Biomedical Informatics 260

Radiomics

Lecture 8

David Paik, PhD

Spring 2019

Today: Radiomics

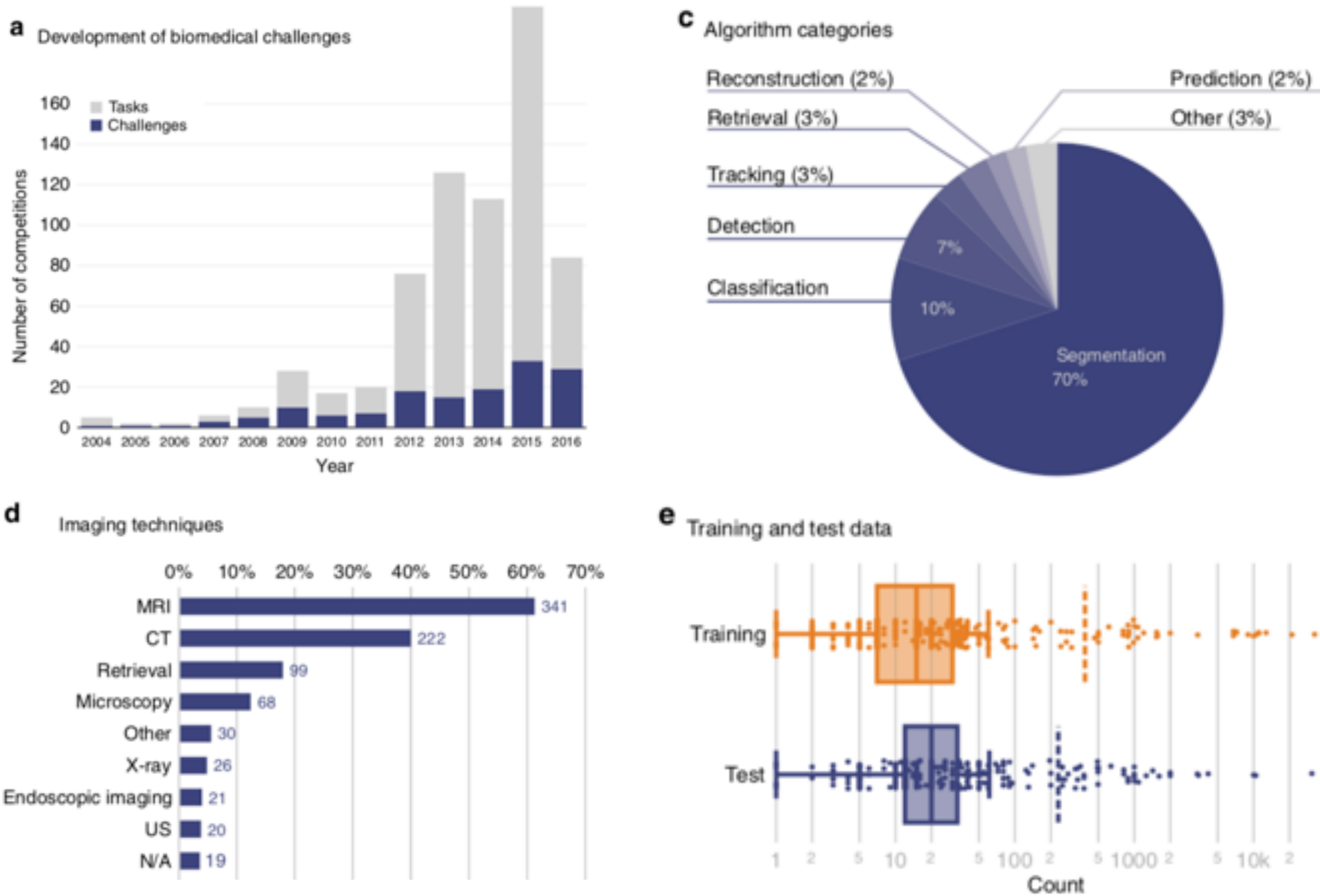
- Medical Imaging Datasets
- Content Based Image Retrieval (CBIR)
- Imaging Biomarkers
- Radiomics and Radiogenomics
- Quantitative Imaging
- Radiomics Applications
- Prelude to Deep Learning: Biological Neural Networks

Medical Image Datasets

Large-scale Medical Image Datasets

- Challenges and Competitions
  - Kaggle: numerous competitions
  - Grand-Challenge.org: numerous competitions
- Collections and Directories
  - NBIA/NCIA: numerous datasets
  - XNAT: numerous datasets
  - ACR DSI Dataset Directory
  - Aylward open access medical image repository list
- Individual Datasets
  - Osteoarthritis Initiative: 431k X-ray & MR studies
  - CheXpert: 224k CXR
  - NIH CXR: 112k CXR
  - MURA: 40k MSK X-rays
  - DeepLesion: 33k bookmarked CT images
  - DDSM: 2.5k mammography studies
  - fastMRI: 1.5k knee MRI
  - MRNet: 1.3k knee MRI
- *And many more…*

Biomedical Image Analysis Challenges



Maier-Hein et al, Nat Comm 2018

Biomedical Image Analysis Challenges

- Praise:
  - Heightens interest in medical imaging research
  - Makes research more accessible
  - Stimulates algorithm development and performance
- Critique:
  - Maier-Hein et al, Nat Comm 2018
    - Analysis of 150 challenges up to 2016
    - No commonly respected quality control exists
    - Half of relevant information not reported
      - How winner was determined
      - If training data could be supplemented
      - How reference standard annotation was done
    - Large variability in design
      - Radically different results with different metric, different annotator, different data

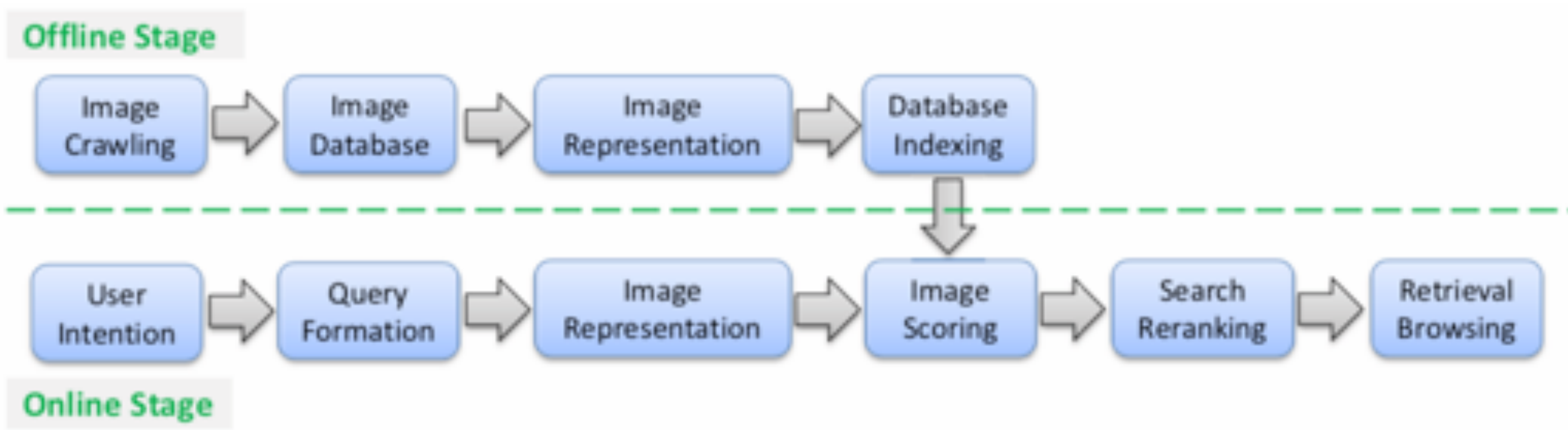
Content-Based Image Retrieval (CBIR)

Content Based Image Retrieval

- **Intention Gap**: difficulty for user to express the expected visual content

- **Semantic Gap**: difference between low-level visual information and high-level semantic information as perceived by humans

