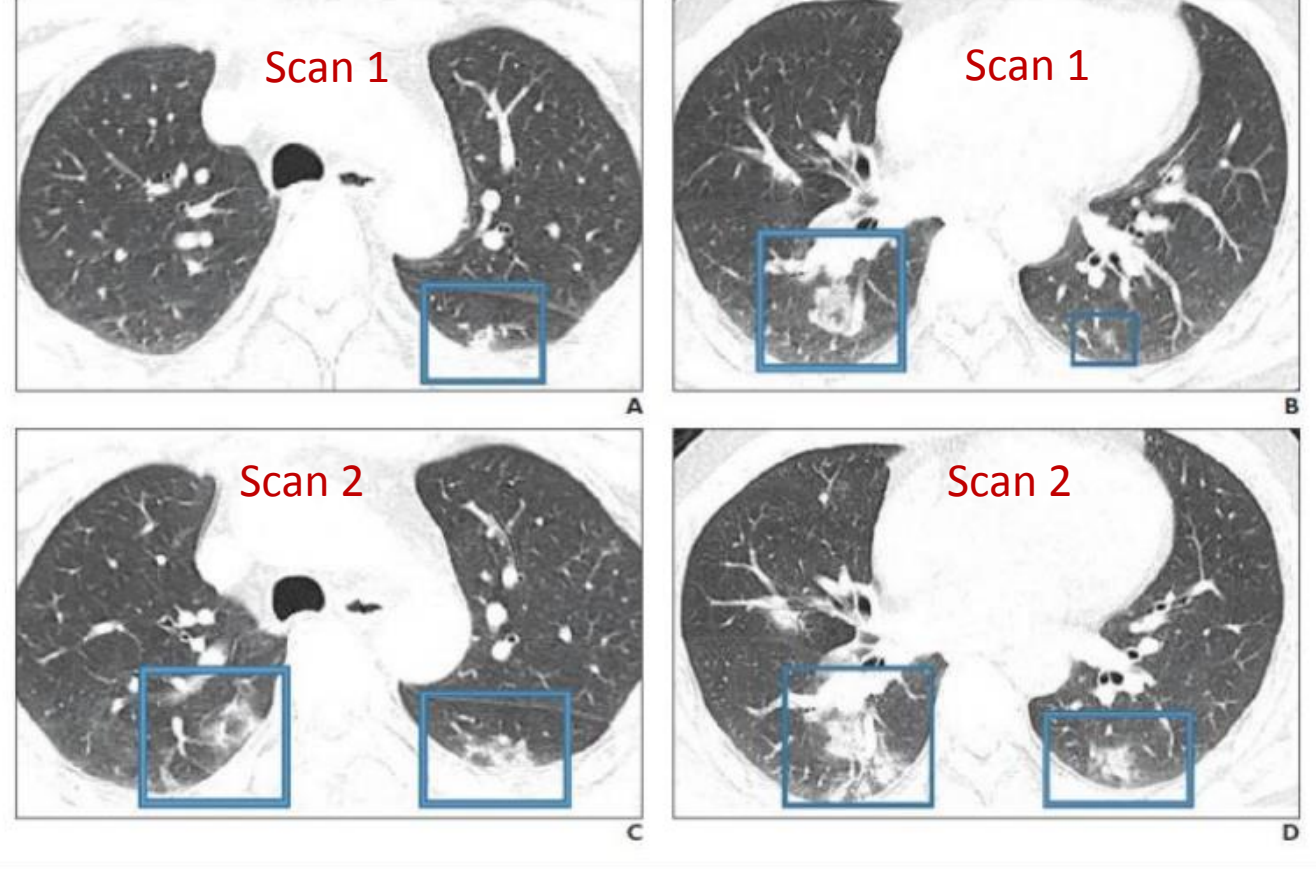1. Radiologist annotates region of interest with consolidation in scan 2. AI system finds all pixels (voxels) with consolidation in scan 2
OR:
Automatic Evaluation:
AI system detects & measures the volume of the consolidation in scan 1 and scan 2

AI system evaluates change in size of region: Increase: Patient fares worse
            Decrease: Patient is getting better

Scan 1   Scan 1

Scan 2   Scan 2

CAPTION
A and B, Initial CT images obtained show small round areas of mixed ground-glass opacity and consolidation (rectangles) at level of aortic arch (A) and ventricles (B) in right and left lower lobe posterior zones. C and D, Follow-up CT images obtained 2 days later show progression of abnormalities (rectangles) at level of aortic arch (C) and ventricles (D), which now involve right upper and right and left lower lobe posterior zones.

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Additional Terminology:

- 2D Landmarks = 2D Feature Locations in Image (pixels)
- 3D Landmarks = 3D Feature Locations in 3D Scan (voxels)

Other Use Cases

Photogrammetry = Analysis of images (often photographs) to extract geometric information (often for map building) about (typically) physical objects and their environment

Biomedical Image Analysis = Computer Vision for Medicine (diagnosis, prognosis, treatment, and prevention of disease)
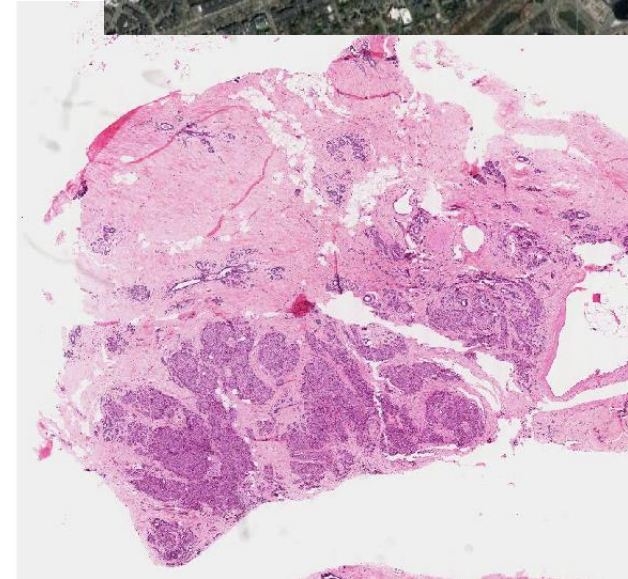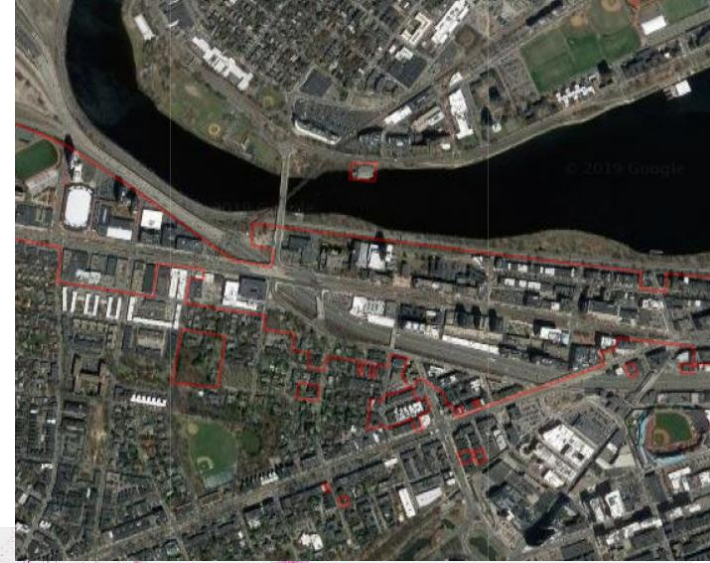
2D Alignment (= Absolute Orientation in 2D)

Definition:

Compute the parameters that describe a "2D rigid body alignment"

= Compute an angle that describes the rotation of the object in the image plane and a 2D translation vector that moves the object into the desired location.

Practical Use Cases:

- Registration of anatomical structures on images of the same patient taken at different times for measuring response to treatment

   Lung cancer patients (Patent: "Method and system for the detection, comparison and volumetric quantification of pulmonary nodules on medical computed tomography scans." Inventors Margrit Betke and Jane P. Ko., US Patent 7,206,462, issued on April 17, 2007.)

   In the future: COVID 19 patients (?)

- Match left and right images in a stereo camera system

- Photogrammetry = Build maps from overlapping photographs

- Compute rigid body motion of objects under the microscope

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Absolute Orientation in 2D

Specific Definition:

Compute the parameters that describe a 2D rigid body alignment

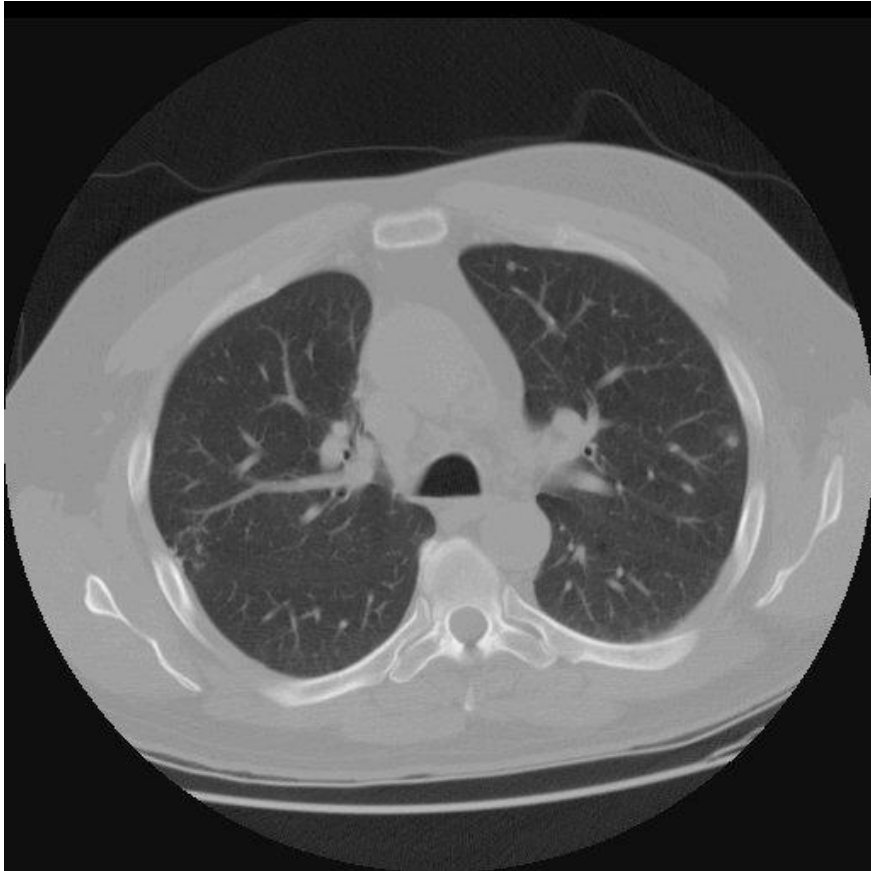= Compute a rotation angle θ and a 2D translation vector $(x_o, y_o)^T$

