Pythagoras, Plato and Eratosthenes:

Greek Models for Imaging Informatics

Brian E. Chapman, Ph.D.

Departments of Biomedical Informatics, Radiology, and Bioengineering

University of Pittsburgh

Imaging Informatics at the University of Pittsburgh

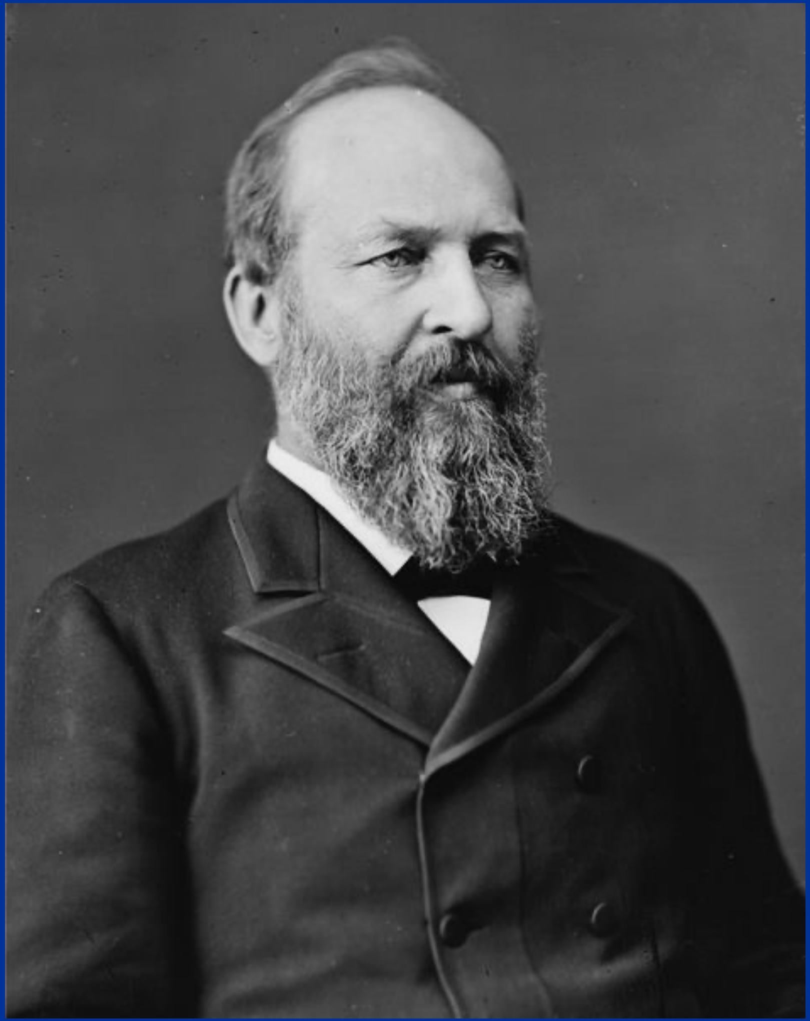
- Radiology Informatics
  - Clinical support, very little research
- Pathology Informatics
  - Clinical support ,some research
- Radiology Imaging Research
- Bioengineering
  - Visualization and Image Analysis Lab
- Biomedical Informatics?

Name it then Build it

- QUantitative Imaging Informatics Lab: QUIIL
  - Brian Chapman, PhD
  - Post-doc:
    - Xiaofei Song, PhD (soon)
  - Graduate Students: Holly Berty, Rich Wilson, Pooja Chatterjee, Patrice Jamison (hopefully)
  - Undergraduate students: Doug Nelson
  - Medical Students: Sean Lee, Katherin Pepperzak
  - Project Manager: Jeannie Irwin, PhD

Imagine the World Before Medical Imaging

- July 1881
  - President James A. Garfield Shot
    - Where was the bullet?
      - Leave it alone?
      - Go after it?
    - Died 80 days later untreated



Then Along Came Röntgen

And Mrs. Röntgen's Hand

Causing the…

- Repulsion of Mrs. Röntgen
- Banning of X-ray opera glasses in NYC
- Formation of Societies for the preservation of female modesty
- Creation of Radiology as a medical discipline

So the World Was Different

- March 30, 1981
  - Ronald Reagan shot
    - X-ray imaging showed precisely where the bullet was
    - Treated and fully recovered
    - (Maybe other things helped also)

So it is somewhat surprising that…

- Carl Jaffe: "No one in clinical [drug] trials takes radiology seriously." (CaBIG, Dec. 2005)
  1. The inability to quantitatively monitor therapy
  2. The inability to validate findings
  3. Lack of transparency and data sharing between institutions
  4. Failure to integrate clinical information in the image assessment
  5. The unreliability of site interpretations of the imaging studies

Others are not happy with radiology either

"Monumental achievements come with monumental costs."
(Meet You In Hell)

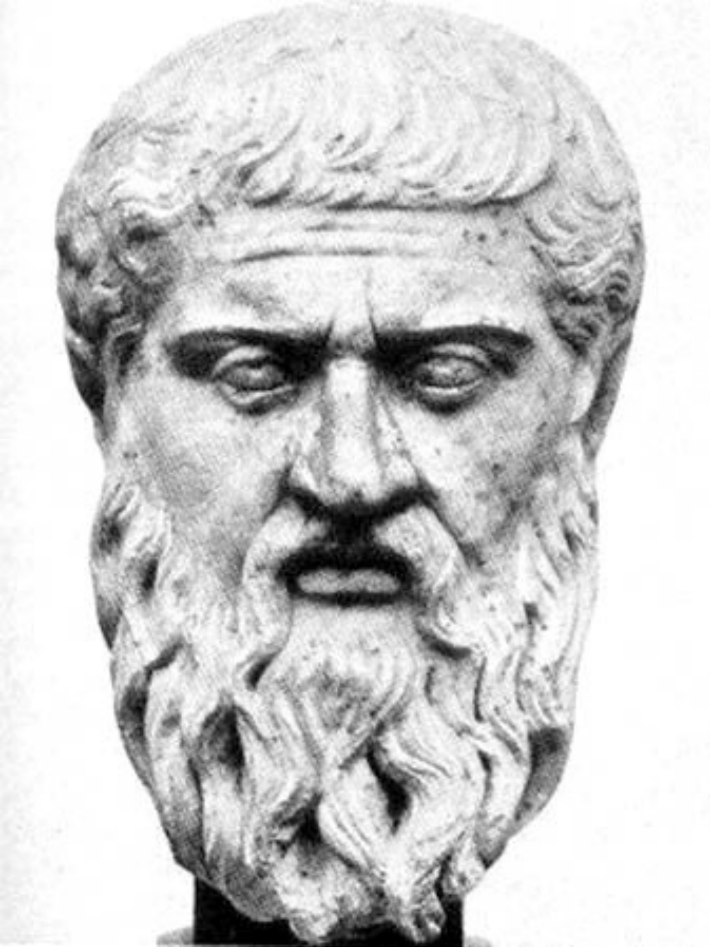
- Medicare medical imaging expenditures increased 20%/year since 1999
- Medicare spent $7 billion in 2005
- Radiation exposure
  - Underappreciated risk (BMJ 2004)
  - Medical sources = Natural sources

If we step back to Pythagoras

- ca. 570 to ca. 490 BCE
- Mystic, philosopher, mathematician?
- "Pythagoras is known for the *honor* he gives to number and for removing it from the practical realm of trade and instead pointing to correspondences between the behavior of number and the behavior of things."

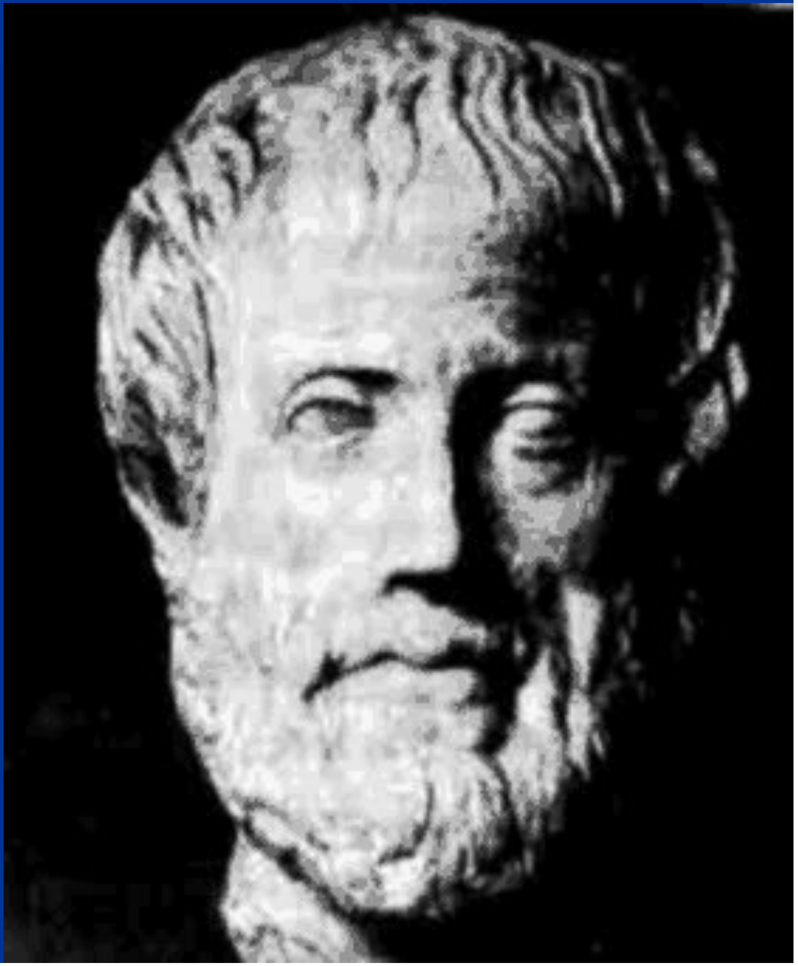
And then Forward a bit to Plato

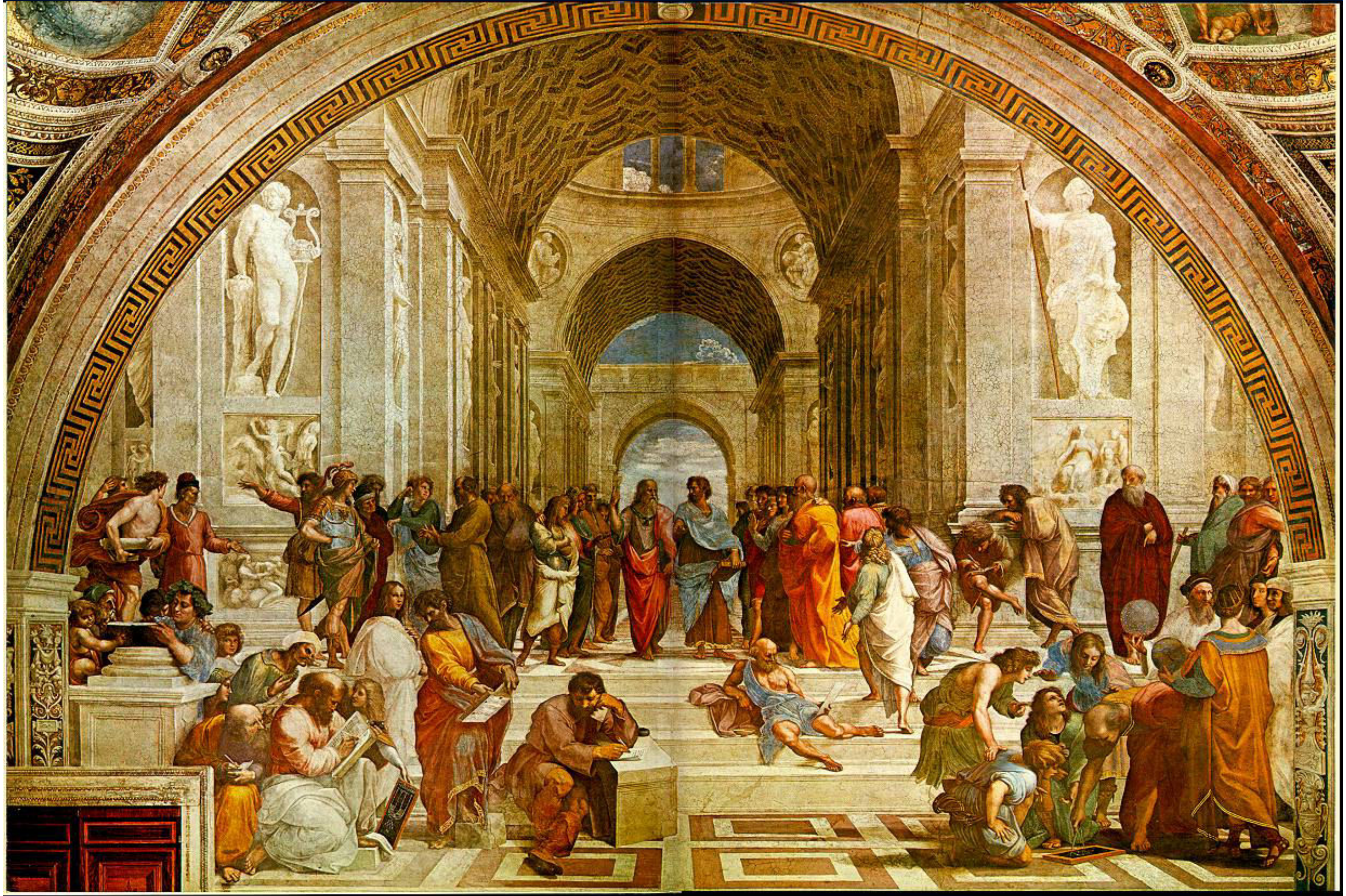
- 429–347 BCE.
- "*let no one ignorant of geometry enter"*
- *Ontology of mathematics*
- *Mostly a promoter*



After Plato, Aristotle

- 384–322 B.C.E.
- Emphasis on logic, empirical classification
  - Collecting constitutions
  - Grounded, systematic thinker





- Plato
  - The mystic pointing up to heaven
- Aristotle
  - The realist keeping things grounded

Plato and Pythagoras stand nearer to modern physical science than does Aristotle. The two former were mathematicians, whereas Aristotle was the son of a doctor, though of course he was not hereby ignorant of mathematics. The practical counsel to be derived from Pythagoras, is to measure, and thus to express quality in terms of numerically determined quantity. But the biological sciences, then and till our own time, have been overwhelmingly classificatory. Accordingly, Aristotle by his Logic throws the emphasis on classification

The popularity of Aristotelian Logic retarded the advance of physical science throughout the Middle Ages. If only the schoolmen had measured instead of classifying, how much they might have learnt!

Classification is necessary. But unless you can progress form classification to mathematics, your reasoning will not take you very far.

~Alfred North Whitehead, *Science and the Modern World*

Eratosthenes, the Model Librarian

- Born circa 285 BCE in Greek north African city
- Appointed head librarian of the Museum in Alexandria in 245 BCE
  - Literary critic
  - Historian
  - Mathematician
  - Pen-pal of Archimedes
  - Geographer

Erastosthenes' Measurements

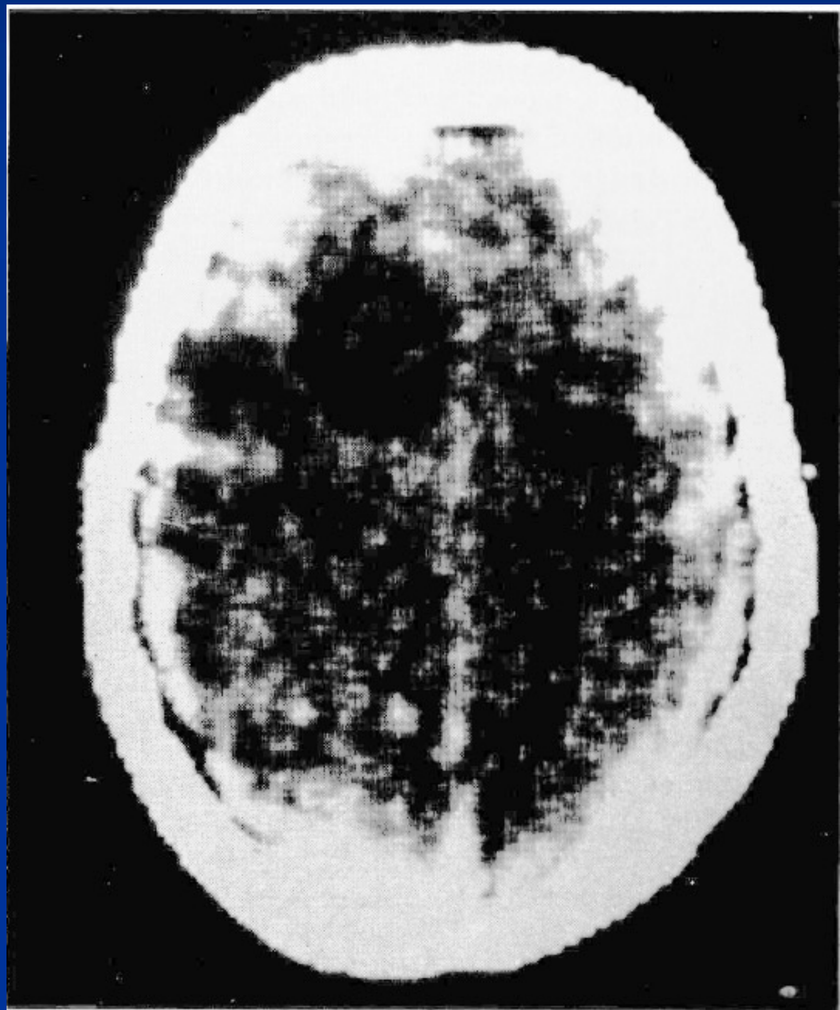
- Eratosthenes estimated the polar circumference of the earth as 252,000 stadia (Greeks liked whole numbers)
  - Depending on definition of stadia, this measurements is between a 1% underestimation or a 16% overestimation
- Also estimated the solar distance to within 16% error
- The patron saint of imaging informatics?

Motivation for Work

- Medical Imaging has developed some phenomenal technologies that have clearly transformed modern medicine.
- The impact of these technologies is not maximized because Radiology remains dominantly a qualitative rather than a quantitative discipline.

Was Quantification Always a Reasonable Expectation?

- Hounsfield didn't believe in images
- Viewed CT as a measuring device for generating a scalar number



What Kinds of Quantification?