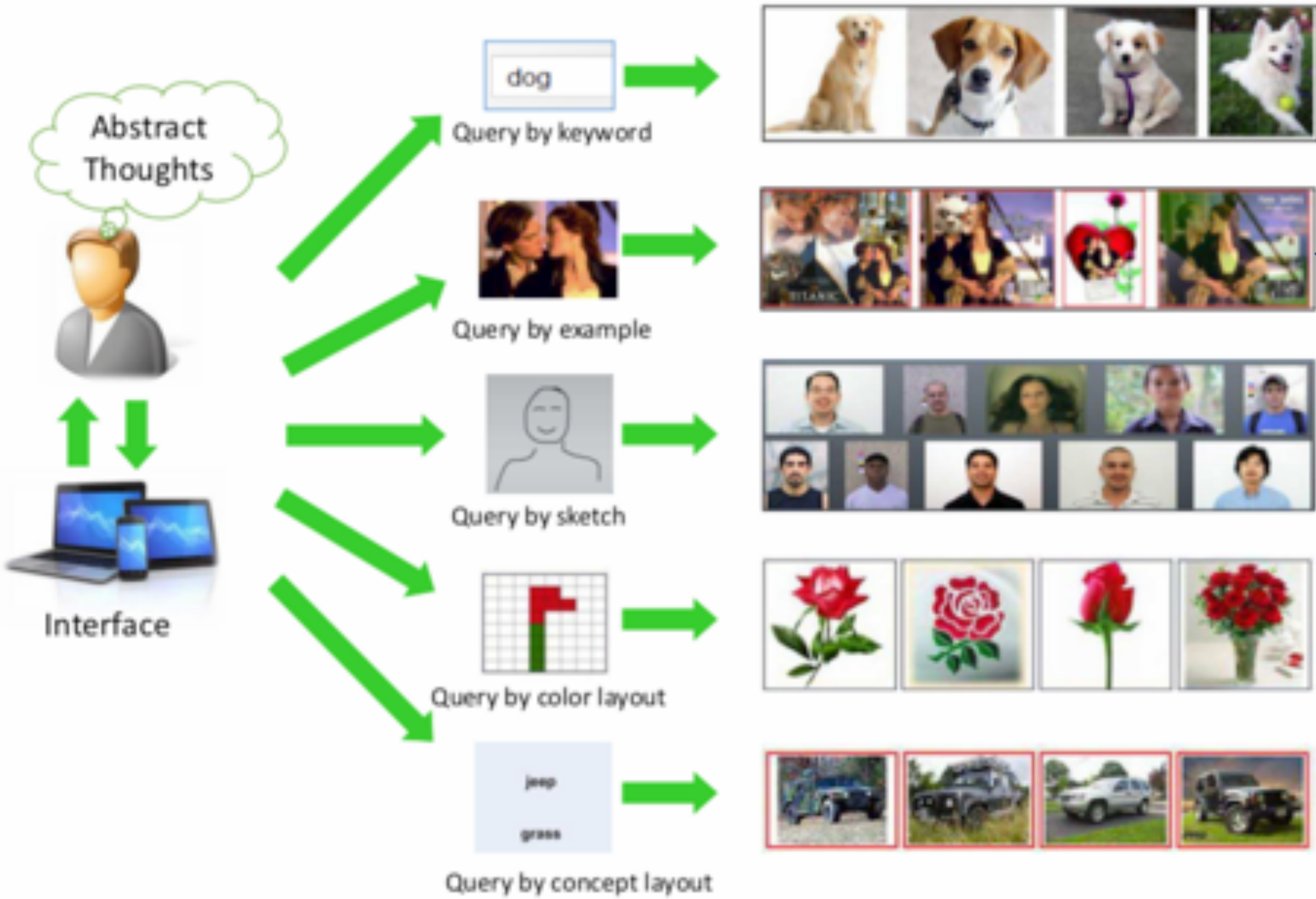
Flowchart and Key Issues



- Three key issues
  - Image representation
    - Define feature space
  - Image organization
    - Database indexing
  - Image similarity
    - Similarity should reflect relevance in semantics

Zhou et al, 2017

Image Query Formation

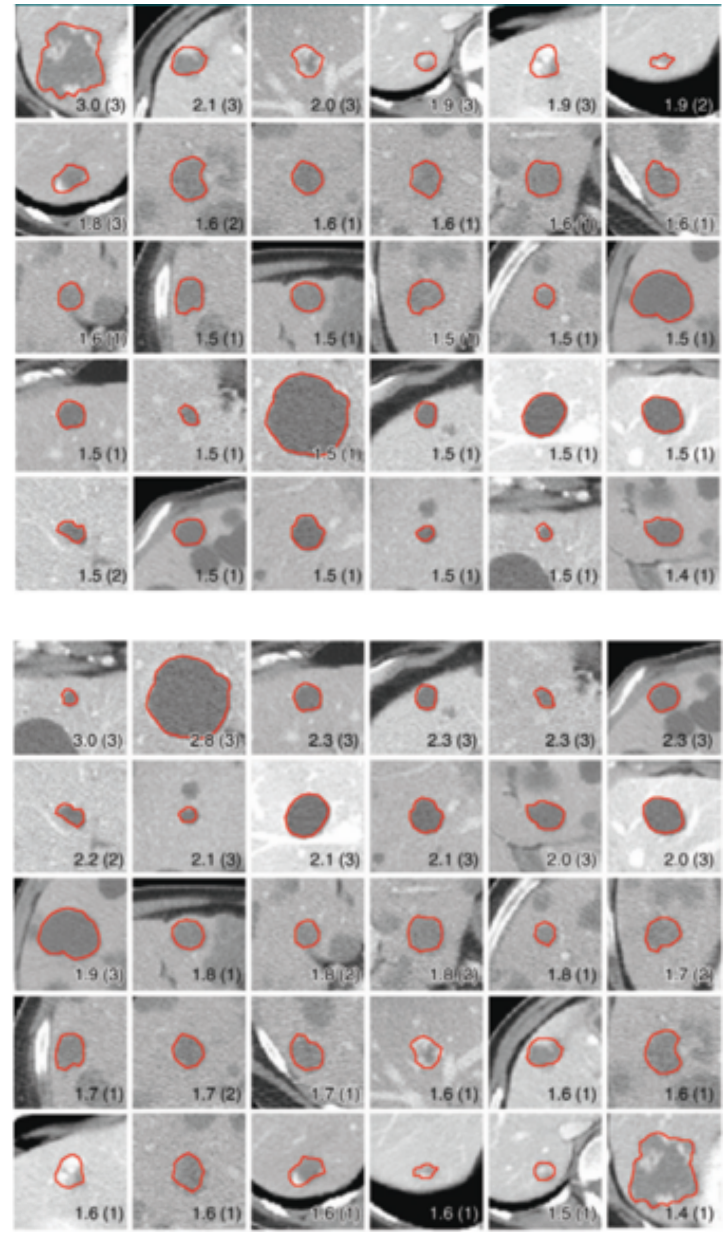


Most relevant
to medical images

Zhou et al, 2017

Retrieval of Similar Liver Lesion CTs

- 30 portal venous phase CT images of liver
- 3 types of liver lesions (cysts, hemangiomas, mets)
- 161 semantic features, 46 texture features, 2 boundary features
- Similarity as inverse weighted sum of differences



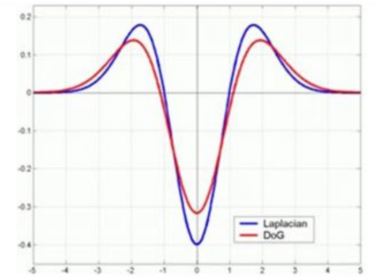
Napel et al, Radiology 2010

SIFT: Hand Crafted Feature Extraction

Scale Invariant Feature Transform

$L(x, y, \sigma) = G(x, y, \sigma) * I(x, y)$ Convolution with Gaussian

$D(x, y, \sigma) = L(x, y, k\sigma) - L(x, y, \sigma)$ Difference of Gaussians (DoG) (approximates Laplacian)



Keypoints are local extrema of DoG (compare to 26 neighbors)

$$D(\mathbf{x}) = D + \frac{\partial D^T}{\partial \mathbf{x}}\mathbf{x} + \frac{1}{2}\mathbf{x}^T \frac{\partial^2 D}{\partial \mathbf{x}^2}\mathbf{x}$$

$$\hat{\mathbf{x}} = -\frac{\partial^2 D}{\partial \mathbf{x}^2}^{-1} \frac{\partial D}{\partial \mathbf{x}}$$

Interpolate keypoints

$if\ D(\mathbf{x})$ < 3% max pixel value Discard low-contrast keypoints

$$H = \begin{bmatrix} D_{xx} & D_{xy} \\ D_{xy} & D_{yy} \end{bmatrix}$$

Eliminate edge responses using Hessian matrix (eigenvalue ratio above threshold)

Lowe, IJCV 2004

SIFT: Keypoint Detection

DoG extrema

Discard low contrast

Eliminate edge responses

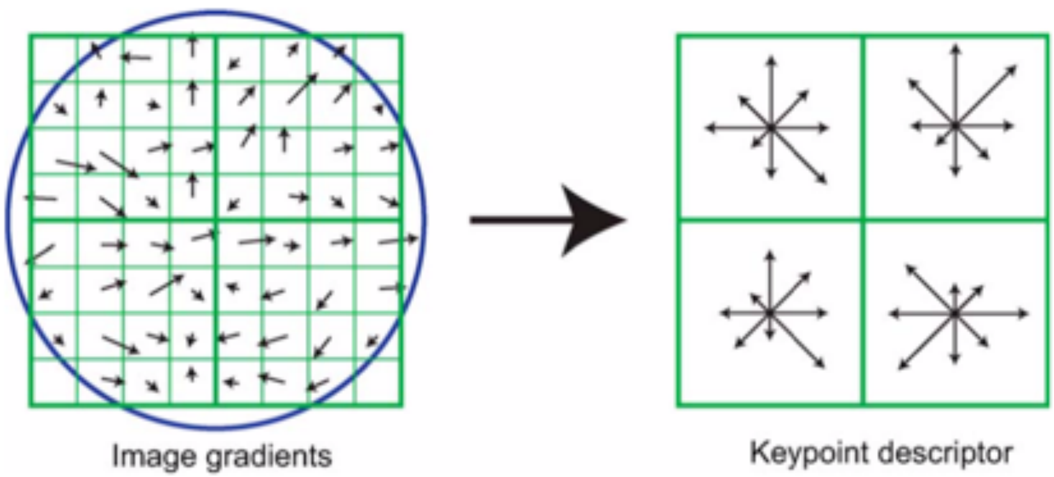
Lowe, IJCV 2004

SIFT: Descriptor Representation

$$m(x,y) = \sqrt{(L(x+1,y) - L(x-1,y))^2 + (L(x,y+1) - L(x,y-1))^2}$$

$$\theta(x,y) = atan2\big(L(x,y+1) - L(x,y-1), L(x+1,y) - L(x-1,y)\big)$$

Orientation histogram computed weighted by $m(x,y)$ and by circular Gaussian window



