Universität Bremen*

Fraunhofer MEVIS

Master Thesis Defense

19th October 2015

Automatic Classification of Non-Mass Breast Lesions in DCE-MRI

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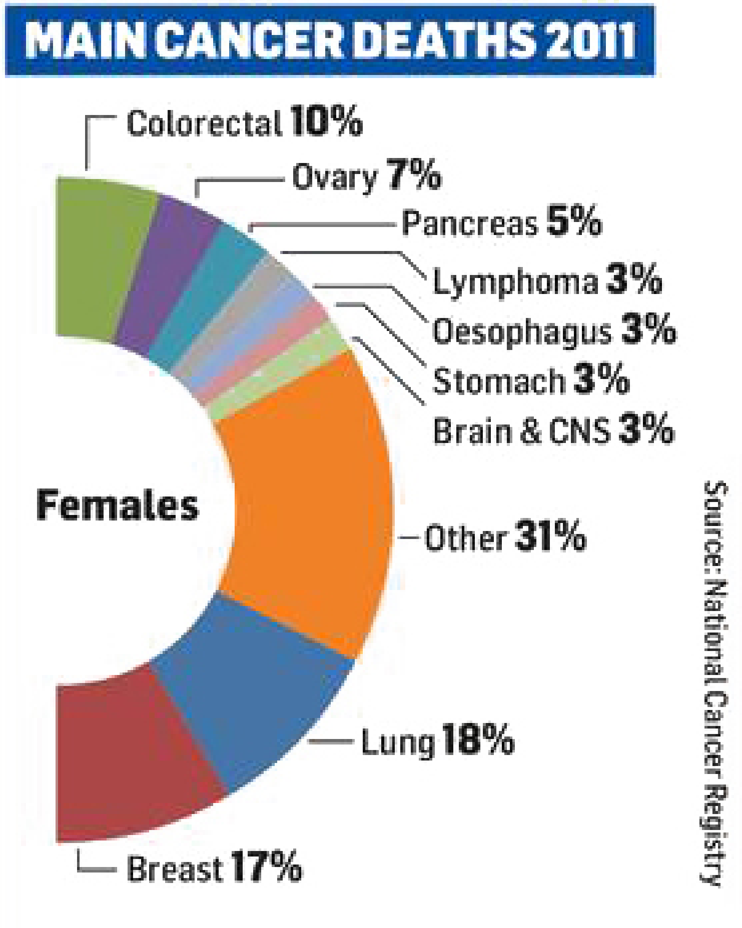
Motivation



A picture is worth a thousand words

Presentation Structure

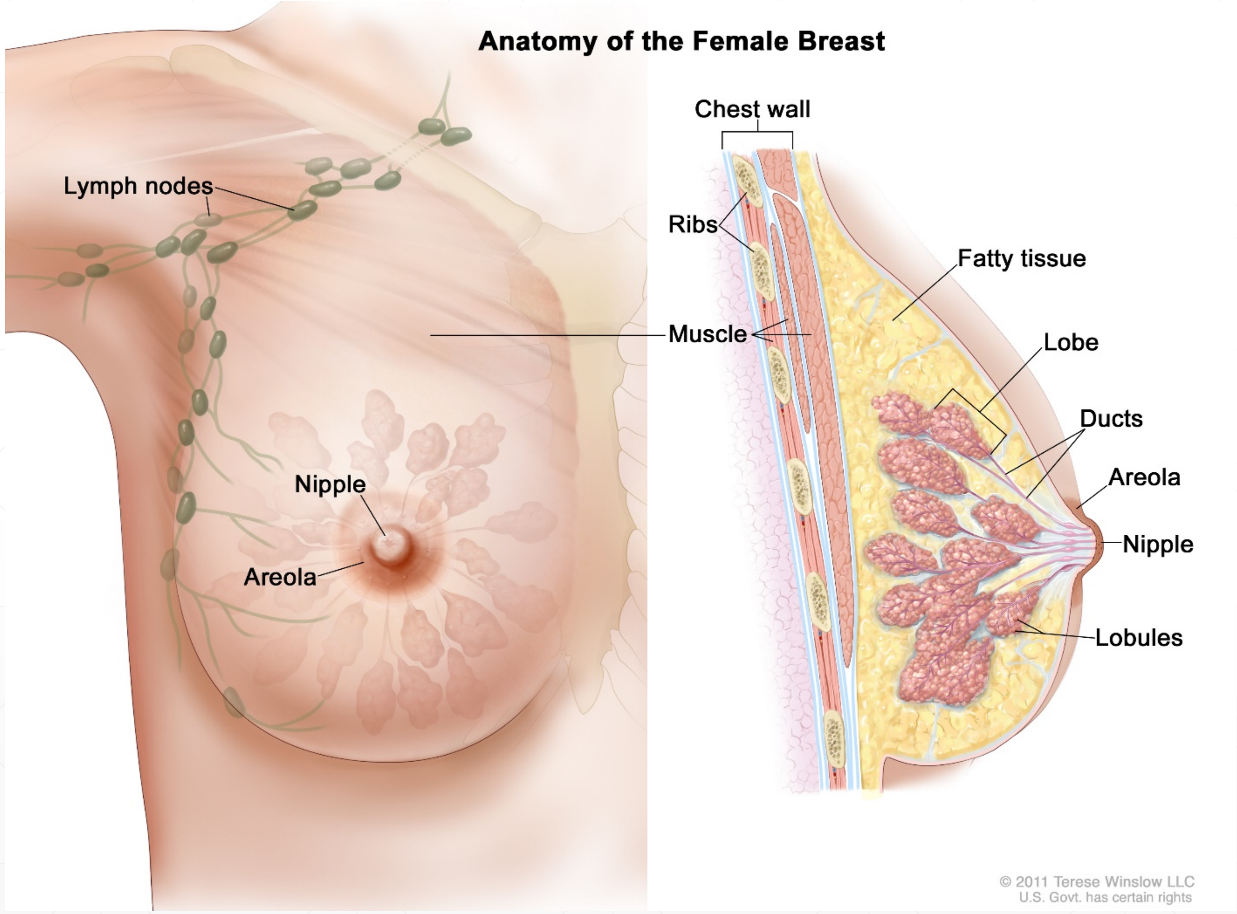
1. Breast Cancer
2. DCE-MRI of Breast
3. Breast Lesion Morphology
4. Materials & Method
5. Framework outline
8. Evaluation & Results
9. Summary & Future Work

Theoretical background

- Breast cancer

Female Breast Structure

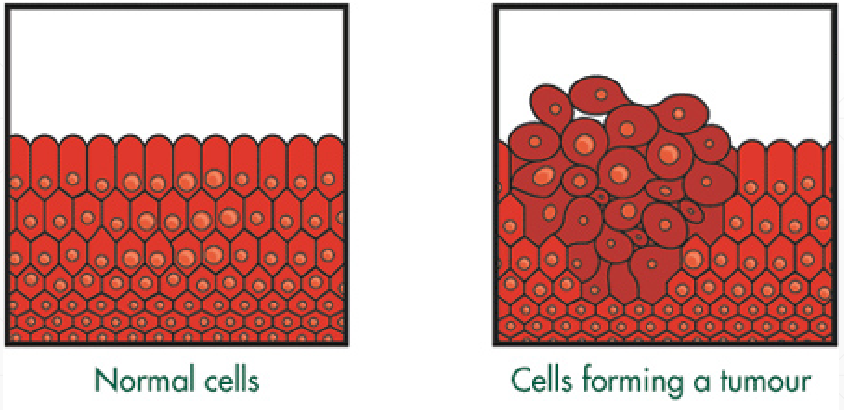
- **Breast tissues**
  1. Fibroglandular tissue (working part)
     - Mammary gland produces milk by lobes
     - Ducts, muscle, and connective tissue
  2. Fatty tissue (non-functioning part)
     - Protecting tissue
     - Often takes the majority of breast
- **Breast density**
  - The ratio of fibroglandular tissue to breast volume
  - The more fat, the less dense the breast
  - Women with dense breasts are at **greater risk** for breast cancer

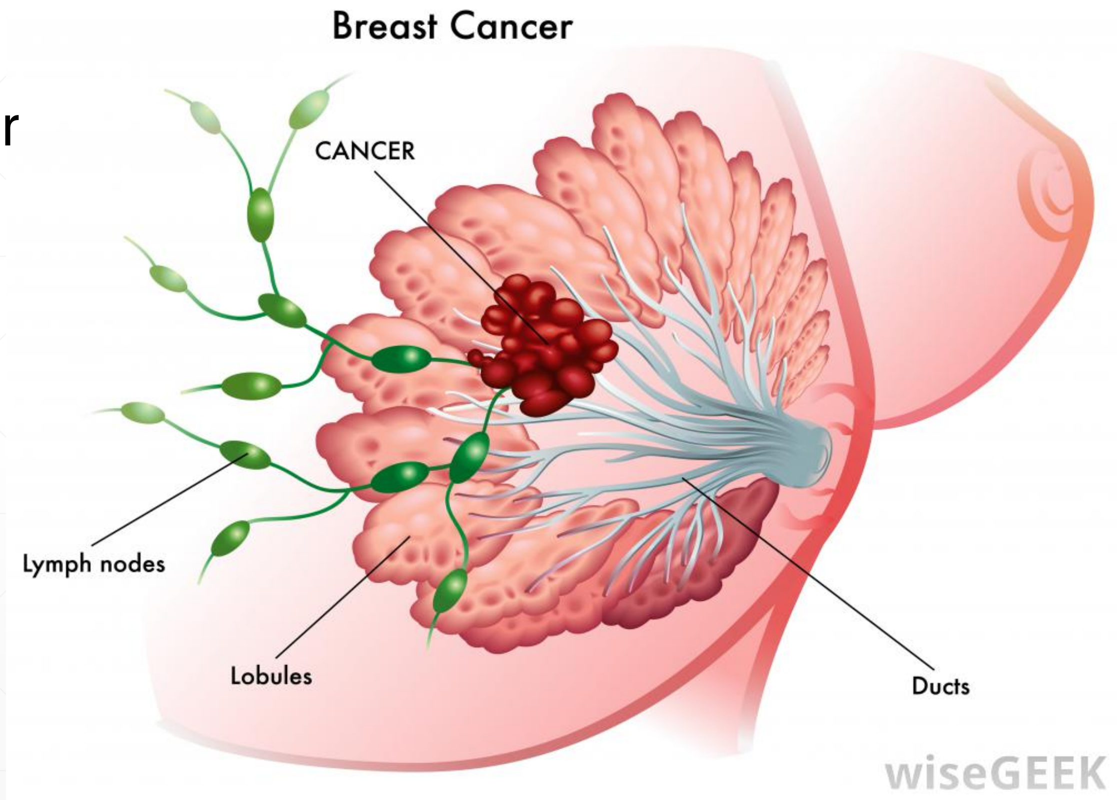


Lobules or **ducts** are the places that cancer develops

Breast Cancer

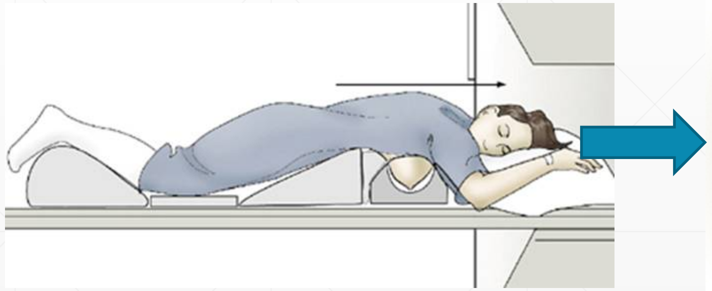
- Normal breast cells are altered in appearance and functionality
- They start growing disorderly and create a tumor
- Breast cancer may take up to 10 or more years

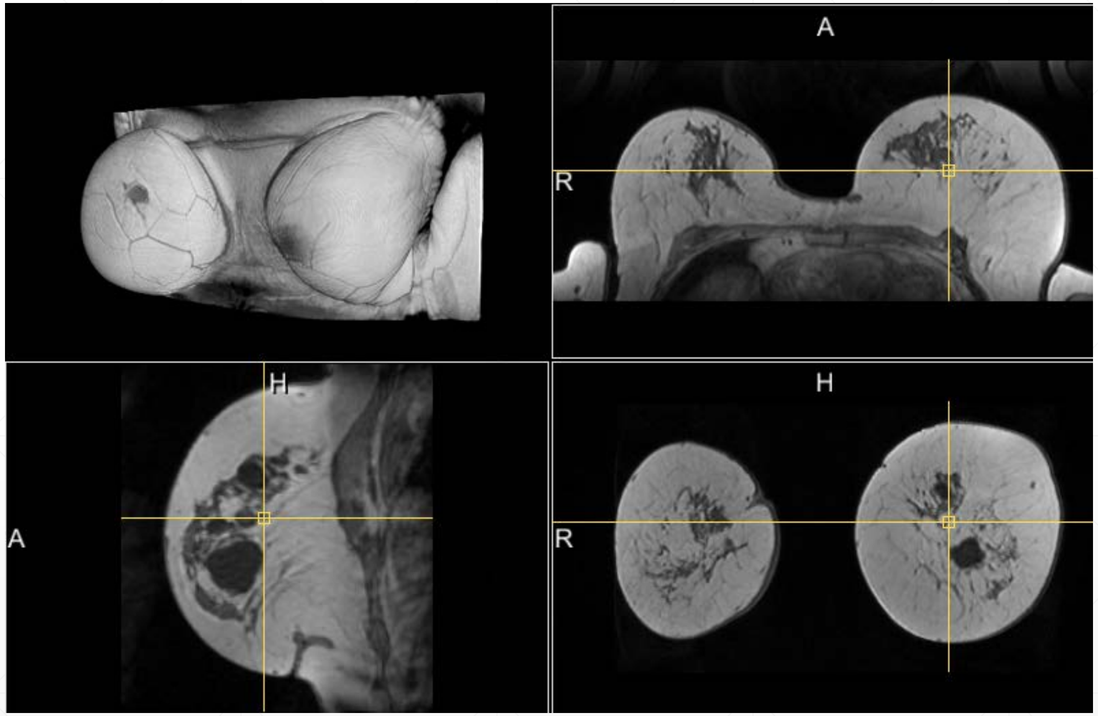




Breast Dynamic contrast-enhanced MRI (DCE-MRI)