- Physiological/functional
  - Xenon CT quantification of perfusion
- Compositional
  - Quantification of interstitial lung disease with HU
  - T2 quantification of HCC
- Morphological
  - Tortuosity of intracranial vessels

Editorial Aside

Addressing Jaffe's critiques is hard

1. Validation

Validation

- How often is a gold standard available?
- When one is available, is it useable?
- Example: Imaging the cirrhotic liver
  - Early detection of HCC important but difficult
    - "What are all those nodes?"
    - If you are trying to see something that isn't easy to see, how do you know whether you are seeing it?
  - Explanted liver often available as a gold standard

But how do you relate this

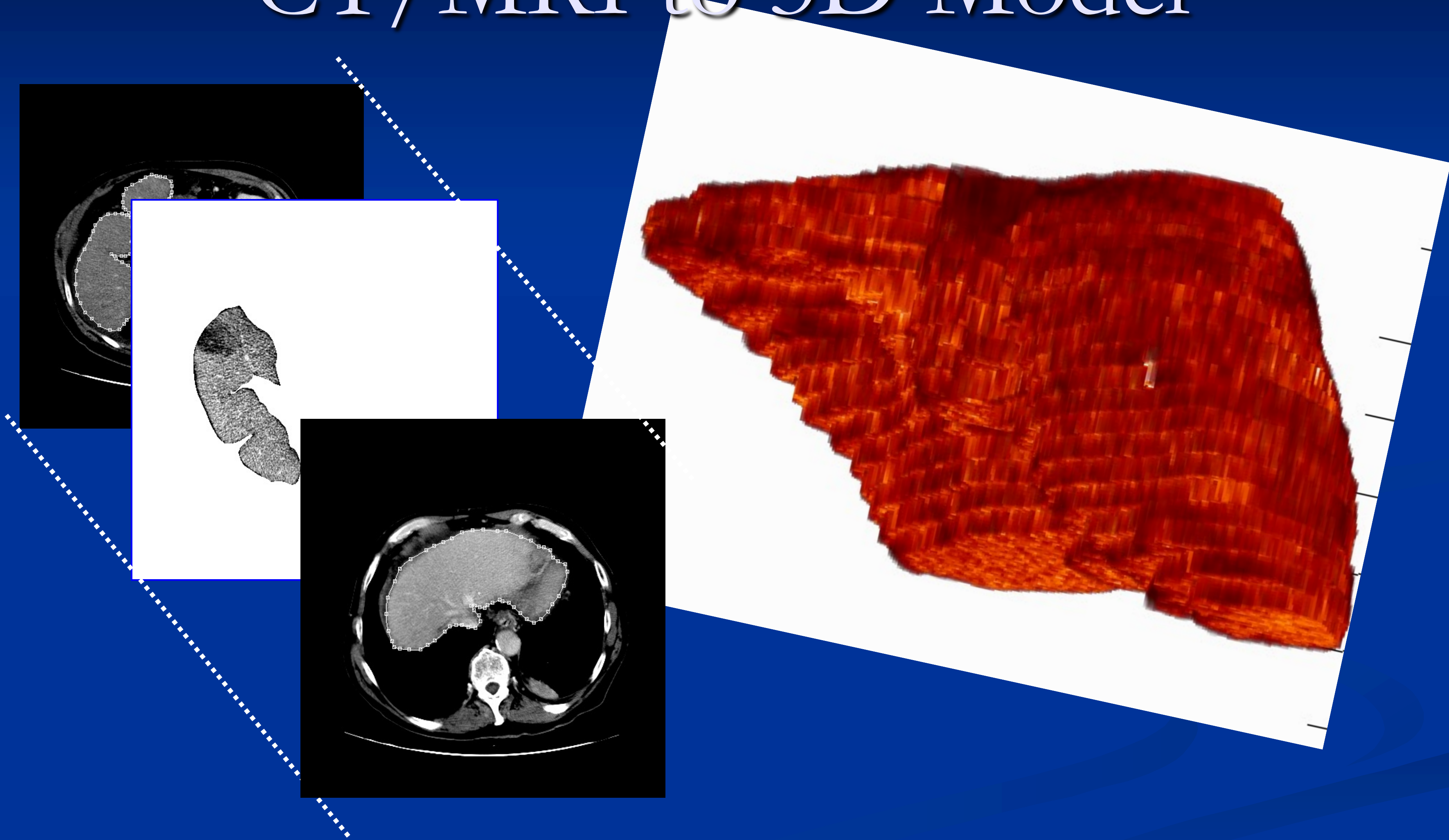
- 23 pound liver
- About two floor tiles long

To this?

- When most Tx pathology reports are worthless for spatial localization

Human meat slicer

CT/MRI to 3D Model



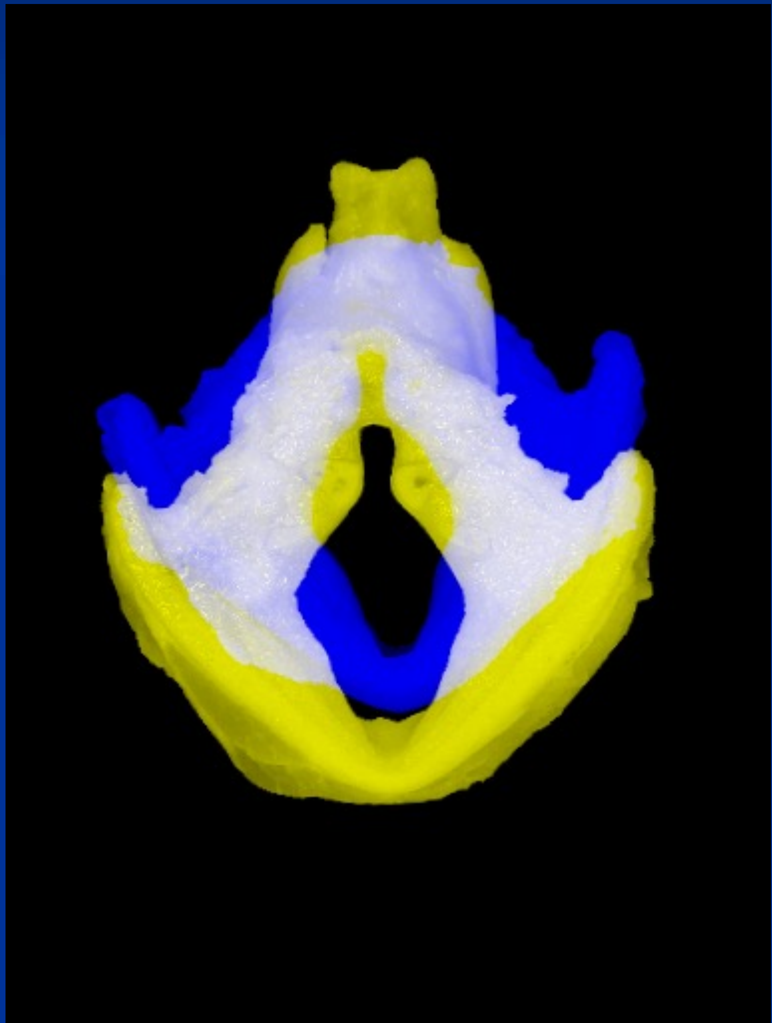
This worked OK but

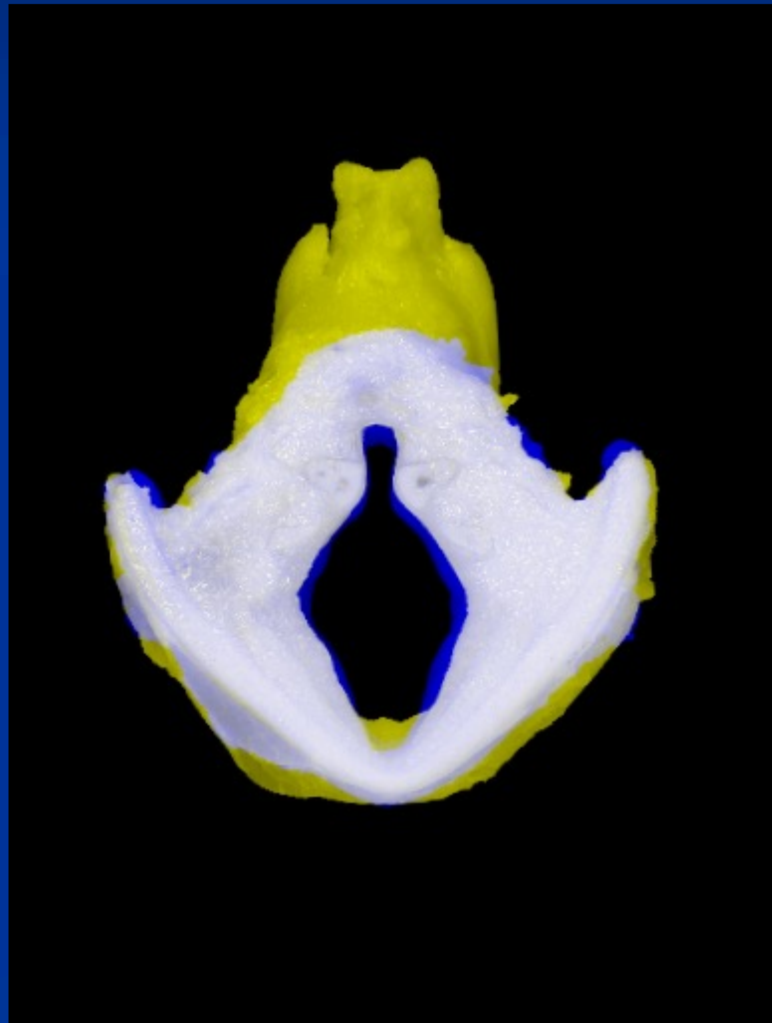
- The liver is big
- And floppy
- And featureless
- And messy
- So…

Try a different organ

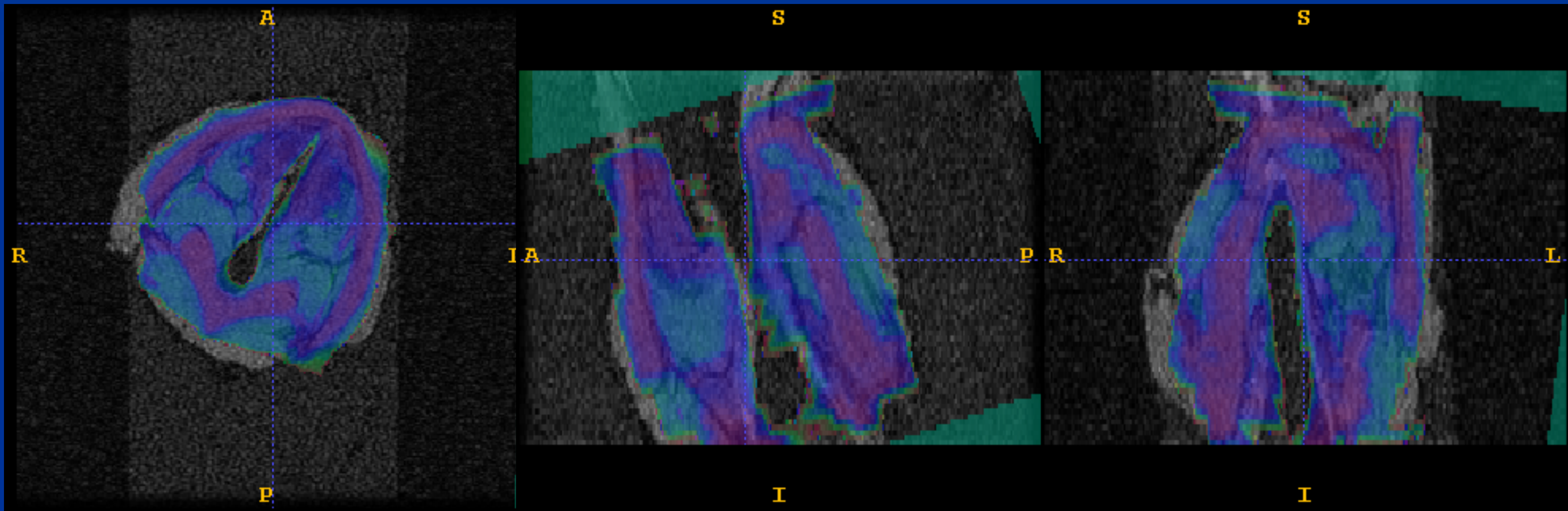
- Like the larynx
  - Small
  - Rigid
  - Feature rich

Slice, Photograph, and Align





Align 3D Model to 3D Image



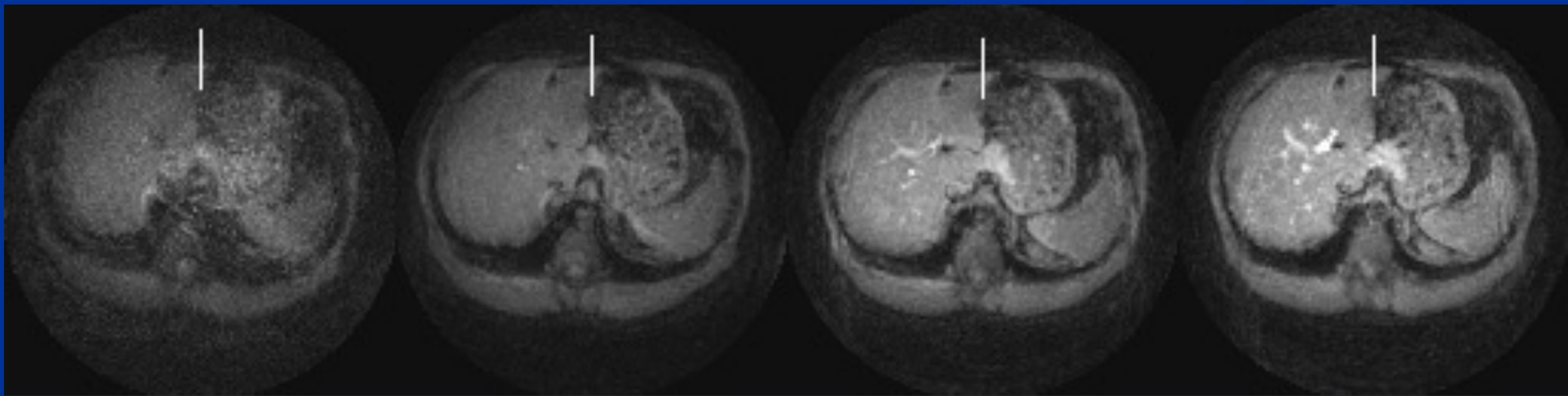
2. Quantification

Compositional Quantification

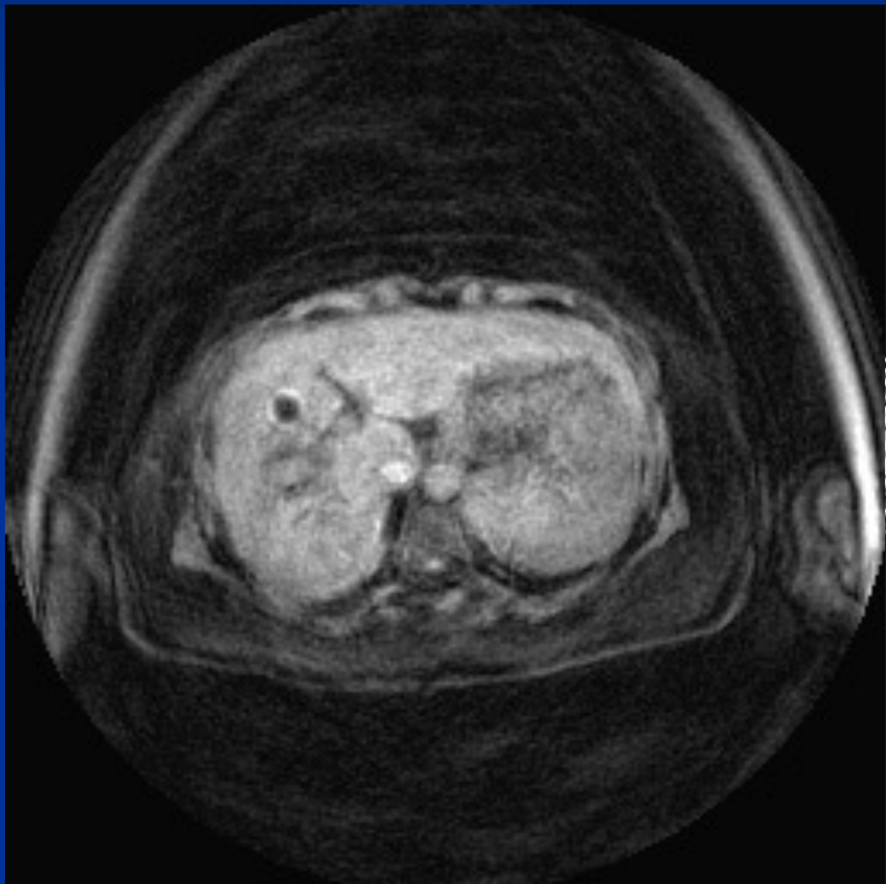
- CT Hounsfield Units a (reasonably) quantitative measure
- But consider MRI
  - Diffusion *weighted*
  - Perfusion *weighted*
  - T2 *weighted*
- Quantification in MRI involves
  - Multiple acquisitions
  - Model fitting

Spiral @ 1.5T: Number of Interleaves

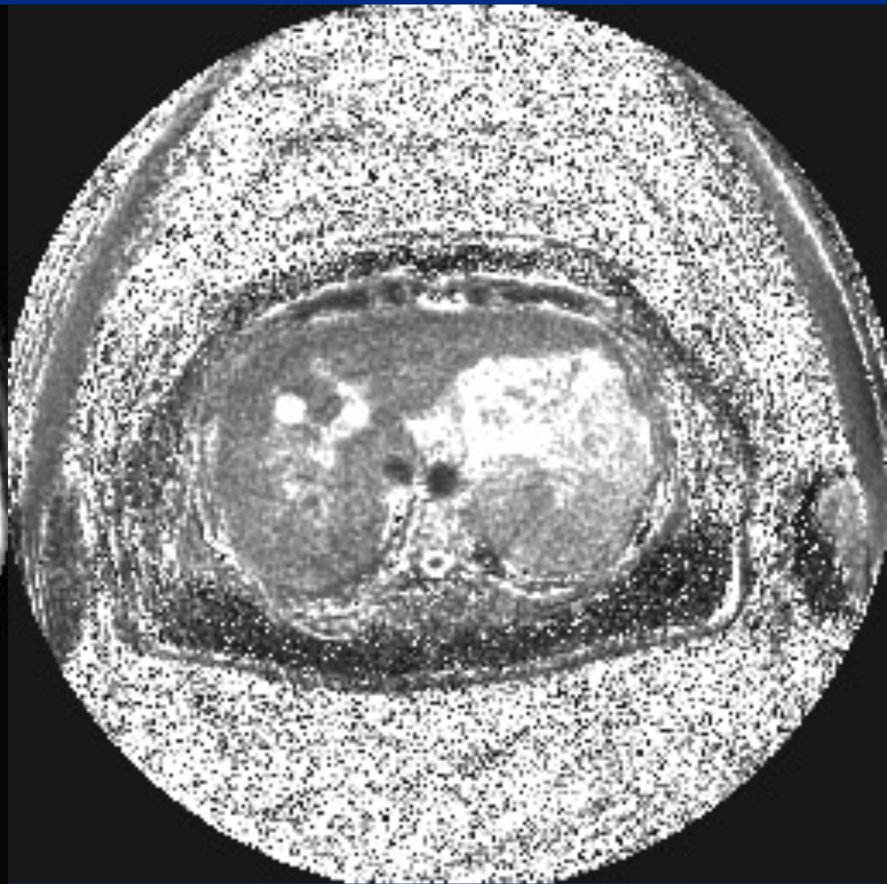
- 128 Matrix
- 2D Interleaved technique
- 1, 4, 8 and 16 spirals/slice