Gradient orientations rotated relative to keypoint orientation

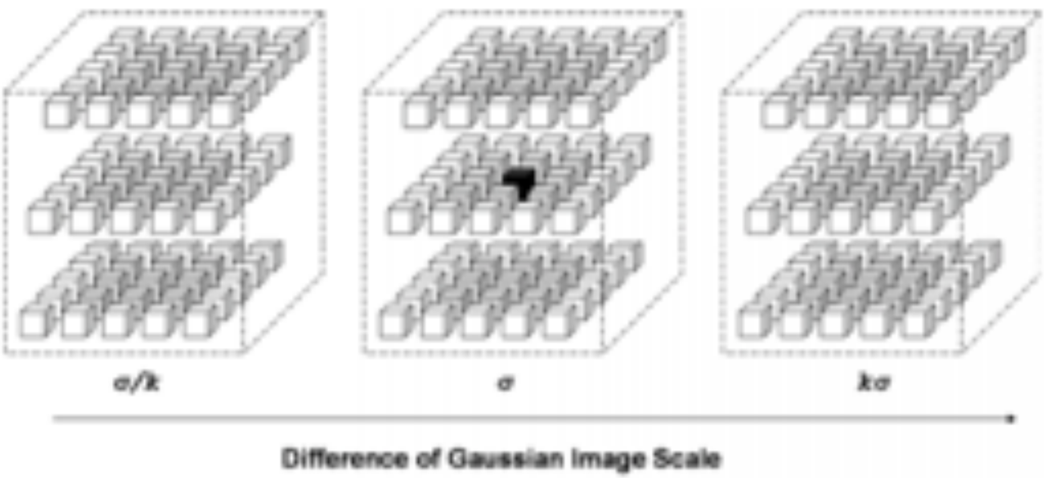
2x2x8 element feature vector (4x4x8 in real practice)

Normalize 128-vector

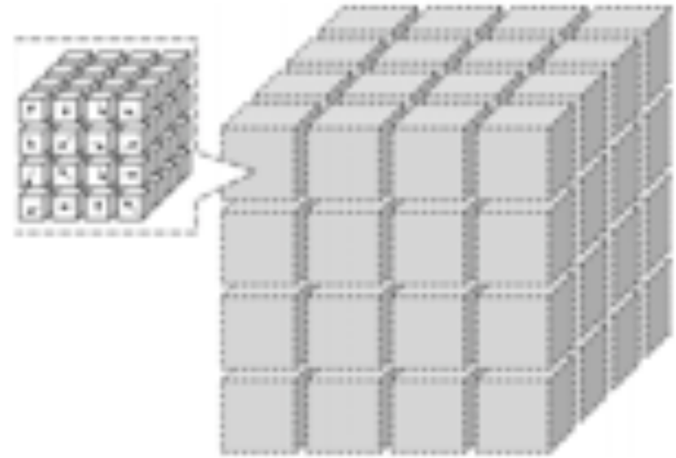
Approximate nearest neighbor matching against database
(uses ratio of distance to best vs to 2nd best match)

Lowe, IJCV 2004

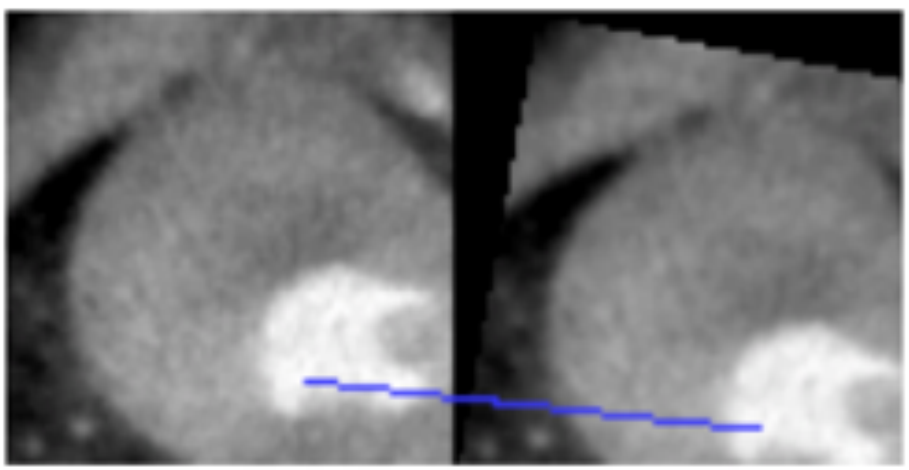
SIFT on 3D Medical Images



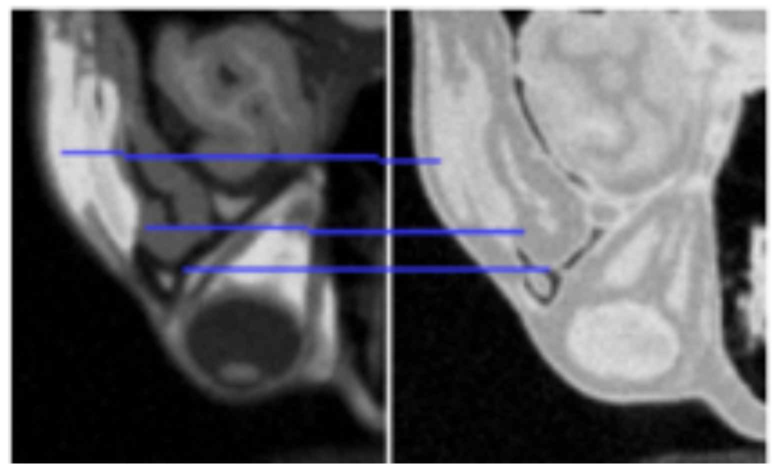
3D DoG



3D Keypoint Descriptor



4D CT (85-90% correct matches)



T1w vs PD matching (80-90% correct)

Cheung et al, ISBI 2007

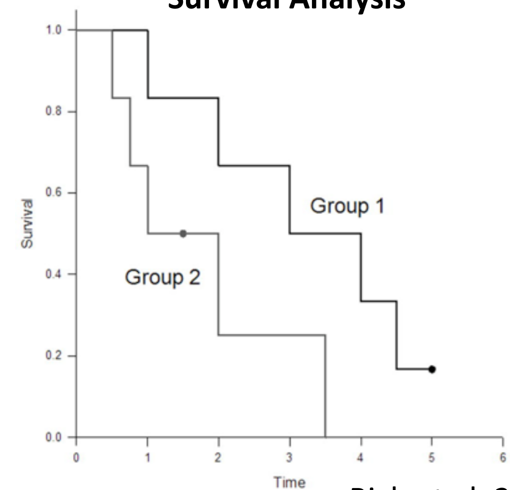
Imaging Biomarkers

Imaging Biomarkers

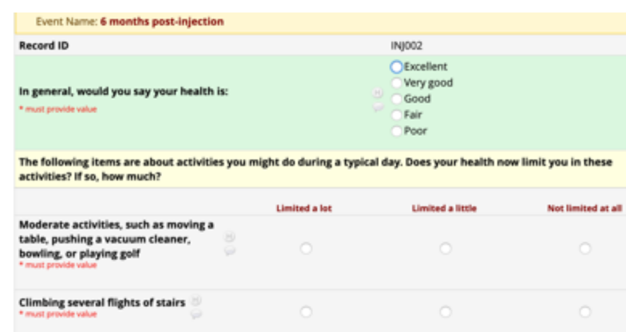
- **Clinical Endpoint**: "A characteristic or variable that reflects how a patient feels, functions, or survives"
  - Can take a long time to measure and can have numerous confounders

  - Survival: overall survival, disease free survival, progression free survival
    - RECIST: complete response, partial response, stable disease, progressive disease
  - Quality of Life: patient reported outcome
    - NIH PROMIS: mental health, physical health, social health, etc.

Kaplan Meier Survival Analysis



Rich et al, 2014


Event Name: 6 months post-injection

Record ID INJ002

In general, would you say your health is:
* must provide value
Excellent
Very good
Good
Fair
Poor

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Limited a lot	Limited a little	Not limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf * must provide value			
Climbing several flights of stairs * must provide value			

Biom. Def. WG, Clin Pharm & Ther, 2001

Imaging Biomarkers

- **Biomarker**: “A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”
  - e.g., cardiac troponins (cardiotoxicity), plasmodium rRNA (malaria), LDL cholesterol (cardiovascular risk)
  - Some dramatic failures of conventional wisdom:
    - suppression ventricular arrhythmia != reduced sudden death after MI

Biom. Def. WG, Clin Pharm & Ther, 2001

Imaging Biomarkers

- **Imaging Biomarker**:
  - Biomarkers measured from imaging (aka high-level image features)
  - "…consist of both qualitative biomarkers, which require expert interpretation, and quantitative biomarkers which are based on mathematical definitions"
  - e.g., tumor volume, ^{99m}Tc-sestamibi (myocardium)

Image Biomarker Standardisation Initiative Reference Manual 2018

Imaging Biomarkers

- **Surrogate Endpoint**:
  - In context of clinical trials, for toxicity or efficacy
  - “A biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence”
  - Stand-in for an endpoint (not “surrogate marker”)

Biom. Def. WG, Clin Pharm & Ther, 2001

FDA Qualified Imaging Biomarkers

- Groups Researching and Promoting Biomarkers
  - Academic Medical Centers & Consortia
  - Industry
  - Critical Path Institute (C-Path), International Life Sciences Institute (ILSI), Health and Environmental Sciences Institute (HESI), Foundation for NIH (FNIH), Radiologic Society of North America (RSNA) QIBA, NCI Quantitative Imaging Network (QIN), etc.