- Analyzes the vessels (tumor vessels structurally differ from the normal ones)
  - **Rapidly growing** in tumors:
    - Heterogeneous vasculature
    - Leaky & fragile capillaries with openings in walls
    - permeability let **fast diffusion** of **contrast agent** to the tumor





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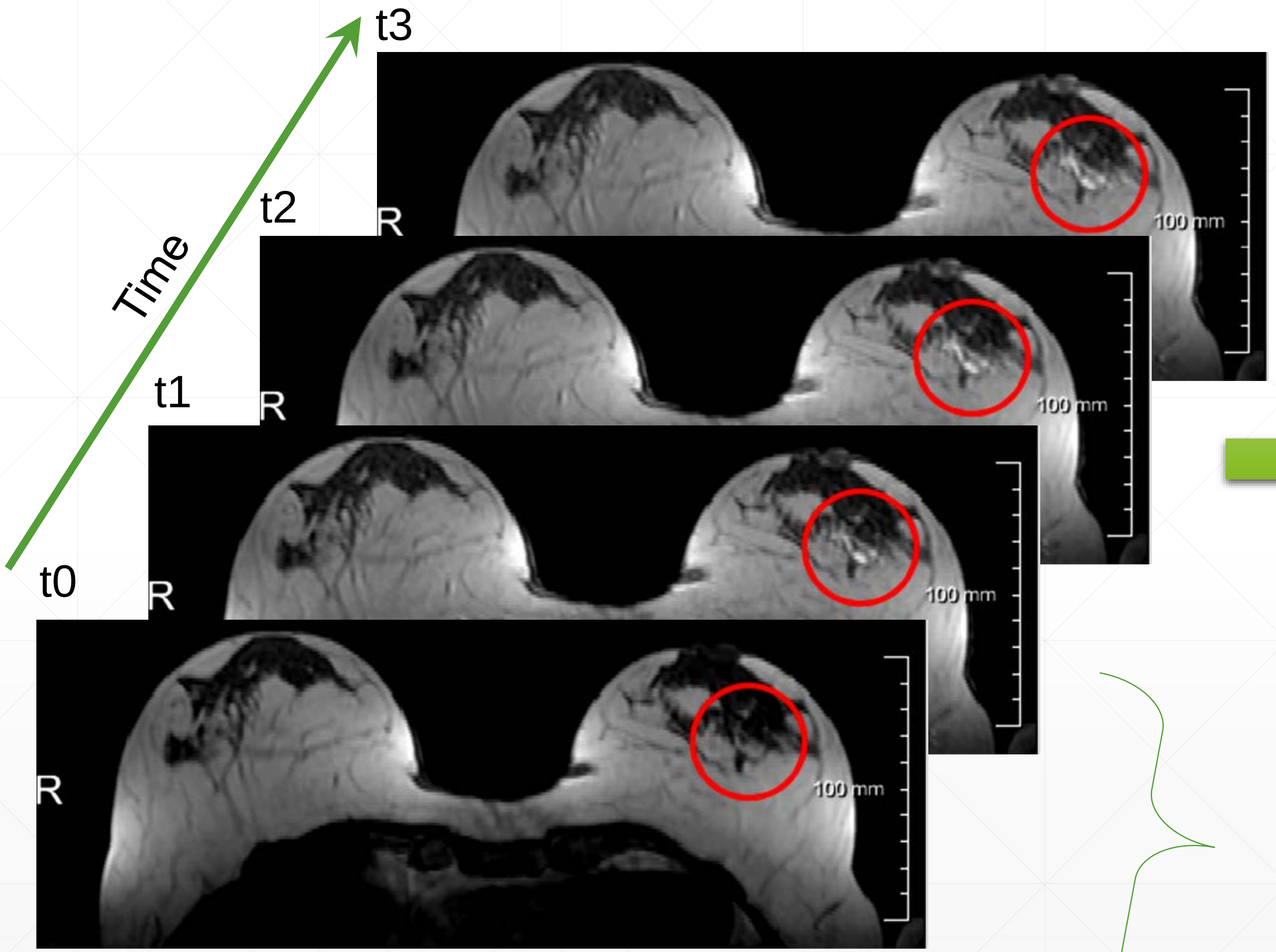
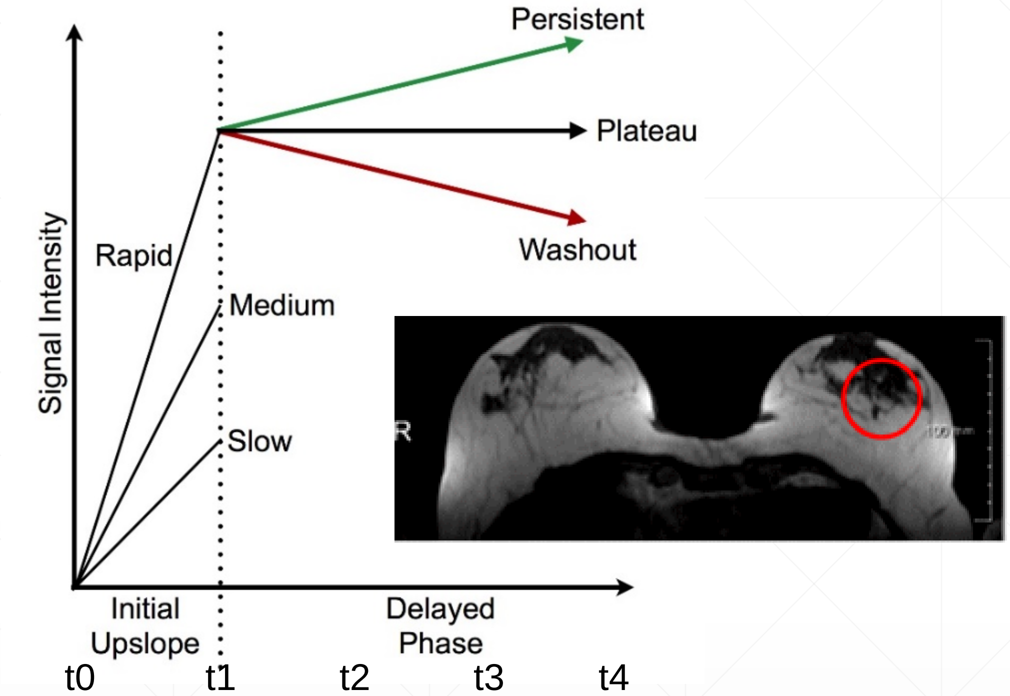
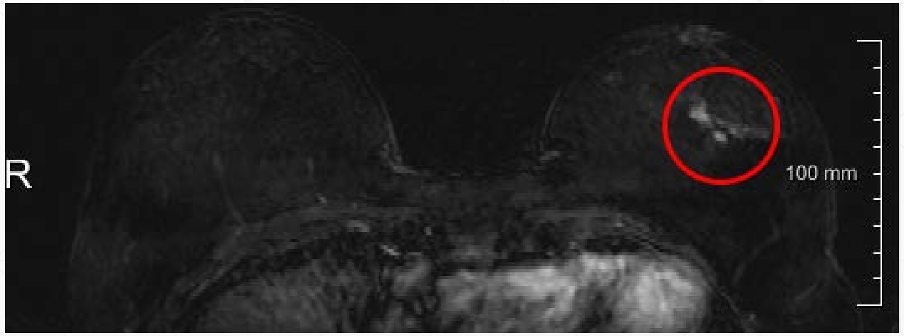
Breast Dynamic contrast-enhanced MRI (DCE-MRI)





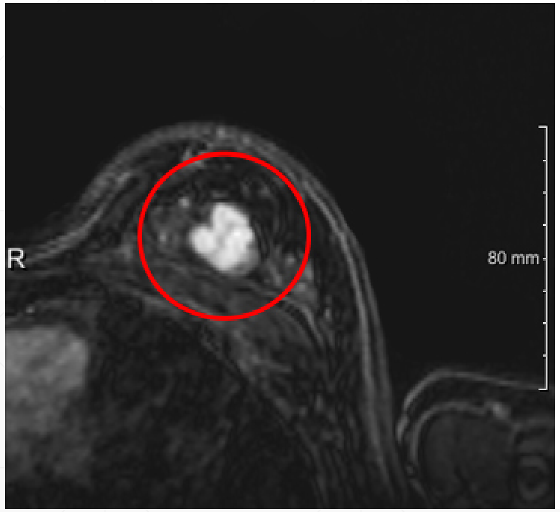


Subtraction image (T1-T0)

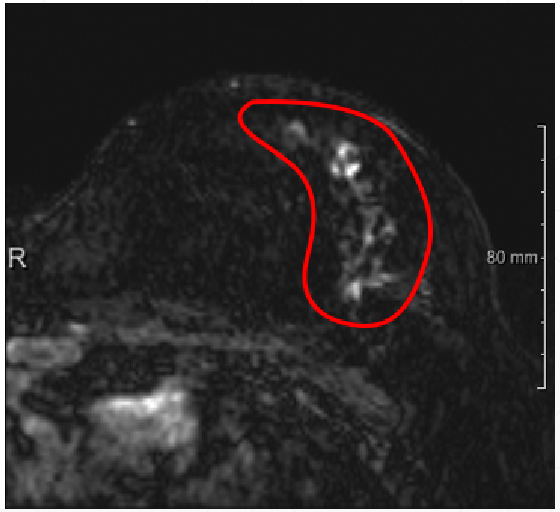
Types of breast tumors

- **By Invasiveness:**
  1. Invasive: Tending to spread to other tissues
  2. Non-invasive: Abnormalities in cells, have not spread to outer tissues

- **By Mass:**
  1. Mass-like
     - Compact regions
     - Noticeable from the healthy tissue
  2. Non-mass-like
     - Complex distribution patterns
     - Dispersed among normal tissue.



Mass-like enhancement

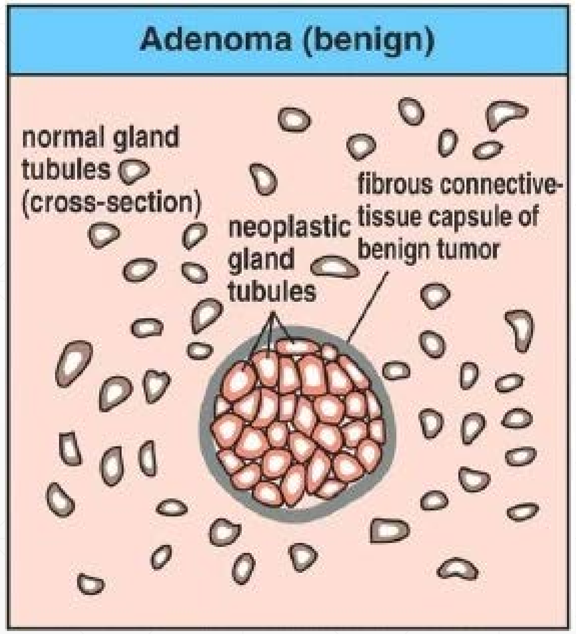


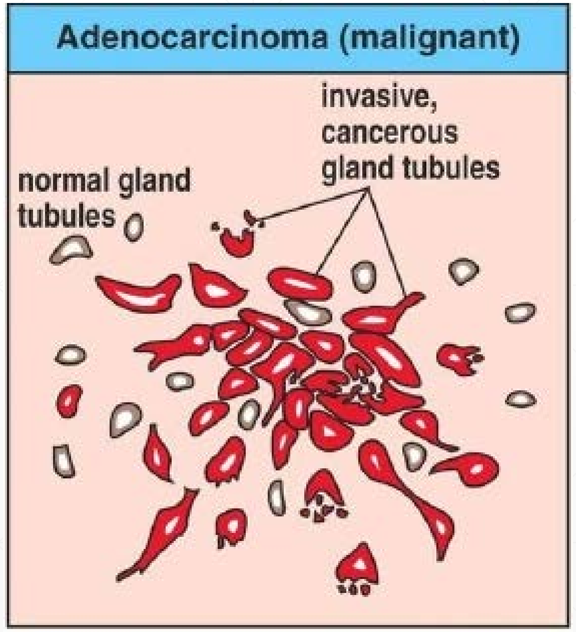
Non-Mass-like enhancement

Benign vs Malignant lesions

- **Benign tumors (non-cancerous)**
  - Non-spreadable
  - Removable

- **Malignant tumors (cancerous)**
  - Uncontrollable growth
  - Tend to metastasize