T2* Maps



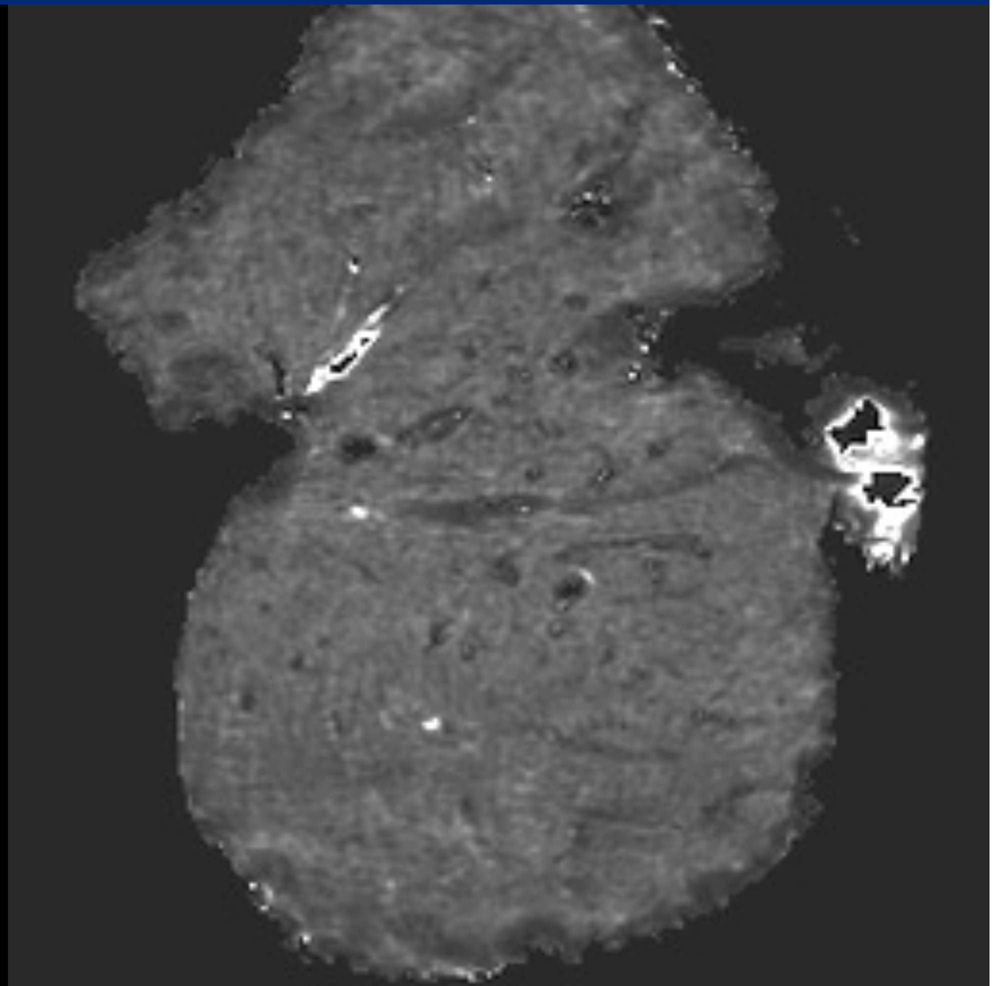
Raw Data



Parameter Map

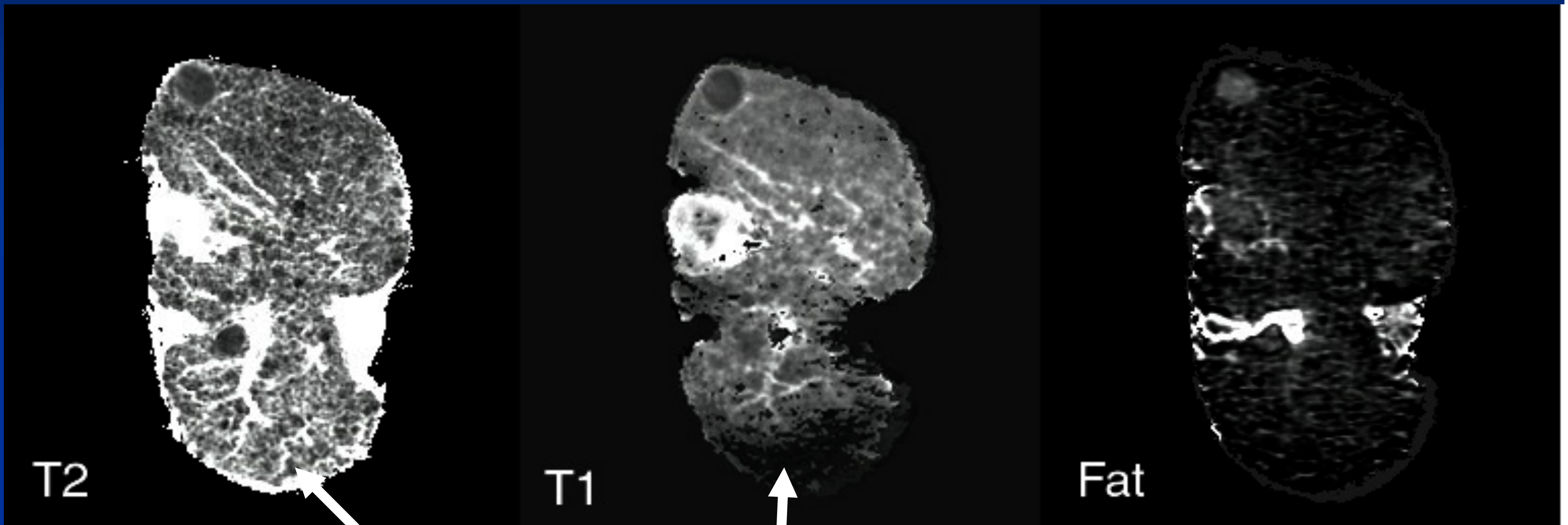
Ex vivo quantification

T2 Map



T2* Map

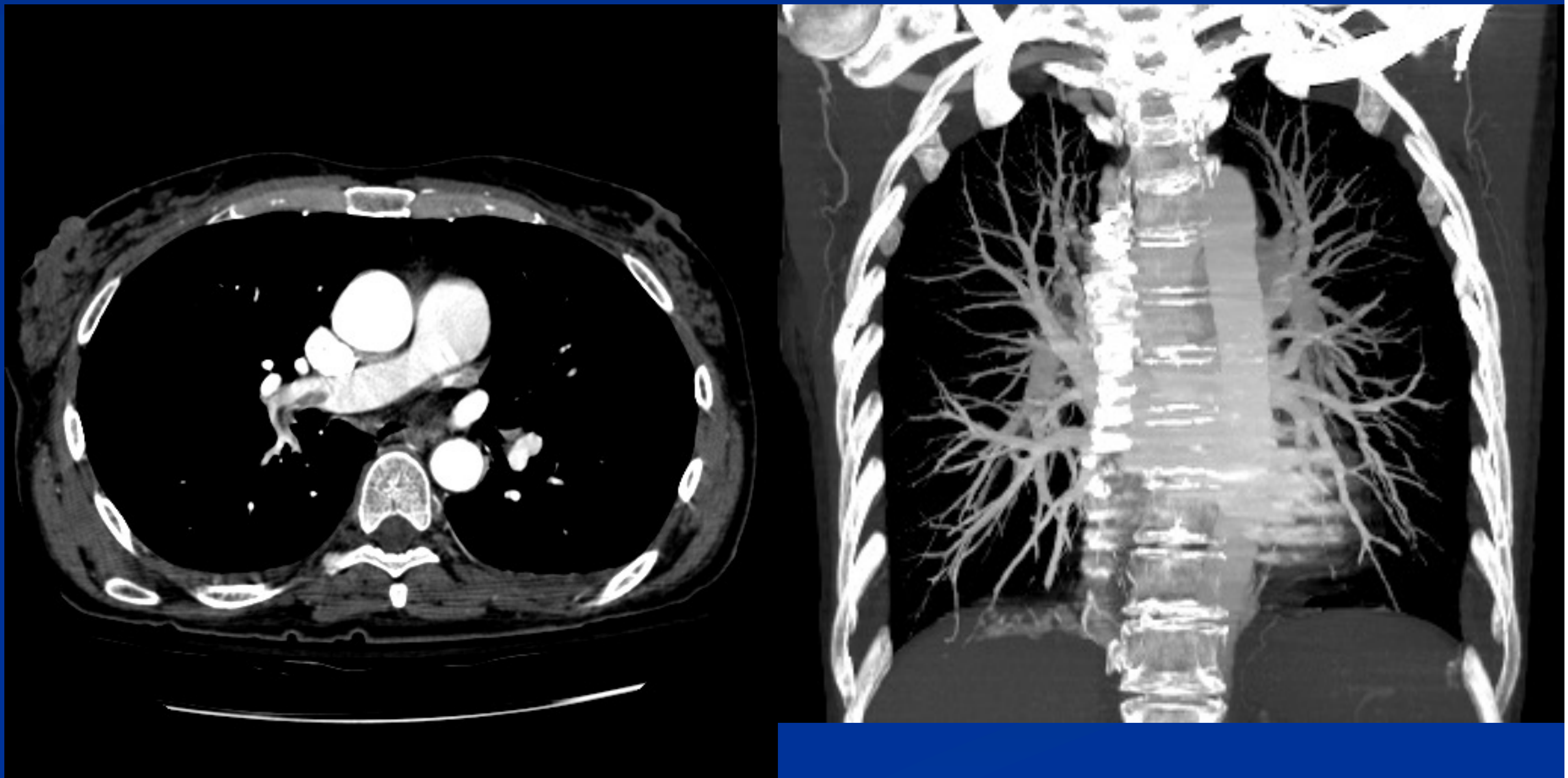
Mapping Using Explanted Livers



?

Morphological Quantification

Certainly Exquisite Detail Now Affords Quantification



What is Needed for Morphological Quantification?

- Segmentation
  - Labeling pixels/voxels as in or out of a set
- Feature Extraction
  - Grouping segmented voxels into related structures
- Registration
  - Following temporal course
  - Mapping to a standard atlas

Insight Toolkit

- National Library of Medicine initiative to create a comprehensive open-source imaging toolkit
  - C++ generic programming
  - Michael Ackerman: ITK far too complex for anyone to use
  - Thankfully there are wrappers
    - Tcl, Python, Java

Image Processing Development

- Use ITK via Python wrappers (when available) for existing algorithms
- Use Python to develop new algorithms (unless speed limited)
- Use C++ when we must
- Avoid commercial solutions
  - Matlab
  - IDL

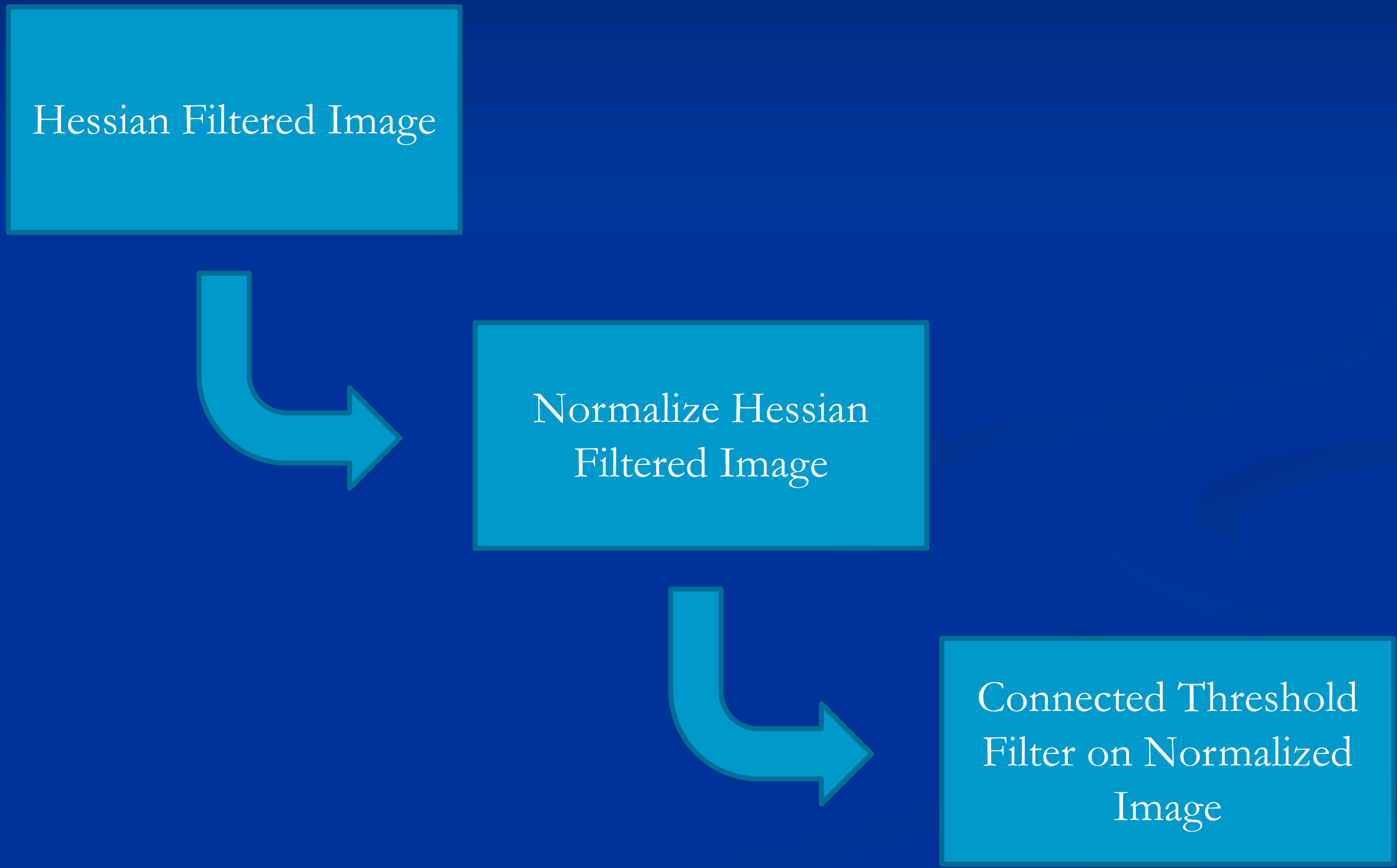
Vascular Segmentation

- Do existing algorithms provide sufficiently accurate vascular segmentations for a pulmonary embolism computer aided detection algorithm?
- Can a novel (Spheres and Shells) algorithm provide more accurate vascular segmentation?
- Can 2D projection images speed up 3D processing?

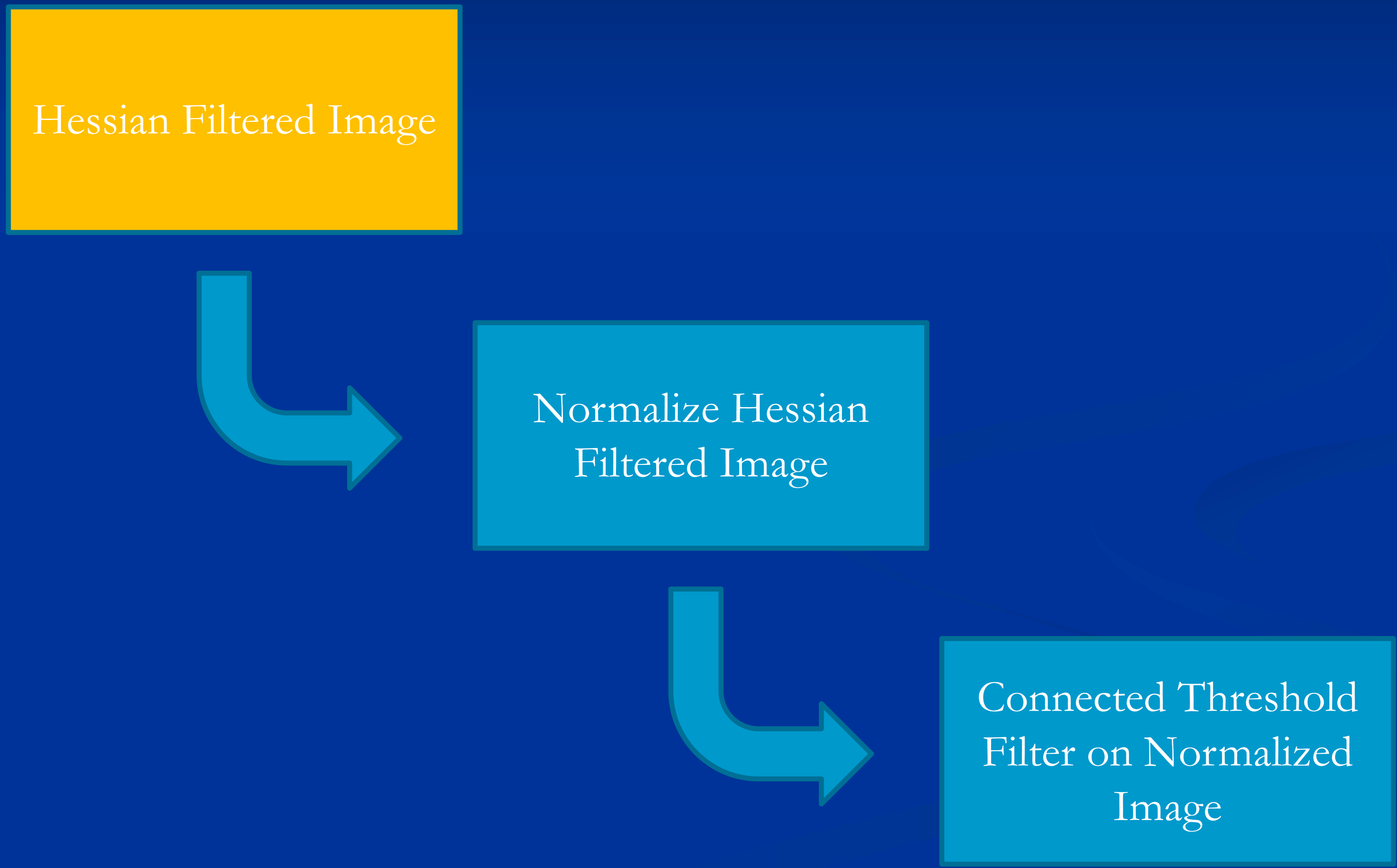
Existing Segmentation Tools

- Approach 1: Estimate the arterial and venous HU values from the right and left ventricles of the heart
    - HU dependent on injection
  - Region growing from seed point
  - Lung mask to exclude non-vascular structures captured with region growing
- Approach 2: Preprocess with vessel enhancement filter