FDA Qualified Imaging Biomarkers

- Accepted
  - Total Kidney Volume by MR, CT, US (2016)
  - Ileum/Large Bowel Features by MR (2017)
- Under review
  - PET SUV
  - Tumor Volume and Tumor Volume Change by CT
  - Hippocampal Volume by MR
  - Lung Structure/Function Parameters by CT
  - Cartilage Thickness by MR
  - BMD by DXA
  - Liver Tissue by Iron Corrected T1 MR
- Not accepted
  - Lower Lung Lobe Volume by CT

Radiomics and Radiogenomics

Radiomics

- **Radiomics**:
  - "high-throughput extraction of quantitative features that result in the conversion of images into mineable data and the subsequent analysis of these data for decision support"
  - Epitomizes precision medicine (right treatment for the right patient at the right time)
  - Utilizes large-scale image databases
  - Data mining, hypothesis generation
  - Main focus on oncology
    - tumor heterogeneity, therapeutic resistance

Gillies et al, Radiology 2016

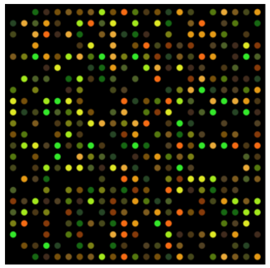
Radiogenomics

- **Radiogenomics**
  - “mining of radiomic data to detect correlations with genomic patterns”
  - Note: some confusion with radiation oncology where radiogenomics is whole-genome analysis of effect of radiation exposure

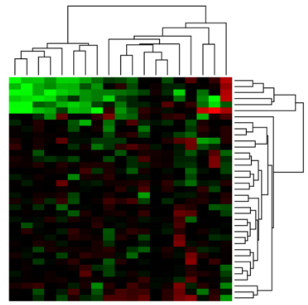
Gillies et al, Radiology 2016

Radiogenomics Data Sources

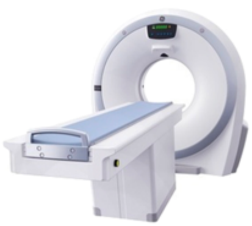
Tissue sample



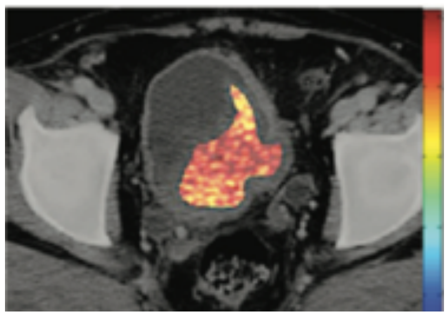
Genomic features



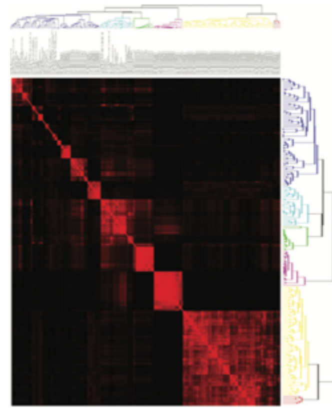
Genomic analysis



CT Scanner



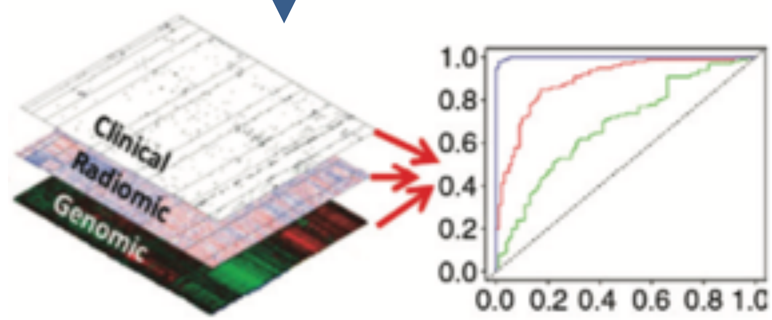
Bladder texture feature



Radiomic analysis

EHR

Data Mining



Gillies et al, Radiology 2016

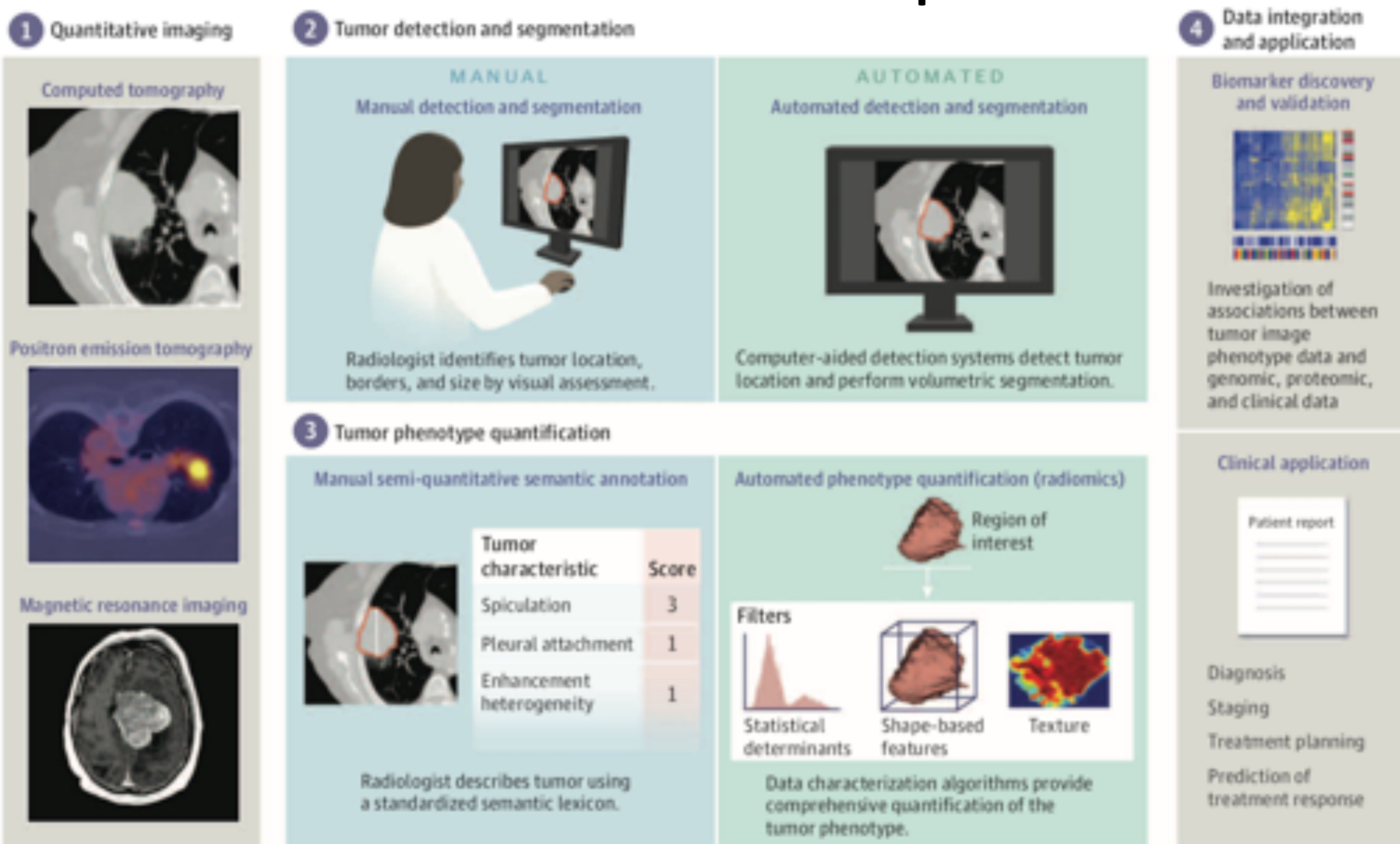
Radiogenomics Uses

- 1) Suggest gene expression or mutation status that warrants further testing
- 2) Radiomic features that are not correlated with genomic features could provide independent information

Process of Radiogenomics

- Image Acquisition
  - Lack of standardized acquisition protocols; non-biological pattern of changes in data
- Identifying Volumes of Interest
- Segmentation
- Feature Extraction
- Populate Database
- Mine Data to Develop Classifier/Prediction

Radiomics Steps



Aerts, JAMA Onc 2016

Quantitative Imaging

Quantitative Imaging

Non-reproducible and Redundant Features

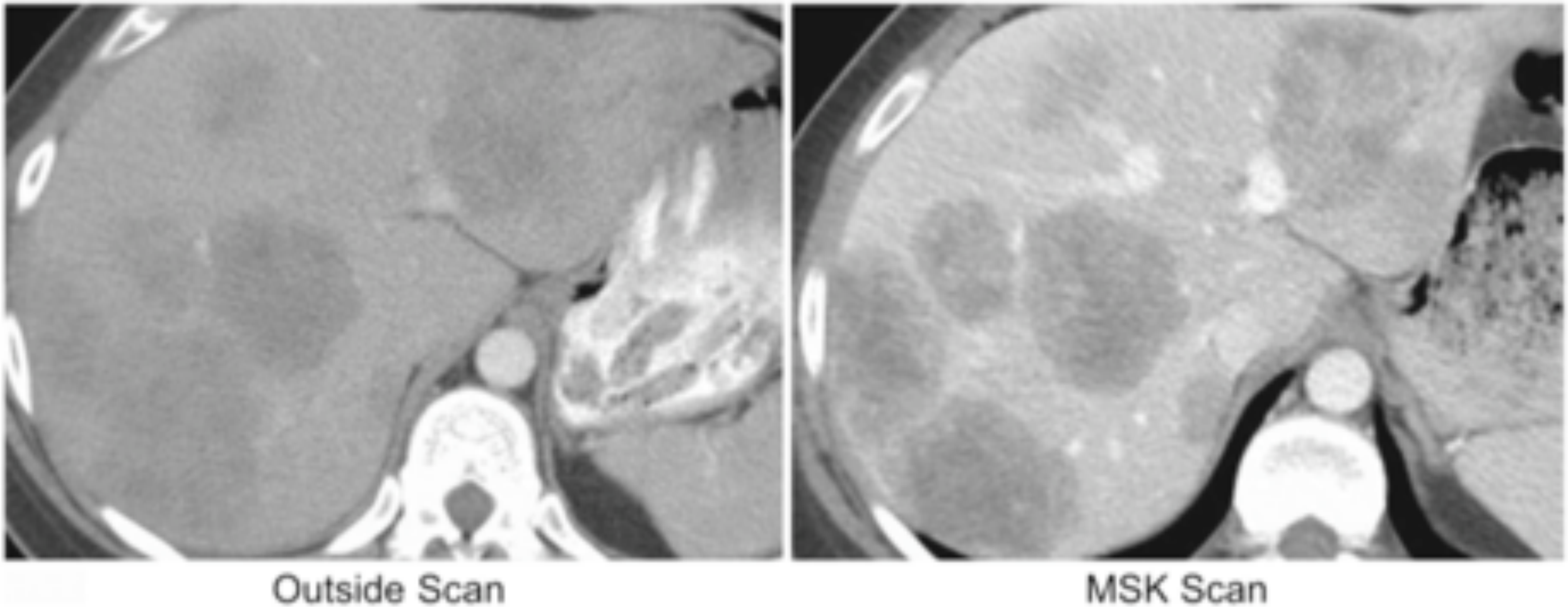


Fig. 1 Comparison of imaging protocol differences: portal venous phase CT acquired of the same patient 10 days apart.