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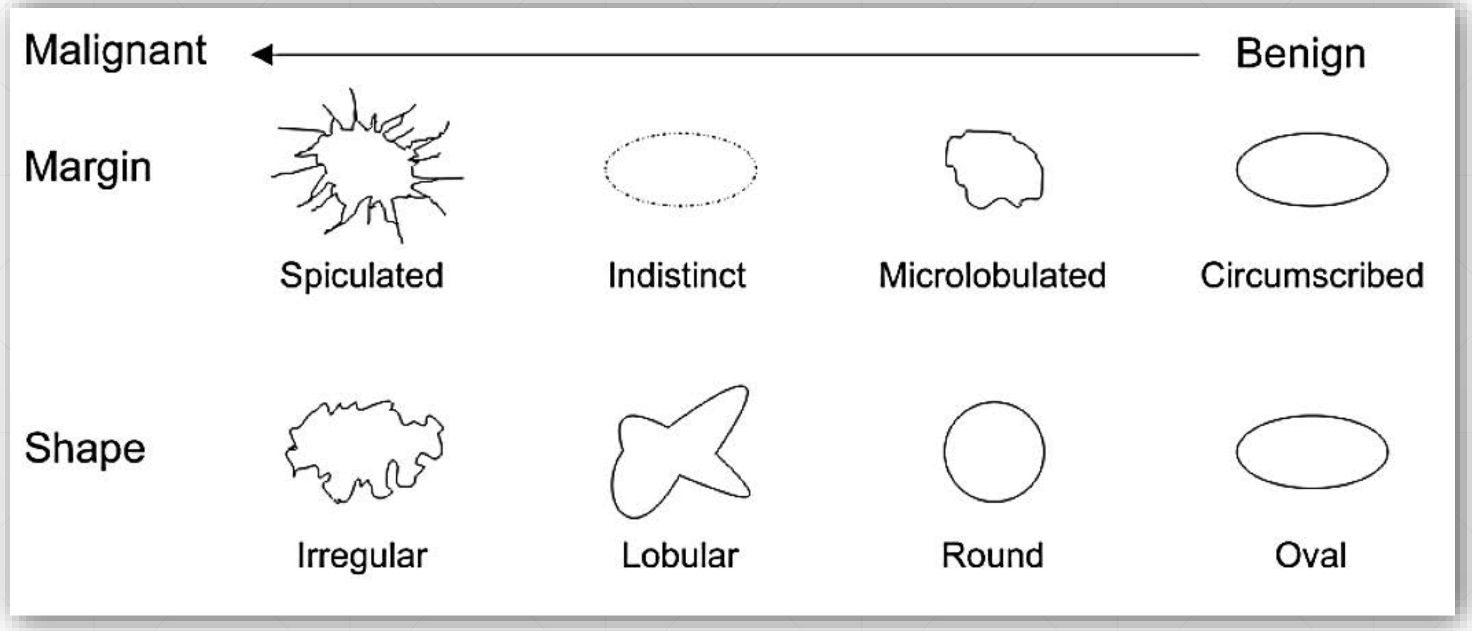
Morphological differences of lesions

Malignant

- **Shape**
  - Irregular
  - No capsule
  - Ulcerating
- **Margin**
  - Spiculated
  - Indistinct

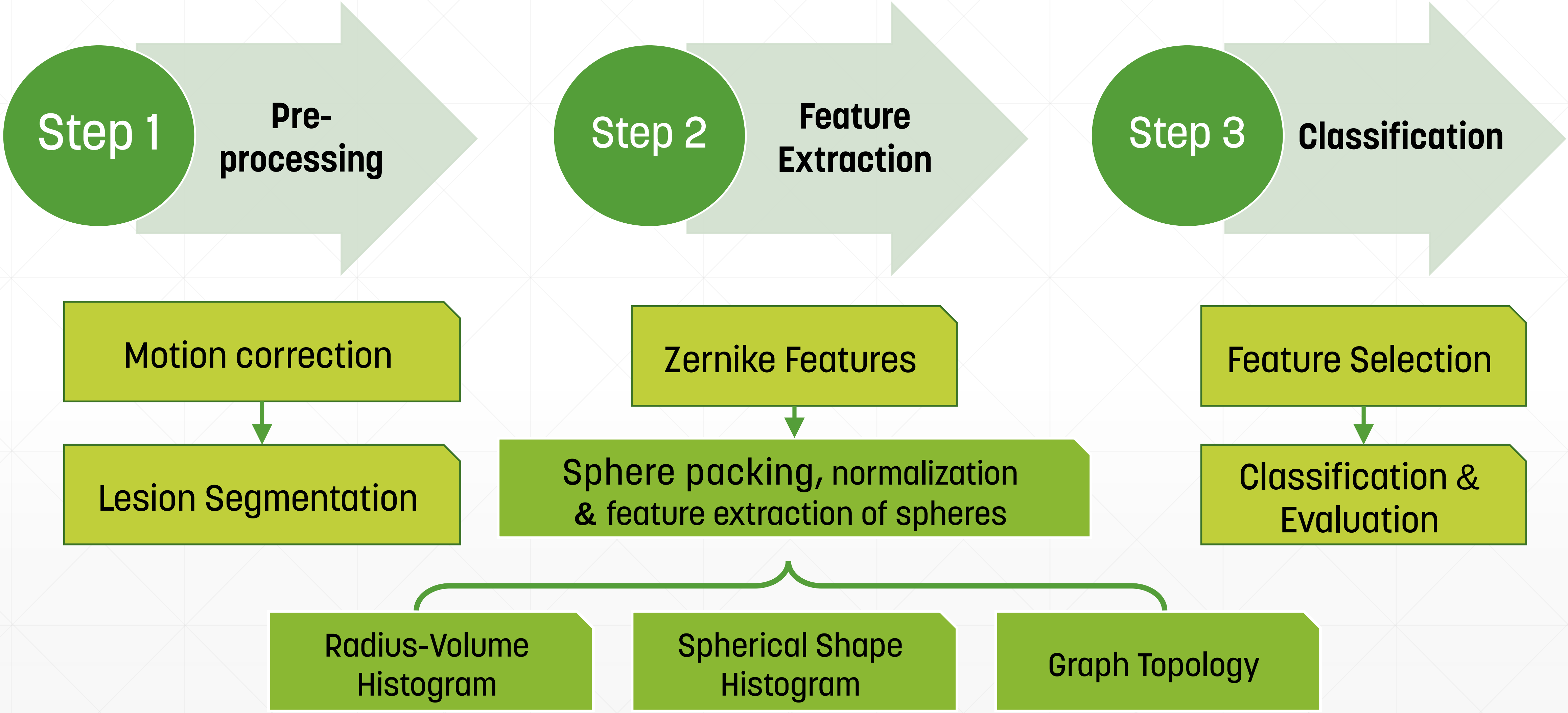


Benign

- **Shape**
  - Round
  - Oval
  - Lobulated
  - Regular
- **Margin**
  - Circumscribed
  - Micro-lobulated

Method outline

Method outline

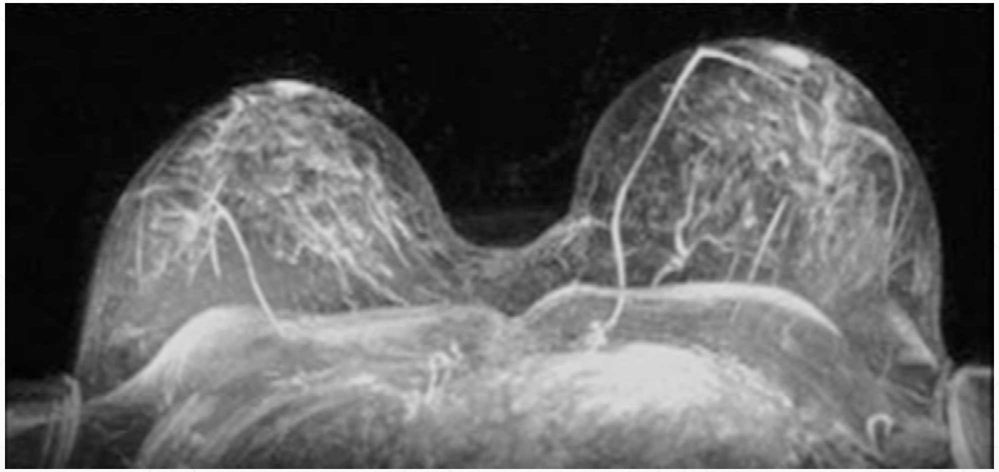


Motion Correction

- Purpose:
  - Compensates motions occurred during image acquisition
  - Improves **difference image** quality

- Possible patient motions
  1. Respiratory motion
  2. Muscle relaxation
  3. Coughing

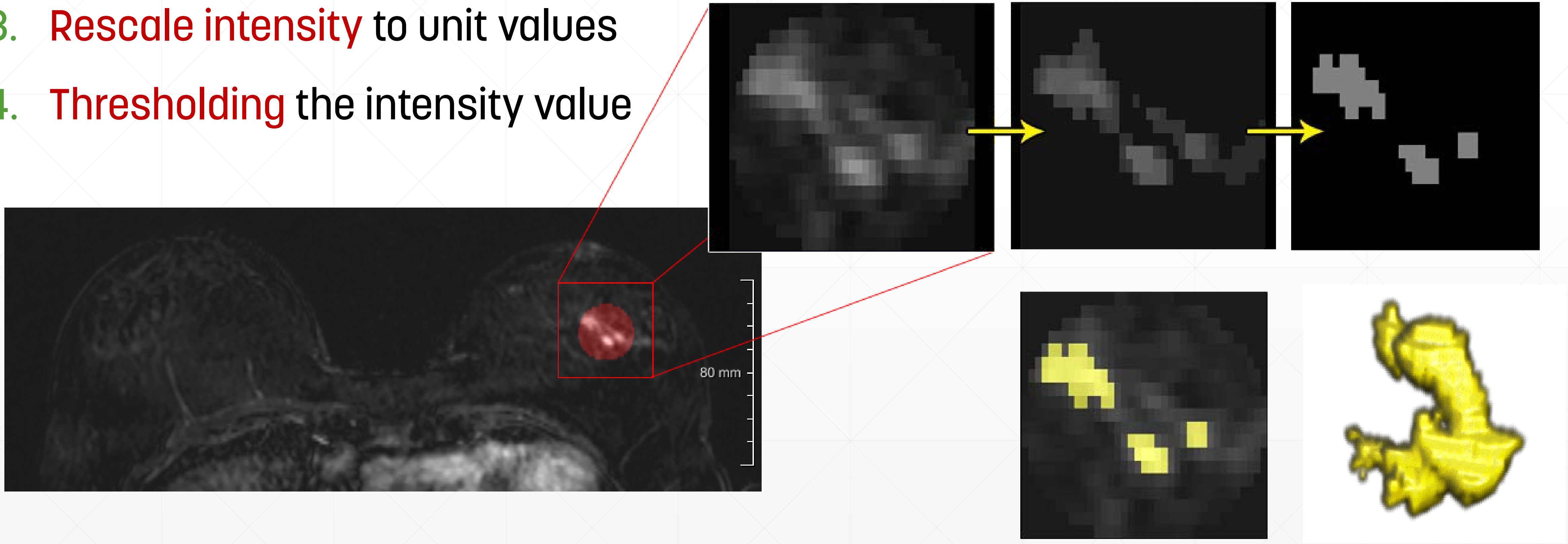
No motion



Moderate motion in both breasts

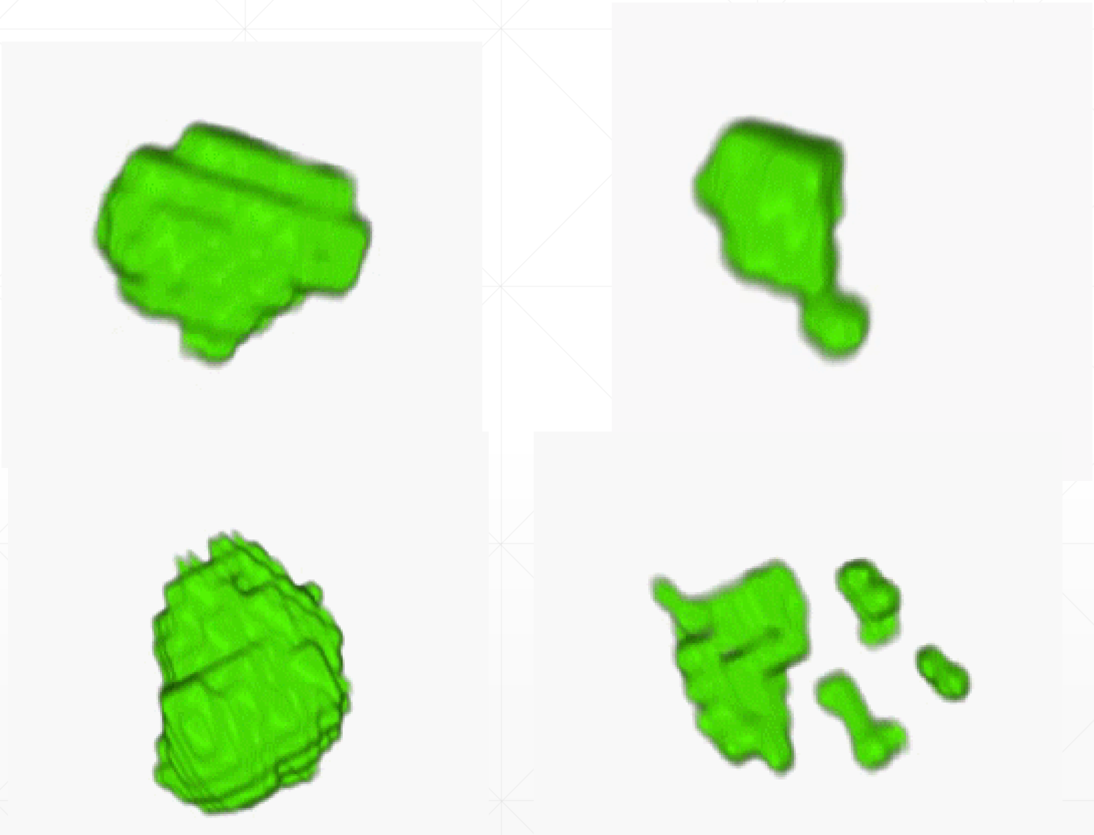
Semi-automatic lesion Segmentation

1. Bounding box separation from subtraction image
2. Applying mean shift segmentation
3. Rescale intensity to unit values
4. Thresholding the intensity value