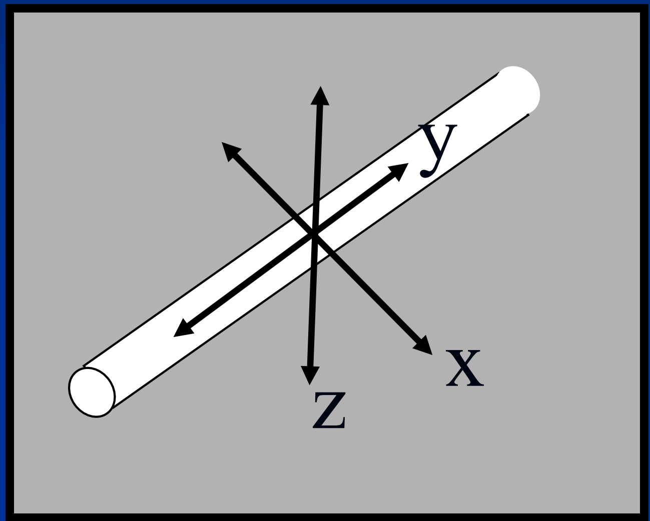
Segmentation Outline

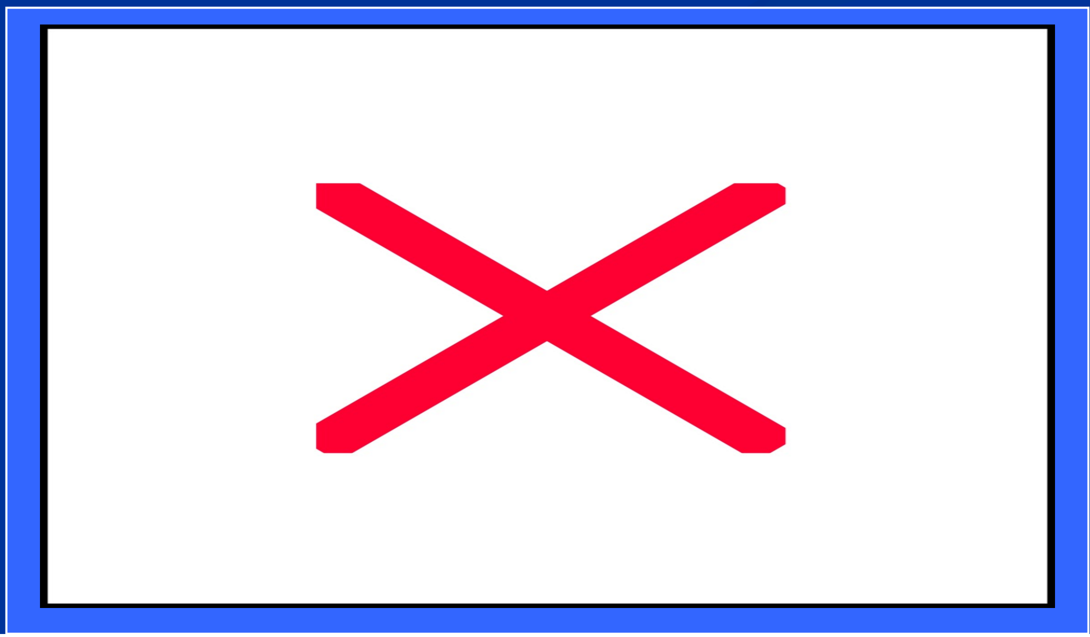


Segmentation Outline



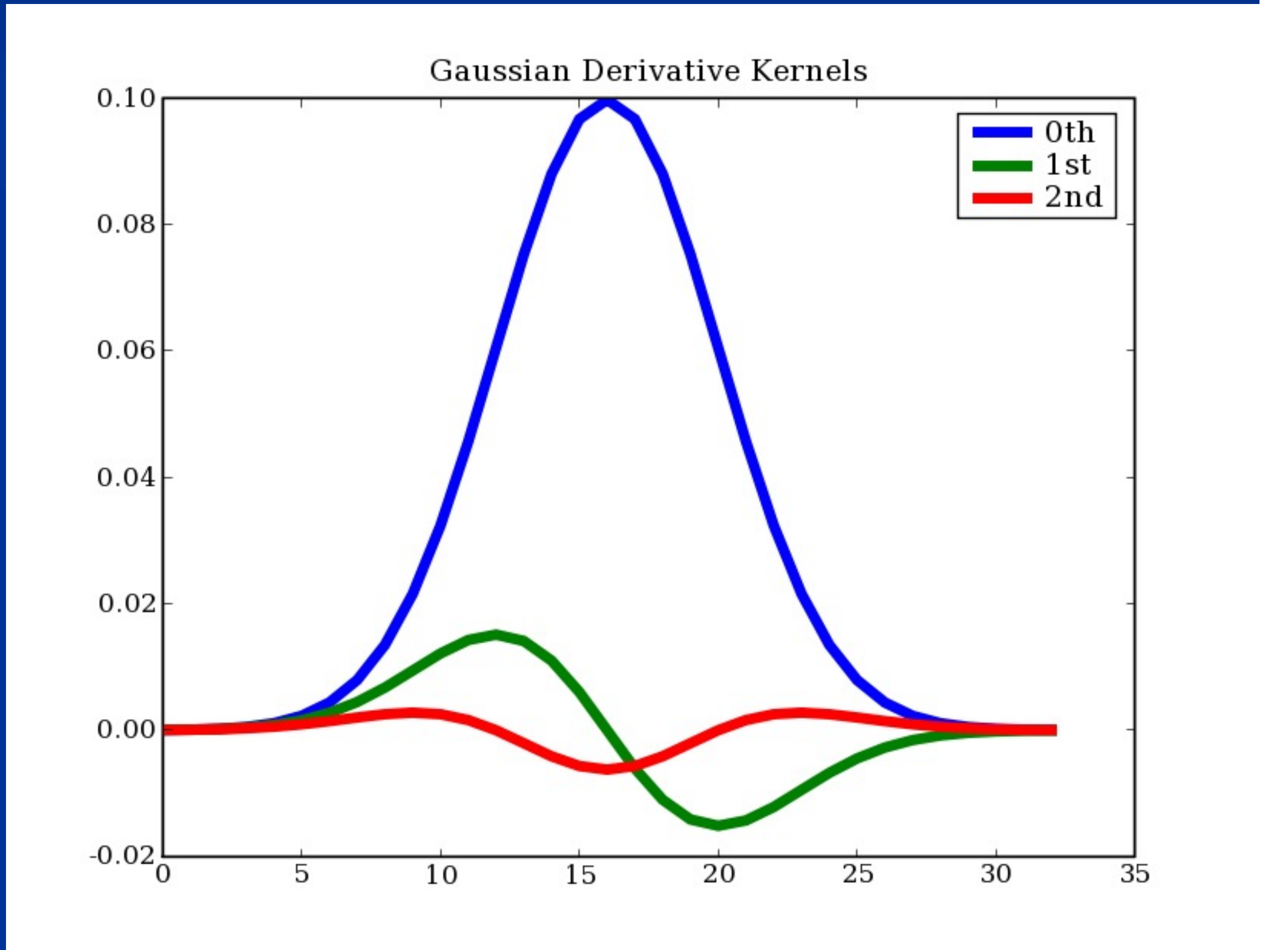
Mathematical Model of Vessels



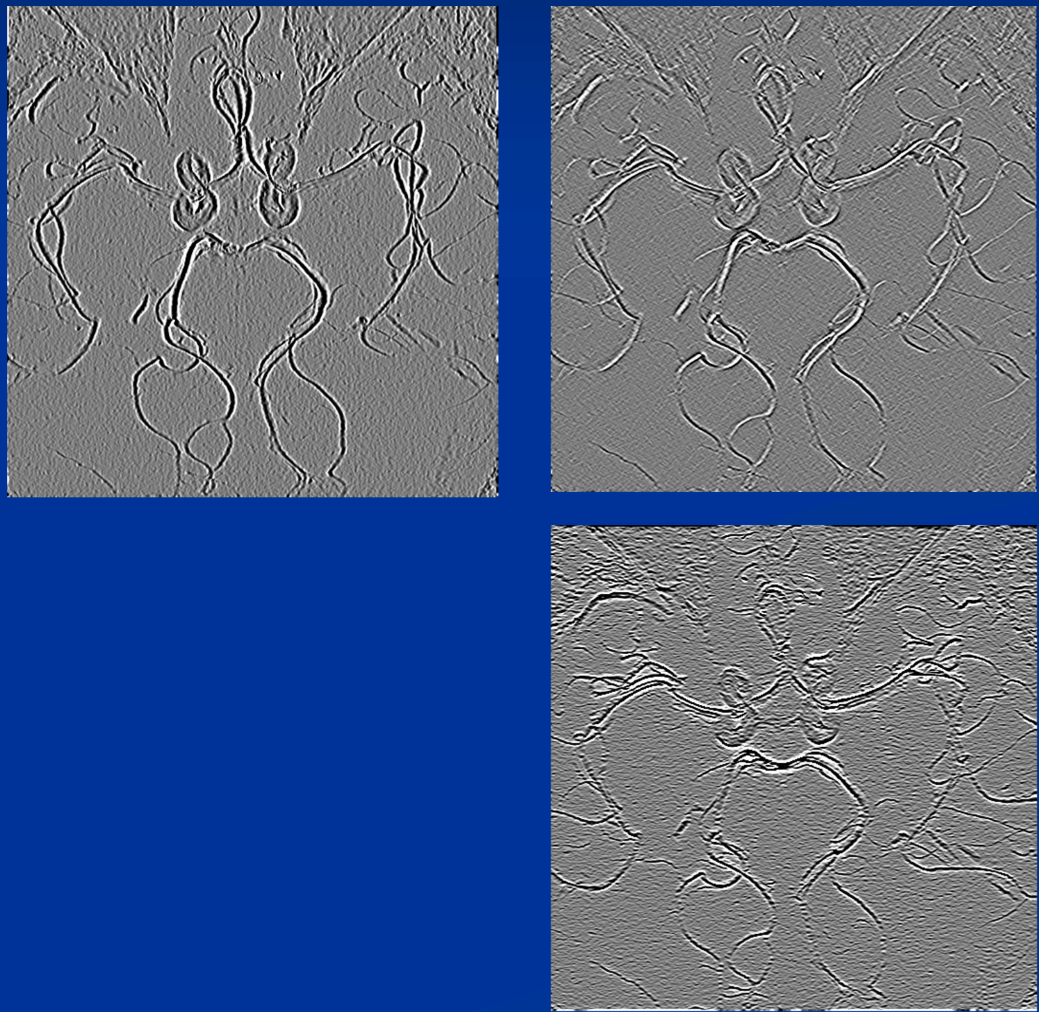


How Do We Compute the Hessian?

- 3D Matrix has six independent terms:
  - Ixx, Ixy, Ixz, Iyy, Iyz, Izz
- Convolve Image with series of differential kernels
  - Generate from Gaussian functions



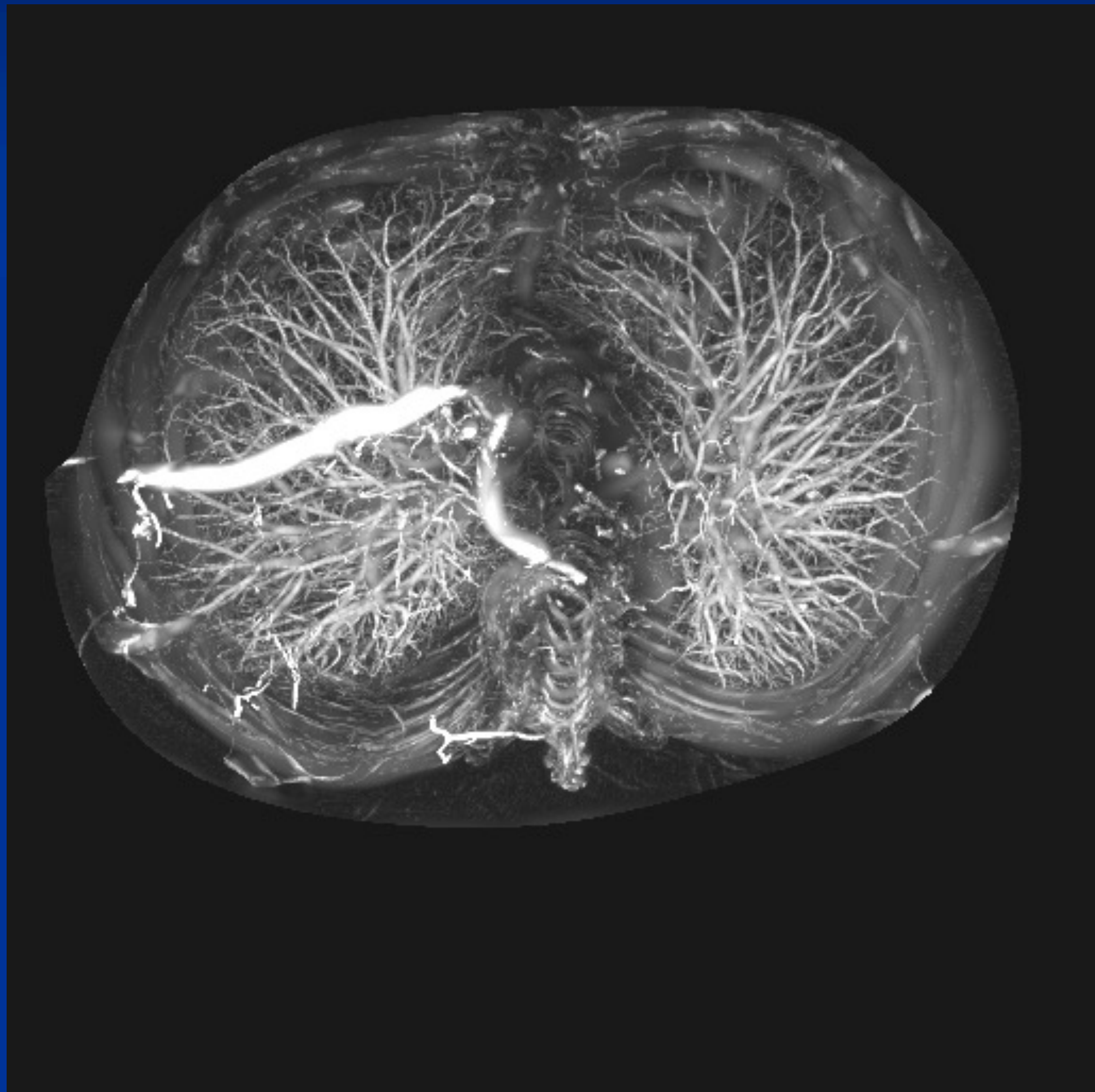
Example Hessian (2D)



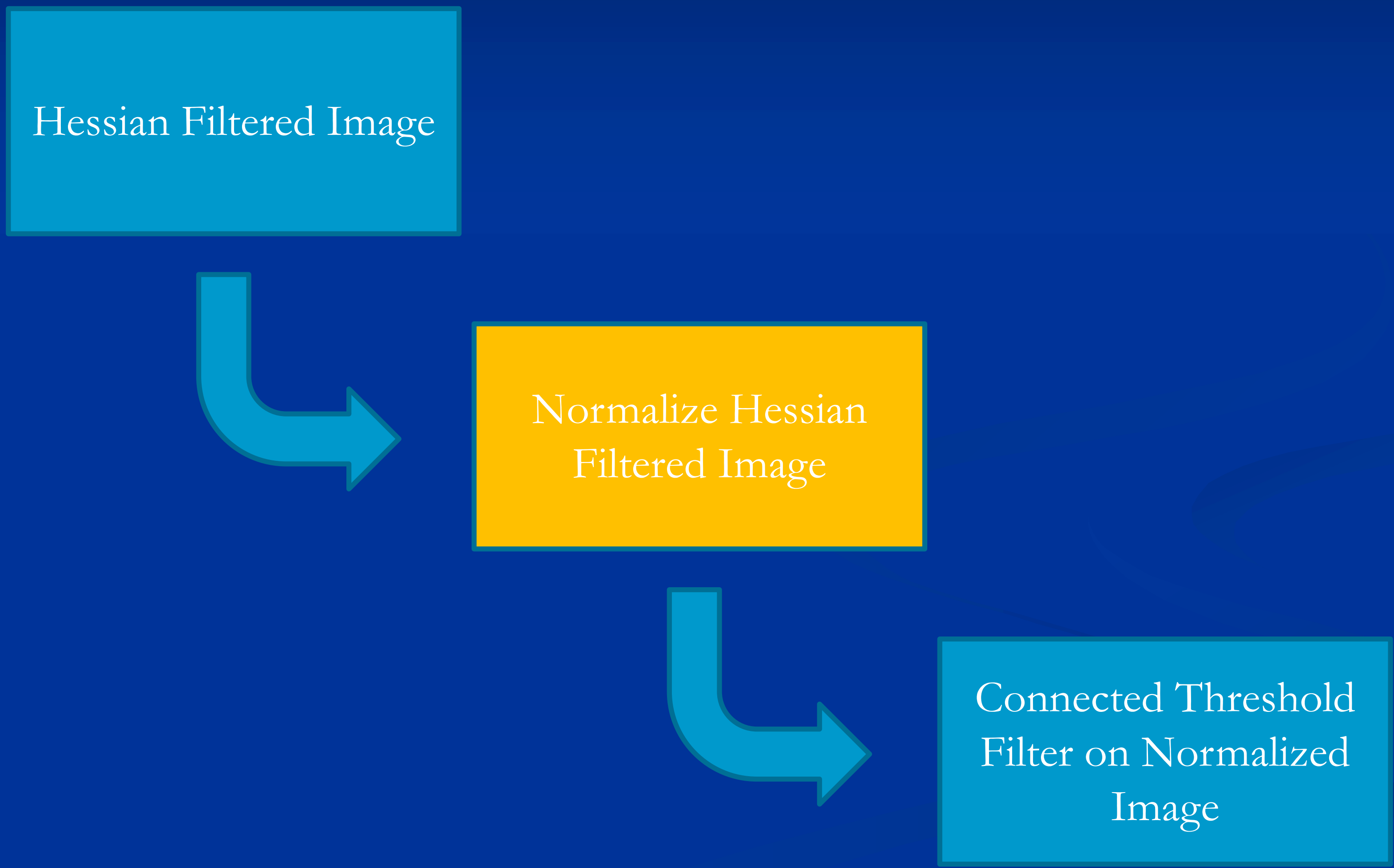
Compute Eigenvalues of Hessian matrix

- Order eigenvalues by increasing magnitude
  - $|\lambda_1| \leq |\lambda_2| \leq |\lambda_3|$
- For bright-blood images
  - $\lambda_2 << 0$ and $\lambda_3 << 0$, $\lambda_1 \sim 0$
- Model a vessel as (something like)
  - $V = (|\lambda_3| - |\lambda_1|)(|\lambda_2| / |\lambda_3|)$

Lung CT



Segmentation Outline



Normalize Hessian Filtered Image

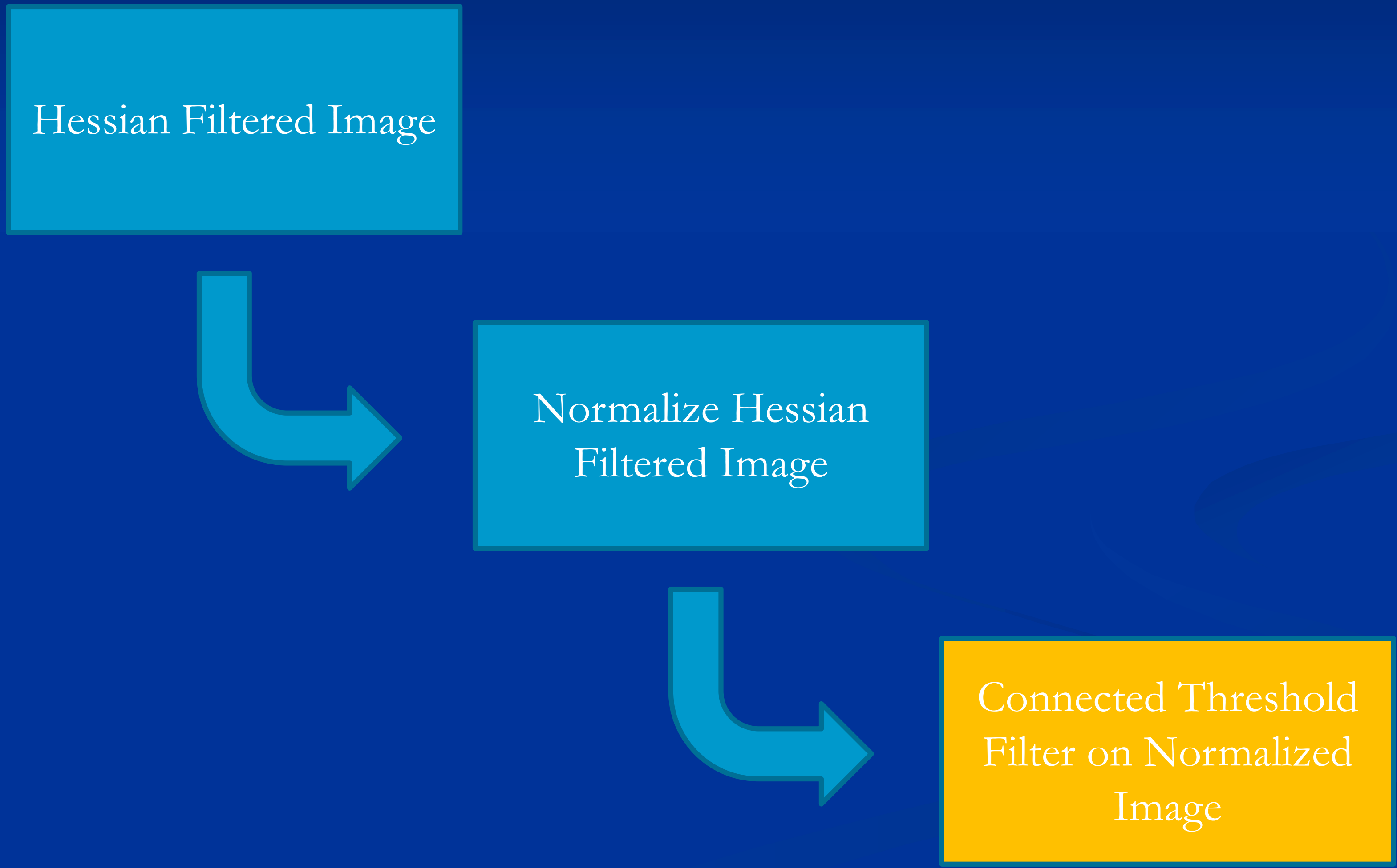
- Dynamic range of Hessian Filtered Image = too large
- Using itkNormalizeImageFilter
  - Normalizes image by setting its mean to zero and variance to one.
  - Shifts and scales an image so that the pixels in the image have a zero mean and unit variance