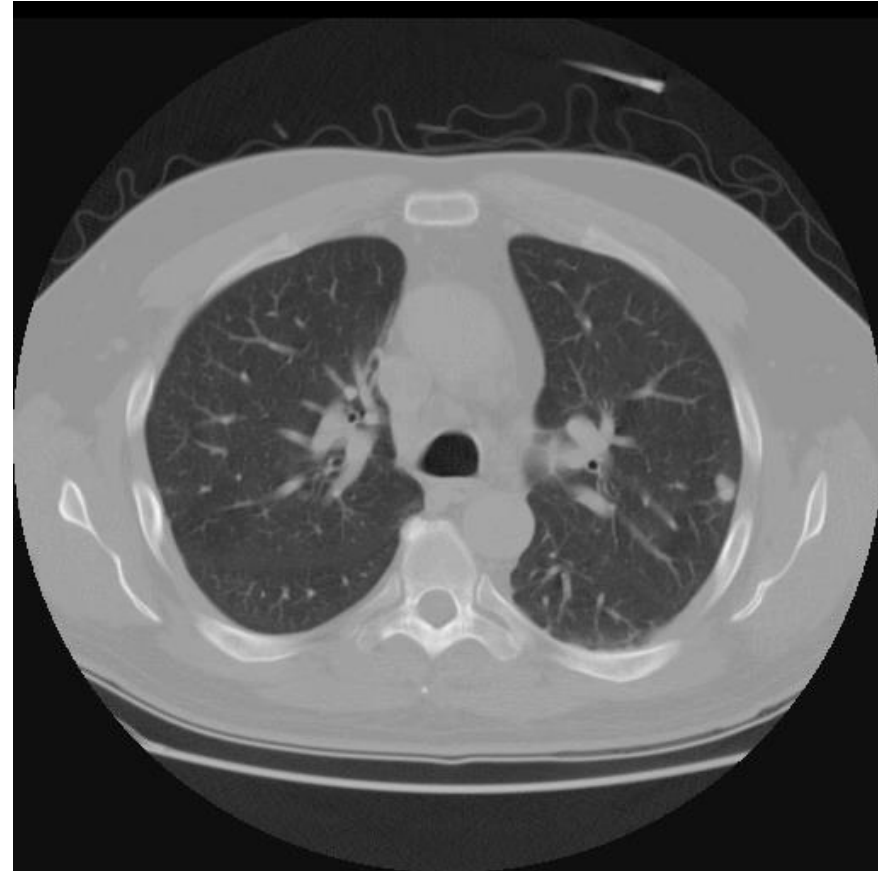# Example: Registration of Lung Images
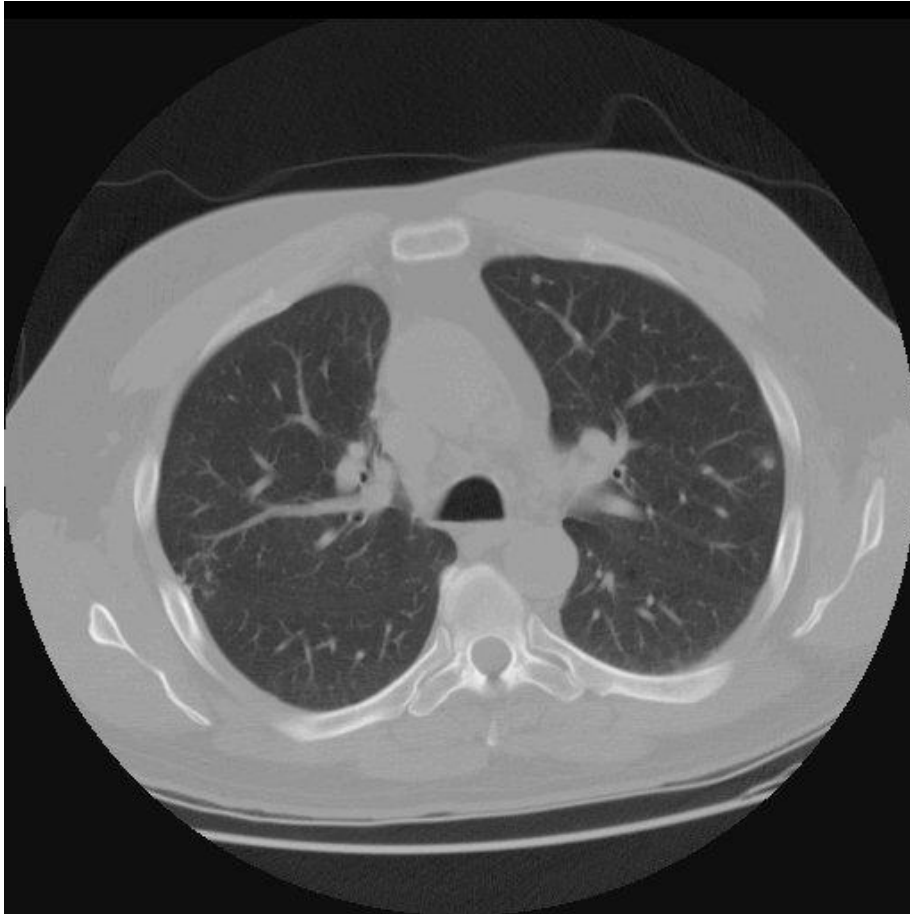
Registration of lung images of a cancer patient taken three months apart to measure nodule growth
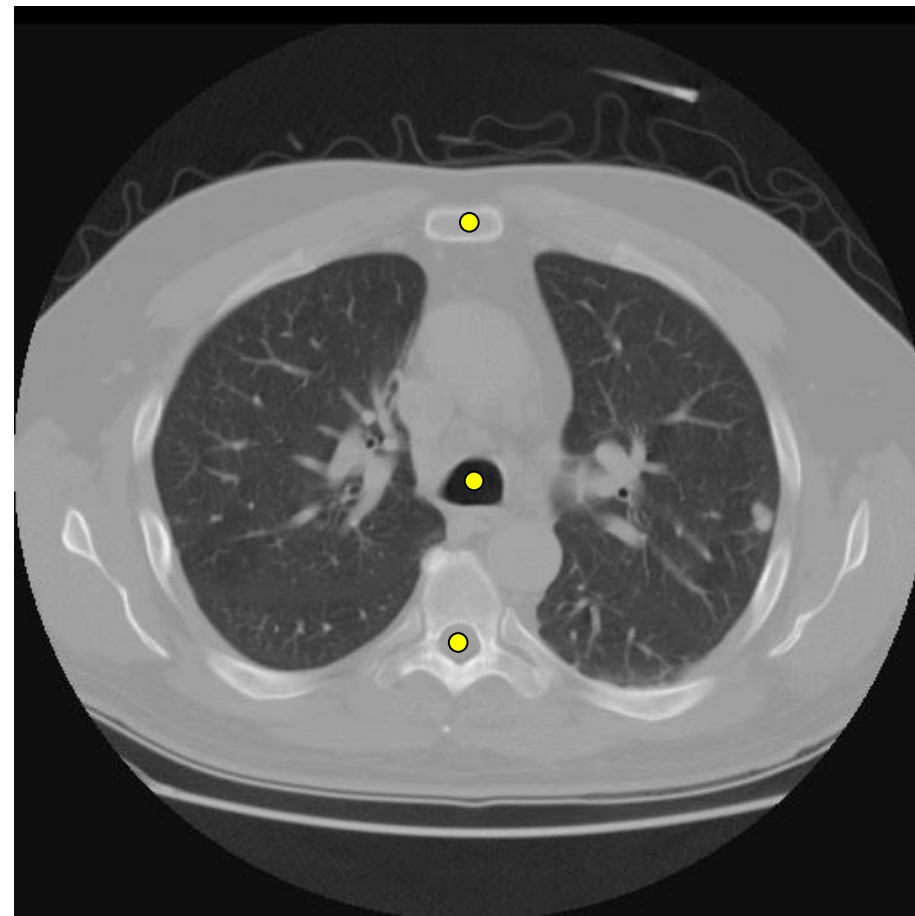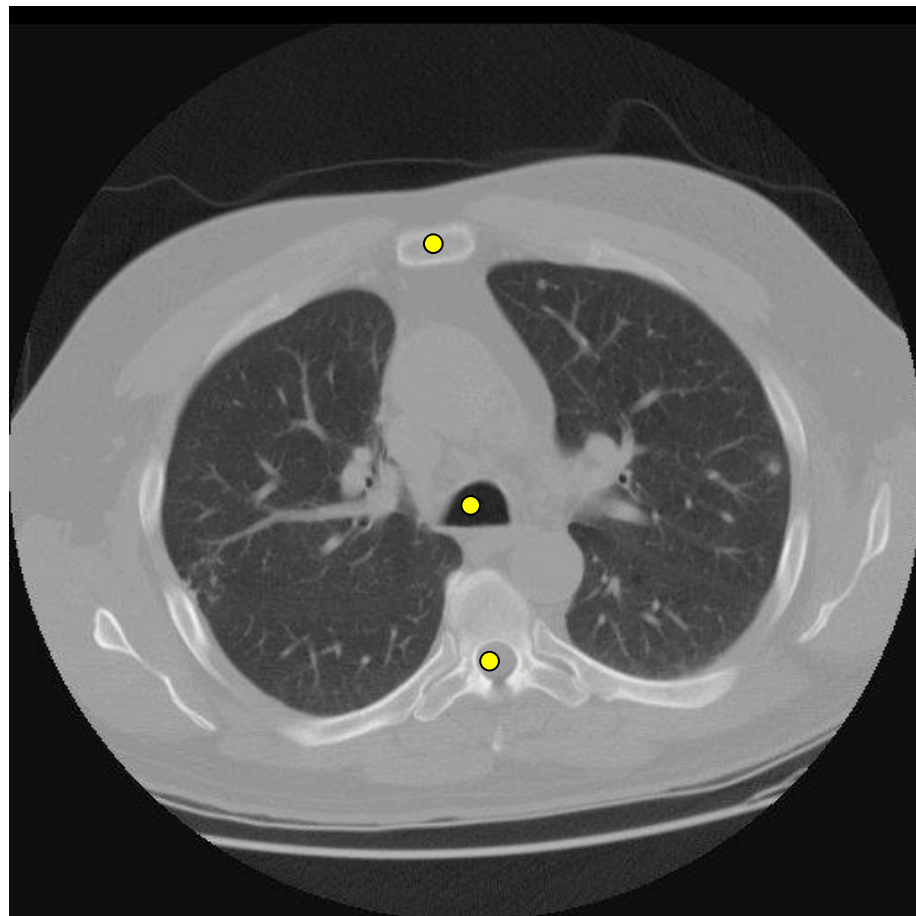
Scan 1

Scan 2

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2D Absolute Orientation

Unknowns: Rotation angle θ and translation vector $(x_o, y_o)^T$
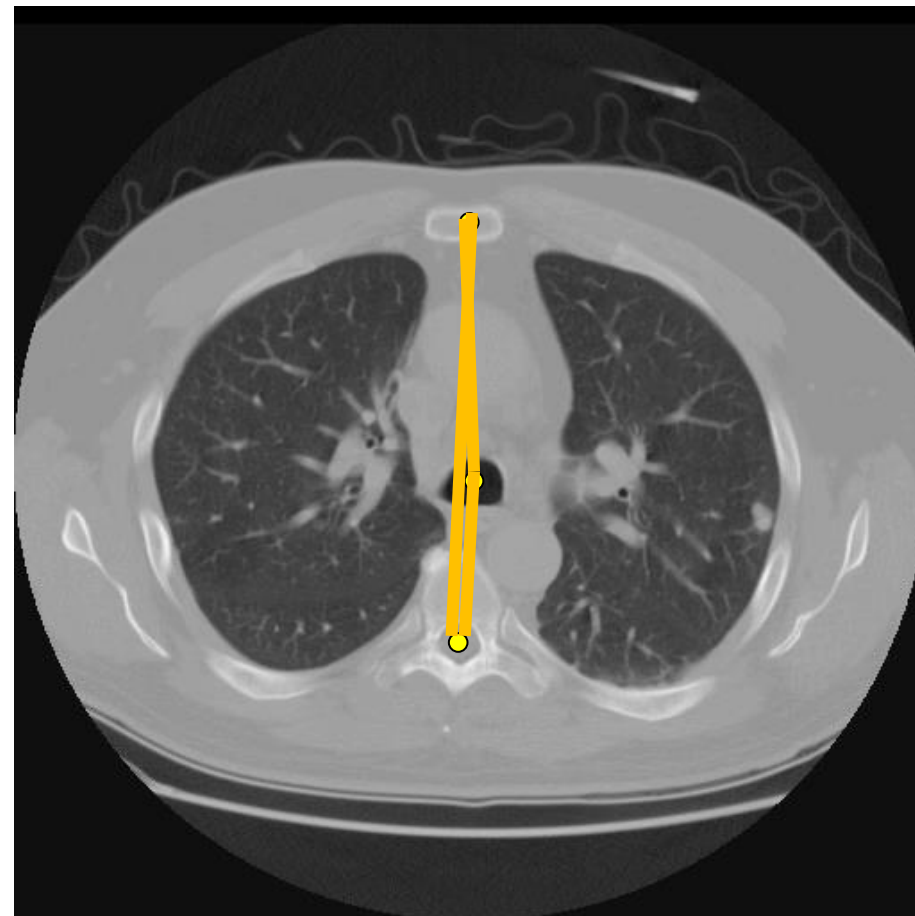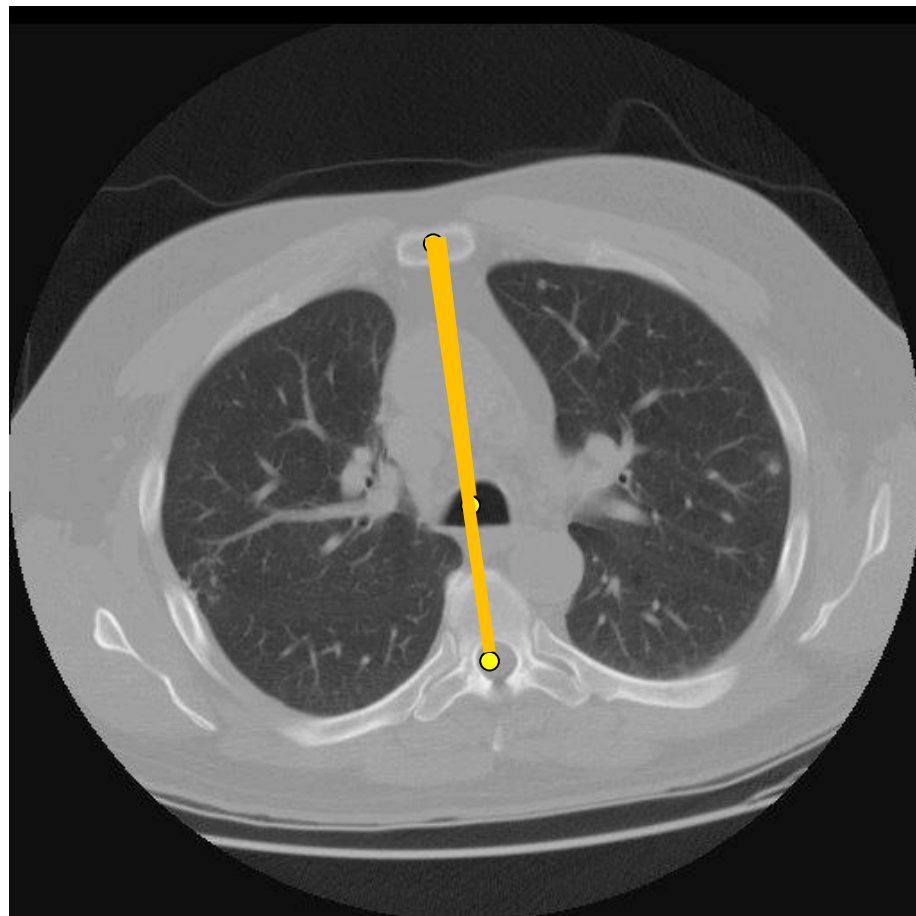
Number of unknowns: 3