Image Acquisition Protocols Not Standardized Across Institutions (and sometimes not even within institutions)

Midya et al, J Med Im 2018

Quantitative Imaging

Non-reproducible and Redundant Features

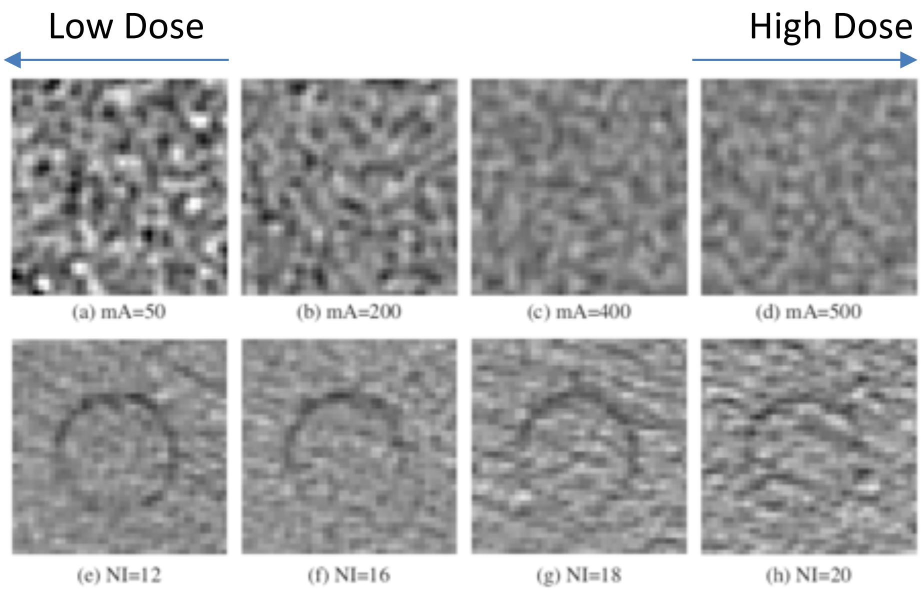


Fig. 5 CT pixel pattern appearance variation with increasing (a)–(d) tube current and (e)–(h) noise index in the UWP and anthropomorphic phantom, respectively. The circle in the anthropomorphic phantom is a rod designed to hold dosimeter.

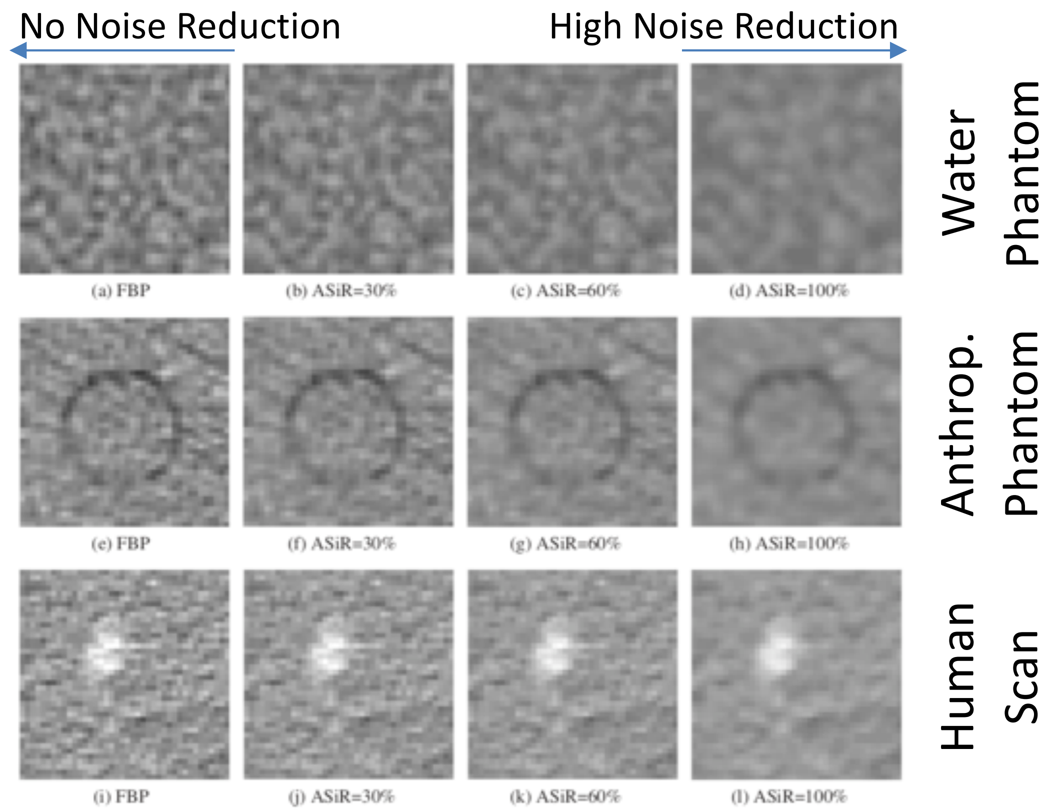


Fig. 7 CT pixel pattern appearance variation with increasing ASiR levels in (a)–(d) UWP, (e)–(h) anthropomorphic phantom, and (i)–(l) human scan, respectively.