Uses itkStatisticsImageFilter to compute mean and variance of input

Then applies itkShiftScaleImageFilter to shift and scale the pixels

- Each voxel intensity represents a bin of unit variance

Segmentation Outline

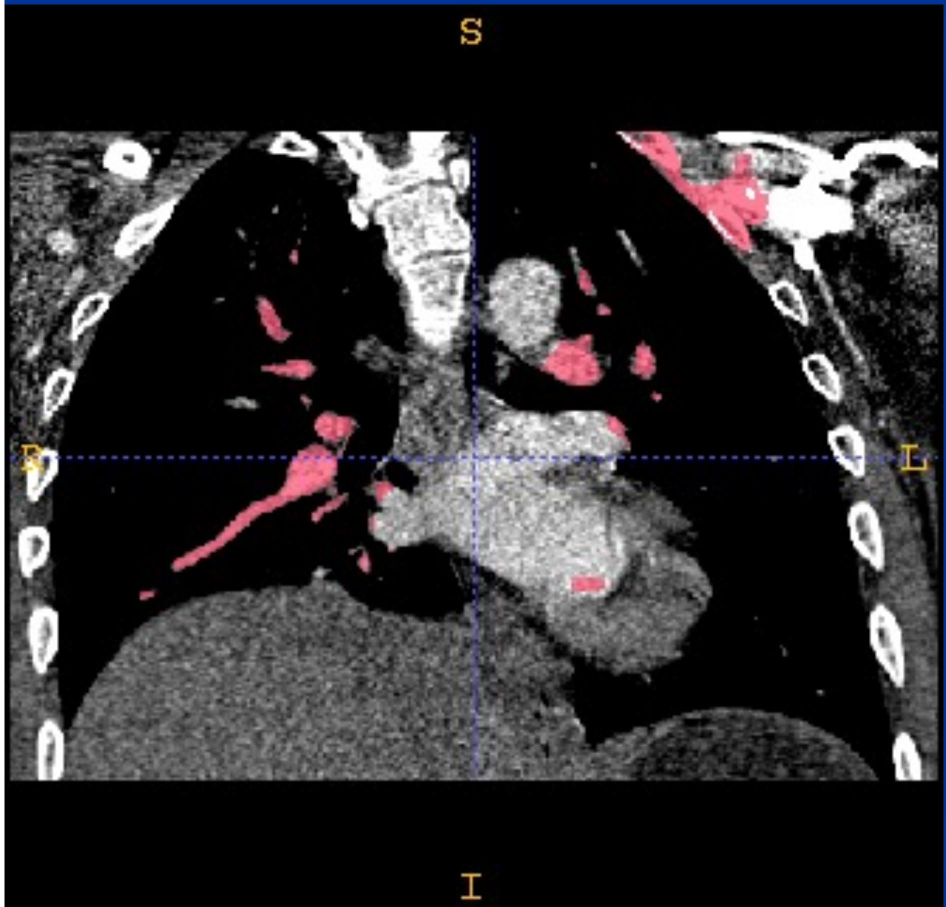


Connected Threshold Filter

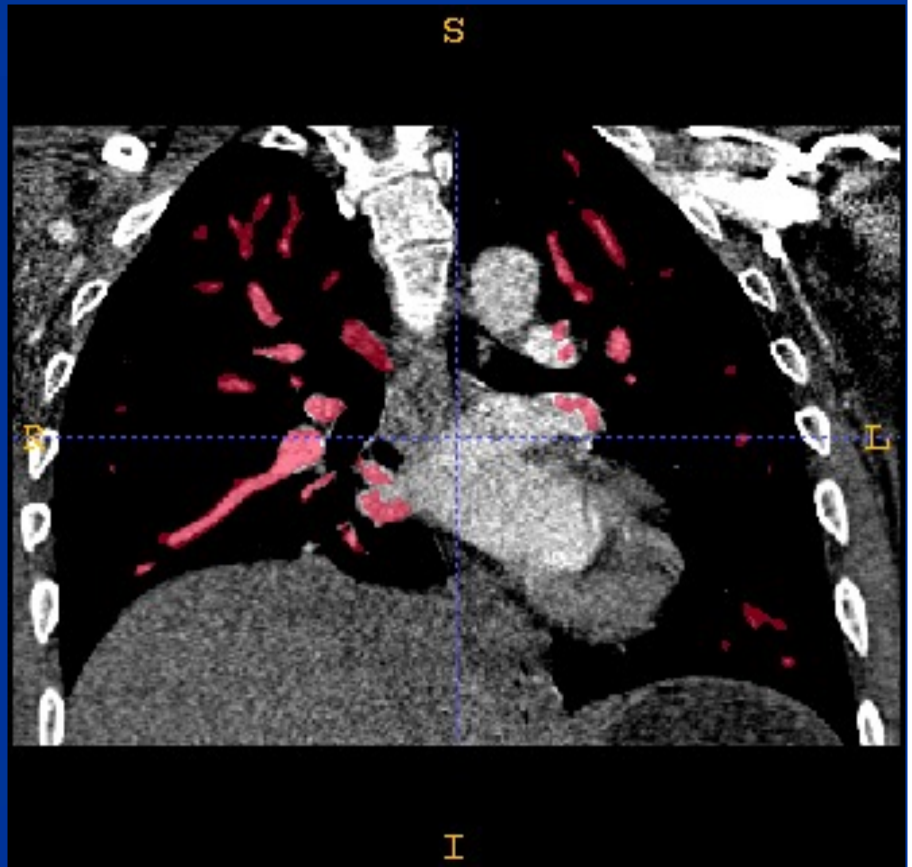
- Apply itkConnectedThresholdImageFilter to the normalized hessian filtered image
  - UpperThreshold = max(normalizedImage)
  - LowerThreshold = 2
    - If = 1, get too much peripheral soft tissue
    - If = 0, background image intensity (since predominant)
  - 3 seeds chosen by visual inspection
    - One in left lung vasculature
    - One in right lung vasculature
    - One in mediastinum