$\Rightarrow$ We need at least 3 equations and 3 landmarks
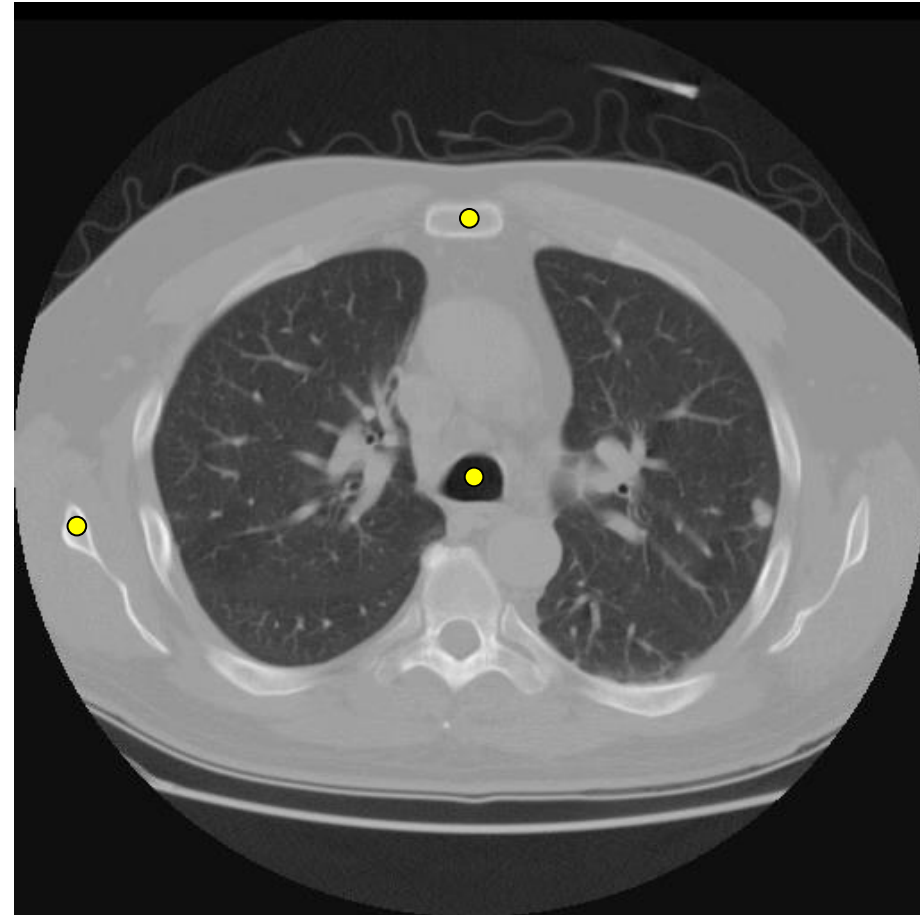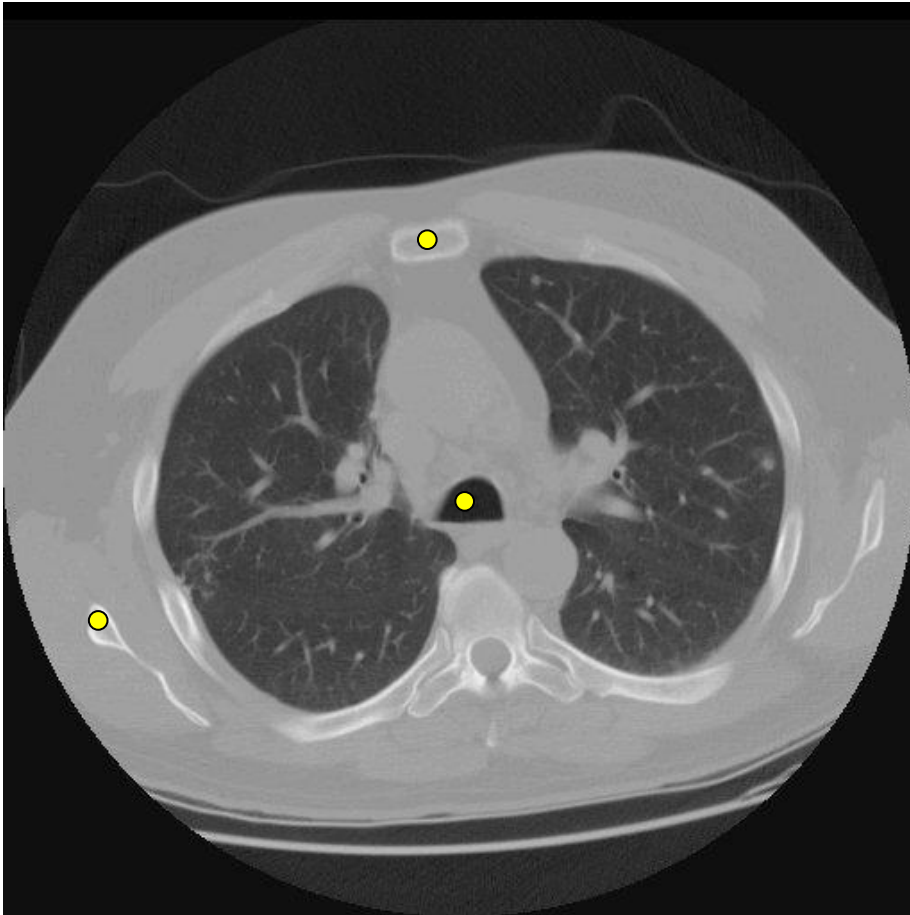
How about these three landmarks?

Angle difficult to discern:

Better these three landmarks:

Better these three landmarks:
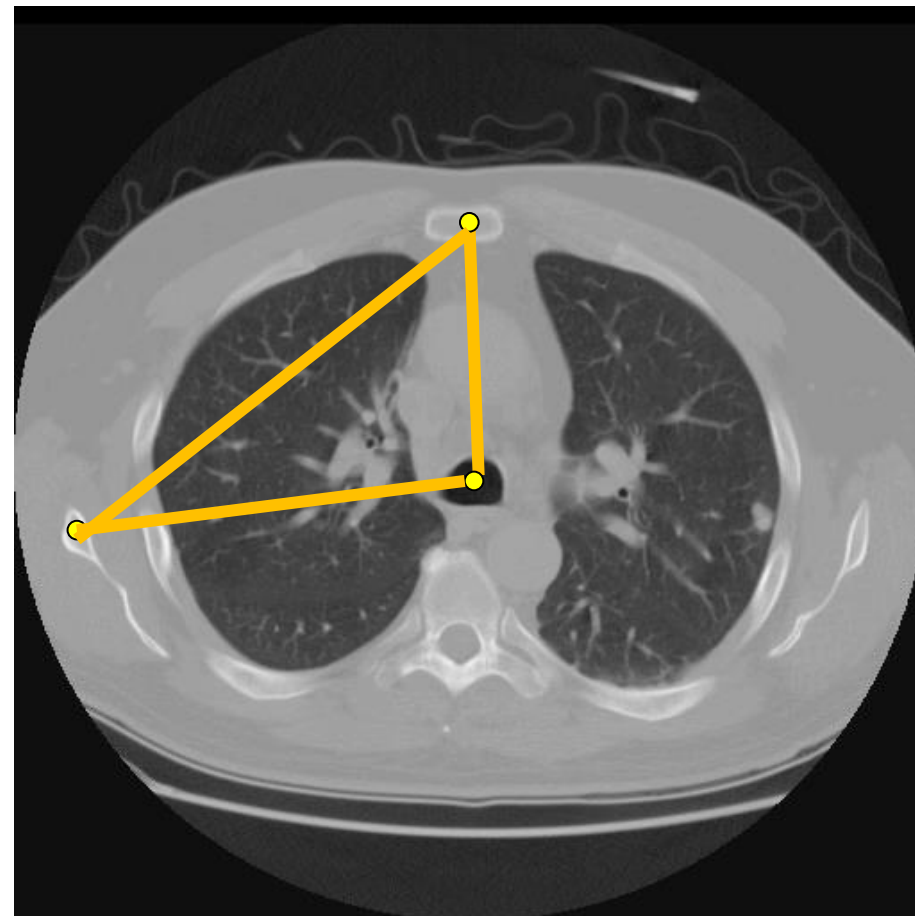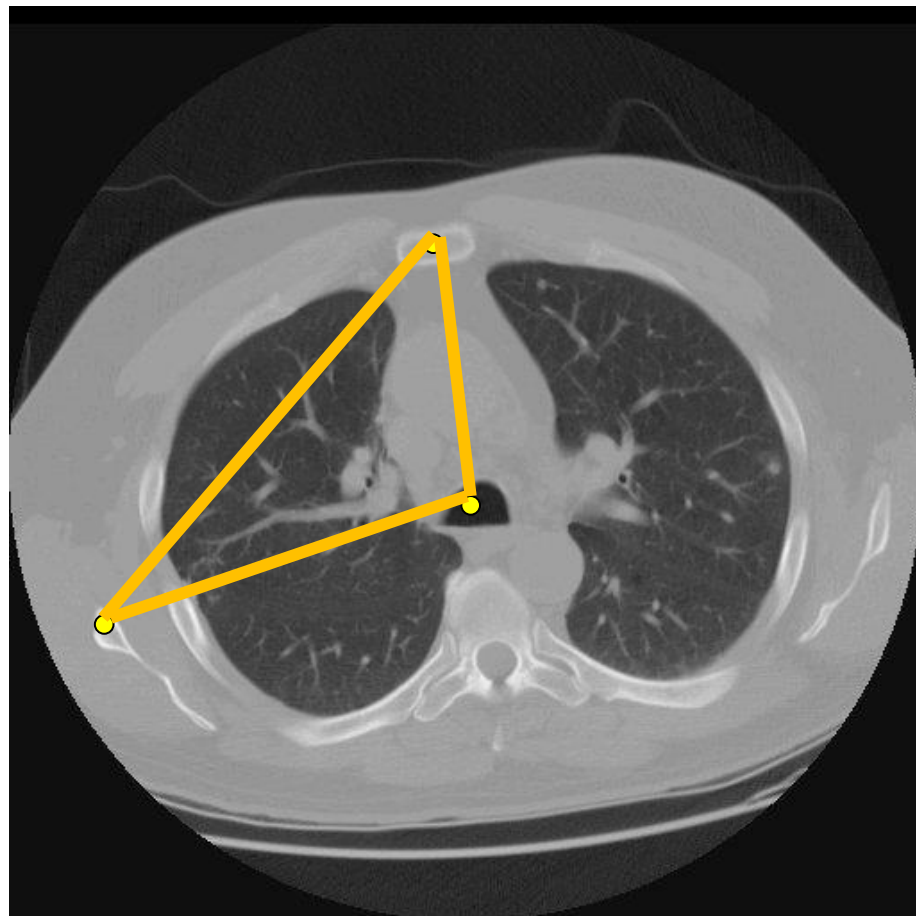
Algorithm Idea for 2D Alignment

First translation, then rotation:
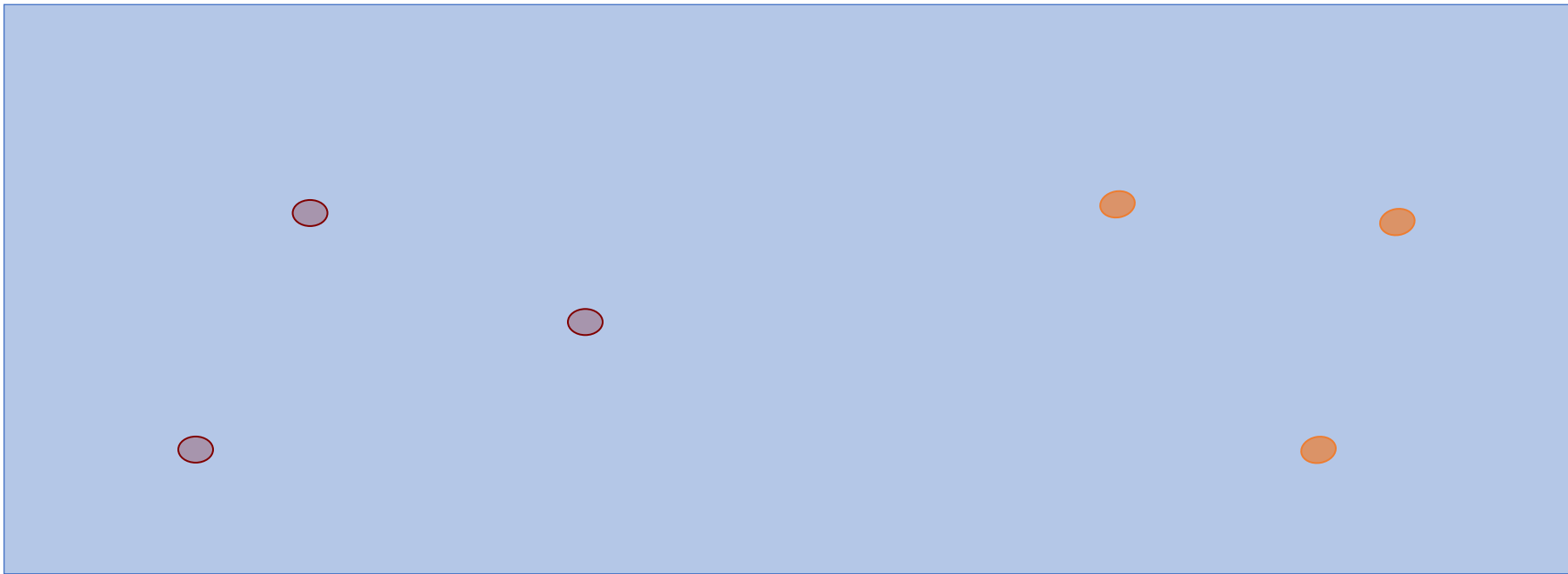
How can we represent rotation?