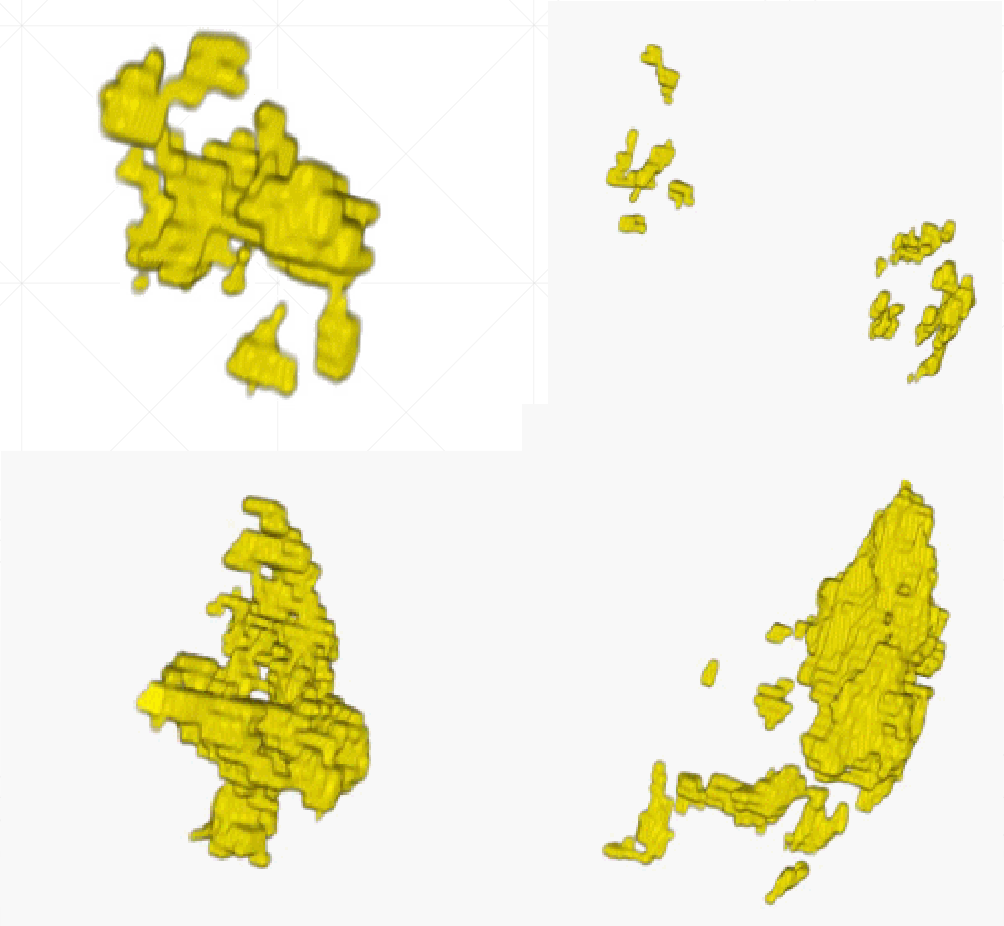


Segmentation results

Benign Lesions



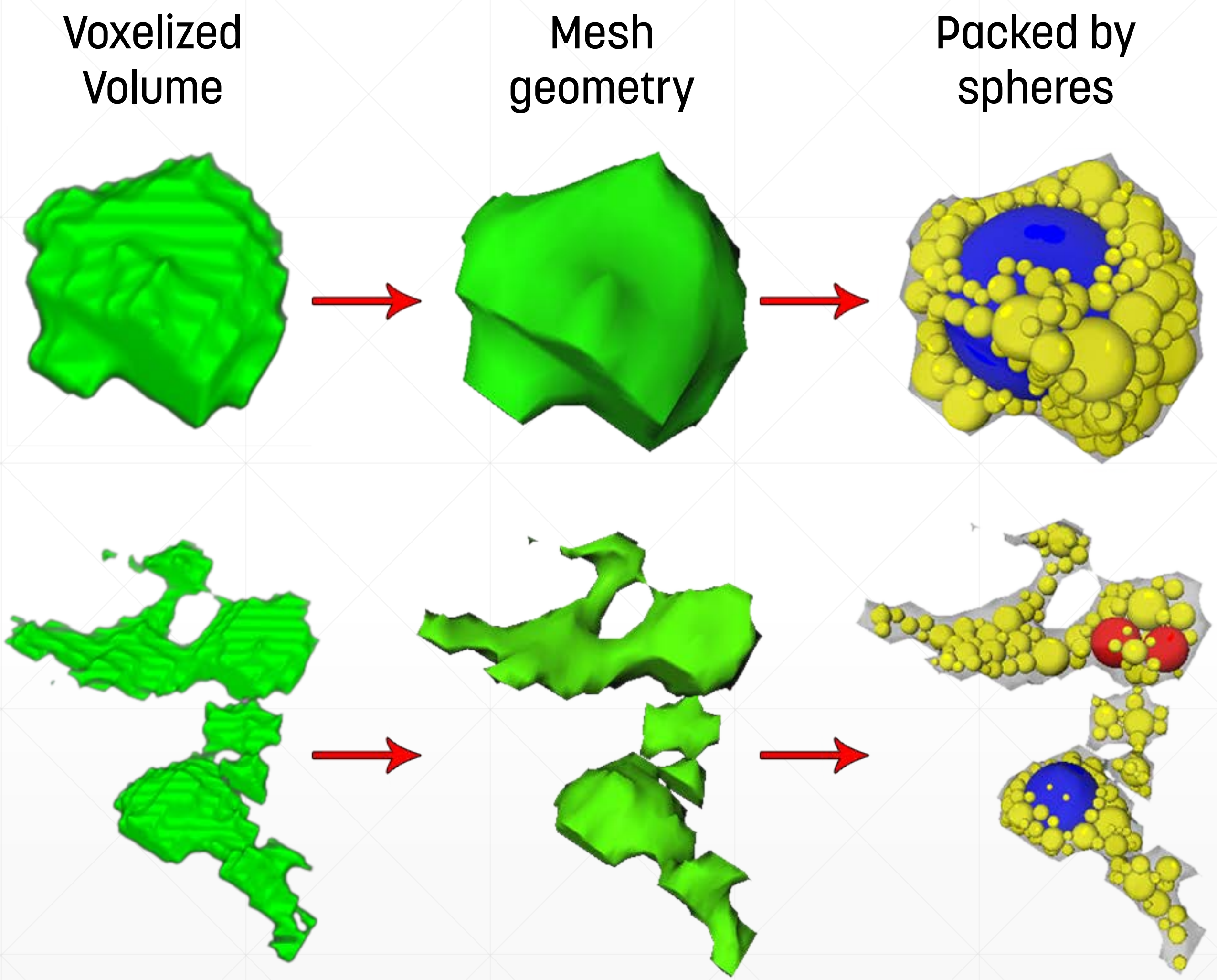
Malignant Lesions



Sphere Packing

Filling an object with **non-overlapping spheres** with arbitrary radii

1. Embedding the **largest possible sphere** into the object
2. Inserting new spheres iteratively:
   A. Must **not intersect** already existing ones
   B. Be completely inside the object



Normalization

- **Scaling by overall maxima** method

Mapping spheres' components (*x, y , z and radius*) to the unit range

For all components:

1. *Maximum* and *Minimum* values are computed
2. subtracted by Minimum value
3. Divided by difference value

$$x_0 = \frac{(x_0 - \min)}{(\max - \min)}$$

#	x	y	z	R
0	-75.3692	-37.7979	11.8563	2.1406
1	-85.1198	-29.7031	6.5474	0.7516
2	-85.8355	-37.0971	8.0866	0.5956
3	-84.9846	-33.1219	11.8964	1.1526
4	-74.7476	-35.0559	11.9773	0.673

Not normalized sphere components

#	x	y	z	R
0	0.107003	0.491118	0.998763	0.0218847
1	0.00731704	0.573876	0.944487	0.00768407
2	0	0.498282	0.960223	0.00608918
3	0.00869927	0.538923	0.999173	0.0117837
4	0.113358	0.519151	1	0.00688049

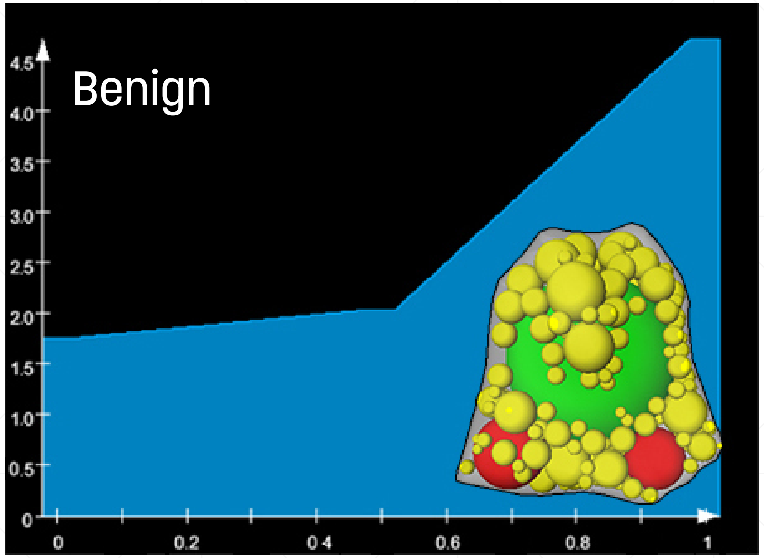
Normalized sphere components

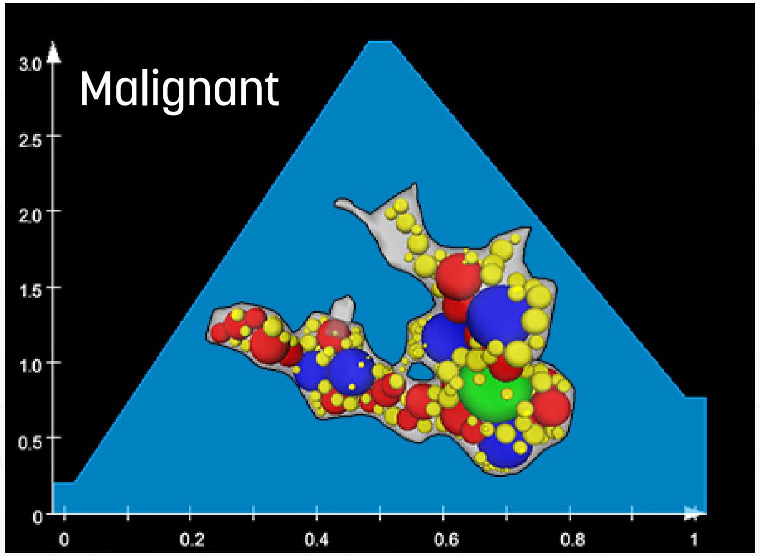
Feature extraction

- Volume-Radius Histogram
- 3D Spherical Shape Histogram
- Graph Topological Features
- Zernike Invariant Moments

Volume-Radius Histogram

- benign Lesions
  - **Big spheres** filled most of their volume
- malignant Lesions
  - **Middle size spheres** filled most of their volume
- Histogram is formed by
  - **X-axis:** radius range of spheres divided by number of bins
  - **Y-axis:** summation of spheres' volume with radius in bin range

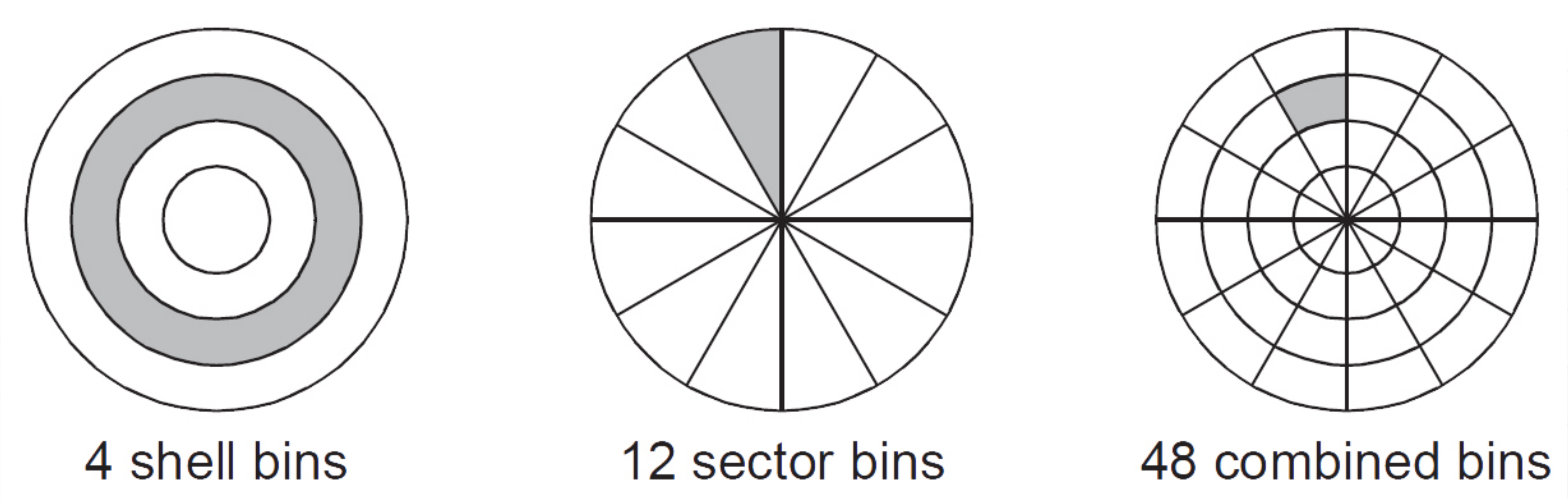




2D Shape Histogram – The Idea

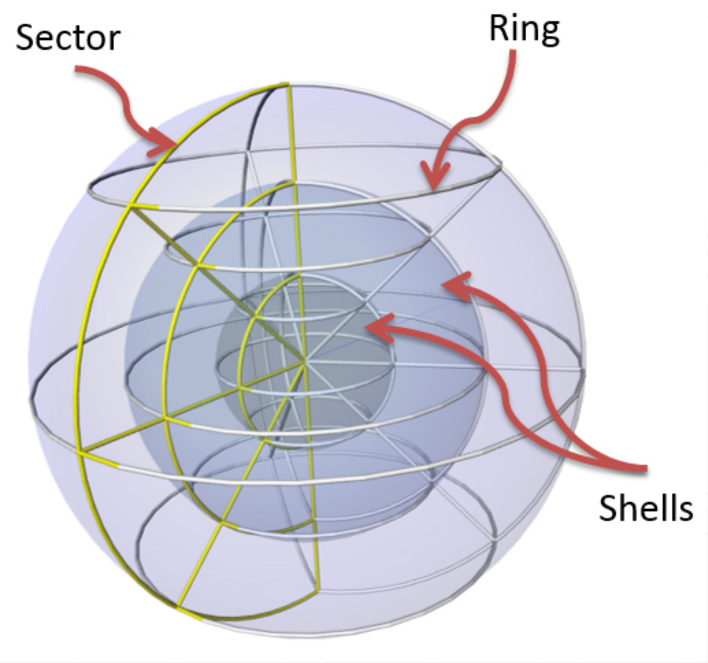
- Uses uniformly distributed elements of a shape.
- A histograms based on a partitioning of the space in which the objects reside
- A complete and disjoint decomposition into cells, which correspond to the bins of the histograms