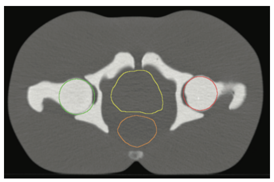
Effect of Acquisition Parameters

Effect of Reconstruction Algorithm

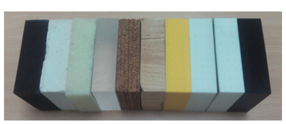
Midya et al, J Med Im 2018

Quantitative Imaging

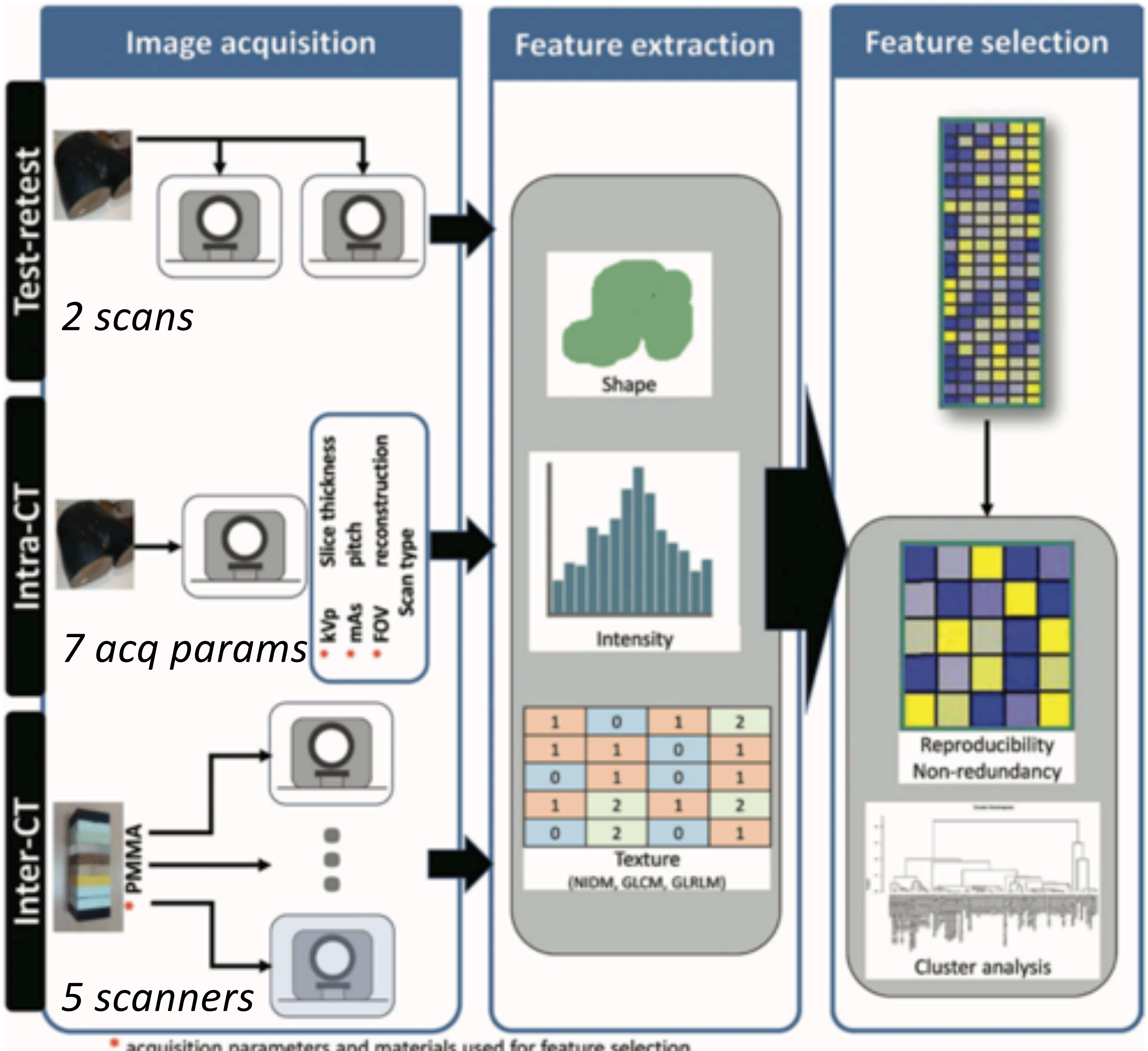
Non-reproducible and Redundant Features



Anthropomorphic Pelvis Phantom



Multi-material Phantom



177 Features

Test-retest

161 Features
-9%

Intra-CT
Inter-CT

71 Features
-56%

Redundancy

10 Clusters
-86%

Berenguer et al, Radiology 2018

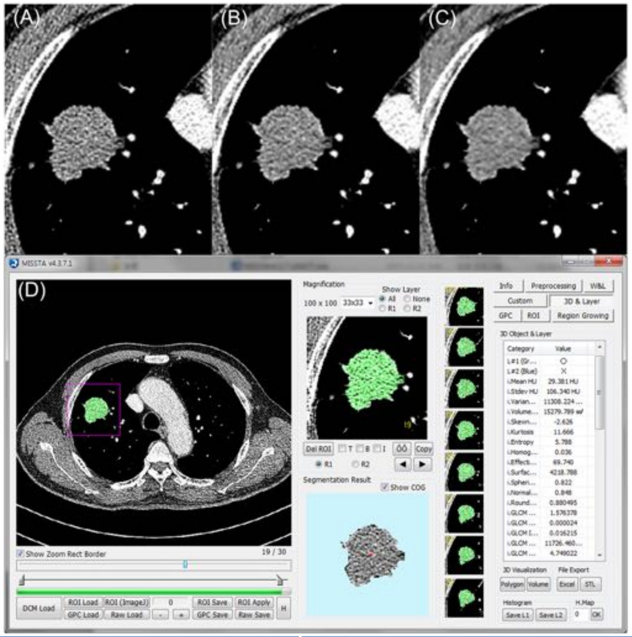
Quantitative Imaging

Impact of Reconstruction Algorithms

- 42 patients
  - 42 lesions across various organ sites
- Contrast-enhanced CT scans
  - Consistent acquisition parameters
  - 3 reconstruction algorithms (FBP, iteratative w/low and high noise reduction)
- Segmentation by 2 different readers on FBP
  - 15 features: 6 intensity, 5 size/shape, 4 texture
- Variability
  - Intra-reader, inter-reader, inter-recon alg

Kim et al, PLOS One 2016

Quantitative Imaging
Impact of Reconstruction Algorithms



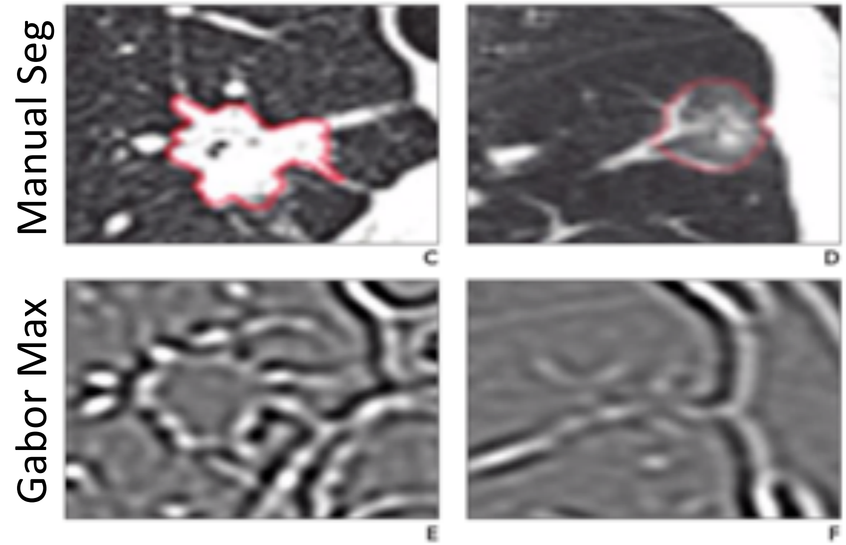
	Inter-recon alg $p < 0.05$	Intra-reader CV > 5%	Inter-reader CV > 5%
Intensity Features	5/6	4/6	4/6
Size/Shape Features	0/5	2/5	2/5
Texture Features	4/4	1/4	1/4

Kim et al, PLOS One 2016

Example Radiomics Applications

Predicting Brain Mets in Lung Adenocarcinoma

- 89 patients with T1 lung adenocarcinoma
  - 35 with brain mets, 54 without
- Semi-automated segmentation of target lesion
  - Level set with refinement by Markov random field
- 1160 quantitative features from unenhanced CT
  - Shape, size, boundary sharpness, texture
  - Hierarchical clustering and feature ranking
  - Random forest
- Three models with AUC for predicting brain metastases
  - Clinical (.759), radiomics (.847), hybrid (.871)



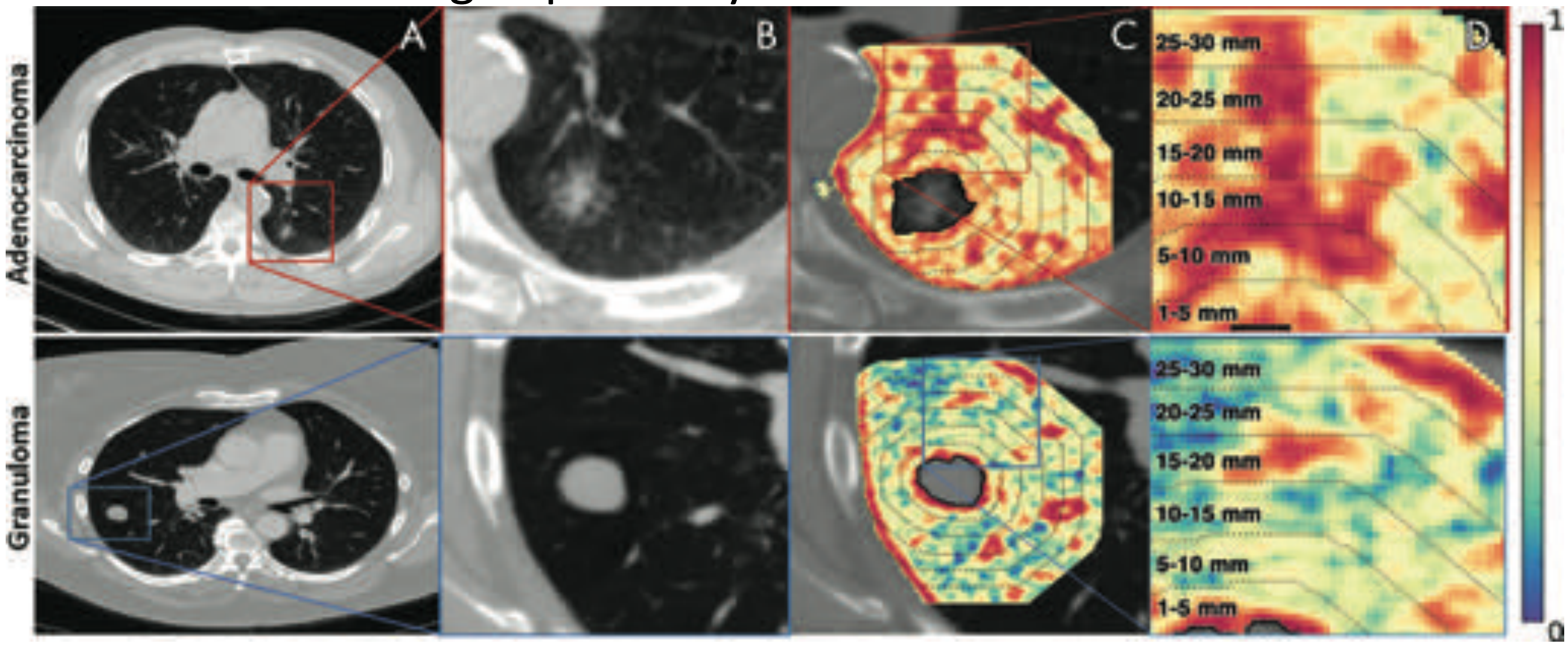
With brain mets | No brain mets

Parameter	Clinical Model	Radiomics Model	Hybrid Model
Variable	Age	Gabor_Max	
	Sex	LoG_Z_Uniformity	LoG_Z_Uniformity
	Smoking status	LoG_Z_Entropy	LoG_Z_Entropy
	Tumor diameter	Sigmoid_Offset_Std	Clinical_Lymph Node
	Tumor position		
	CT-reported N category		
Sensitivity	0.829	0.8	0.829
Specificity	0.574	0.815	0.833
AUC value (95% CI)	0.759 (0.643–0.867)	0.847 (0.739–0.915)	0.871 (0.767–0.933)

Chen et al, AJR 2019

Perinodular + Intranodular Lung CT Radiomics:
Adenocarcinoma vs. Granuloma

- 290 patients from 2 institutions
  - Either adenocarcinoma (145) or granuloma (145)
  - Determined by histopathology
- Nodule segmentation
  - Manual nodule identification and segmentation in all 2D slices
  - 30mm dilated ring of parenchyma around nodule in 5mm increments



Beig et al, Radiology 2018

Perinodular + Intranodular Lung CT Radiomics:
Adenocarcinoma vs. Granuloma

- 1776 Features
  - 252 intranodular
  - 1512 perinodular
  - 12 shape
  - 2D textures from slice with largest nodule area
  - ***Only 12 features used (with $p < 0.05$)***
- Look closely at the Gabor features selected!