Derivation of Rotation Matrix:

Rotation in the image plane by angle θ :

Original
Position:

$$\begin{pmatrix} x_1 \\ y_1 \\ z_1 \end{pmatrix} = \begin{pmatrix} r \cos \alpha_1 \\ r \sin \alpha_1 \\ 1 \end{pmatrix}$$

Rotated
Position:

$$\begin{pmatrix} x_2 \\ y_2 \\ z_2 \end{pmatrix} = \begin{pmatrix} r \cos \alpha_2 \\ r \sin \alpha_2 \\ 1 \end{pmatrix}$$

$$\alpha_2 = \alpha_1 + \theta$$

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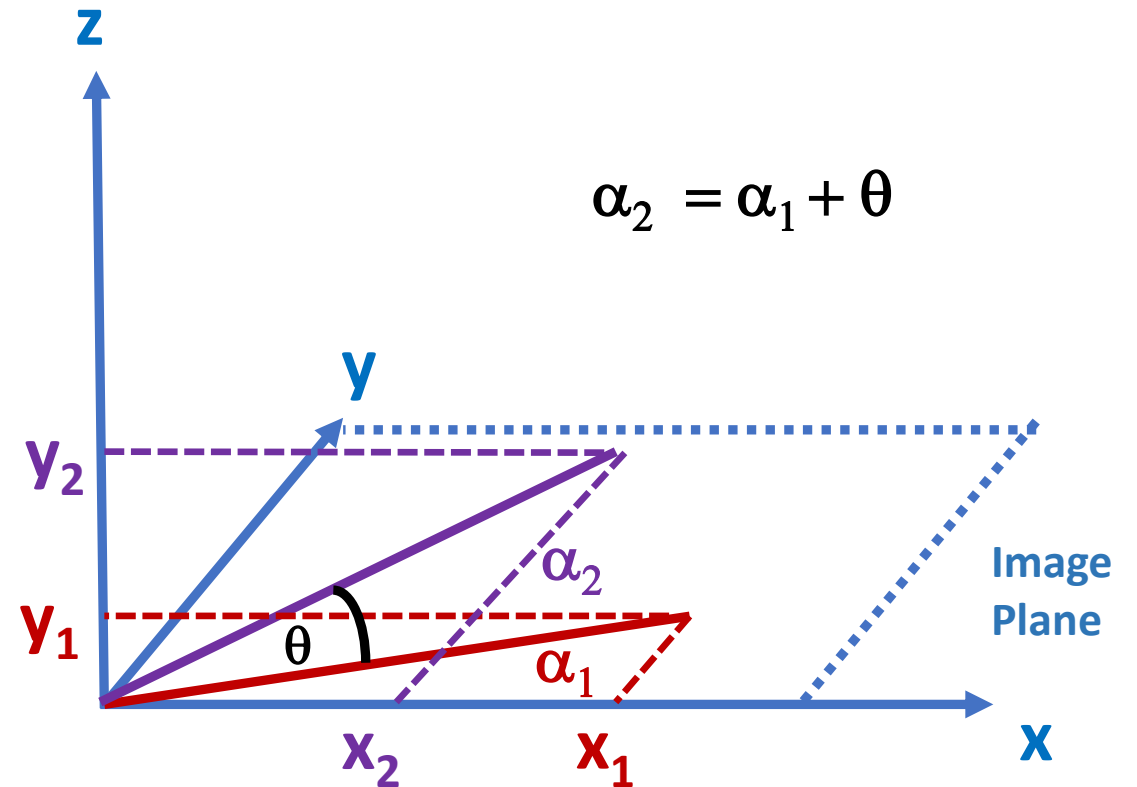
$$\alpha_2 = \alpha_1 + \theta$$

$$\begin{pmatrix} x_2 \\ y_2 \\ z_2 \end{pmatrix} = \begin{pmatrix} r\cos\alpha_2 \\ r\sin\alpha_2 \\ 1 \end{pmatrix}$$

Image Plane

$$\begin{pmatrix} x_2 \\ y_2 \\ z_2 \end{pmatrix} = \begin{pmatrix} r\cos\alpha_2 \\ r\sin\alpha_2 \\ 1 \end{pmatrix}$$

$$\alpha_2 = \alpha_1 + \theta$$

Image Plane
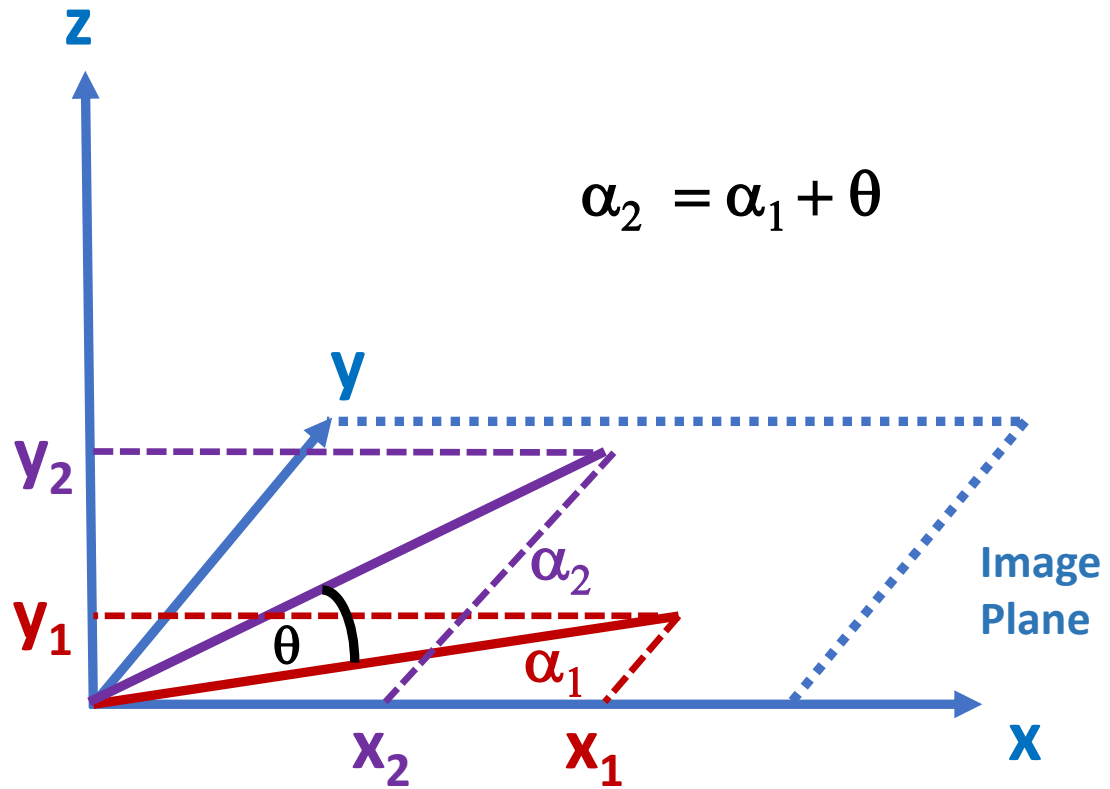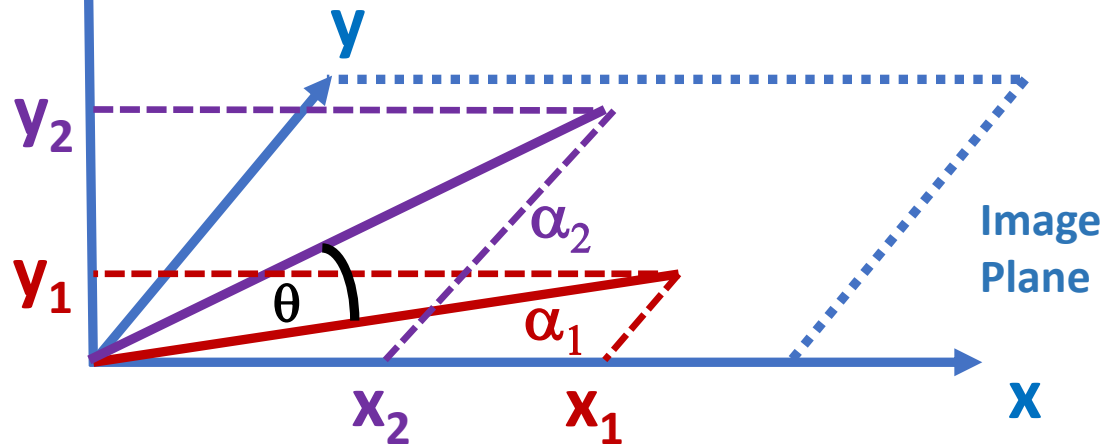
$$R = \begin{pmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

R is an orthonormal matrix = columns (rows) add up to 1 and are perpendicular to each other (dot product = 0)

Algorithm Idea for 2D Alignment

First translation, then rotation:
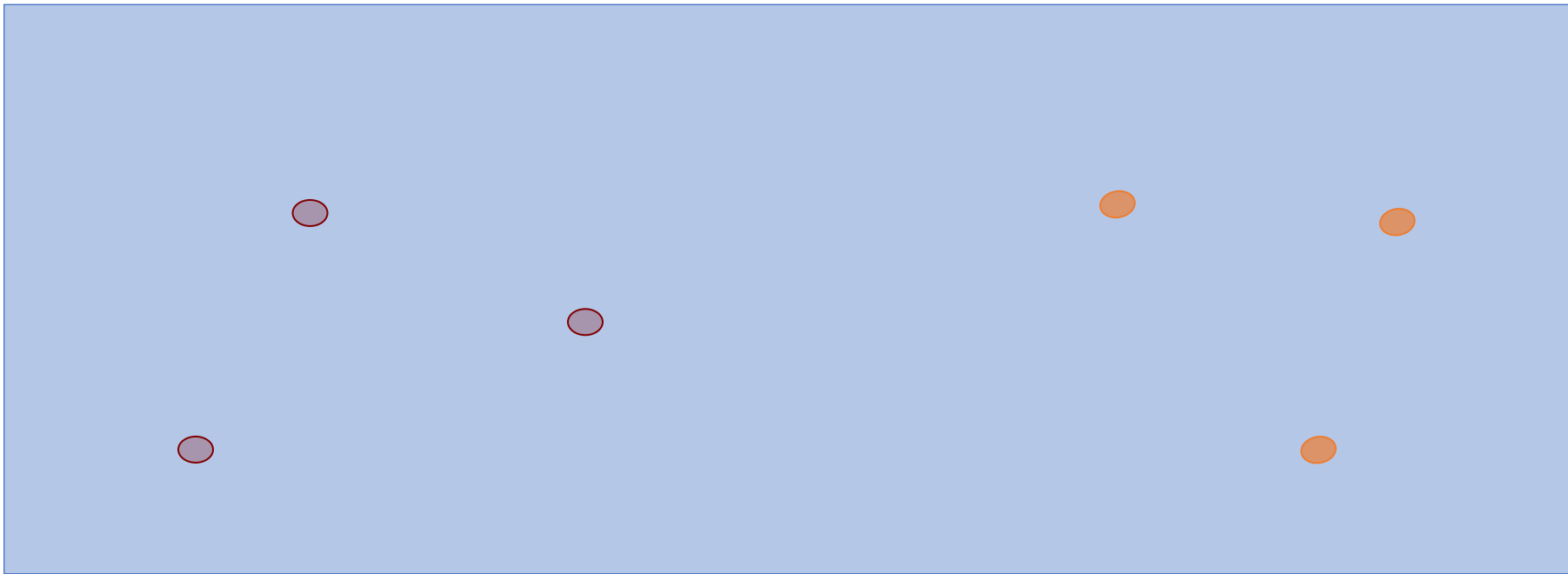
Right & Left Coordinate Systems

$$R = \begin{pmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

$$\mathbf{R}\, \boldsymbol{r}_l + \boldsymbol{r}_o = \boldsymbol{r}_r$$

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Which Equation Describes the 2D Alignment?
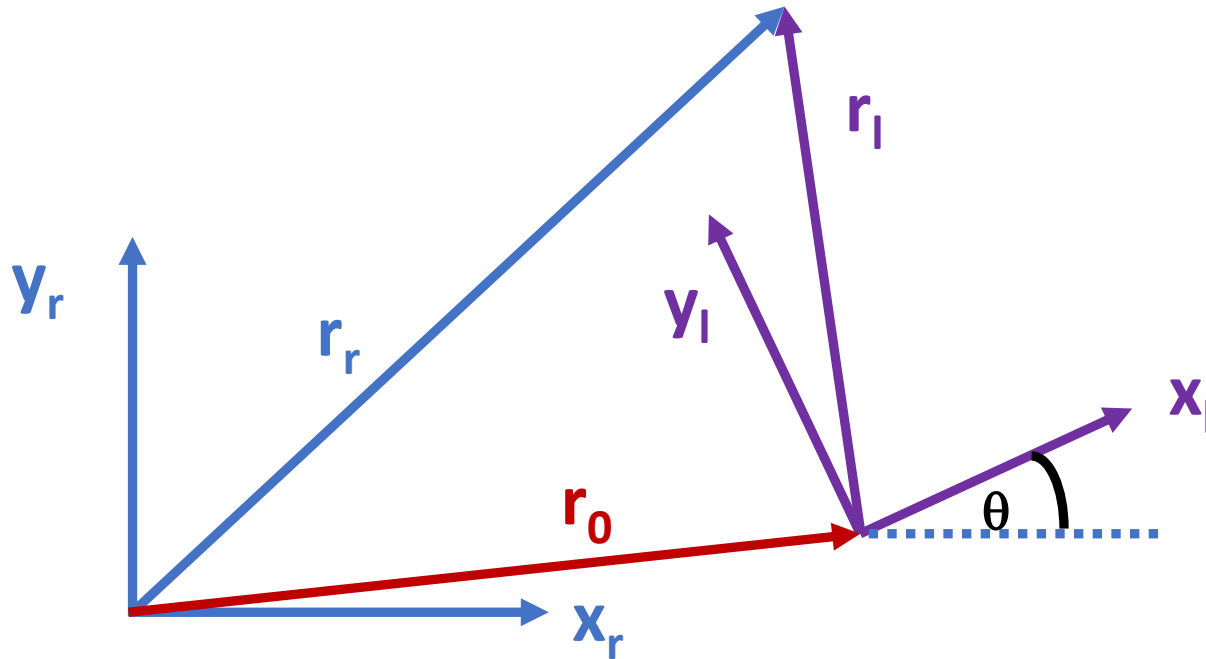
$$R = \begin{pmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

$$\mathbf{R}\, \boldsymbol{r}_l + \boldsymbol{r}_o = \boldsymbol{r}_r$$

How Many Unknowns, How Many Equations?

Unknowns: Rotation angle θ and translation vector $r_0 = (x_o, y_o)^T$

Number of unknowns: 3

We need at least 3 equations and 3 landmarks

R = rotation matrix, r_l = left landmark, r_r = right landmark

$$\mathbf{R}\,\boldsymbol{r}_l + \boldsymbol{r}_o = \boldsymbol{r}_r$$

2D Absolute Orientation

Unknowns: Rotation angle θ and translation vector $(x_o, y_o)^T$

Number of unknowns = 3

Equation not linear: $\mathbf{R}\, \boldsymbol{r}_l + \boldsymbol{r}_o = \boldsymbol{r}_r$

$$R = \begin{pmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

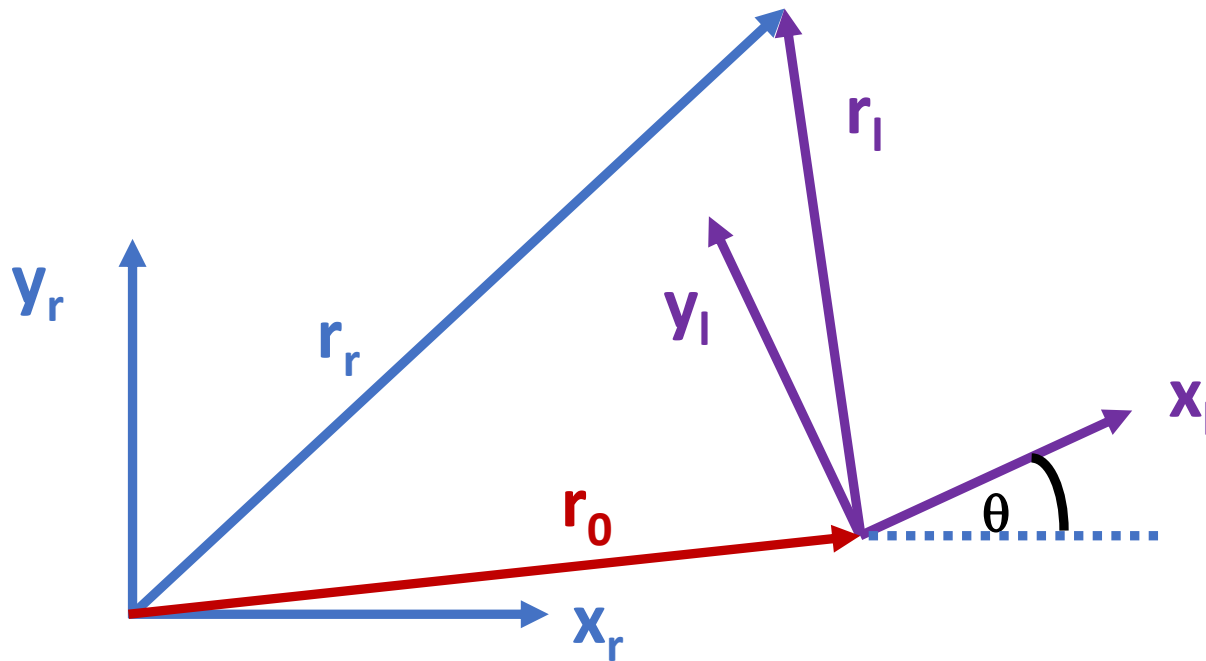1 equation per landmark pair $\boldsymbol{r}_{l,i},\, \boldsymbol{r}_{r,i}$ for i = 1, 2, and 3 ?