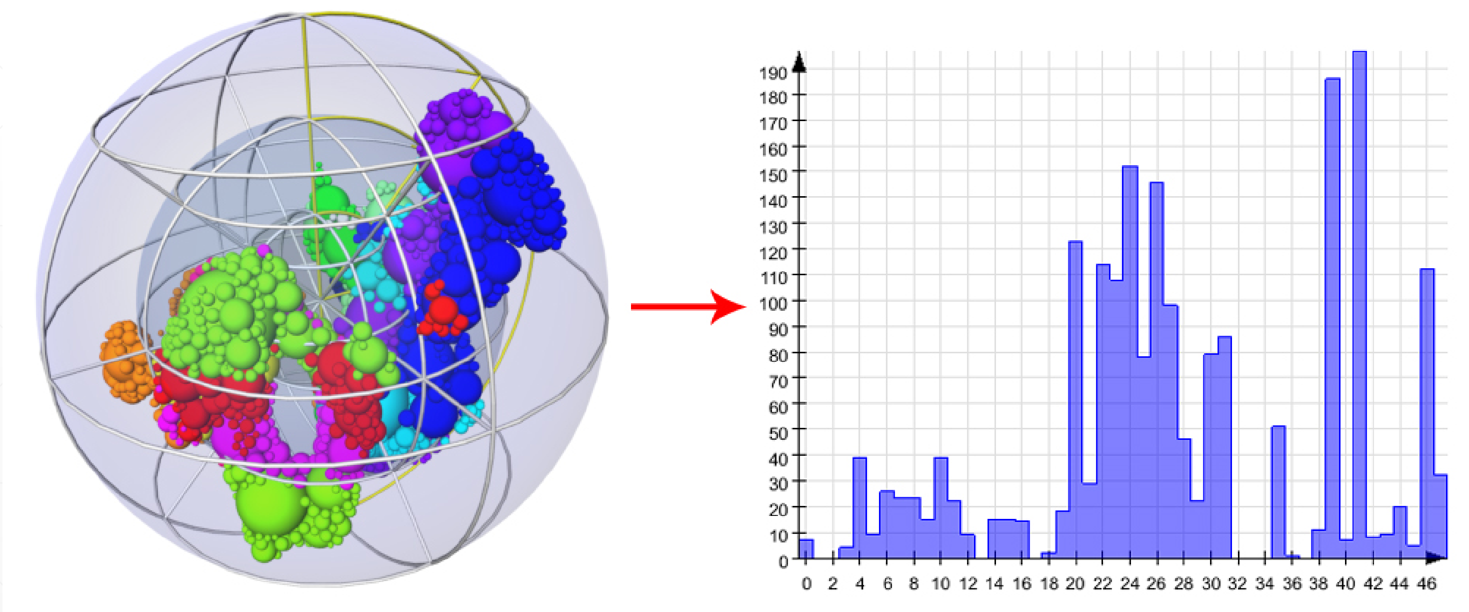
2D section coding



3D Spherical Shape Histogram

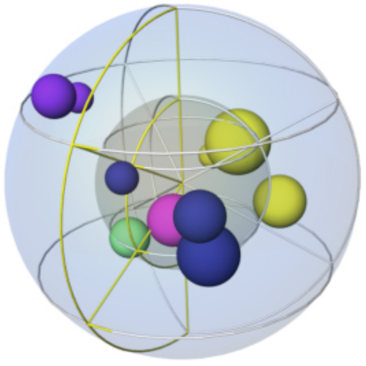
- A surrounding wireframe with internal space partitioning:
  - **Sectors:** vertical lines (longitude); **Rings:** horizontal lines (latitude); **Shells:** concentric spheres
- **Histogram x-axis:** the bins represent each partition, starting from the most centric one
- **Histogram y-axis:** the number of spheres' center points inside each partition



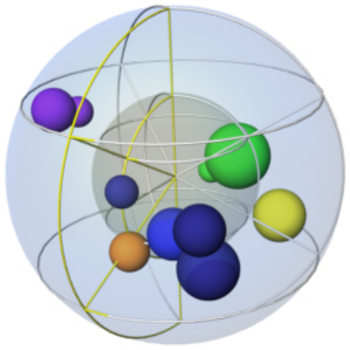


Strategies for choosing spherical wireframe center point

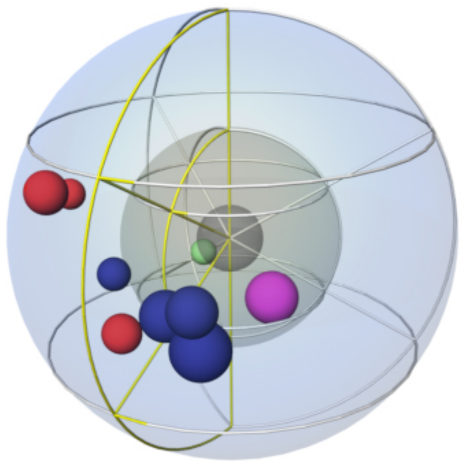
1. In the mean distance of the all spheres' center points
2. In the middle of the two most distant spheres
3. In the center of the biggest sphere
4. According to the Smallest Enclosing Ball of Balls algorithm



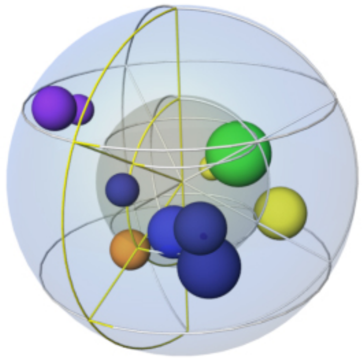
(1)



(2)



(3)

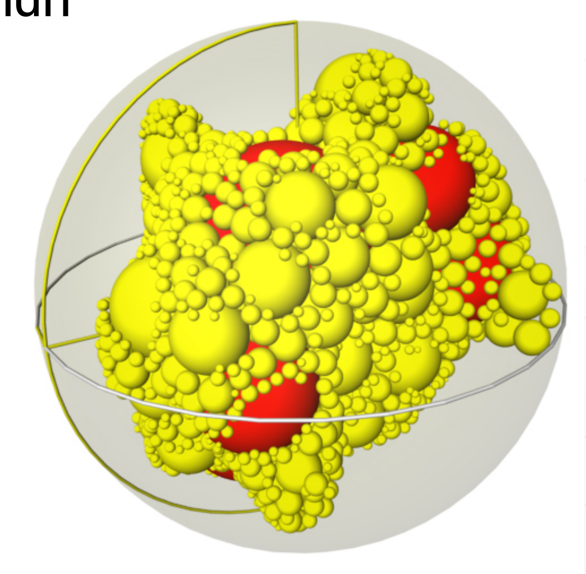


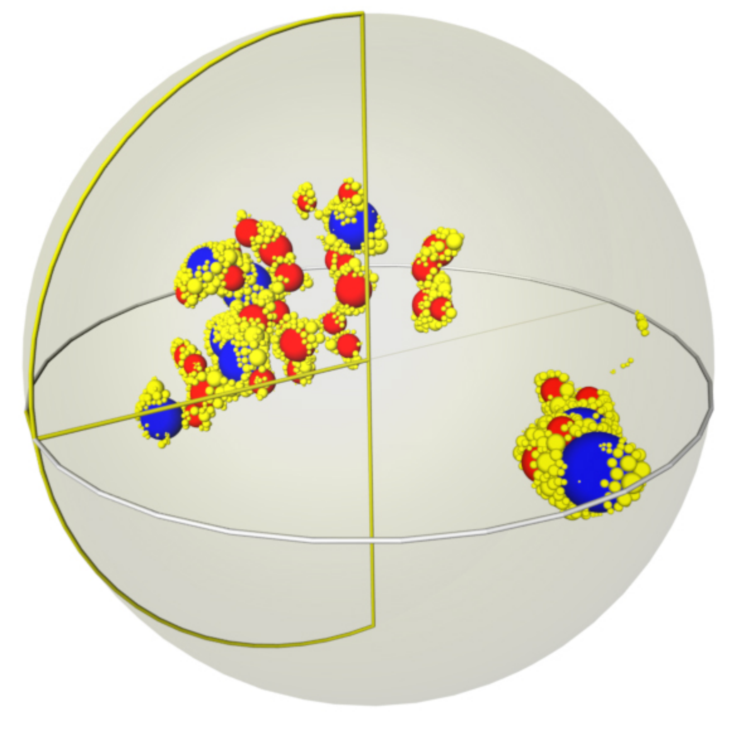
(4)

The filled-portion feature

- Occupied proportion of the surrounding wireframe sphere

- **In benign lesions**
  - the surrounding sphere is more occupied than the malignant ones.



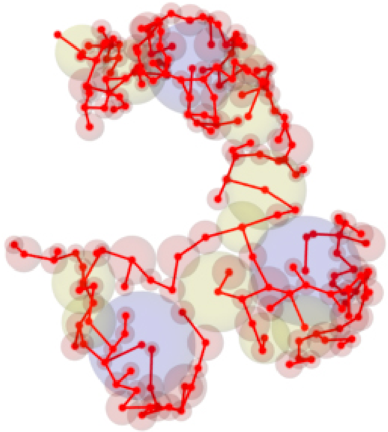


- Benign lesions -> closer to one
- Malignant lesions - > closer to zero

Graph construction

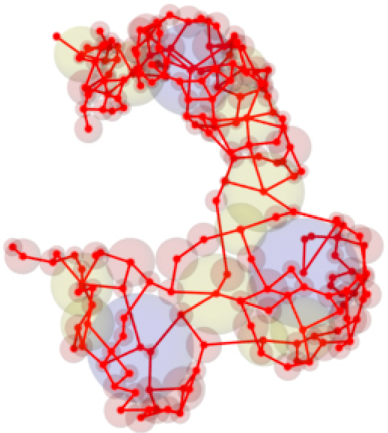
- For each packed lesion:
  - Center point of embedded spheres are considered as **nodes**
  - Spatial relationship between nodes is translated into **edges**

Fireworks Graph



Kruskal's Minimum Spanning Tree

Prim's Minimum Spanning Tree



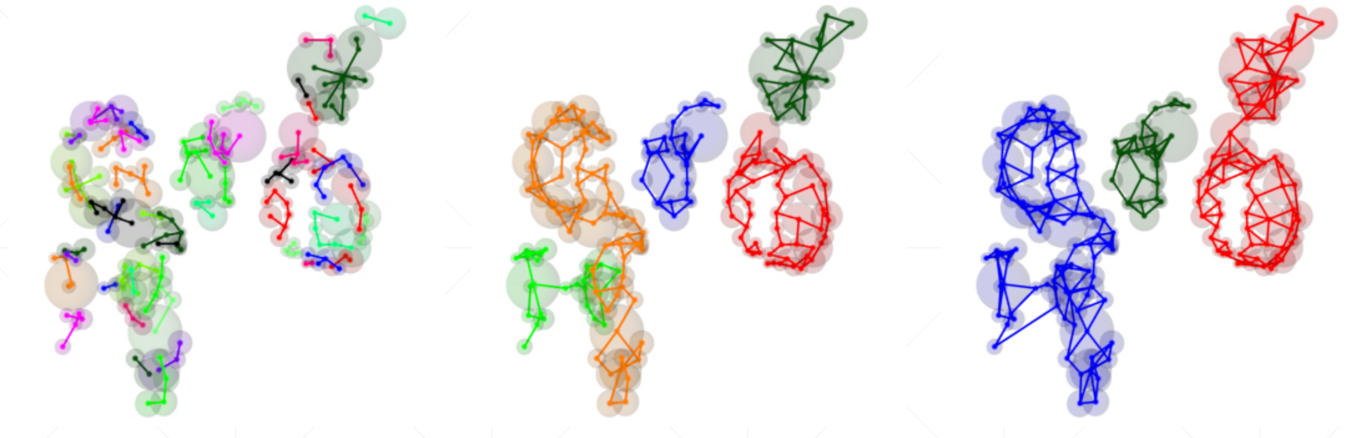
Relative Neighborhood Graph

Gabriel Graph

Beta-Skeleton Graph

Graph clustering

- Spatial constraints deconstruct graph into subgraphs
- K_{max}: the neighborhood distance
  - Low values -> more clusters



Kmax = 2, *c* = 51 | *Kmax* = 3, *c* = 5 | *Kmax* = 4, *c* = 3

Kmax = 8, *c* = 2 | *Kmax* = 19, *c* = 1 | *Kmax* = 200, *c* = 1

Global and local graph based features can be extracted

Graph characteristics

- Graph compactness:
  - The completeness and being dense

Compactness based on edge density: $\frac{E}{N}, \frac{E}{N^2}$

Compactness index: $$Cp = \frac{Max - \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} d(v_i, v_j)}{Max - Min}$$