Feature No.	Feature Family	Descriptor*	Statistic	Nodule Region of Feature Extraction†	P Value‡
	Perinodular Radiomic Features				
1	Gabor	$f = 16, \theta = \pi/8$	Skewness	Perinodular	<.001
2	Laws energy	R5S5†	Median	Perinodular	<.001
3	Gabor	$f = 8, \theta = \pi/2$	SD	Perinodular	<.001
4	Gabor	$f = 8, \theta = 3\pi/4$	Kurtosis	Perinodular	.001
5	Gabor	$f = 2, \theta = \pi/2$	Skewness	Perinodular	.001
6	Gabor	$f = 2, \theta = 3\pi/4$	Kurtosis	Perinodular	<.001
7	Gabor	$f = 4, \theta = \pi/4$	Median	Perinodular	<.001
8	Gabor	$f = 4, \theta = \pi/8$	Kurtosis	Perinodular	<.001
9	Gabor	$f = 4, \theta = \pi/8$	Median	Perinodular	<.001
10	Gabor	$f = 2, \theta = 3\pi/4$	Skewness	Perinodular	<.001
11	Gabor	$f = 4, \theta = \pi/8$	SD	Perinodular	<.001
12	Gabor	$f = 2, \theta = 3\pi/4$	Skewness	Perinodular	<.001
	Combined Radiomic Features				
1	Gabor	$f = 16, \theta = \pi/8$	Skewness	Perinodular	<.001
2	Gabor	$f = 32, \theta = 3\pi/4$	Kurtosis	Intranodular	<.001
3	Gabor	$f = 4, \theta = 3\pi/4$	Skewness	Intranodular	<.001
4	Gabor	$f = 4, \theta = \pi/2$	Median	Intranodular	.001
5	Laws energy	R5 W5§	Median	Perinodular	<.001
6	Laws energy	W5E5§	Median	Intranodular	<.001
7	Laws energy	S5E5§	Median	Intranodular	<.001
8	Gabor	$f = 32, \theta = 3\pi/4$	Median	Intranodular	<.001
9	Gabor	$f = 8, \theta = \pi/2$	SD	Perinodular	<.001
10	Gabor	$f = 32, \theta = \pi/2$	Median	Intranodular	<.001
11	Gabor	$f = 32, \theta = 3\pi/8$	Skewness	Intranodular	.003
12	Gabor	$f = 8, \theta = 3\pi/4$	Kurtosis	Intranodular	<.001

Beig et al, Radiology 2018

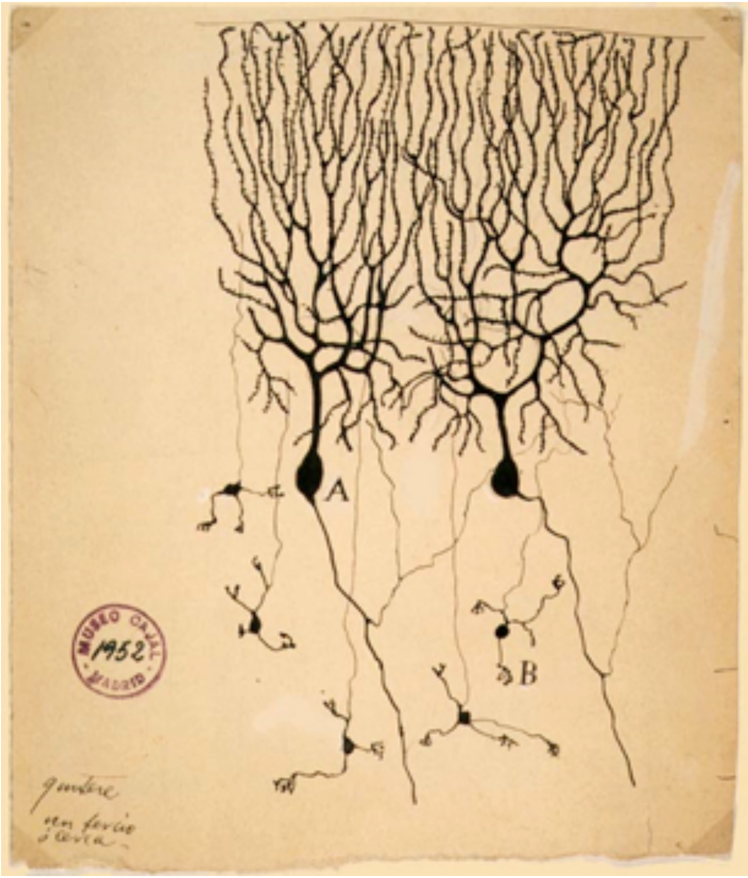
Perinodular + Intranodular Lung CT Radiomics:
Adenocarcinoma vs. Granuloma

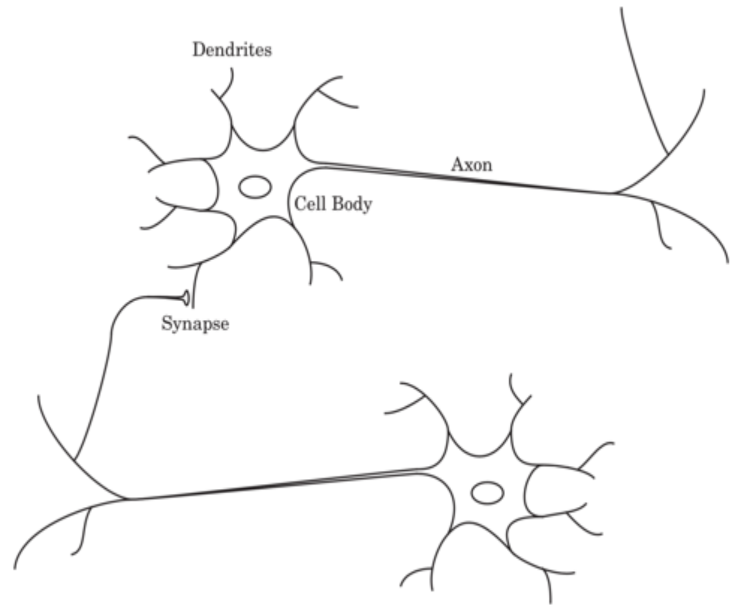
- Classified with LDA, QDA, SVM (linear+RBF), RF
  - Perinodular radiomics: SVM lin. AUC 0.74 (0.57,0.90)
  - Intra+Perinodular radiomics: SVM lin. AUC 0.80 (0.65,0.94)
- For comparison
  - LeNet CNN AUC 0.76 (0.60,0.92)
  - Readers AUC 0.60-0.61
- Scanner manufacturer comparison
  - Siemens: AUC 0.82 (0.64,0.99)
  - Philips: AUC 0.72 (0.43,0.99)
- By CT image type
  - Diagnostic (slice thickness ≤ 3mm): AUC 0.73 (0.53,0.93)
  - Screening (slice thickness > 3mm): AUC 0.66 (0.20,1.11)
- Takeaway: analyze lesions *and their surrounding context*

Beig et al, Radiology 2018

Prelude to Deep Learning: Biological Neural Networks

Bio-inspired Computing



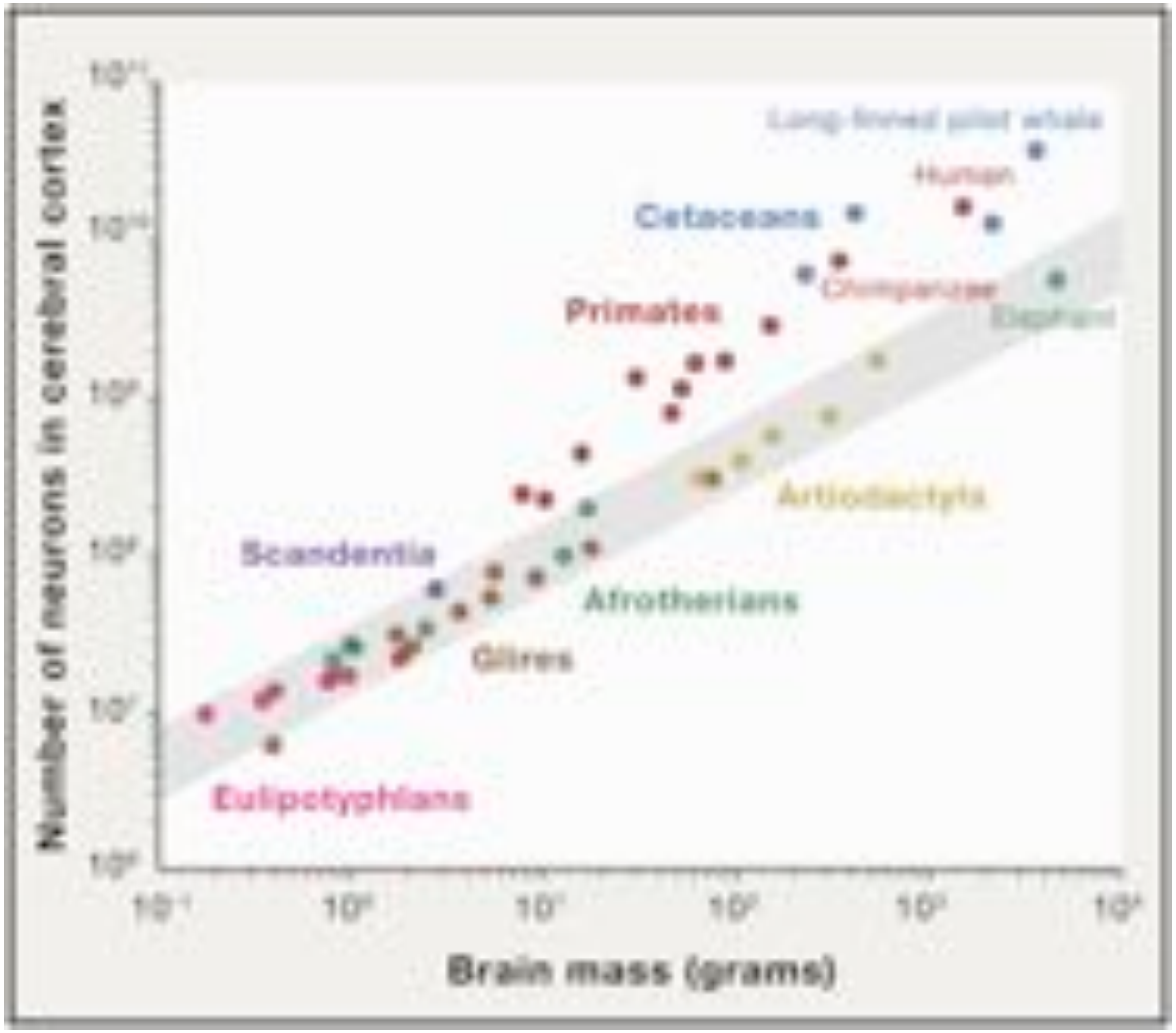


Hagan et al, Neural Network Design

Pigeon cerebellum (A: Purkinje cells, B: granule cells)
Santiago Ramon y Cajal 1899
1906 Nobel Prize for discovery of discrete neurons