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Three landmarks to be found in both scans:
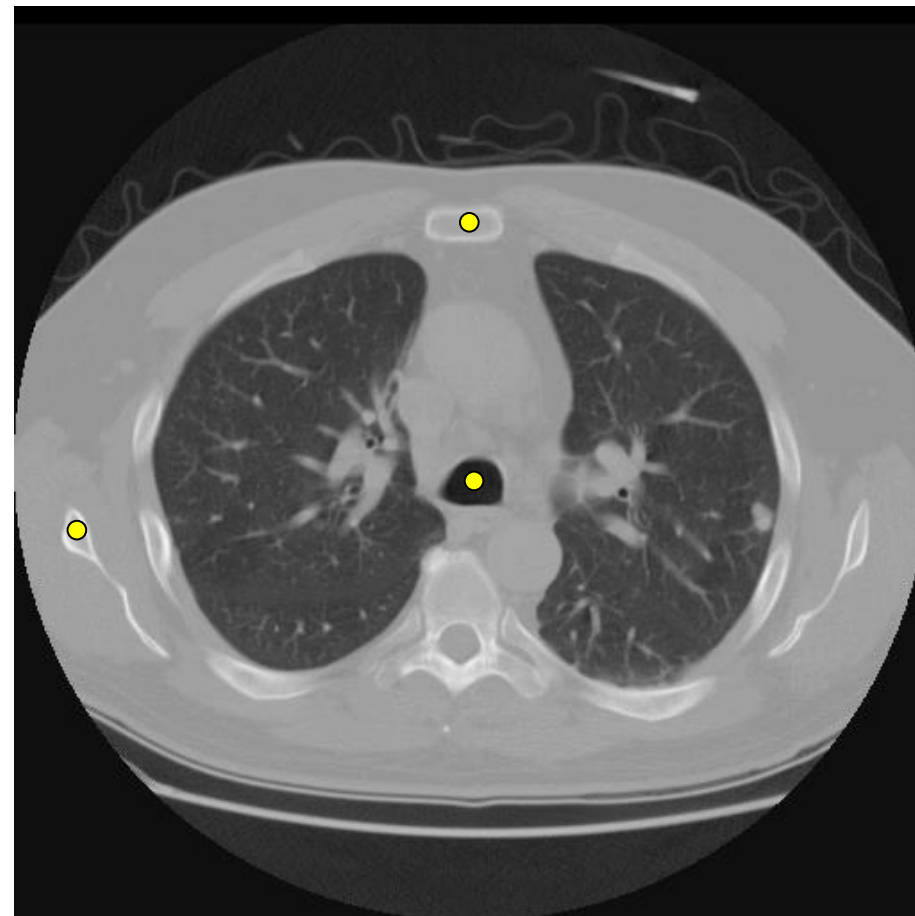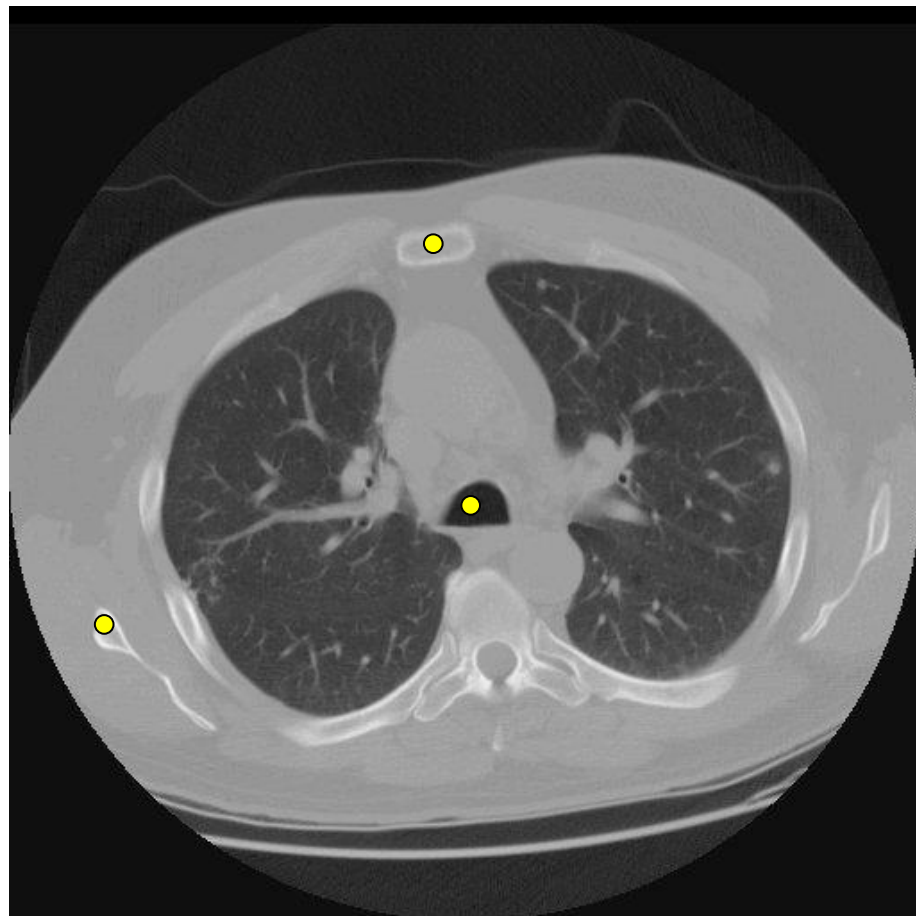
Use > 3 Landmarks, e.g.:
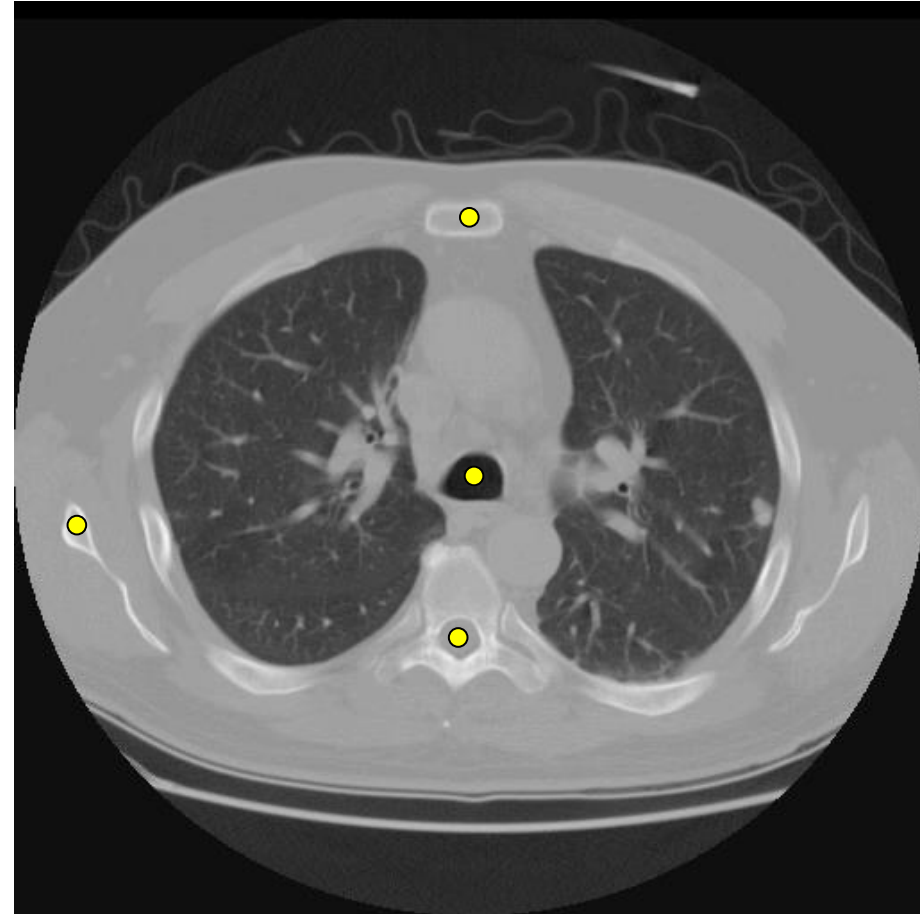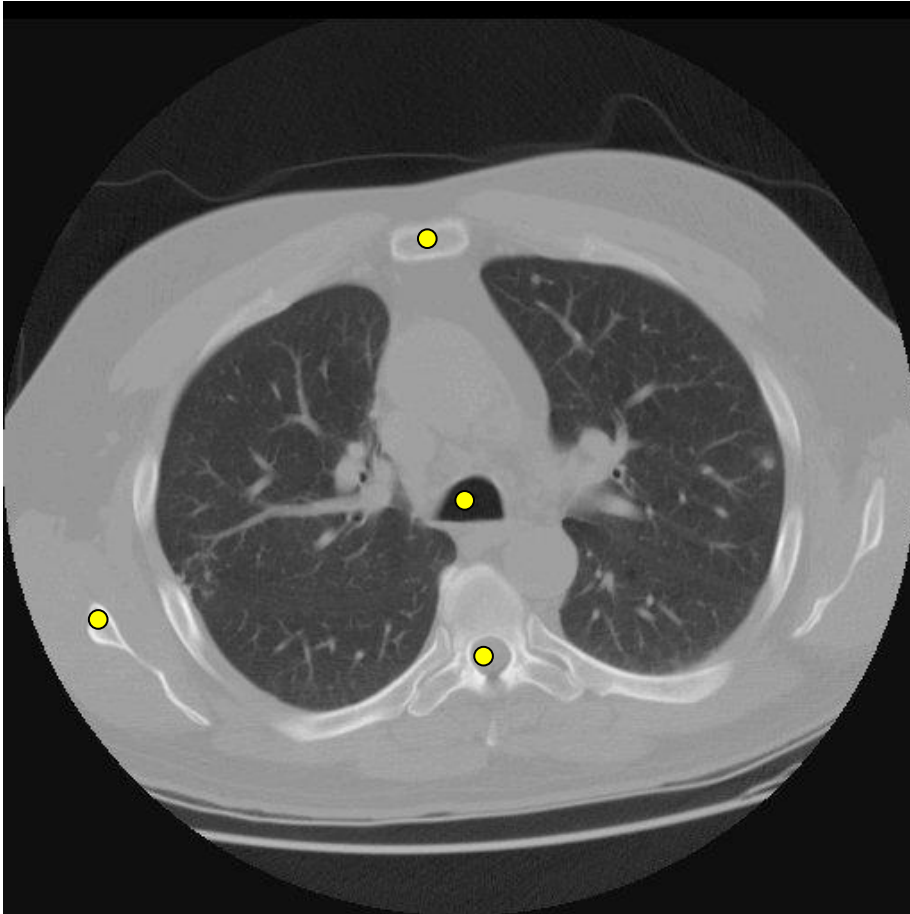
2D Absolute Orientation

Unknowns: Rotation angle θ and translation vector $(x_o, y_o)^\mathsf{T}$

We need at least 3 equations and 3 landmarks

$$\mathbf{R}\, \boldsymbol{r}_l + \boldsymbol{r}_o = \boldsymbol{r}_r$$

Better: Use n equations

1 equation per landmark pair $\boldsymbol{r}_{l,i}, \boldsymbol{r}_{r,i}$ for i = 1, …, n

How do you combine n versions of the equation above?