New compactness Index: $$Cp^* = \frac{\sum_{i=1}^{N-1} \sum_{j=i+1}^{N} sim(v_i, v_j)}{N(N-1)/2}$$

- The Stratum (St)
  - Captures the linear structure of the graph
    - Zero -> circular structure
    - One -> linear structure
  - Linear Absolute Prestige (LAP)

$$\mathrm{LAP} = \begin{cases} \frac{n^3}{4}, & \text{if} \quad n \text{ is even.} \\ \frac{n^3 - n}{4}, & \text{if} \quad n \text{ is odd.} \end{cases}$$

$$St = absolute\ prestige / \mathrm{LAP}.$$

Famous graph topology indices

Evaluating clustering algorithms

- Indices based on diameter and distance
  - Dunn's index

$$D(C) = \frac{d(C_i, C_j)}{diam(C_h)}$$

  - Davies Bouldin index

$$DB = \frac{1}{K}\sum_{i=1}^{K} \max_{j \neq i}\left[\frac{diam(C_i) + diam(C_j)}{d(C_i, C_j)}\right]$$

- Indices based on inter & intra-cluster edges
  - MinMaxCut

$$MinMaxCut = \sum_{i=1}^{K} \frac{E_i'}{E_i}$$

- Indices using number of nodes and links
  - Modularization quality MQ

$$\mathrm{intra}(C_i) = \frac{E_i}{N_i(N_i - 1)/2} \qquad \mathrm{inter}(C_i, C_j) = \frac{E_{ij}}{N_i N_j}$$

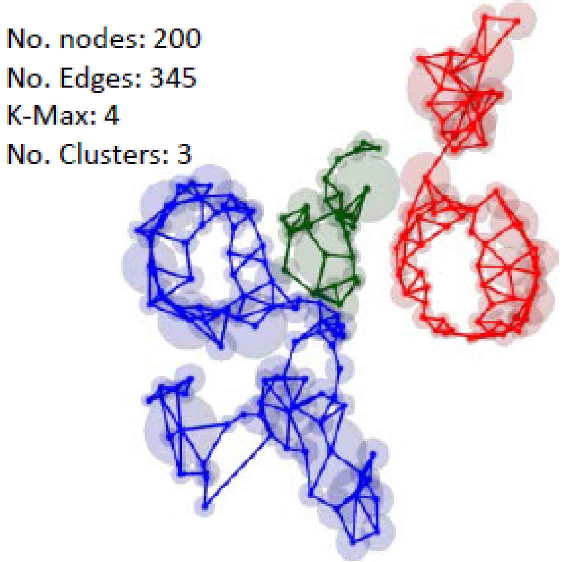
$$Let\ define\ \overline{\mathrm{intra}} = \frac{\sum_{i=1}^{K} \frac{E_i}{N_i(N_i-1)/2}}{K}\ and\ \overline{\mathrm{inter}} = \frac{\sum_{i<j}^{K} \frac{E_{ij}}{N_i N_j}}{K(K-1)/2}$$

$$MQ = \overline{\mathrm{intra}} - \overline{\mathrm{inter}} = \frac{\sum_{i=1}^{K} \frac{E_i}{N_i(N_i-1)/2}}{K} - \frac{\sum_{i<j}^{K} \frac{E_{ij}}{N_i N_j}}{K(K-1)/2}$$

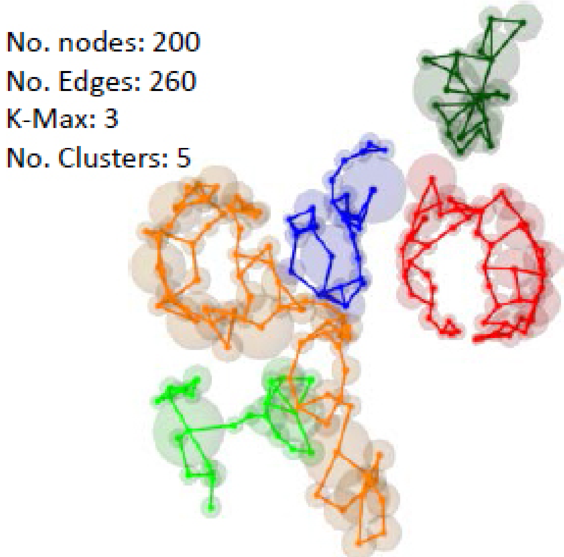
  - A new index denoted MQ*

$$MQ^* = \frac{\sum_i E_i}{\sum_i \frac{N_i(N_i-1)}{2}} - \frac{\sum_{i<j} E_{ij}}{\sum_{i<j} N_i N_j}$$

All calculated graph features



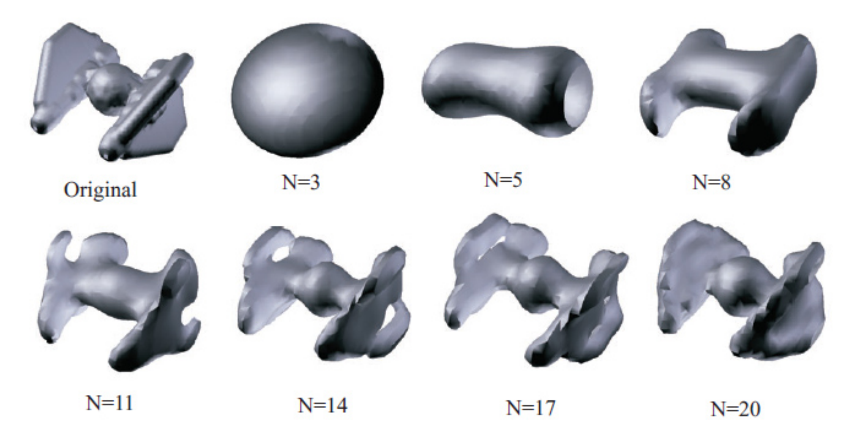
Feature	Value	Feature	Value
Edge Density	1.725	Coverage	0.57971013
Edge Density*	0.0086249998	Modularization quality MQ	-34.993408
Compactness Index Cp	0.24017853	New MQ*	0.037906155
New Cp*	0.13441421	Global Silhouette index (GS)	0.48201945
Linear Structure (Stratum)	0.080078728	New GS*	0.44905704
Dunn's Index	0.37598059	Jaccard Coefficient	0
Davies Bouldin	2.3165514	Folkes and Mallows index	0
MinMaxCut	0.0077294684	Rand Statistic	0.61100501
Cohesion	20.242949	Hubert and Arabie's statistic	0



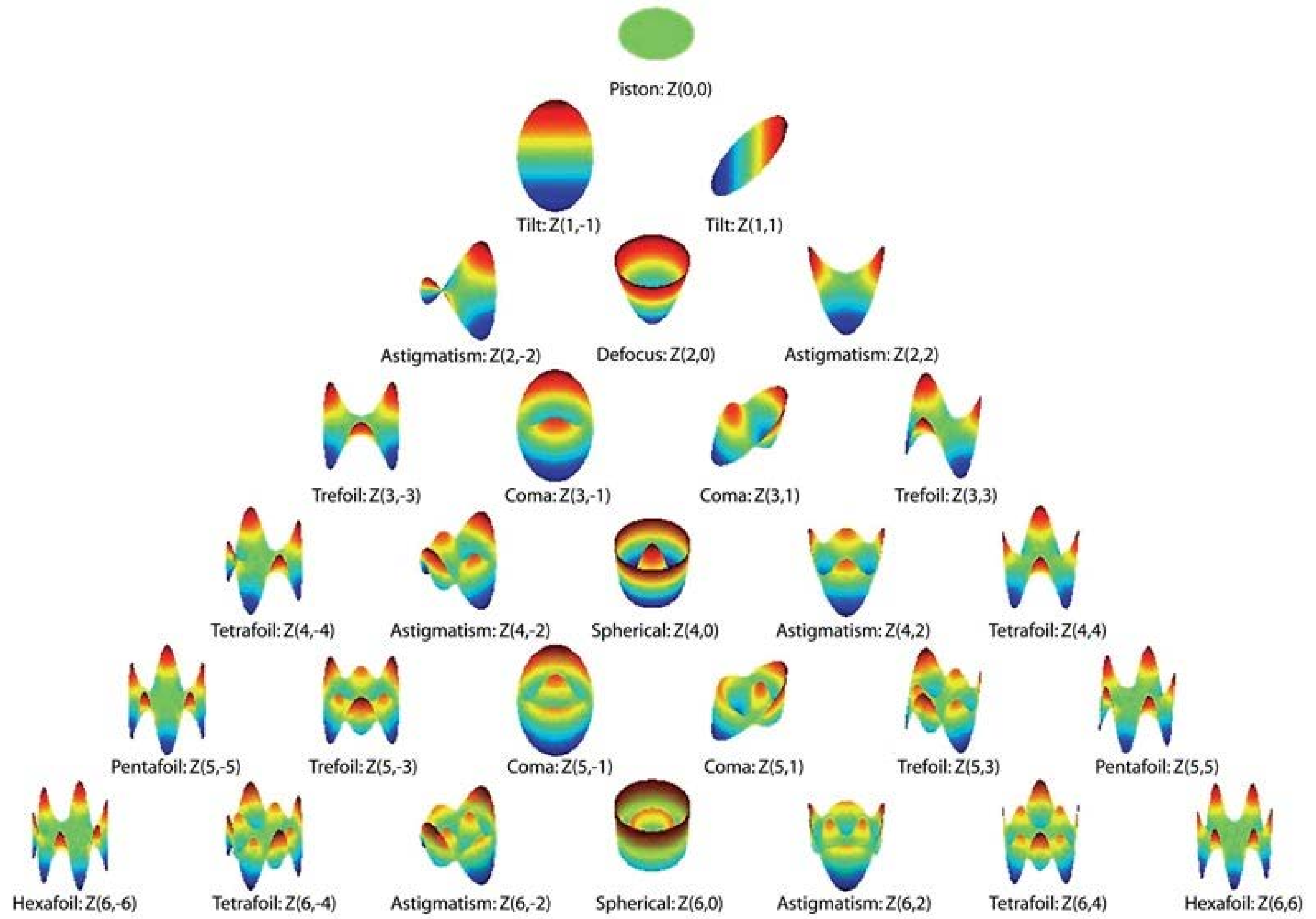
Feature	Value	Feature	Value
Edge Density	1.3	Coverage	0.76923078
Edge Density*	0.12267283	Modularization quality MQ	-14.527812
Compactness Index Cp	0.12267283	New MQ*	0.044762693
New Cp*	0.09278556	Global Silhouette index (GS)	0.50787872
Linear Structure (Stratum)	0.048521247	New GS*	0.44993725
Dunn's Index	0.31838393	Jaccard Coefficient	0
Davies Bouldin	2.4751117	Folkes and Mallows index	0
MinMaxCut	0.016153846	Rand Statistic	0.75879395
Cohesion	13.591794	Hubert and Arabie's statistic	0

3D Zernike Descriptors

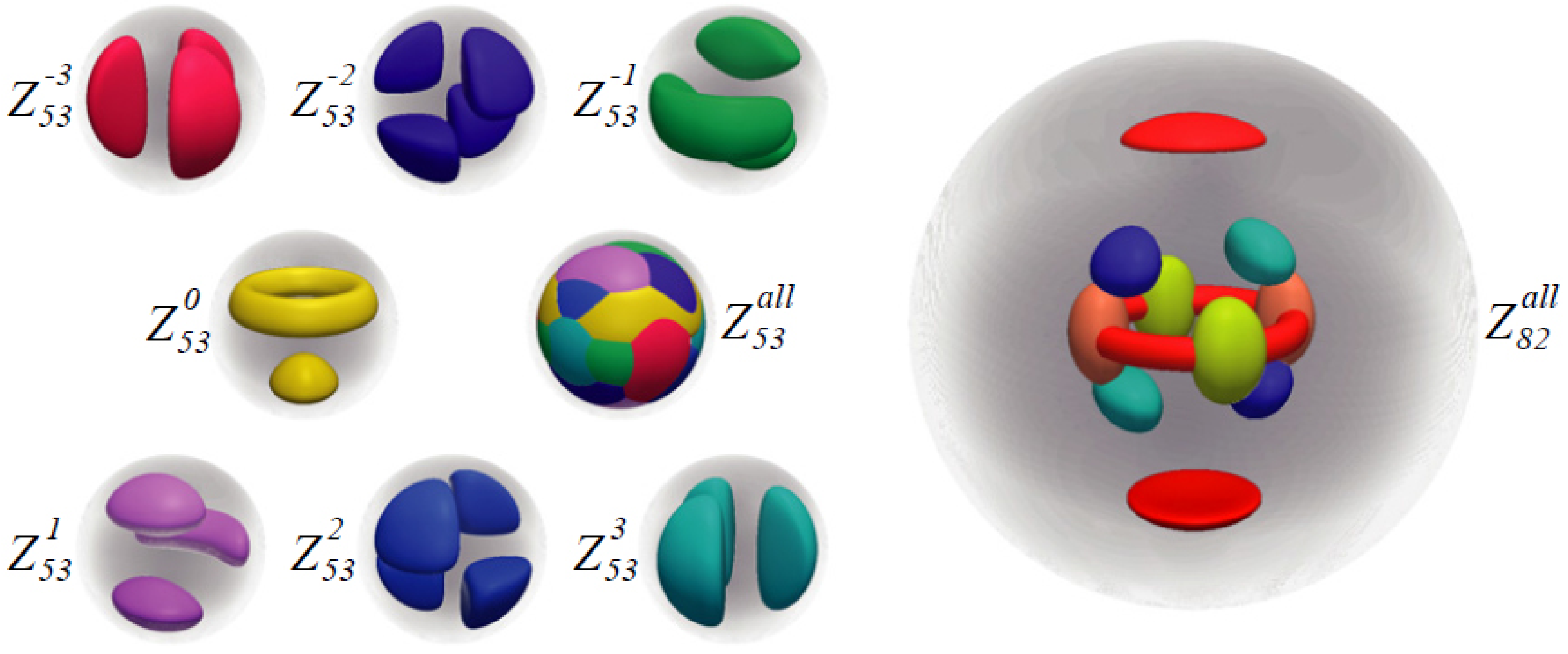
- A rotation, translation and scale invariant numerical expression of a 3D object
- Zernike Moments
  - The projection of the voxelized image onto orthogonal basis functions.