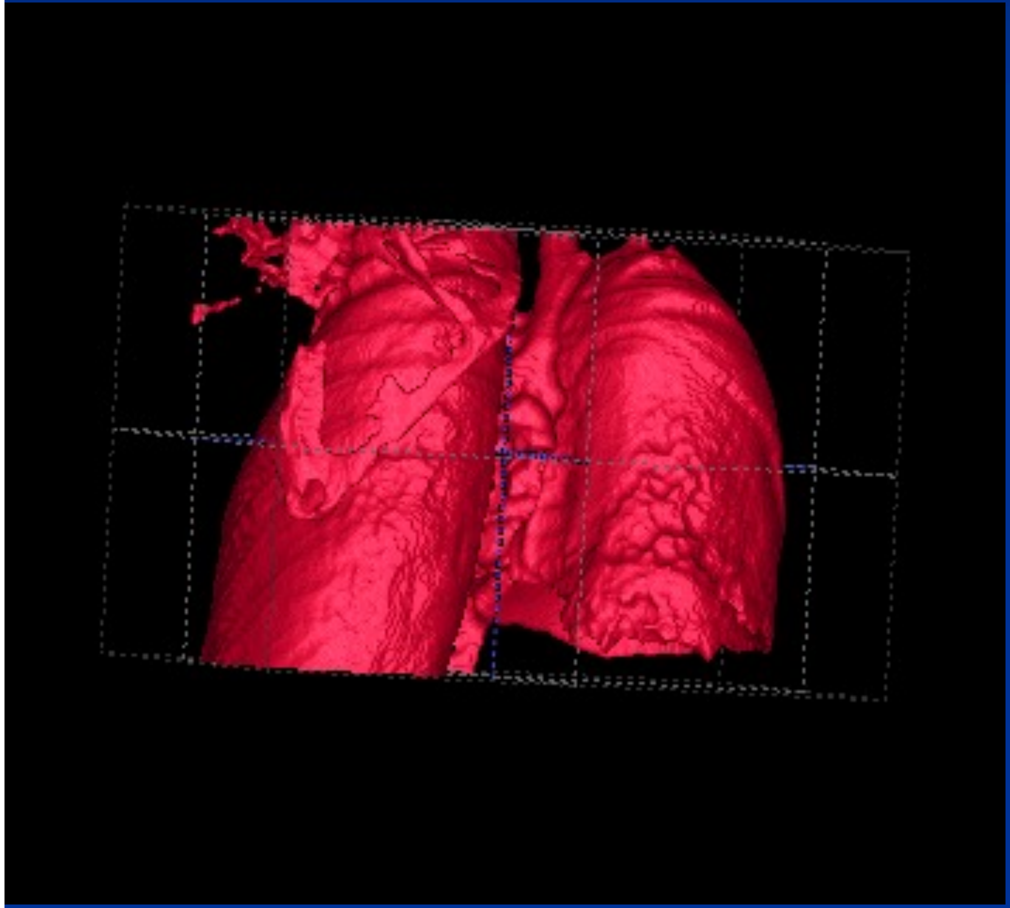
Segmentation of Pulmonary CTA

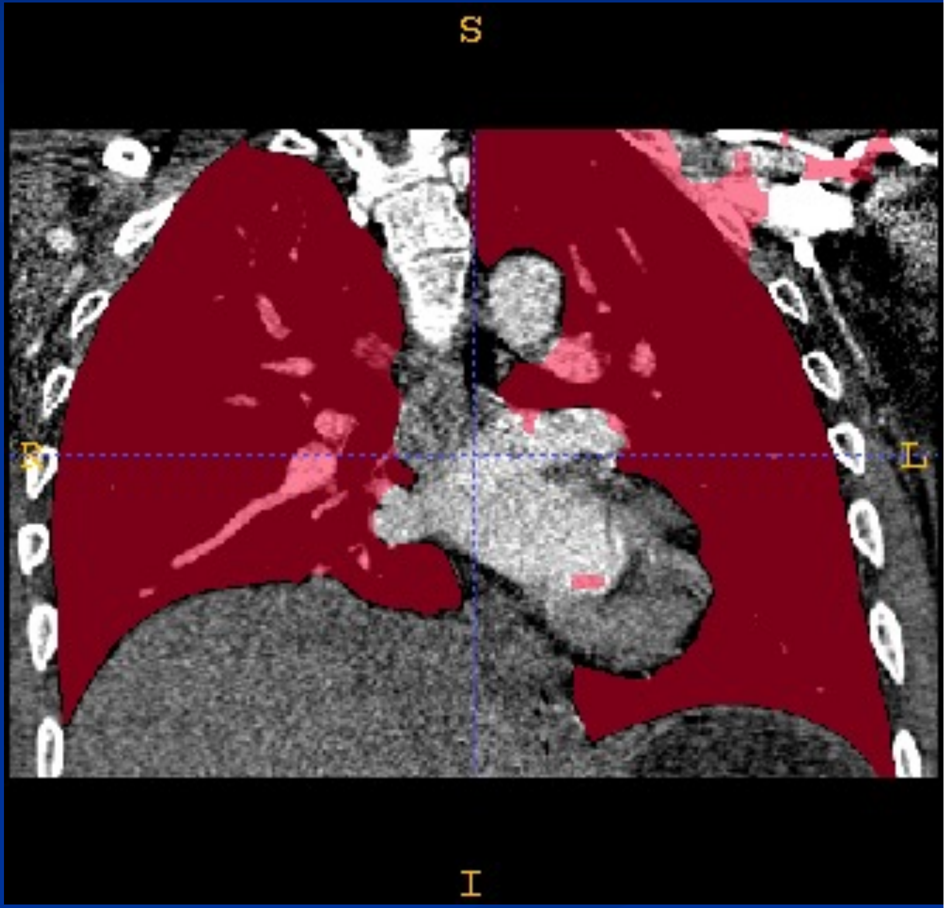
Original



Filtered

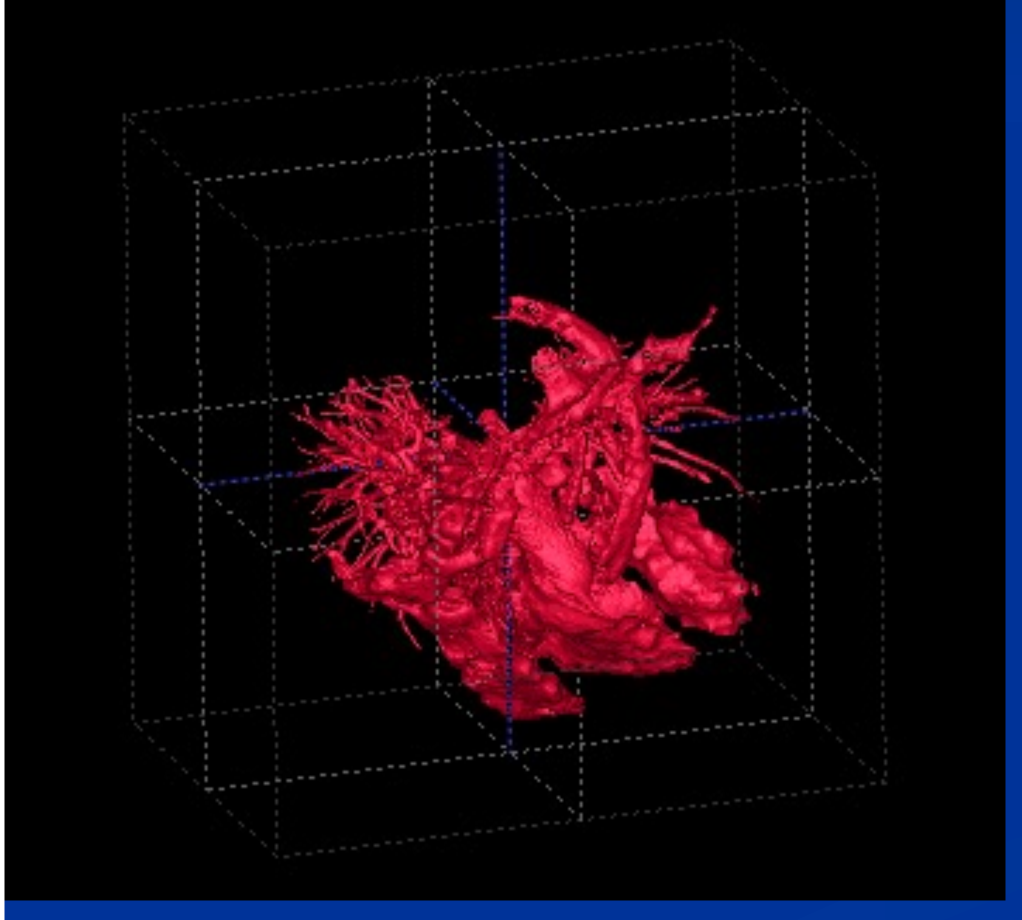




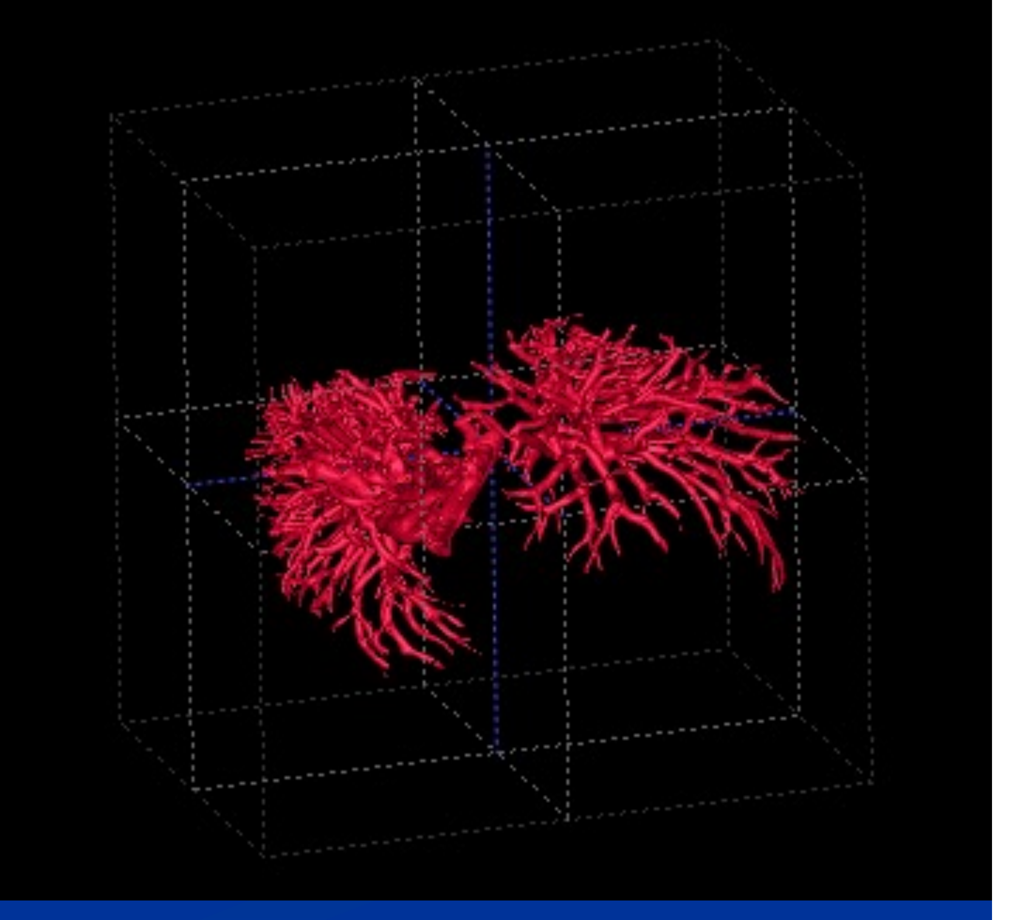

S
R
L
I

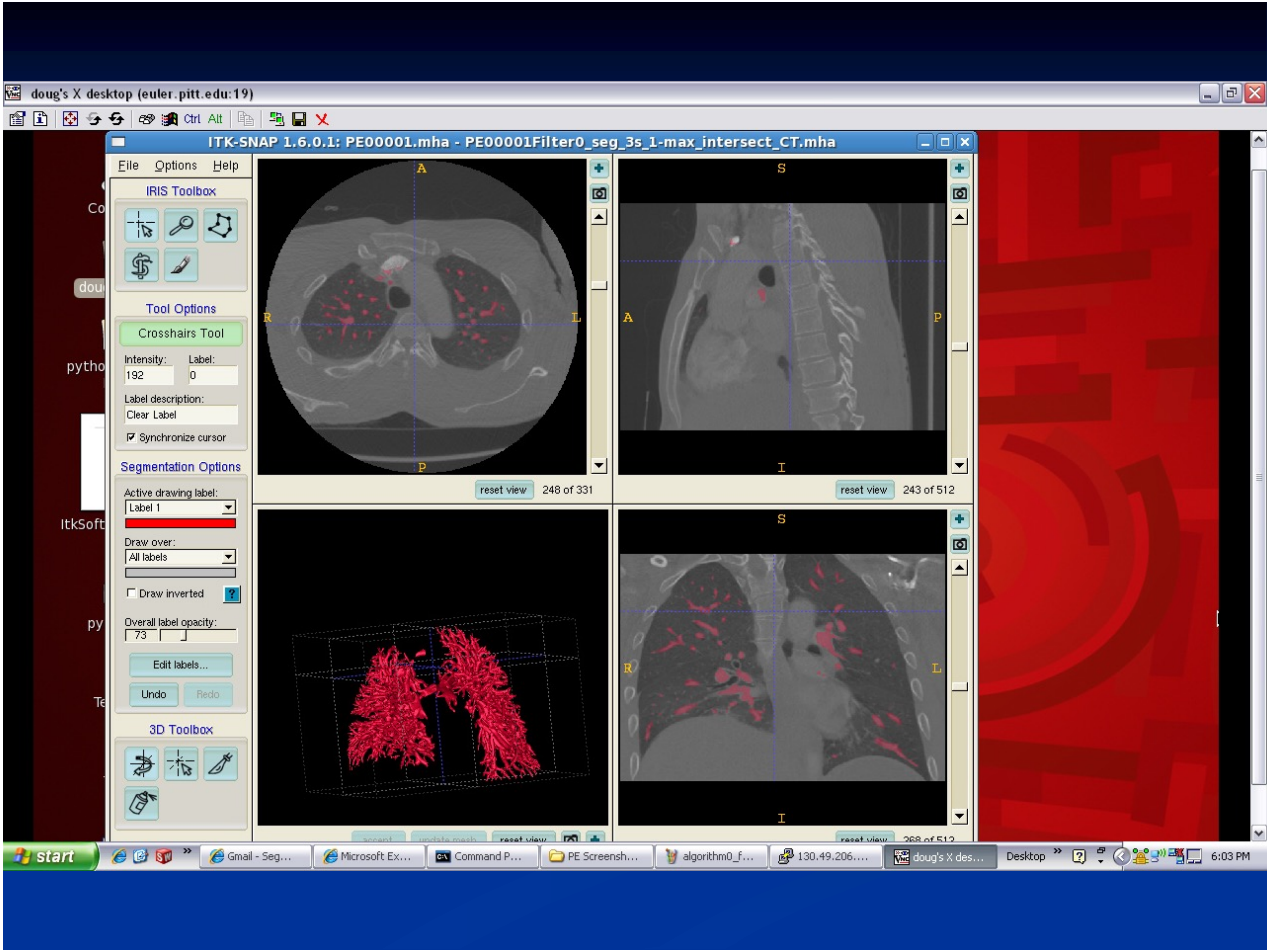
Segmentation of Pulmonary CTA

Original



Filtered





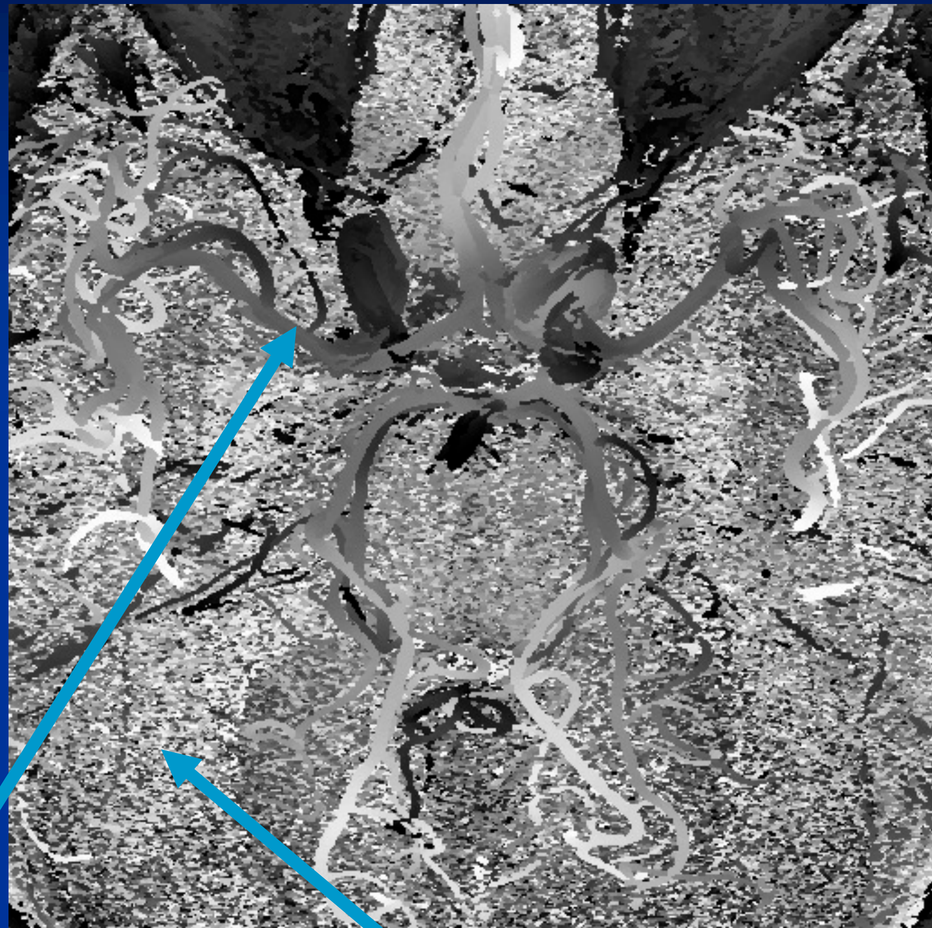
doug's X desktop (euler.pitt.edu:19)
ITK-SNAP 1.6.0.1: PE00001.mha - PE00001Filter0_seg_3s_1-max_intersect_CT.mha
File Options Help
IRIS Toolbox
Tool Options
Crosshairs Tool
Intensity: 192
Label: 0
Label description: Clear Label
Synchronize cursor
Segmentation Options
Active drawing label: Label 1
Draw over: All labels
Draw inverted
Overall label opacity: 73
Edit labels...
Undo
Redo
3D Toolbox
reset view 248 of 331
reset view 243 of 512
reset view 268 of 512
start
6:03 PM

3D Segmentation with cheating from 2D Images

- 3D Images are large meaning computations are slow
- Vascular structures often represent a small portion of image
- Can we do a cheap first-pass vascular segmentation based on the 2D image?

MIP Image

Corresponding Depth Buffer



Vessels Appear Smooth

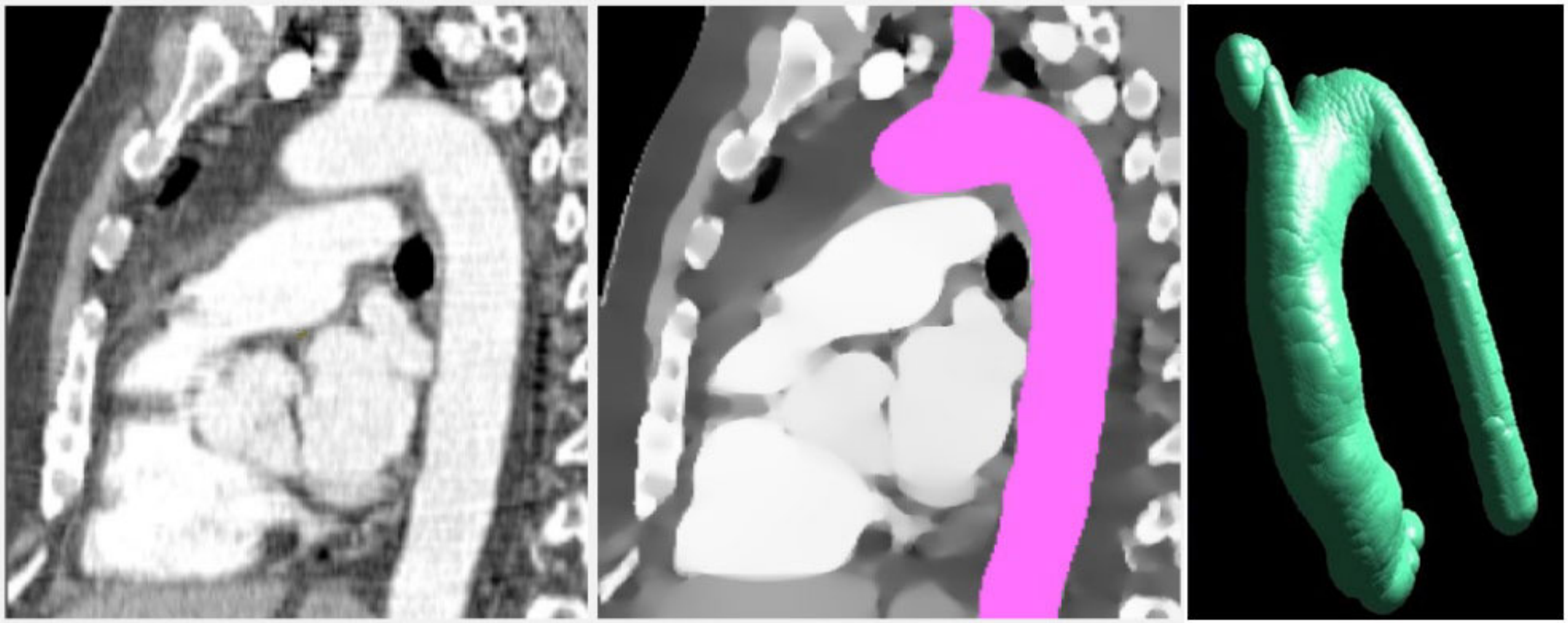
Background Appears Rough

Example Segmentations

- Simple-minded segmentations work quite well
  - Region growing with a global threshold
- Can we do this better?
  - Principled estimates of parameters (Garrick Wallstrom)

A More Elegant Approach: Shells and Spheres

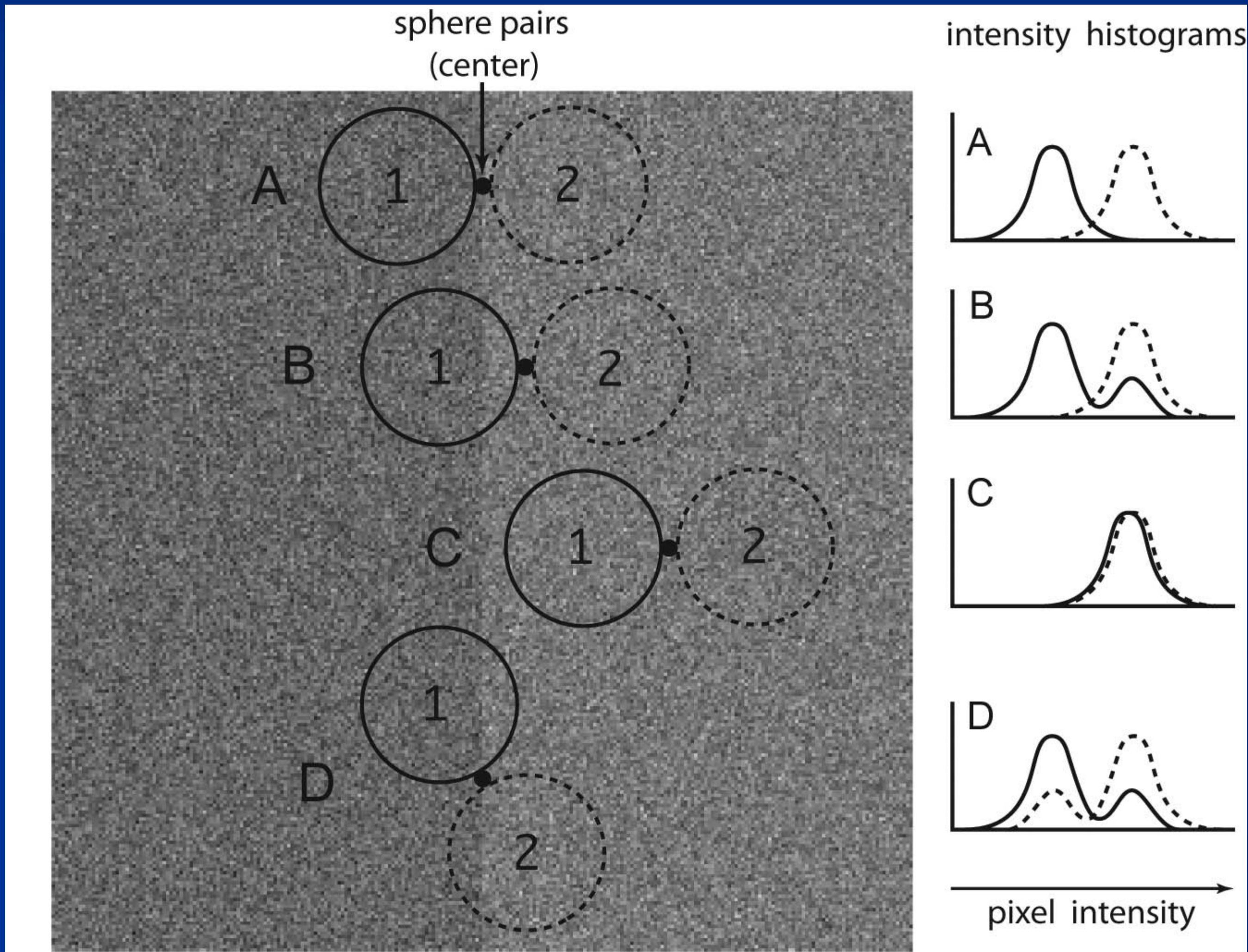
Automated segmentation using statistical analysis
of variable scale spherical regions

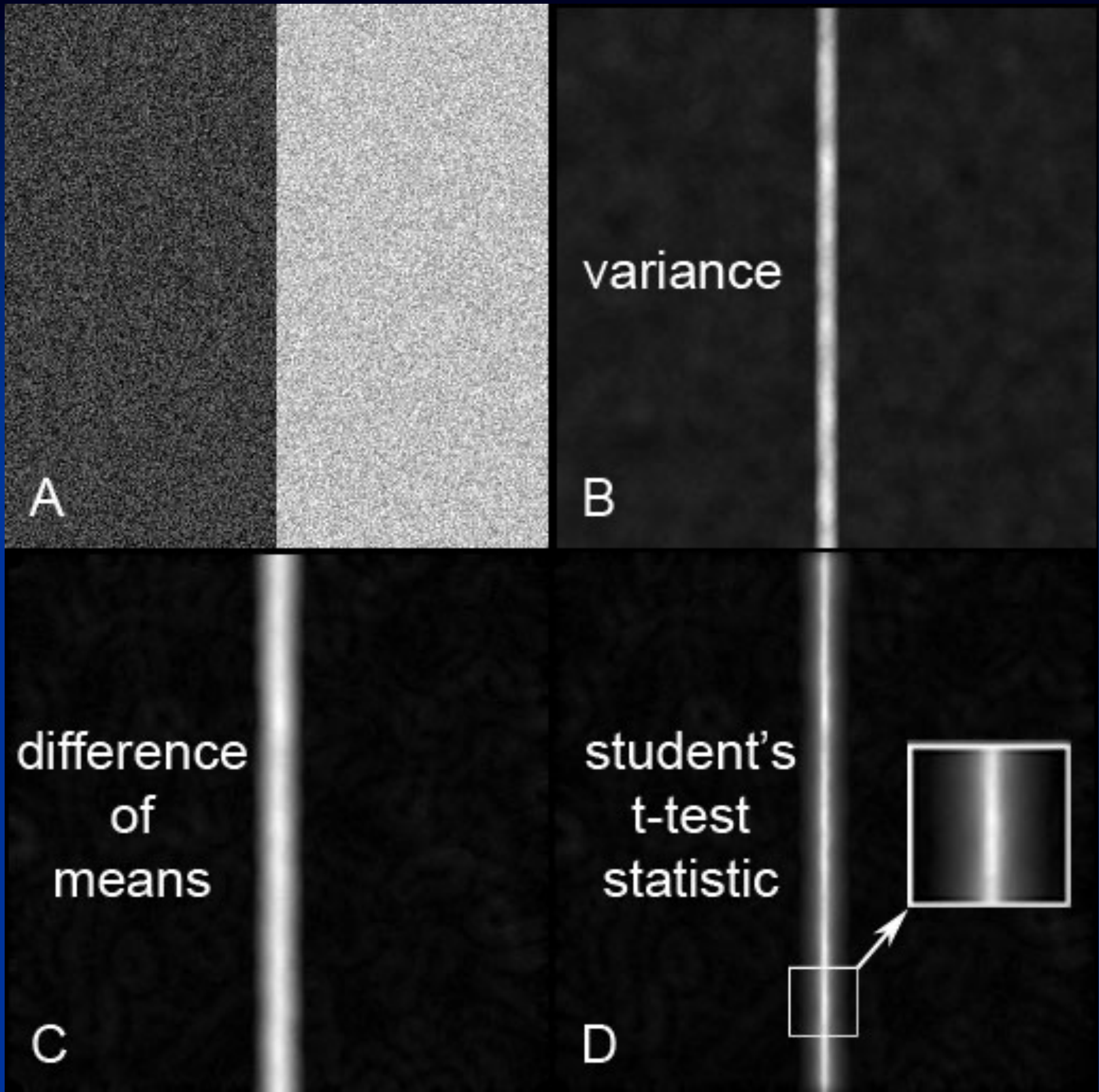


left: noisy CT slice of thorax; *center*: 2D segmentation of aorta with Shells and Spheres;
right: 3D segmentation with rendered surface.

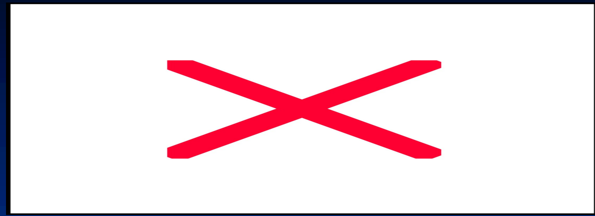
Cois, et al., ISBI 2007

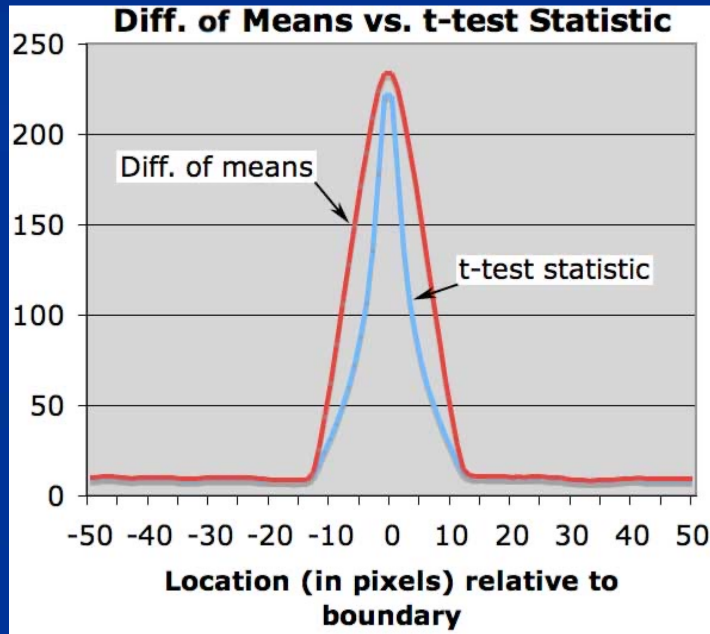
Sphere pairs on an image with a noisy edge. Each pair consists of two spheres (1 and 2) with a center point between them. Corresponding intensity histograms shown to the right.