2D Absolute Orientation

n versions of the equations combined: Σ somehow?

$$\mathbf{R}\,\boldsymbol{r}_l + \boldsymbol{r}_o = \boldsymbol{r}_r$$

2D Absolute Orientation

n versions of the equations combined: Σ somehow?

$$\mathbf{R}\, \boldsymbol{r_l} + \boldsymbol{r_o} = \boldsymbol{r_r}$$

Subtract from r_r: $\qquad r_r - R\, r_l - r_0 = 0$

Computer Vision, Margrit Betke

2D Absolute Orientation

n versions of the equations combined: $\sum$ somehow?

$$\mathbf{R}\,\boldsymbol{r}_l + \boldsymbol{r}_o = \boldsymbol{r}_r$$

Subtract from r_r: $\qquad r_r - R\,r_l - r_0 = 0$

Sum: $\qquad \sum_{i=1}^{n} (r_{r,i} - R\,r_{l,i} - r_0) = 0$

for n landmark pairs, $\boldsymbol{r}_{l,i}, \boldsymbol{r}_{r,i}$, $i=1,..,n$

Least Squares Method (LSM)

Unknowns: Rotation angle θ and translation vector $(x_o, y_o)^{\mathsf{T}}$

Algorithm to determine unknowns may yield errors in equations:

$$r_{r,i} \ - \ R \, r_{l,i} - \ r_0 \ = \ ERROR$$

Goal of LSM: Minimize the error:

$$\min_{x_o, y_o, \theta} \sum_{i=1}^{N} \left\| \boldsymbol{r}_{r,i} - R \, \boldsymbol{r}_{l,i} - \boldsymbol{r}_o \right\|^2$$

Right (= Scan 1) & Left (= Scan 2) Landmarks

n landmarks

y_r

$r_{r,i}$

$r_{l,i}$

$r_{r,j}$

y_l

$r_{l,j}$

x_l

θ

r_0

x_r
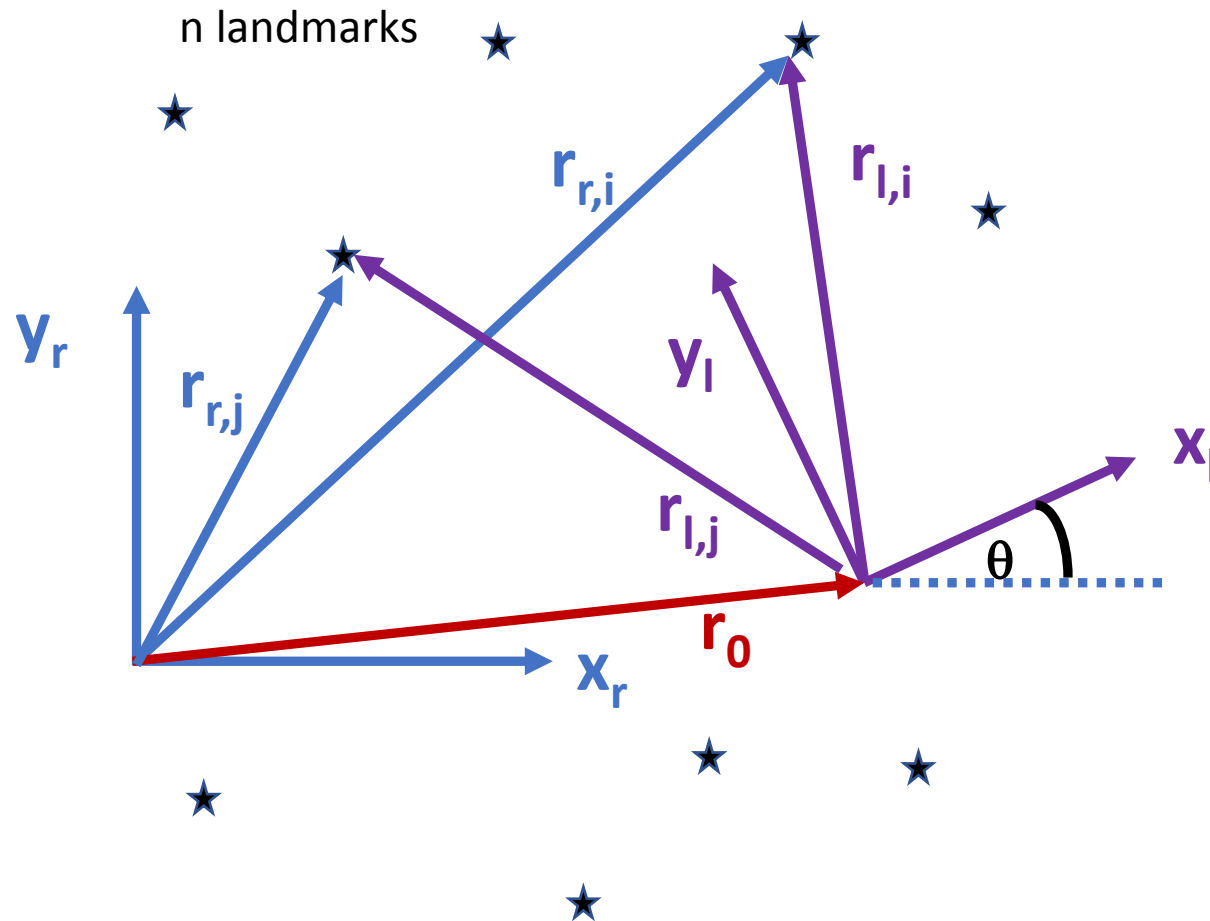
n landmark pairs:

$$r_{l,i}, r_{r,i}$$

for i=1,.., n

Least Squares Method (LSM)

Minimize the error:

$$\min_{x_o,y_o,\theta} \sum_{i=1}^{N} \|\boldsymbol{r}_{r,i} - R\,\boldsymbol{r}_{l,i} - \boldsymbol{r}_o\|^2$$

which is equivalent to:

$$\min_{x_o,y_o,\theta} \sum_{i=1}^{N} \left\| \begin{pmatrix} x_{r,i} \\ y_{r,i} \end{pmatrix} - \left(\begin{pmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{pmatrix} \begin{pmatrix} x_{l,i} \\ y_{l,i} \end{pmatrix} + \begin{pmatrix} x_0 \\ y_0 \end{pmatrix} \right) \right\|^2$$

or

$$\min_{x_0,y_0,\theta} \sum_{i=1}^{N} \left((x_{r,i} - (x_{l,i}\cos\theta - y_{l,i}\sin\theta + x_0))^2 + (y_{r,i} - (x_{l,i}\sin\theta + y_{l,i}\cos\theta + y_0))^2 \right)$$

Computer Vision, Margrit Betke

Trick to reduce number of unknowns:

- Compute centroids of landmarks in each image $(x_r, y_r)^T$ and $(x_l, y_l)^T$

  Left centroid $$\bar{\boldsymbol{r}}_l = \sum_{i=1}^{n} \boldsymbol{r}_{l,i}$$ and right centroid: $$\bar{\boldsymbol{r}}_r = \sum_{i=1}^{n} \boldsymbol{r}_{r,i}$$

- Assume: $$\bar{\boldsymbol{r}}_r = (\bar{x}_r, \bar{y}_r)^T \qquad \xleftarrow{\text{No Error!}} \qquad \bar{\boldsymbol{r}}_l = (\bar{x}_l, \bar{y}_l)^T$$

- That means: $$\bar{\boldsymbol{r}}_r - R\,\bar{\boldsymbol{r}}_l - \boldsymbol{r}_0 = 0$$

- Or:

$$\bar{x}_r - (\bar{x}_l \cos\theta - \bar{y}_l \sin\theta + x_0) = 0$$

$$\bar{y}_r - (\bar{x}_l \sin\theta + \bar{y}_l \cos\theta + y_0) = 0$$

CS 585: Image and Video Computing
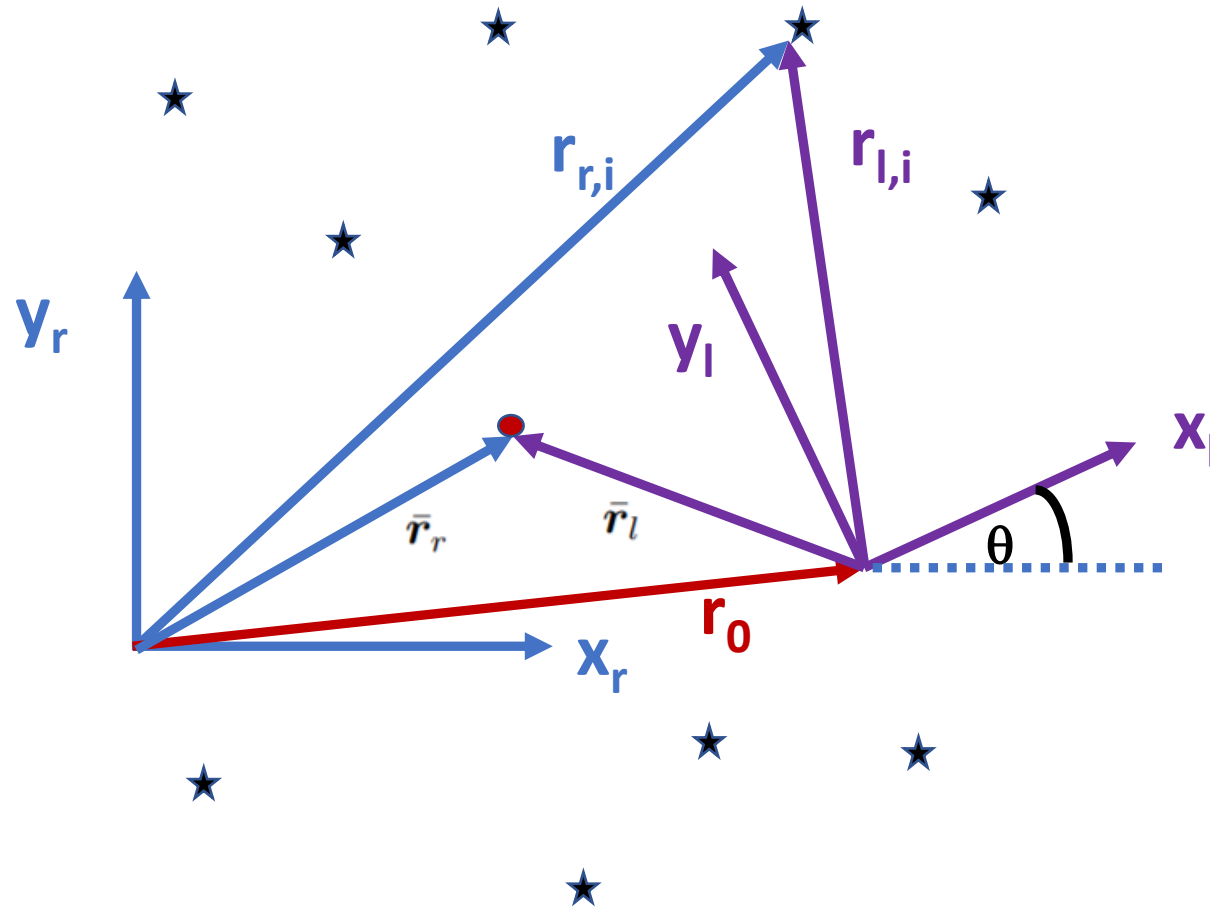
Centroids = Origin of New Coordinate System

$$\bar{r}_r = \sum_{i=1}^{n} r_{r,i}$$

$$\bar{r}_l = \sum_{i=1}^{n} r_{l,i}$$

Centroids = Origin of New Coordinate System
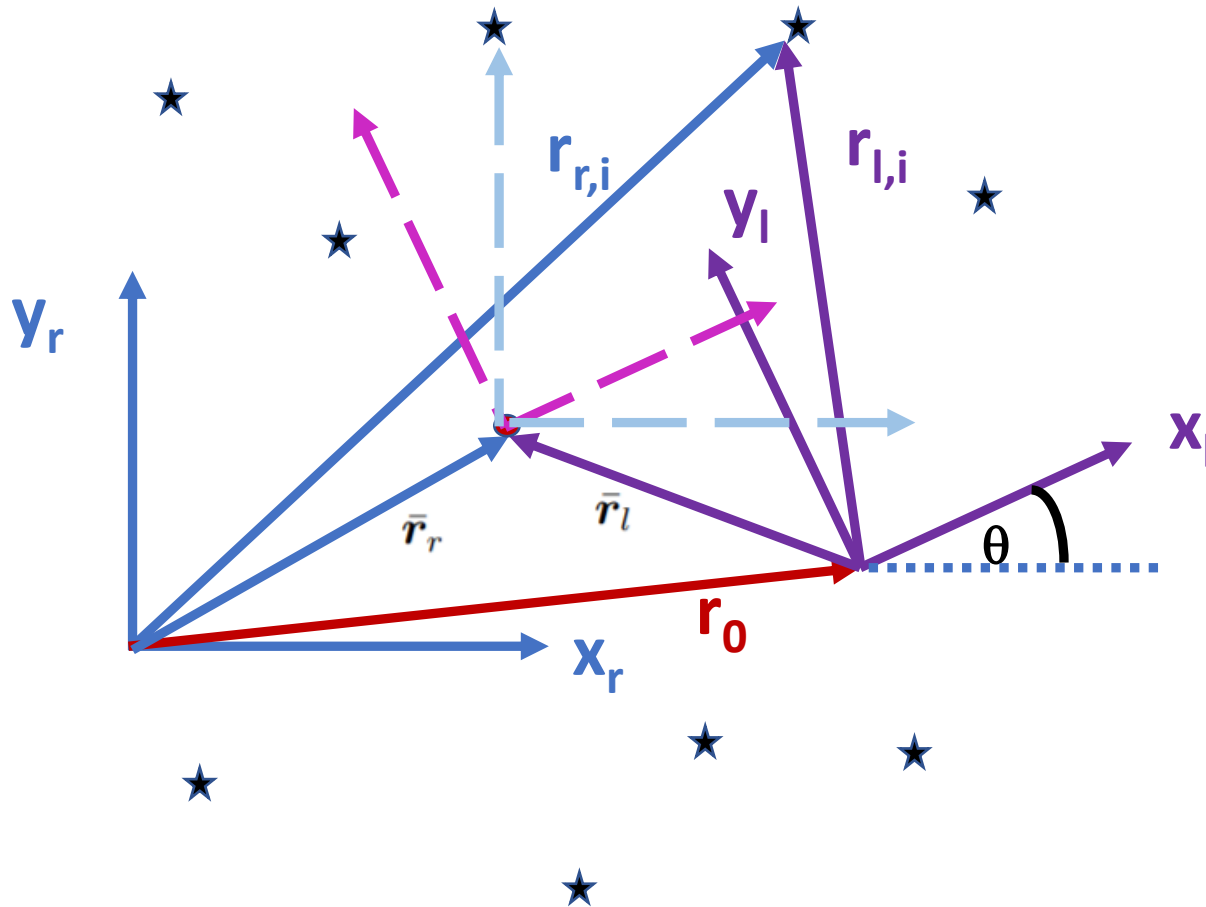
$$\bar{r}_r = \sum_{i=1}^{n} r_{r,i}$$