Object reconstruction (Novotni et al 2003)



3D Zernike functions Z_{53}^{m} and Z_{82}^{m}



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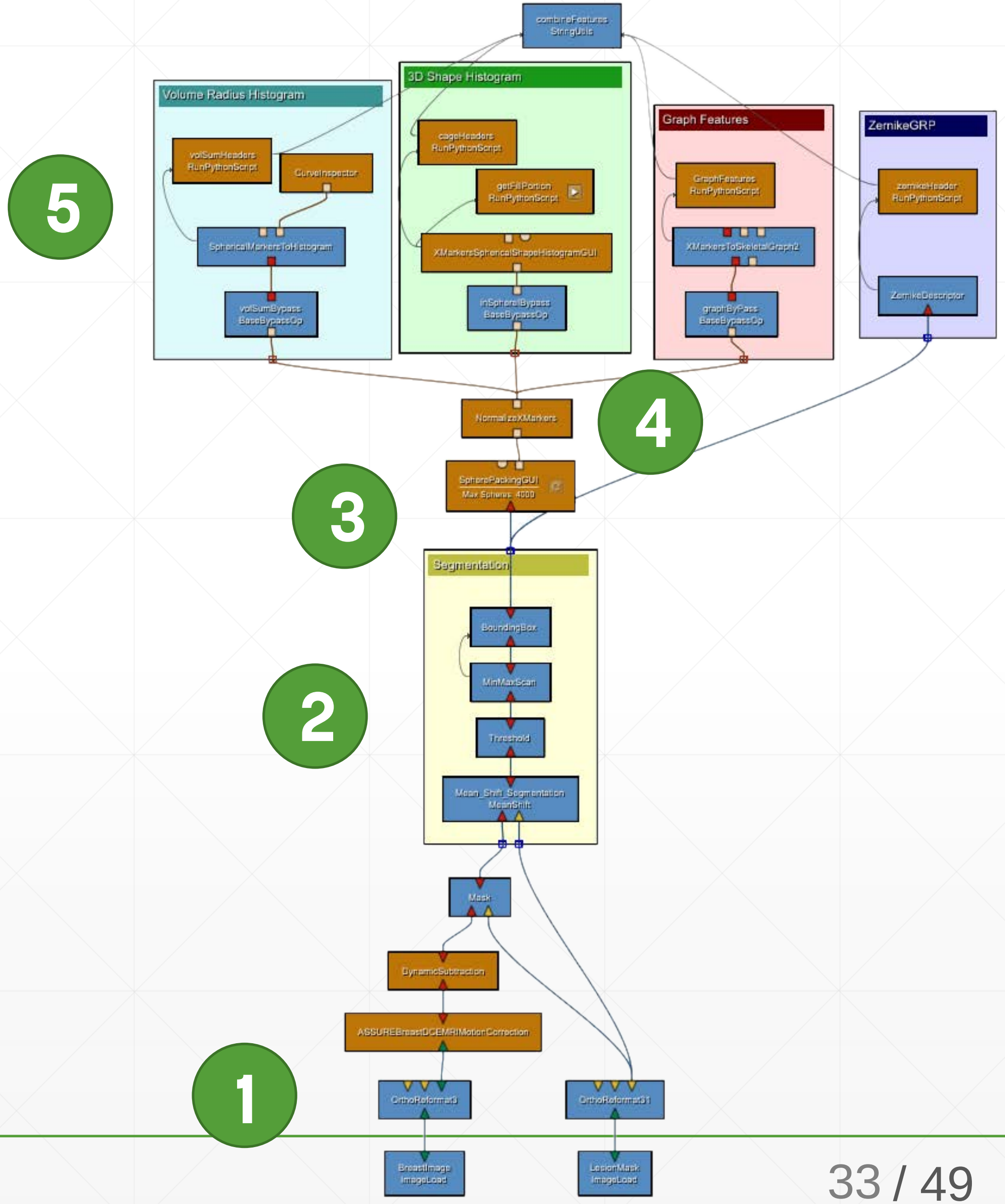
Development

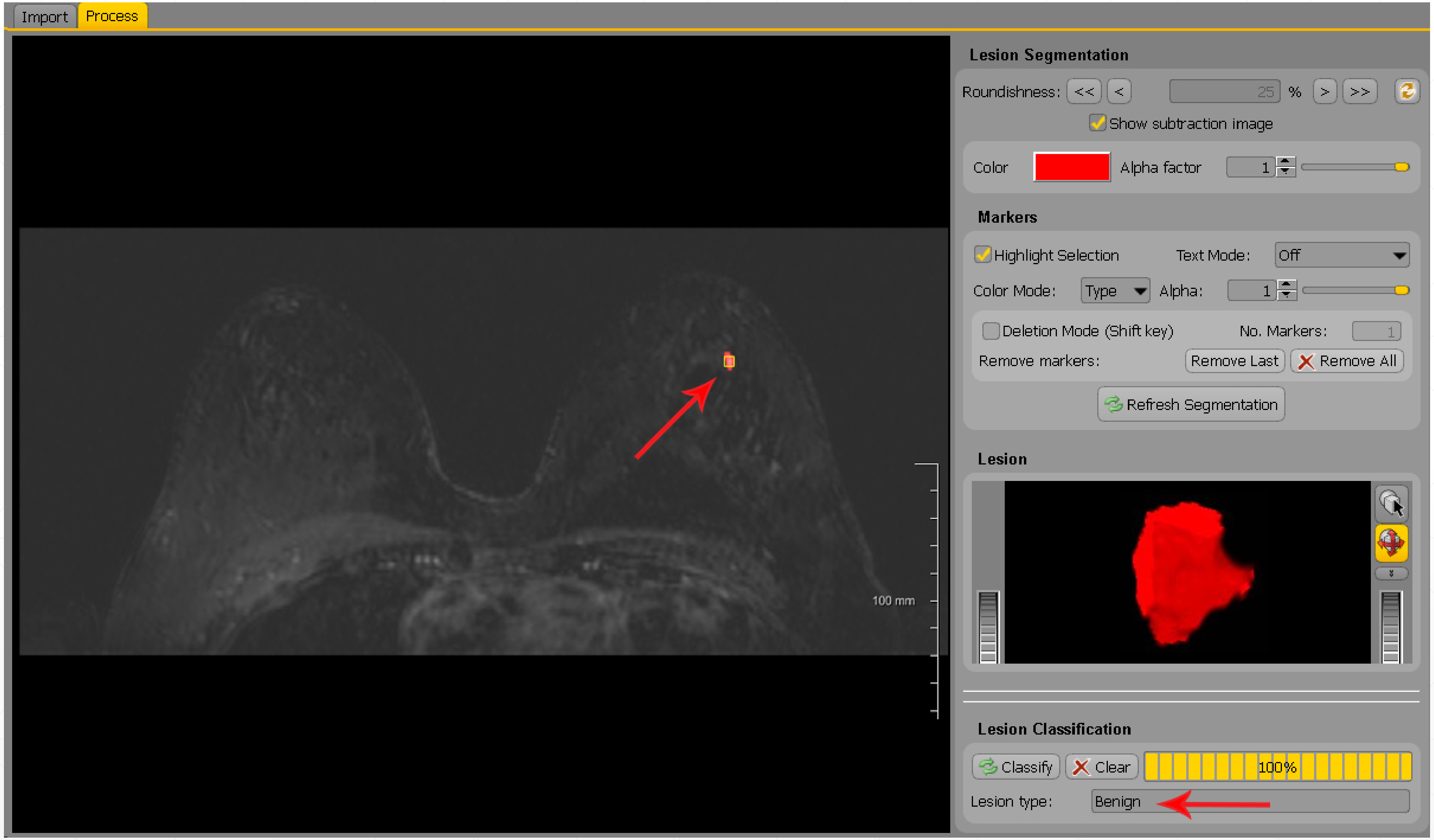
- Processing framework
- Integration in CADx tool

Processing framework in MevisLab

1. Pre-processing
   - Motion correction
2. Segmentation
3. Sphere Packing
4. Normalization
5. Feature Extraction
   1. Volume-Radius Histogram
   2. 3D Shape Histogram
   3. Graph topological features
   4. Zernike Features



Framework integration into CADx tool

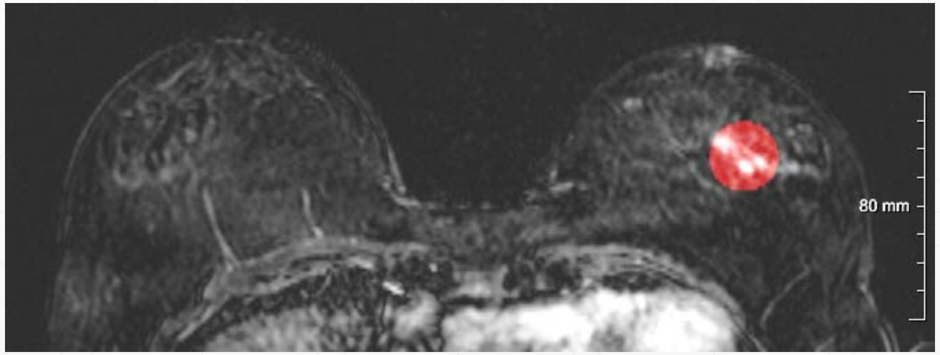


Evaluation

- Dataset
- Machine learning algorithm
- Performance measures
- Feature selection

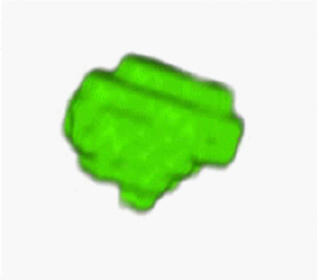
Image Dataset

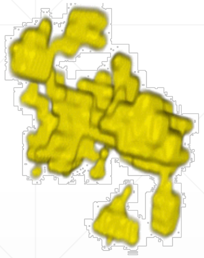
- MR breast volumes from 86 different patients diagnosed having non-mass lesions
- Age: 23 - 76 years (45.84 ± 11.97)
- Within years 2003 - 2009 from the Radboud University Nijmegen in the Netherlands.
- Resolution 256x128x80 to 512x256x16
- Reference lesion binary masks: manually annotated by an experienced radiologist.



Ground truth

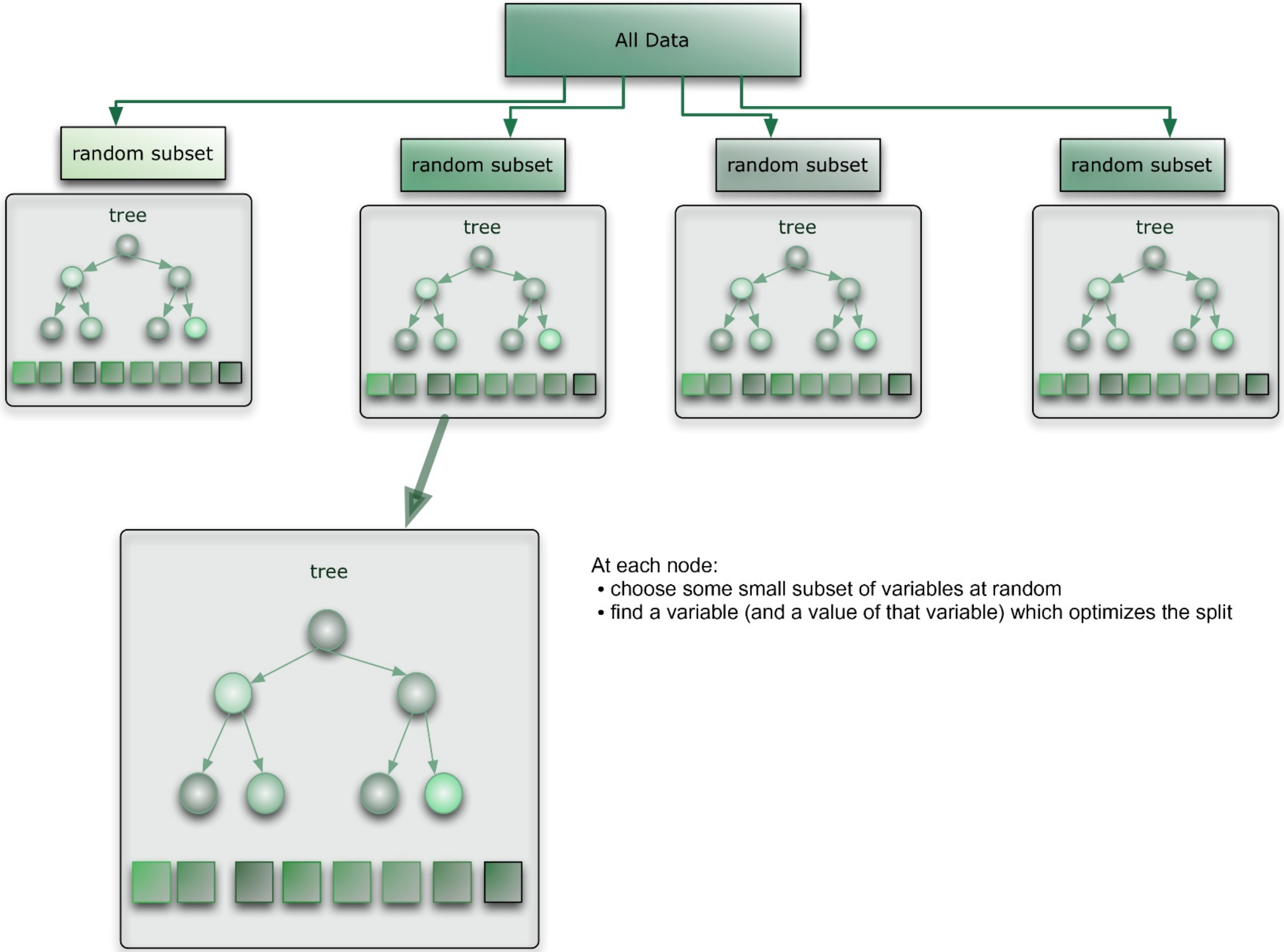
- 106 lesion enhancements acquired from segmentation step
  - 38 benign
  - 68 malignant