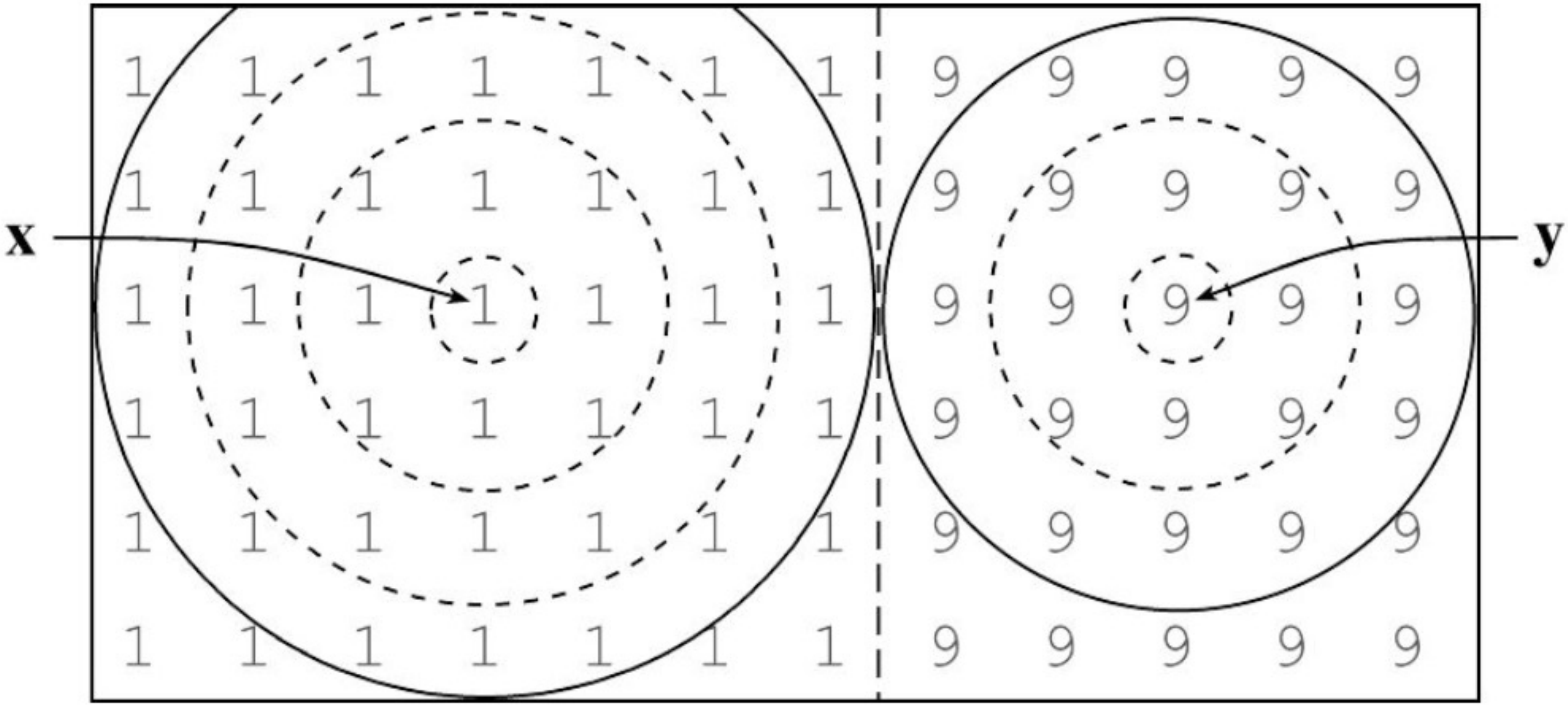
Noisy image (A), variance in a single sphere (B), and statistical measures from pairs of spherical regions (C,D).



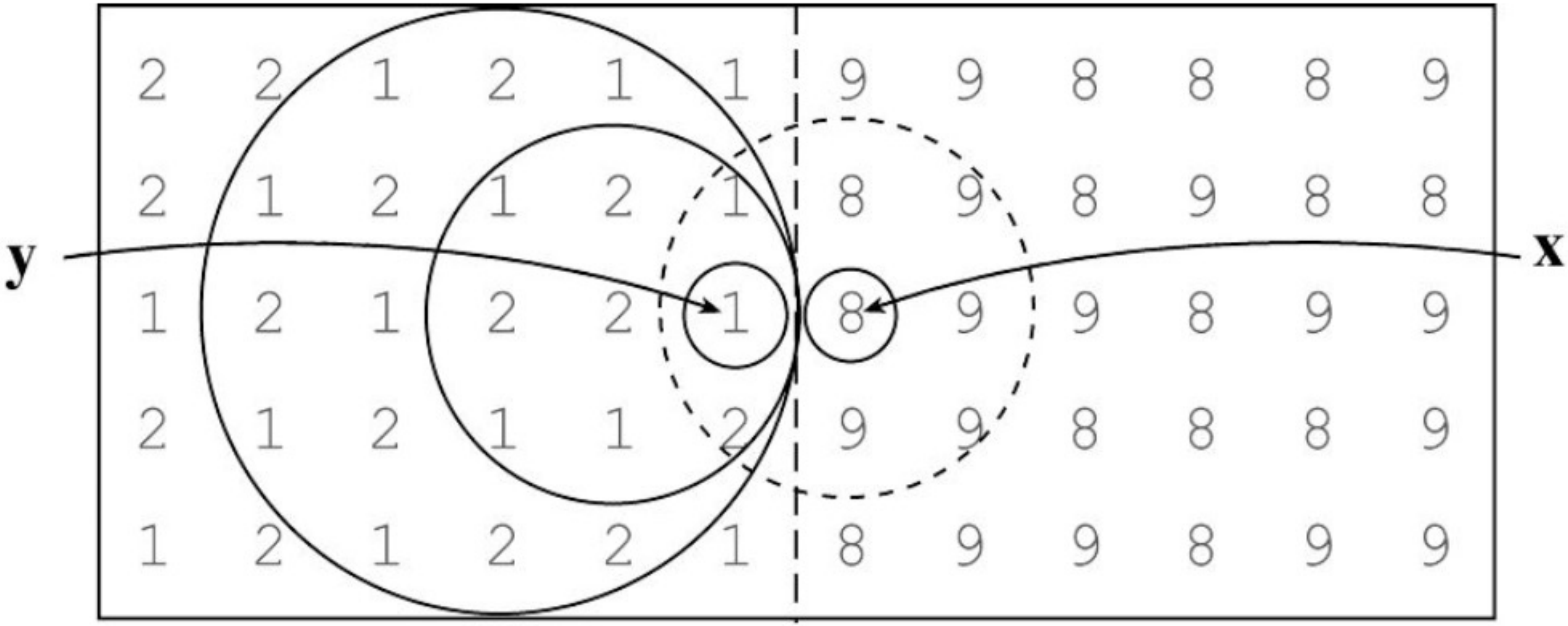


Average measure for all rows in C and D, showing superior resolution for t-test.

Shells and Spheres Framework



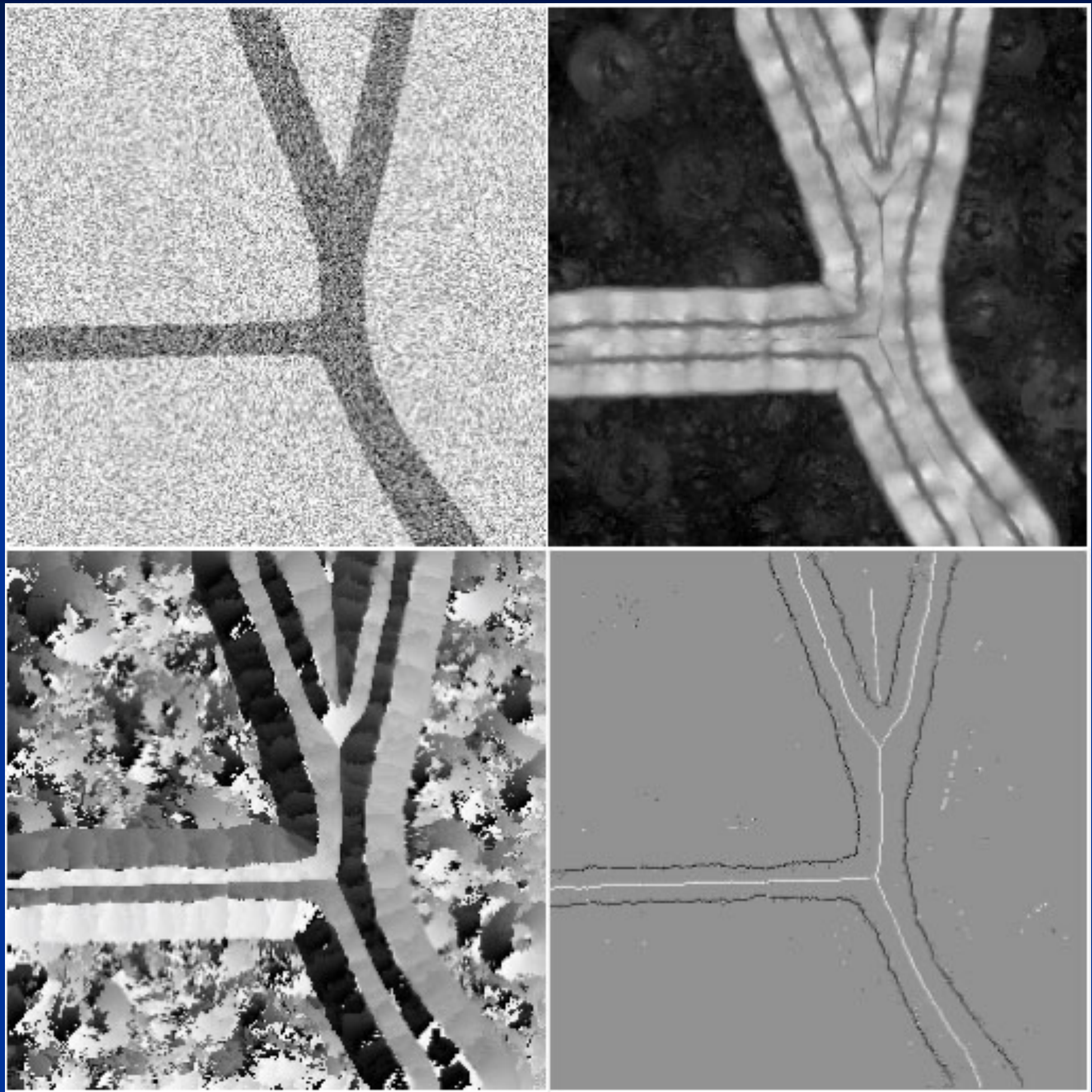
Shells and Spheres Framework



Divergence of the Direction Function

simulated bronchi with noise in 2D (these algorithms will work in 3D)

boundary significance of variable scale spherical regions



distance direction derived from optimal sphere pairs

boundaries and medial ridges derived from divergence of the direction function

Stetten, et al., SPIE Medical Imaging, 2010.

Morphological Quantification

Step 2: Feature Extraction

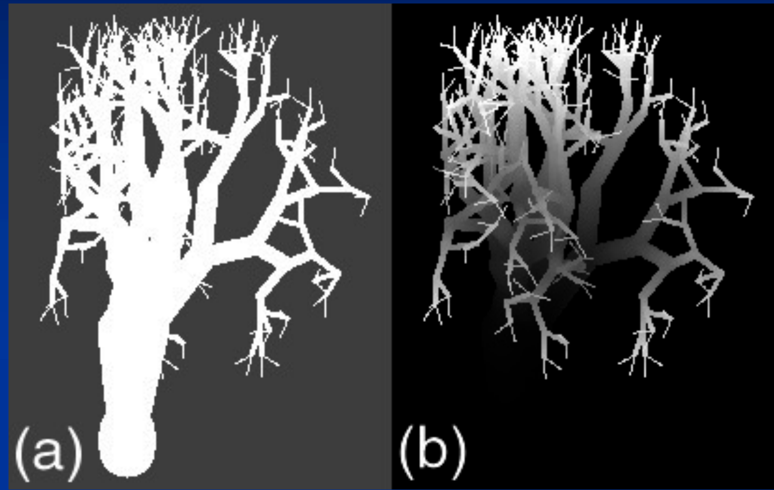
Vascular Feature Extraction

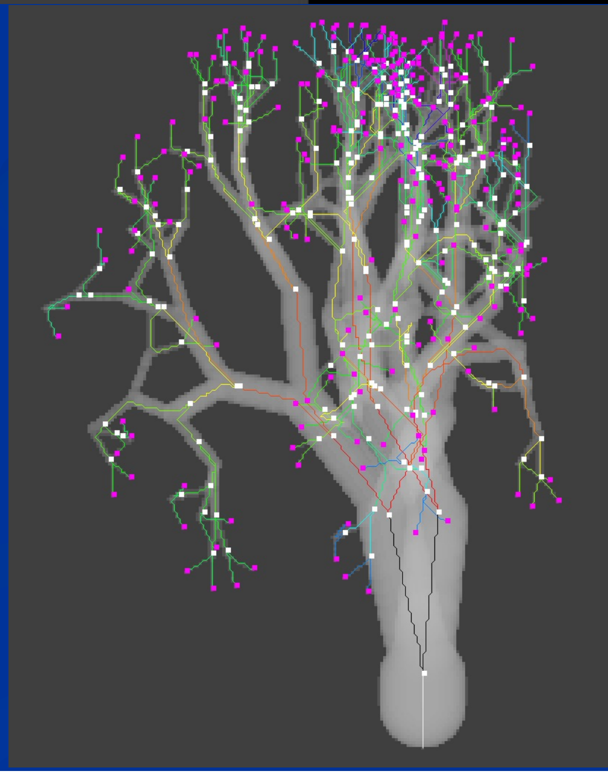
How Can We Generate Vascular Models?

- Morphological operators (Sonka)
- Dynamic programming
  - Generate cost function describing minimum cost to travel from seed-point to each voxel in mask
    - Lowest cost path along vessel center
  - Trace back centerlines
  - Recognize bifurcations

Results: Phantom Trees

- 6 Trees
- Detected 94% of endpoints exactly
  - Mean displacement of 4.6 voxels for remaining endpoints
- Detected 98% of bifurcations
  - Mean displacement 3.2 voxels

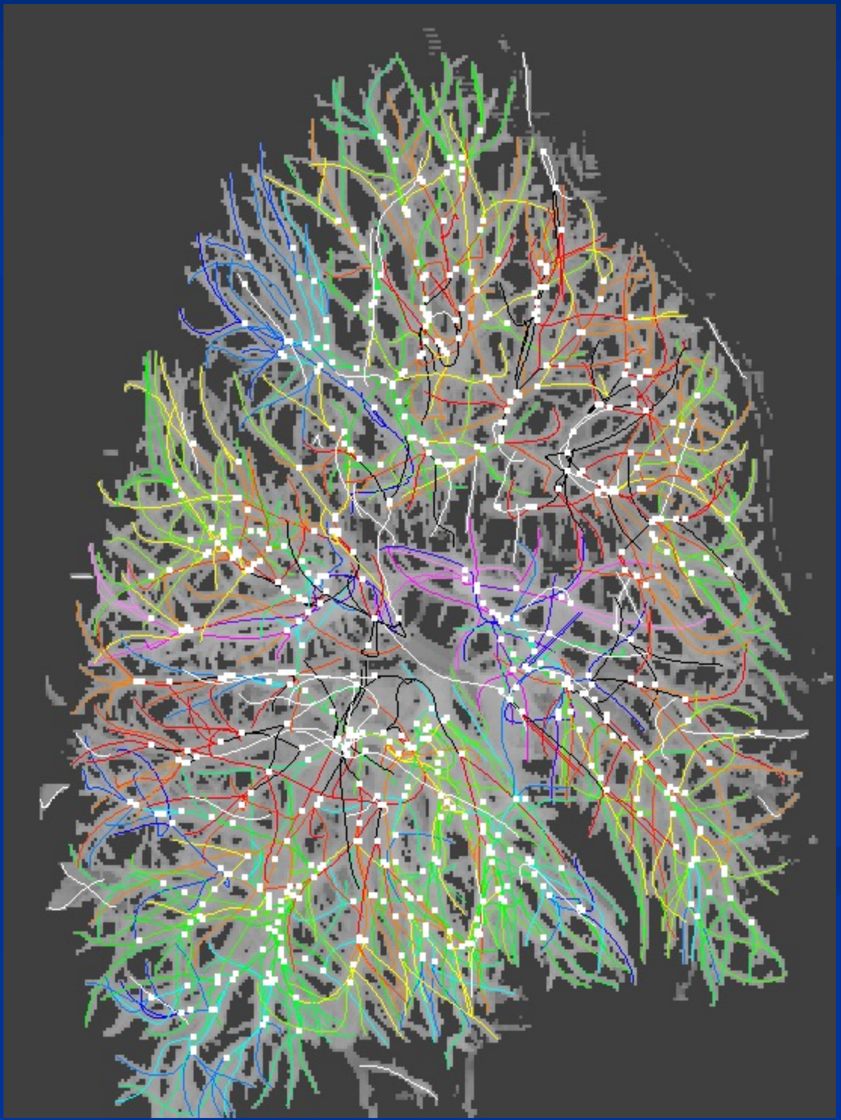




Patient Data: Fitted Vascular Tree

CTA/CTV Analysis

- Challenges
  - Short thick vessels
  - Lots of vessels
  - Poor contrast with other tissue structures
  - Bones



Rewriting Code

- Implemented algorithm using networkx
  - A Python graphs package developed at LANL
- Dijkstra centerline discovery (as before)
  - Directional Dijkstra (twice as fast)
- Resulting graphs very dense
  - Directional Dijkstra still slow
  - Pruning rules not obvious

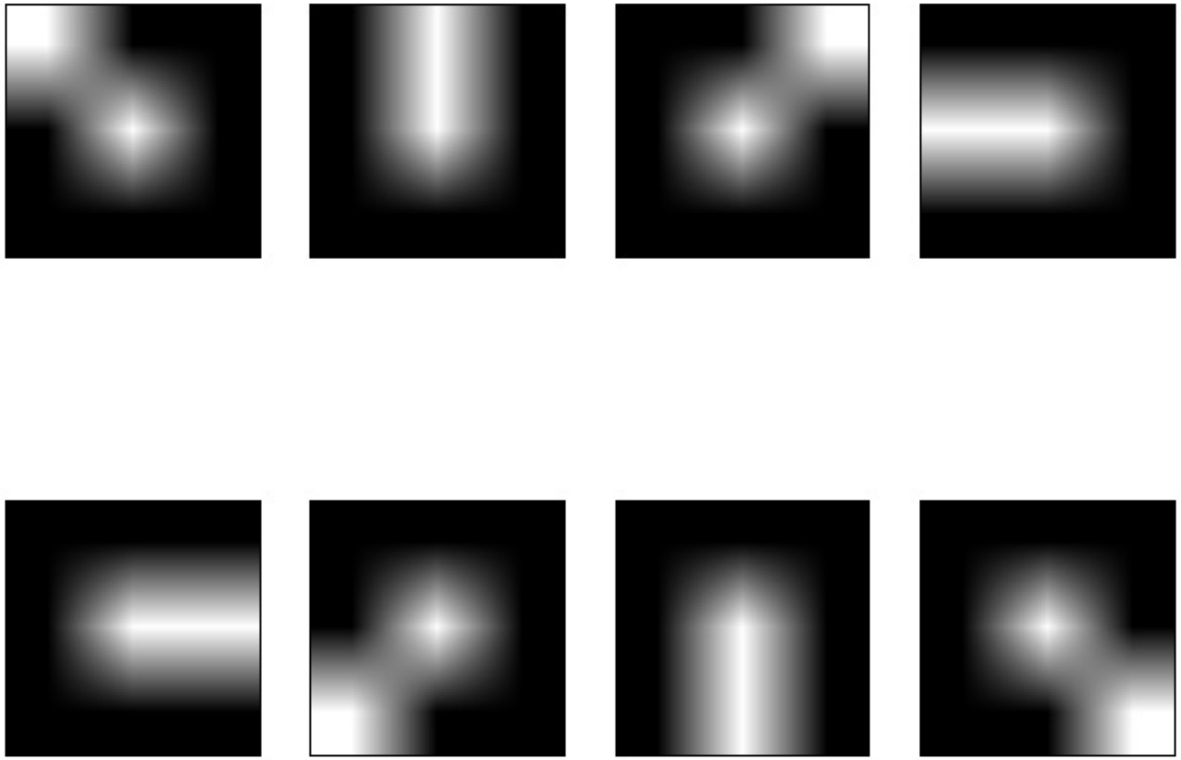
Alternative Approach

- Detect end-points on mask and then use A* algorithm to trace path between end-points and target.
- What constitutes an end-point?