$$\bar{r}_l = \sum_{i=1}^{n} r_{l,i}$$

Centroids = Origin of New Coordinate System
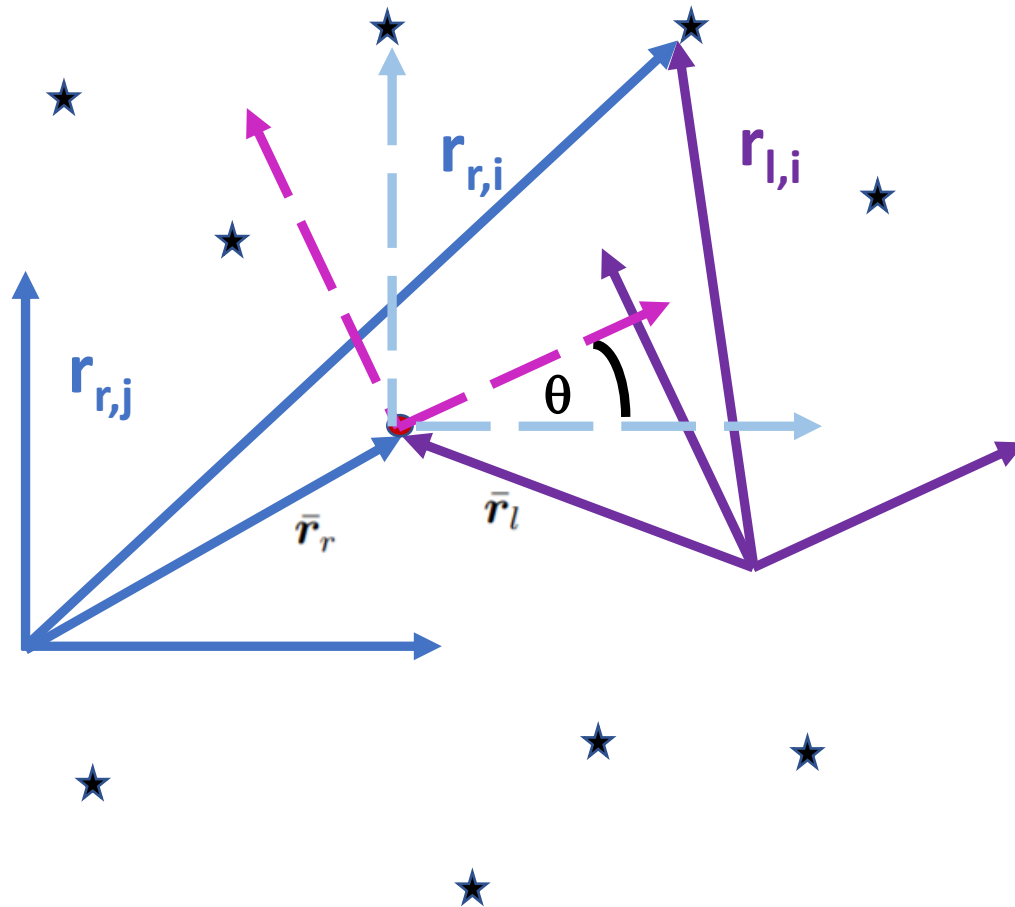
Centroids = Origin of New Coordinate System
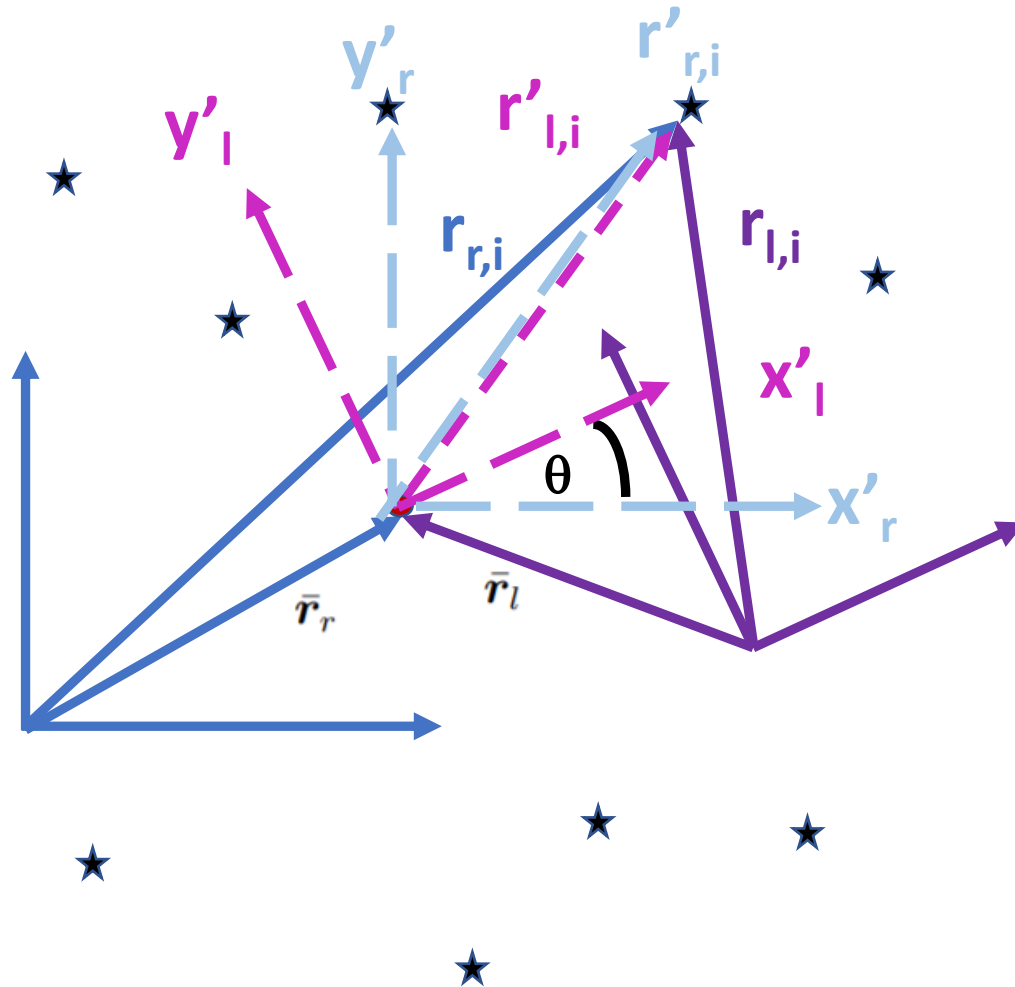
$$x_l = \bar{x}_l + x_l'$$

$$y_l = \bar{y}_l + y_l'$$

$$x_r = \bar{x}_r + x_r'$$

$$y_r = \bar{y}_r + y_r'$$

Centroids = Origin of New Coordinate System
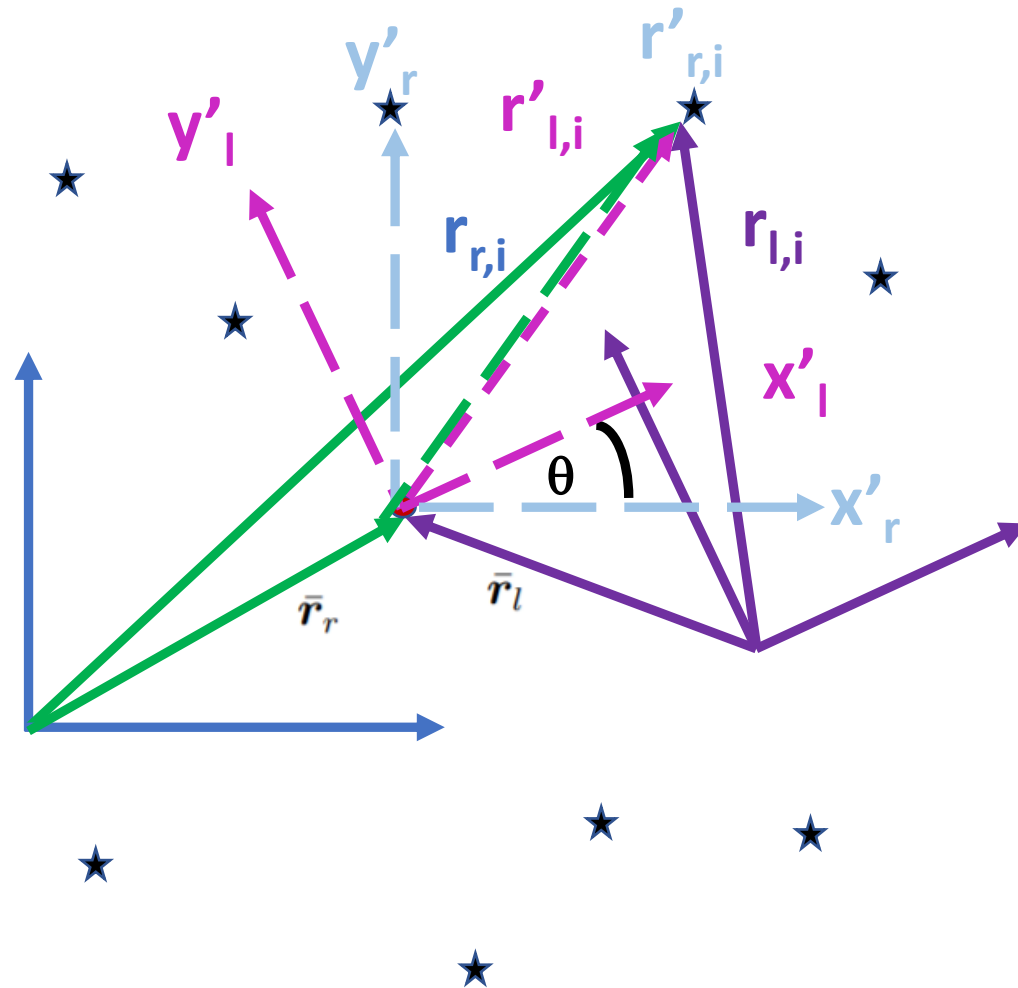
$$x_l = \bar{x}_l + x'_l$$

$$y_l = \bar{y}_l + y'_l$$

$$x_r = \bar{x}_r + x'_r$$

$$y_r = \bar{y}_r + y'_r$$

Centroids = Origin of New Coordinate System
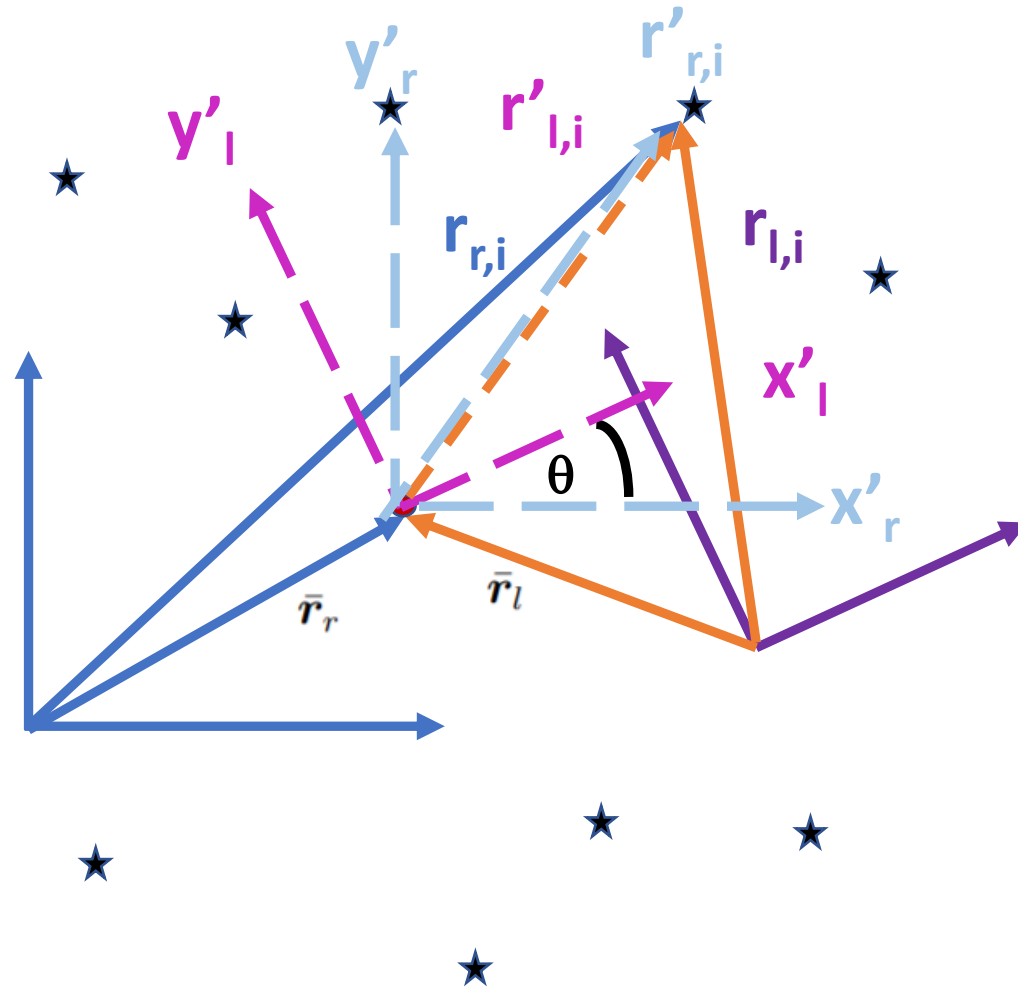
$$x_l = \bar{x}_l + x'_l$$

$$y_l = \bar{y}_l + y'_l$$

$$x_r = \bar{x}_r + x'_r$$

$$y_r = \bar{y}_r + y'_r$$

Convert Original LSM into Coordinate-Transformed LSM:

$$\min_{x_0, y_0, \theta} \sum_{i=1}^{N} ((x_{r,i} - (x_{l,i} \cos\theta - y_{l,i} \sin\theta + x_0))^2 + (y_{r,i} - (x_{l,i} \sin\theta + y_{l,i} \cos\theta + y_0))^2)$$

$$\min_{\theta} \sum_{i=1}^{N} ((x'_{r,i} - (x'_{l,i} \cos\theta - y'_{l,i} \sin\theta))^2 + (y'_{r,i} - (x'_{l,i} \sin\theta + y'_{l,i} \cos\theta))^2$$

Advantage? No translation vector $(x_o, y_o)^\mathsf{T}$
Only one variable θ

$$\min_{x_0,y_0,\theta} \sum_{i=1}^{N} ((x_{r,i} - (x_{l,i} \cos\theta - y_{l,i} \sin\theta + x_0))^2 + (y_{r,i} - (x_{l,i} \sin\theta + y_{l,i} \cos\theta + y_0))^2)$$

$$\min_{\theta} \sum_{i=1}^{N} ((x'_{r,i} - (x'_{l,i} \cos\theta - y'_{l,i} \sin\theta))^2 + (y'_{r,i} - (x'_{l,i} \sin\theta + y'_{l,i} \cos\theta))^2$$

CS 585: Image and Video Computing

Solve Transformed LSM Problem:

- Take derivative with respect to θ.