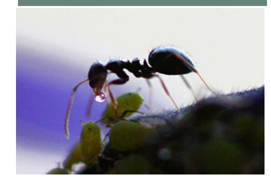
Human brain ~10^{11} neurons
~7000 synapses per neuron

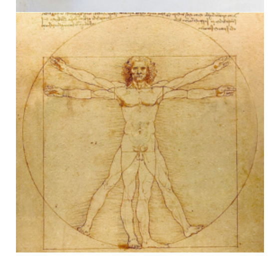
Neuronal Number



Sousa et al, Cell 2017

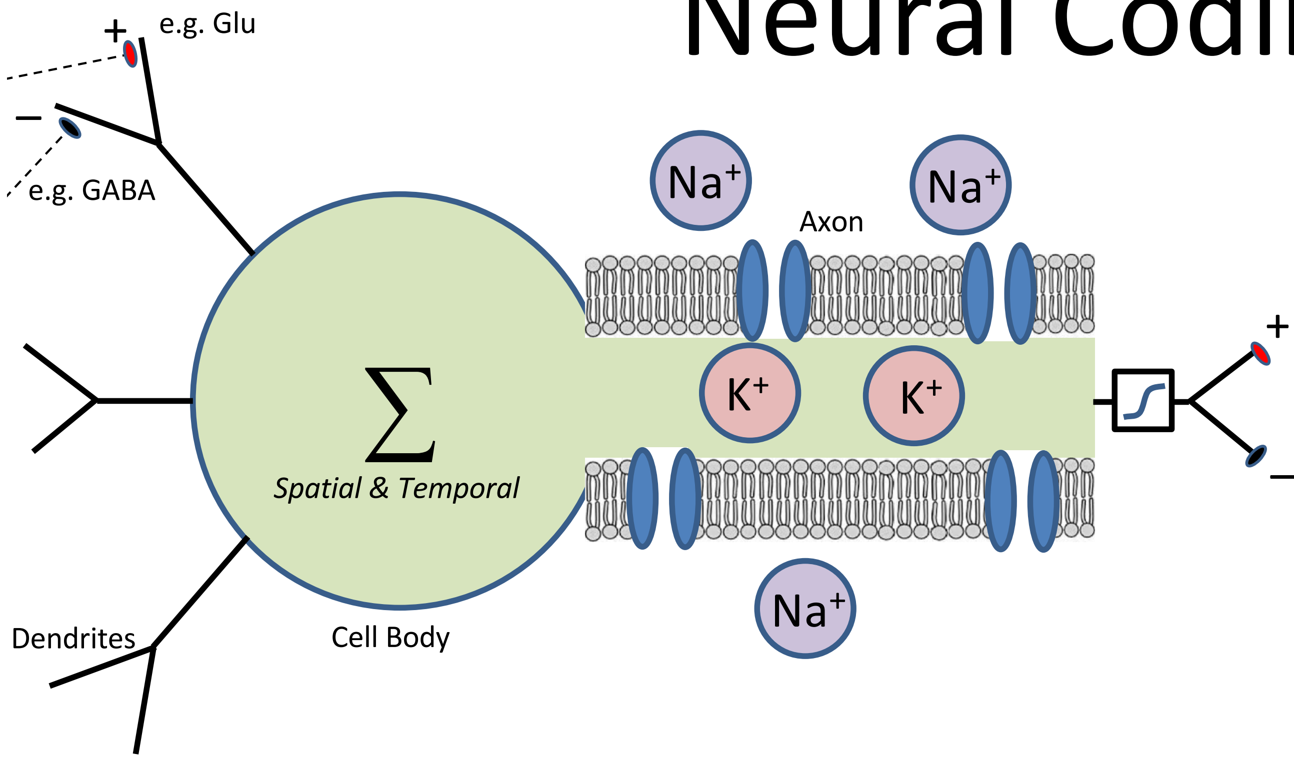
- 302: nematode
- 10K: ant
- 4M: mouse
- 300M: cat
- 100B: human

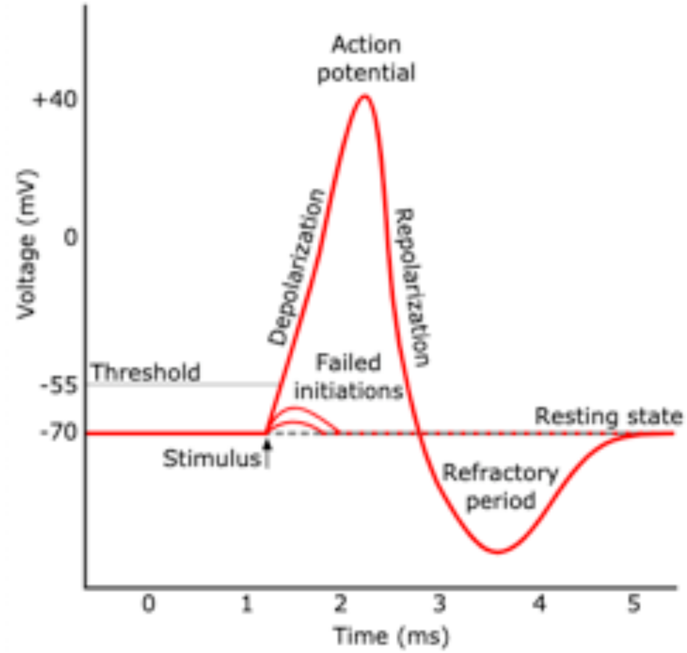



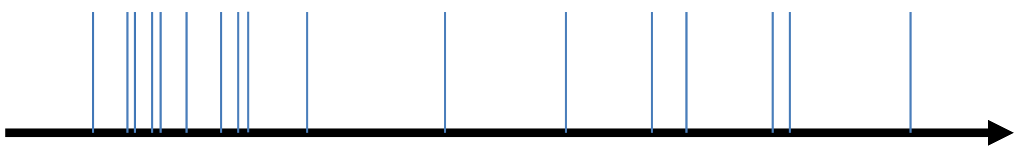



Highly suggested book: "Scale: The Universal Laws…" by Geoffrey West

Neural Coding

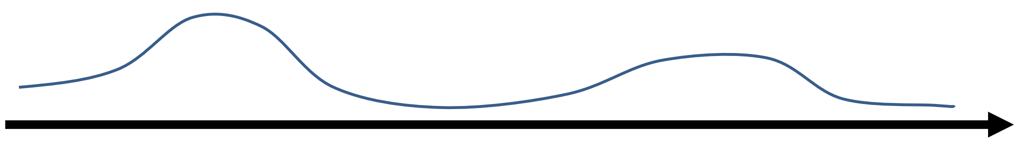






time

Spike train
(min ~5ms apart)



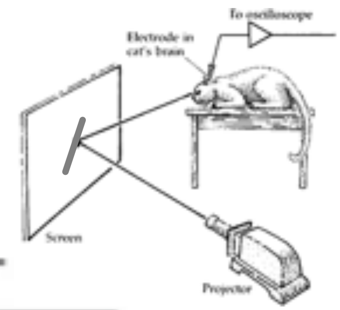
time

Firing rate
(saturates at ~200Hz)

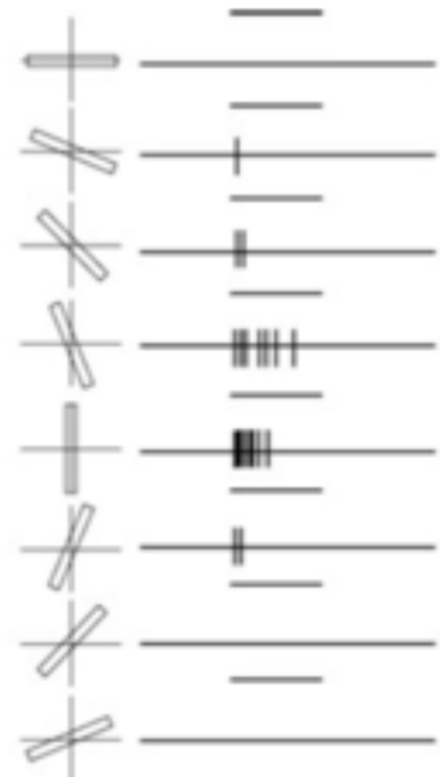
Can model spike trains as an inhomogeneous Poisson process

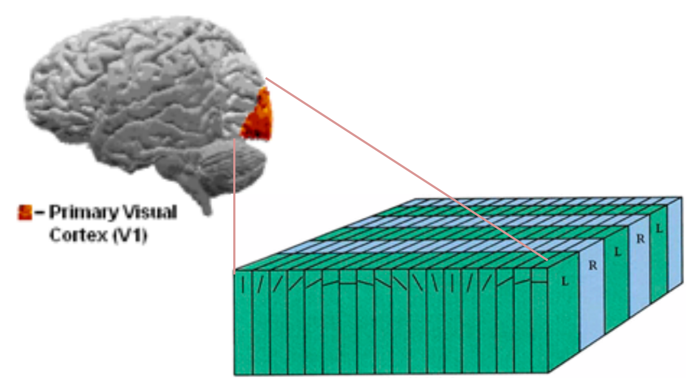
https://soundcloud.com/blake_porter_neuro/anterior-cingulate-principal-cells

Biological Vision



- David Hubel and Torsten Wiesel, Single unit activity in striate cortex of unrestrained cats, J Physiol 1959.
  - Discovery of cells with oriented receptive fields in the primary visual cortex
  - Columnar Architecture of V1
    - Across cortical surface, orientation sensitivity rotates
    - From cortex to white matter, orientation stays the same
  - Nobel Prize in Physiology or Medicine





Columnar Architecture of V1

What does it mean for me?

- Medical Imaging Datasets
- Content Based Image Retrieval (CBIR)
- Imaging Biomarkers
- Radiomics and Radiogenomics
- Quantitative Imaging
- Radiomics Applications
- Prelude to Deep Learning: Biological Neural Networks

Next Lecture:

Deep Learning