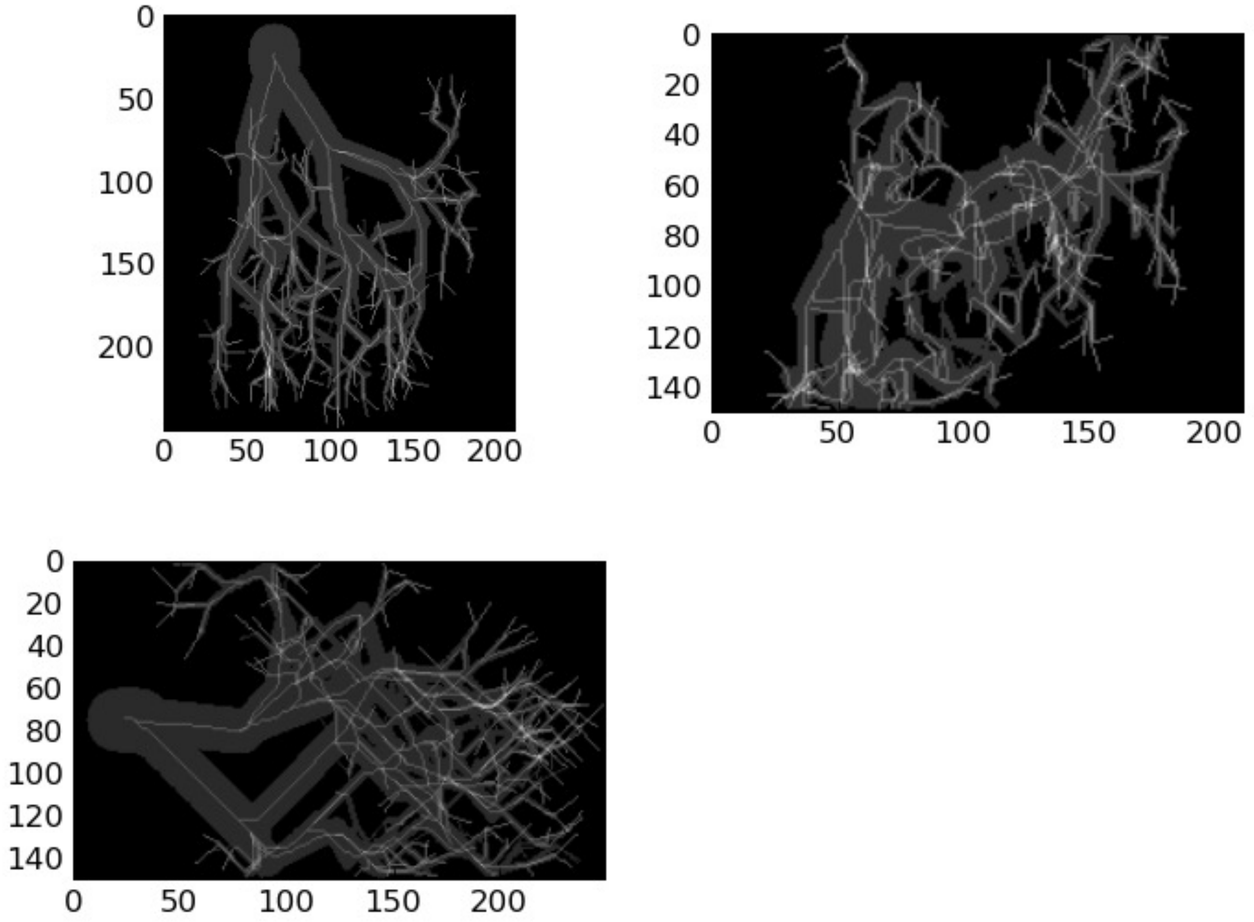
Alternative: End-point Detection

- Detect vascular terminations and only trace paths back from these points
- From the Hessian matrix filter
  - An end-point might be a point where the first derivative along the λ_1 eigenvector is large and negative
- From mathematical morphology
  - An endpoint is the termination of a line
  - So in an ideal world a hit-or-miss filter with a simple structuring element could be used

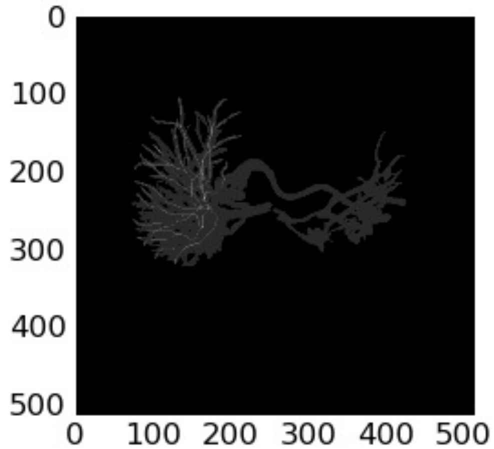
Kernels for 2D End-point Detection

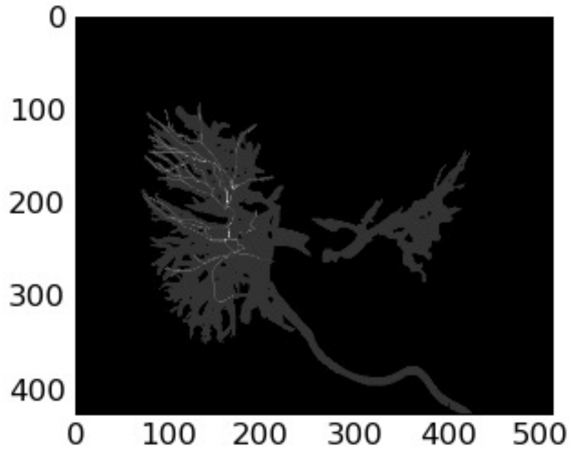


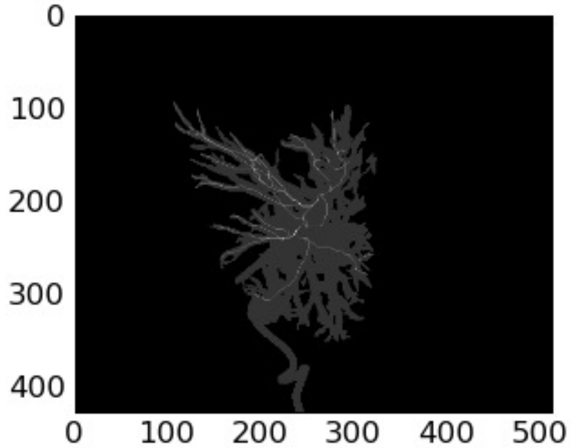
End-point Detection with Phantom



End-point Detection from Segmented Mask

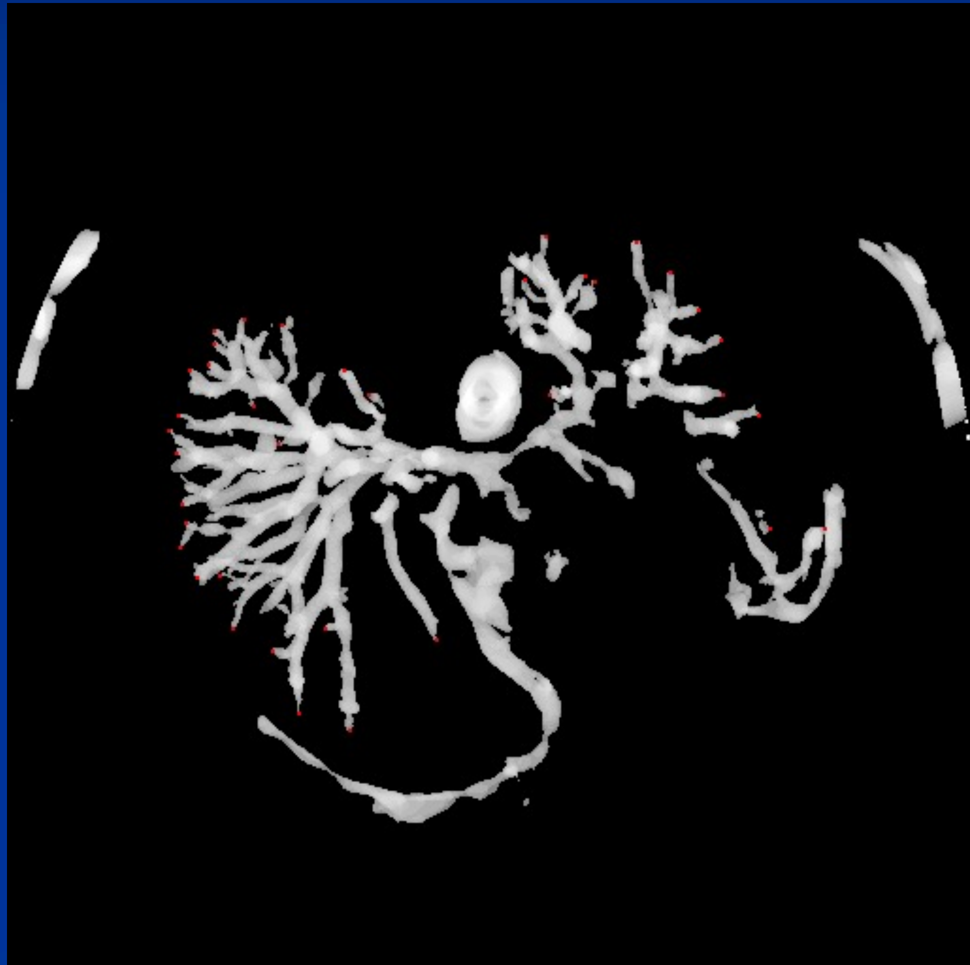






End-point Sampling

- Sampling from filter driven segmentation
- 10 Cases
- About 100 end-points (sampled) per case
- Do end-point morphologies from one segmentation match morphology from another?



Computer Aided Detection

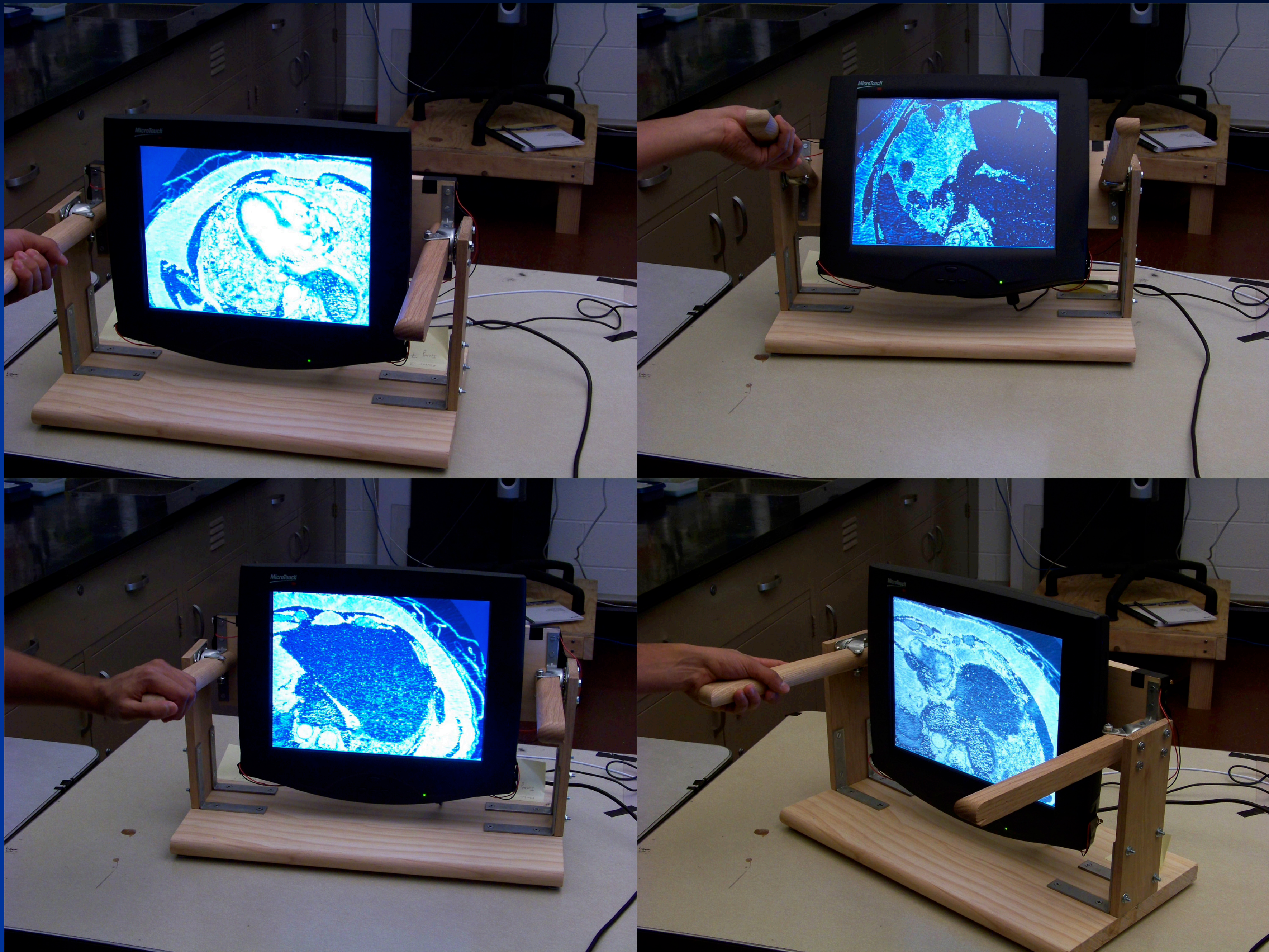
- Vascular models may
  - Increase specificity of CAD for pulmonary emboli
  - Provide additional features for classification
  - Provide more intelligent means to review CAD ques

Visualization

Grab-a-Slice

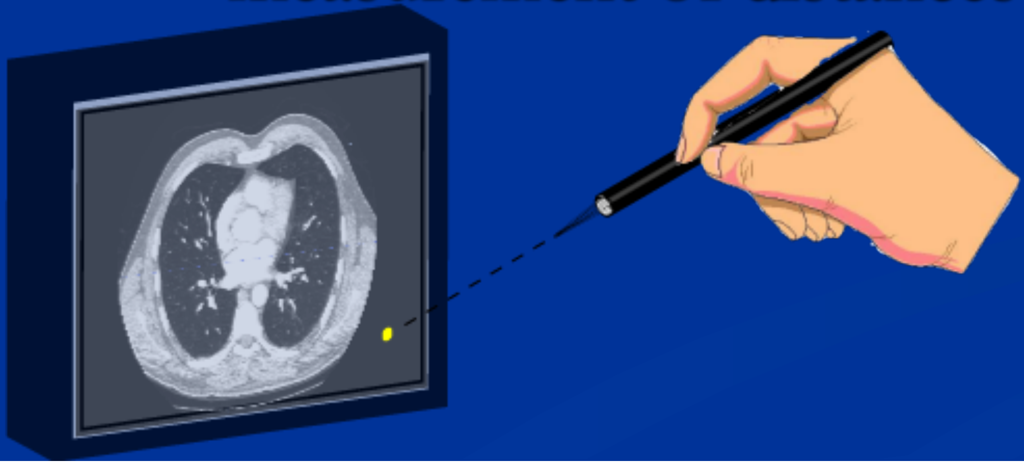
Movable Tomographic Display for 3D Medical Images

Shukla, et al., AMI ARCS workshop, MICCAI 2009



Navigational cues

- Cubic grid to provide coordinate system in which data resides
  - Can be combined with anatomical info to provide powerful context cue
- Tracked stylus as virtual laser pointer
  - Selection of target structures
  - measurement of distances between structures

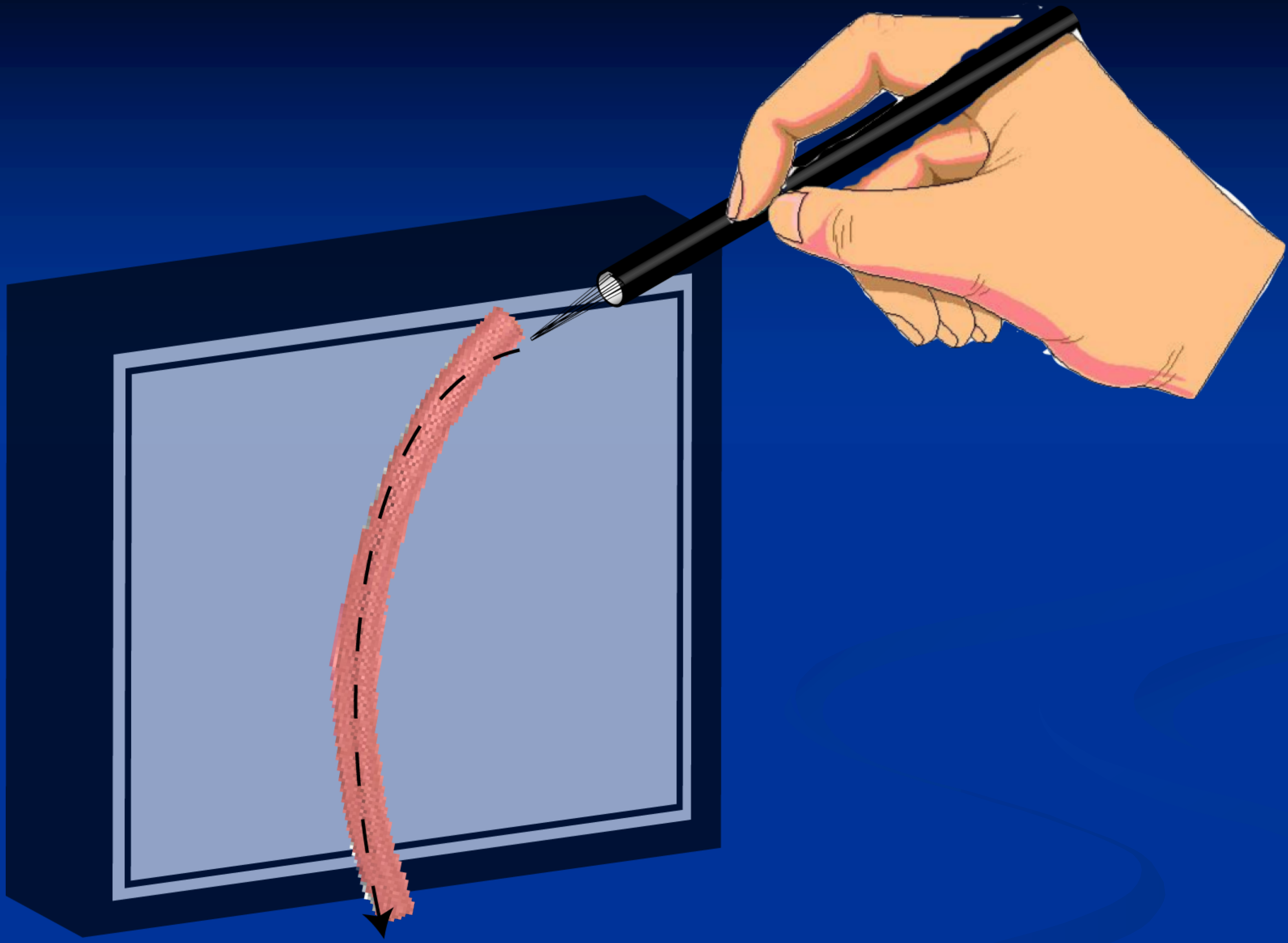


Stereo Display

- Options for stable display of stereo images
  - assumed viewpoint (commercial system)
  - fixed known viewpoint
  - mobile tracked viewpoint

Mental representation of 3D curvature

- Simulated 3D tubes with various curvatures.
- Subjects trace the trajectories of the tubes
  - using a tracked stylus



Computerized Image Analysis

- Segmentation
  - labeling pixels in an organized fashion
- Automated vs. semi-automated
- Promises great benefit to clinicians, but hasn't been widely accepted
  - mostly because it doesn't work (especially totally automated)
  - only *semi-automated* is practical today

Supervised Segmentation

- Use grab-a-slice as segmentation tool
  - to supervise algorithm
- Top-down process
  - human-defined path along axis of object
- Bottom-up process
  - computer analysis at the pixel level

Other Work (Past, Present, Future)

- Radiology involves images and words
  - Analysis of reports, integration with images
- Web computing—liberating the poor researcher
- Expansion of CAD work
  - Annotation!
- Peripheral vasculature
  - DVT, atherosclerosis
- Coronary imaging

The End