- Set result equal to zero.

- The terms with factors $\sin\theta\cos\theta$, $\sin^2\theta$, and $\cos^2\theta$ cancel each other.

- The only remaining terms include $\sin\theta$ and $\cos\theta$.

- Collect the terms that include $\sin\theta$ on one side of the equation and $\cos\theta$ on the other.

- Divide by $\cos\theta$ to yield an expression with $\tan\theta$:

- Equation 1:

$$\tan\theta = \frac{\sum_{i=1}^{n}(y'_{r,i}x'_{l,i} - x'_{r,i}y'_{l,i})}{\sum_{i=1}^{n}(x'_{r,i}x'_{l,i} + y'_{r,i}y'_{l,i})}$$

Equation 2:

$$\boldsymbol{r}_0 = \bar{\boldsymbol{r}}_r - R\,\bar{\boldsymbol{r}}_l$$

Algorithm for Image Alignment in 2D

Input: Landmarks in two images

1. Determine corresponding point pairs.

2. Compute centroids of landmarks in each image $(x_r, y_r)^T$ and $(x_l, y_l)^T$

3. Transform point coordinates into coordinate systems with centroids serving as the origins.

4. Compute θ with Equation 1 (above)

5. Compute $(x_o, y_o)^T$ with Equation 2 (above)

Output: Rotation angle θ and translation vector $(x_o, y_o)^T$

Absolute Orientation in 3D

Definition:

Compute the parameters that describe a 3D rigid body alignment

= Determine 3 rotation angles and a 3D translation vector or

= Determine a 3x3 rotation matrix R and a 3D translation vector r_o or

$$\mathbf{R}\, \boldsymbol{r}_l + \boldsymbol{r}_o = \boldsymbol{r}_r$$

= Determine a unit quaternion $\overset{o}{q}$ and a 3D translation vector

What you need to know about Quaternions:

- Vector with 4 components: 1 scalar, 3 "imaginary" parts
- How multiplications of i, j, and k work
- How multiplications of quaternions work (not commutative)
- How represent a quaternion multiplication by a 4x4 orthogonal skew-symmetric matrix
- What is the magnitude of a quaternion? The conjugate?
- The dot product of two quaternions is the regular 4D dot product.
- What is a unit quaternion? Why does it represent a 3D rotation?
- Rotation preserves length of 3D vectors and angles between them
- Composition of rotations = multiplications of quaternions
- How to compute a rotation matrix from a quaternion

Algorithm for Absolution Orientation in 3D

Input: Landmarks in two 3D scans

1. Determine corresponding point pairs.

2. Compute centroids of landmarks in each image $(x_r, y_r, z_r)^T$ and $(x_l, y_l, z_l)^T$

3. Transform point coordinates into coordinate systems with centroids serving as the origins.

4. Compute quaternion & rotation matrix (on Zoom whiteboard)

5. Compute translation (on Zoom whiteboard)

Output: Rotation matrix R and translation vector $(x_o, y_o, z_o)^T$

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COVID-19 CT Scan Evaluation Process that I am Proposing:

Given a pair of CT scans:
Compute 3D Alignment

Semi-automatic Evaluation:
1. Radiologist annotates regions of interest with consolidation in scan 2. AI system finds all voxels with consolidation in scan 2 OR:
Automatic Evaluation:
AI system detects & measures the volume of the consolidation in scan 1 and scan 2

AI system evaluates change in volume of region: Increase: Patient fares worse
          Decrease: Patient is getting better
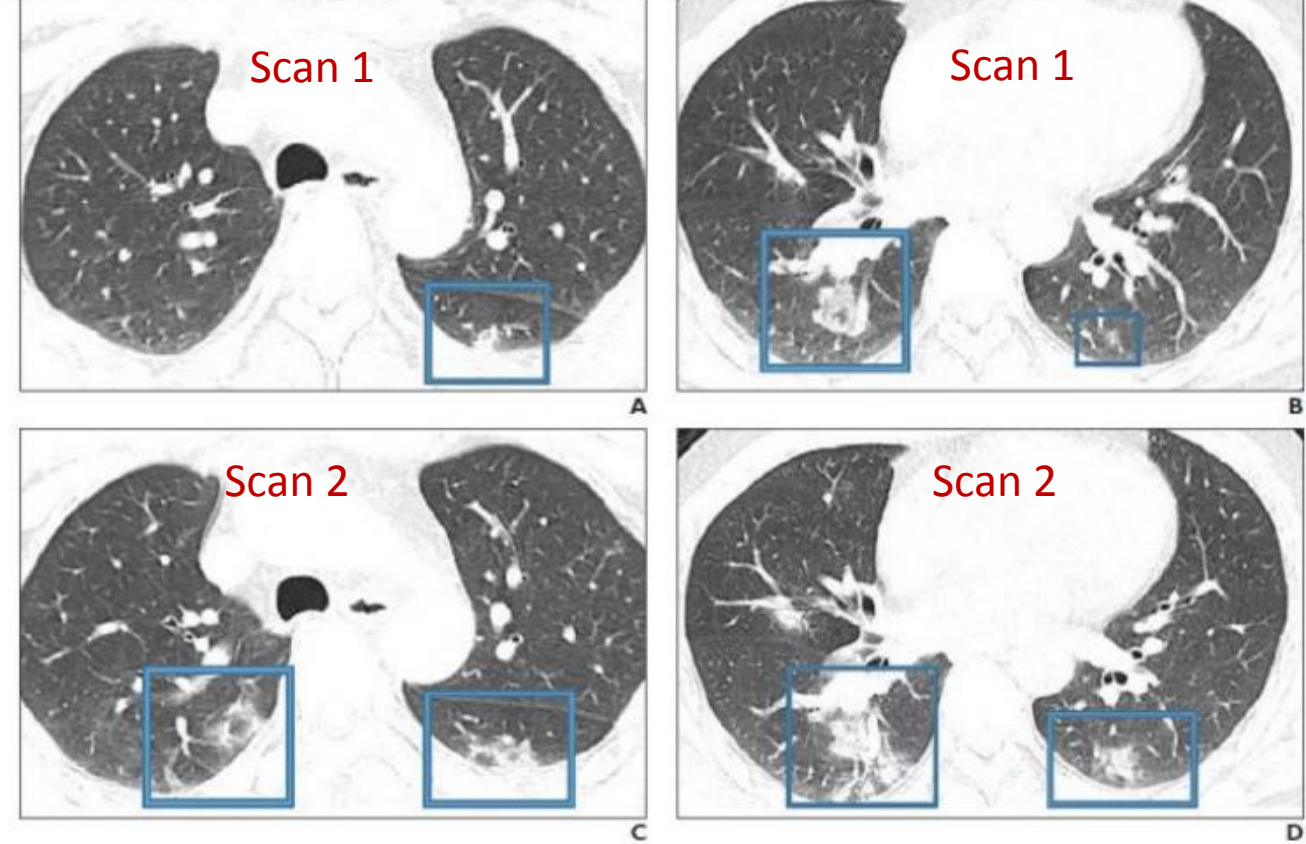
CAPTION
A and B, Initial CT images obtained show small round areas of mixed ground-glass opacity and consolidation (rectangles) at level of aortic arch (A) and ventricles (B) in right and left lower lobe posterior zones. C and D, Follow-up CT images obtained 2 days later show progression of abnormalities (rectangles) at level of aortic arch (C) and ventricles (D), which now involve right upper and right and left lower lobe posterior zones.

CREDIT
American Journal of Roentgenology (AJR)

Research Questions

Devil's Advocate: Such an AI system may not matter – the radiologist can glance at the two CT scans and diagnose the patient's status.

Arguments for AI system:

- AI could quantify the (partial) filling of air spaces more accurately and timely

- AI may be able to predict patient outcome from scan 1 alone, helping to assess COVID19 severity and guide treatment

- AI may be able to combine the interpretation of CT scans with other features (patient's age, preexisting conditions, symptoms, etc)

Research Questions

- How many scan pairs to we need to train an AI system sufficiently?

- Where do we find this data?

- What AI learning model should we use?
  - Deep learning needs lots of data – can we bootstrap by using CT scan pairs published for lung cancer detection project (see Kaggle.com)
  - In lung cancer analysis, deep learning works much better if scans are geometrically aligned -- *This lecture material matters!*
  - Can we adapt our approach on "Acute Respiratory Distress Syndrome:" PhD thesis by my student William Mullally (2009)?

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Computational Models of Airways Trees

Explaining Clustered Ventilation Defects Via a Minimal Number of Airway Closure Locations

W. Mullally, M. Betke, M. Albert, and K. Lutchen

Annals of Biomedical Engineering, 37(2): 286-300, February 2009

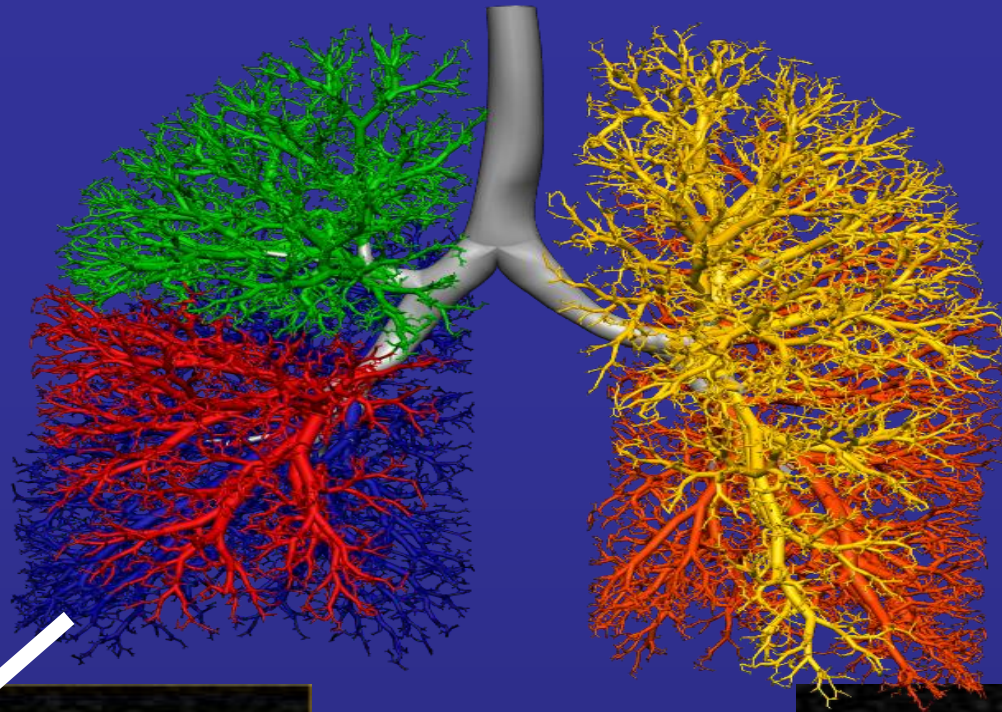**Hyperpolarized Helium MRI**

Non-Constricted Lung

Constricted Lung

Hyperpolarized Helium MRI

Non-Constricted Lung

Constricted Lung

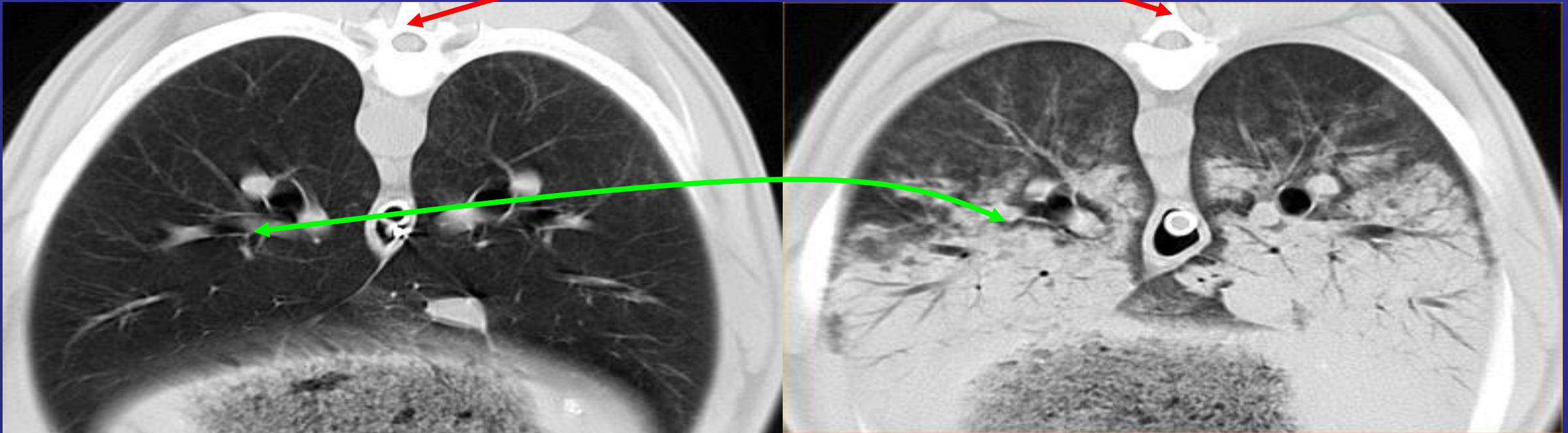Ventilation caused by physical structure of lung and airway tree

Generic airway tree

How can we align physically-changed regions (that look different)?

Healthy Sheep Lung

ARDS inflicted lung under air pressure

Research Questions

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Summary
Research Tasks:

- AI could quantify the (partial) filling of air spaces more accurately and timely

- AI may be able to predict patient outcome from scan 1 alone, helping to assess COVID19 severity and guide treatment

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Research Questions:

- What AI learning model should we use?

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- Where do we find this data?

Potentially: Discovery Viral Infection and Respiratory Illness Universal Study:

COVID-19 Registry and Validation of Critical Care Data Dictionary (C2D2). > 200 ICU's around the world participate. BU's Dr. Allan Walkey is Co-PI.