Random Forest

- By random selection of features constructs a collection of decision trees with controlled variance
- Outputs the class that is the mode of the classes (classification) or mean prediction (regression) of the individual trees



At each node:
- choose some small subset of variables at random
- find a variable (and a value of that variable) which optimizes the split

Performance Measures

- Confusion matrix
- Accuracy
- Precision
- AUC: Area under receiver operating characteristic (ROC) curve

Class \Recognized	as Positive	as Negative
Positive	t_p	f_n
Negative	f_p	t_n

$$accuracy = \frac{t_p + t_n}{t_p + f_p + f_n + t_n}$$

$$precision = \frac{t_p}{t_p + f_p}$$

Machine learning technique

- Random Forest
- 10-fold cross validation

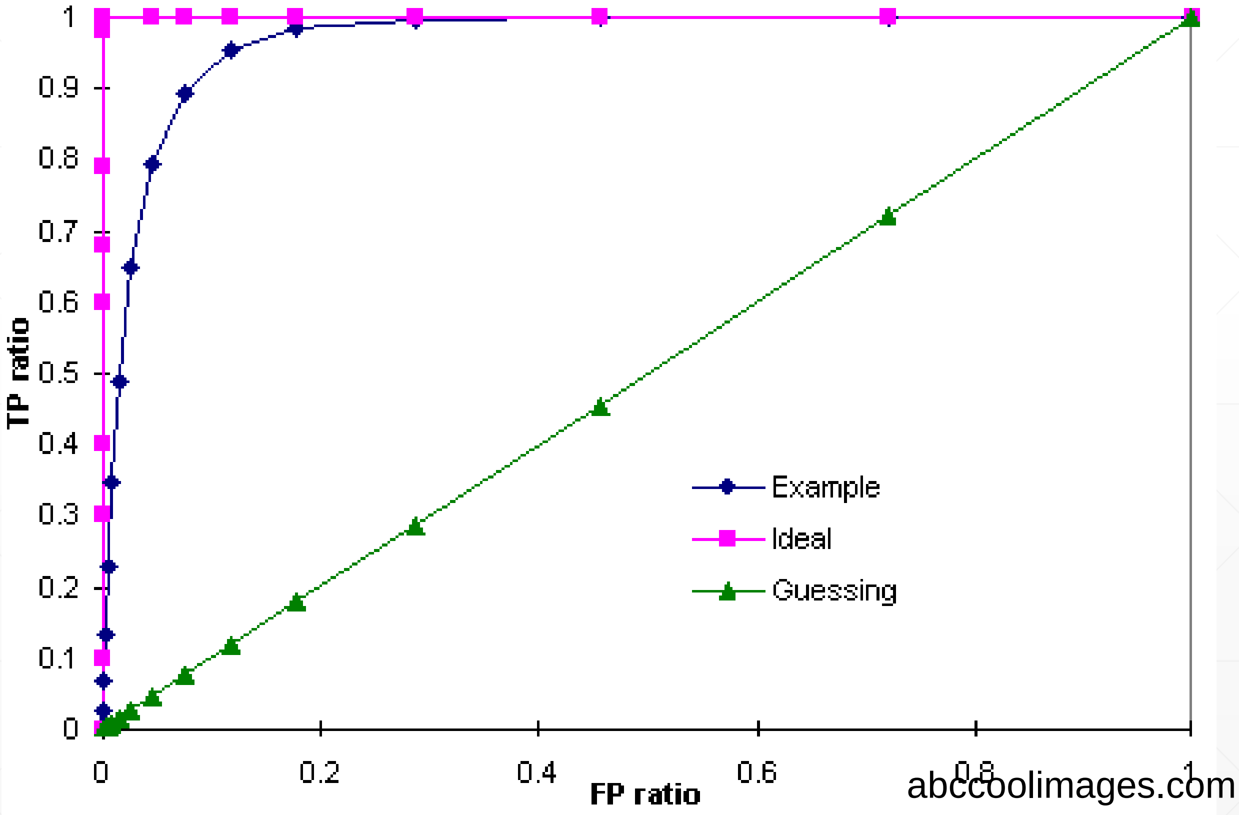
Area Under ROC Curve (AUC)

- Illustrates the performance of a binary classifier
  - How well the test separates the groups
- By plotting the true positive rate (TPR) (sensitivity) against the false positive rate (FPR) (fall-out = 1 - specificity) at various threshold settings
  - y-axis: true positive rate
  - x-axis: false positive rate
    - An area of 1 represents a perfect test
    - An area of 0.5 represents a worthless test

wikipedia.org

$$sensitivity = \frac{t_p}{t_p + f_n}$$

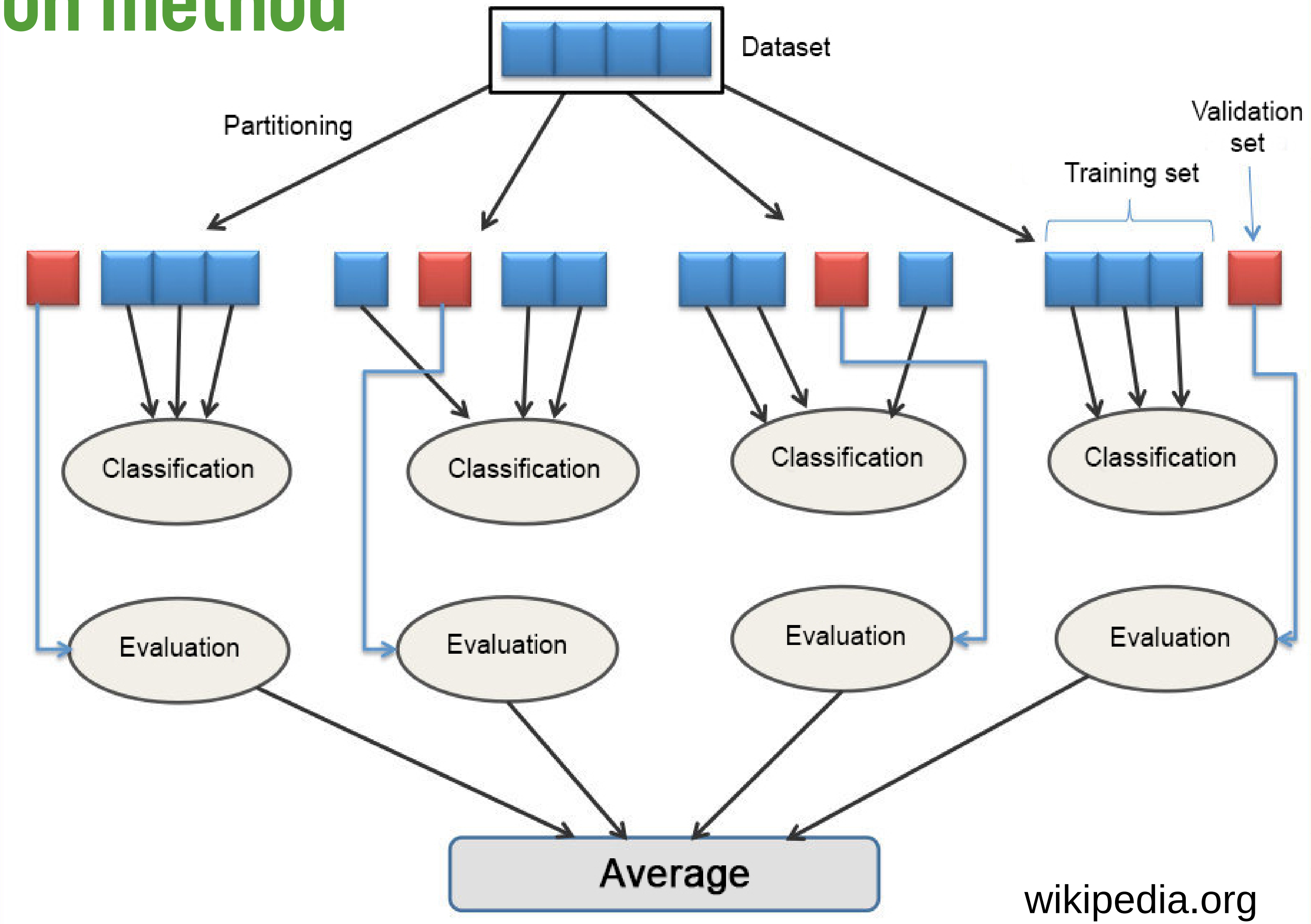
$$specificity = \frac{t_n}{f_p + t_n}$$



abccoolimages.com

K-Fold Cross Validation method

- Partitioning a sample of data into complementary subsets
  - Performing the analysis on one subset (training set)
  - validating using other subset (validation set or testing set).
- Multiple rounds of cross-validation are performed using different partitions
- The validation results are averaged over the rounds
- Here, 10-Fold is used



wikipedia.org

Feature Combination (All features)

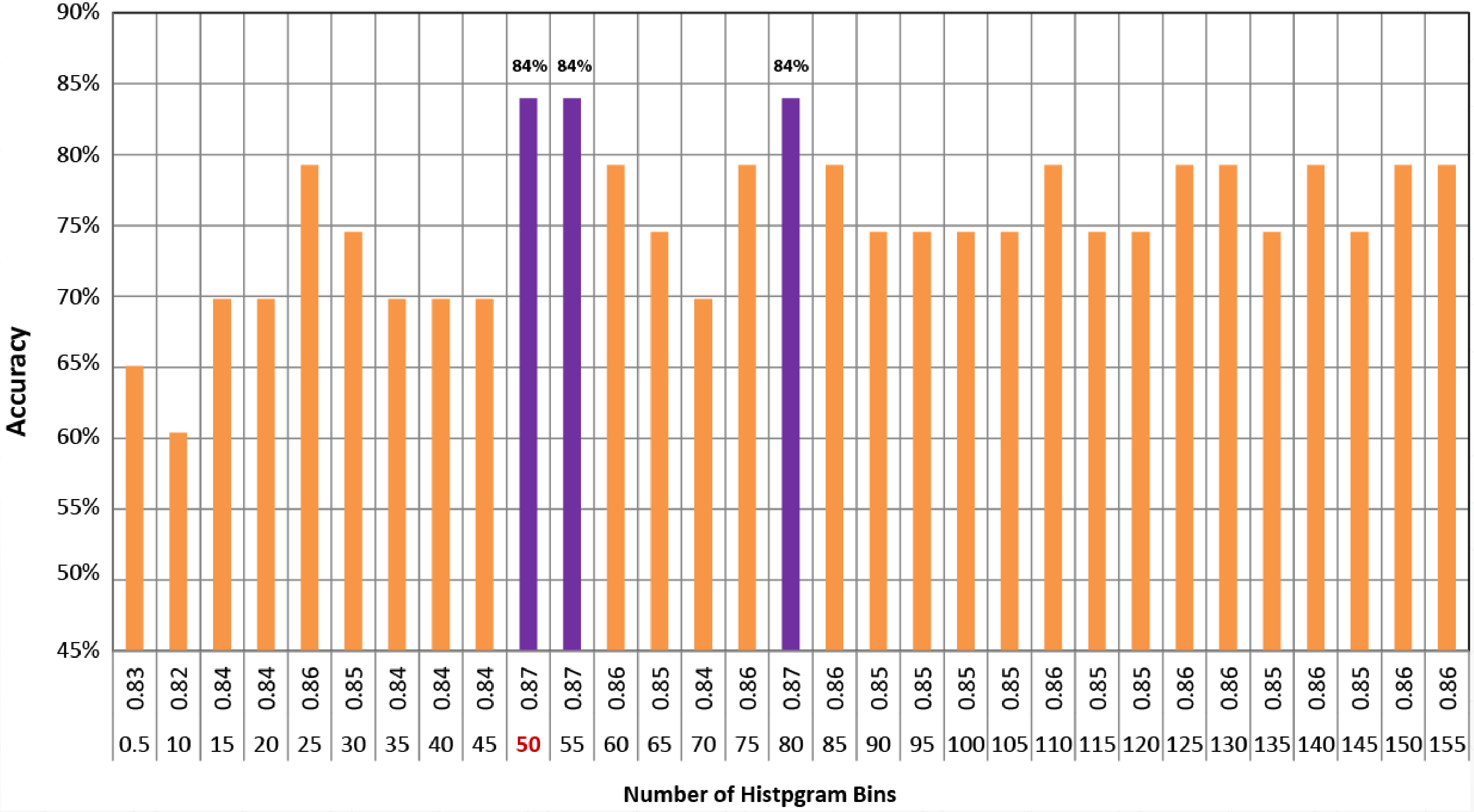
- A serial combination of all 252 best features (brute force search) including:

1. 50 features: volume-radius histogram features
   - 50 histogram bins
2. 111 features: 3D shape histogram features
   - 11 rings, 10 shells, and 1 sector (11x10x1=110)
   - Wireframe center: in middle of the two most distant spheres
3. 72 features: Zernike descriptor features
   - Maximum Order of 15
4. 15 features: graph topological features
   - K_{max} equal to number of nodes (n)
   - A Gabriel graph with no clustering

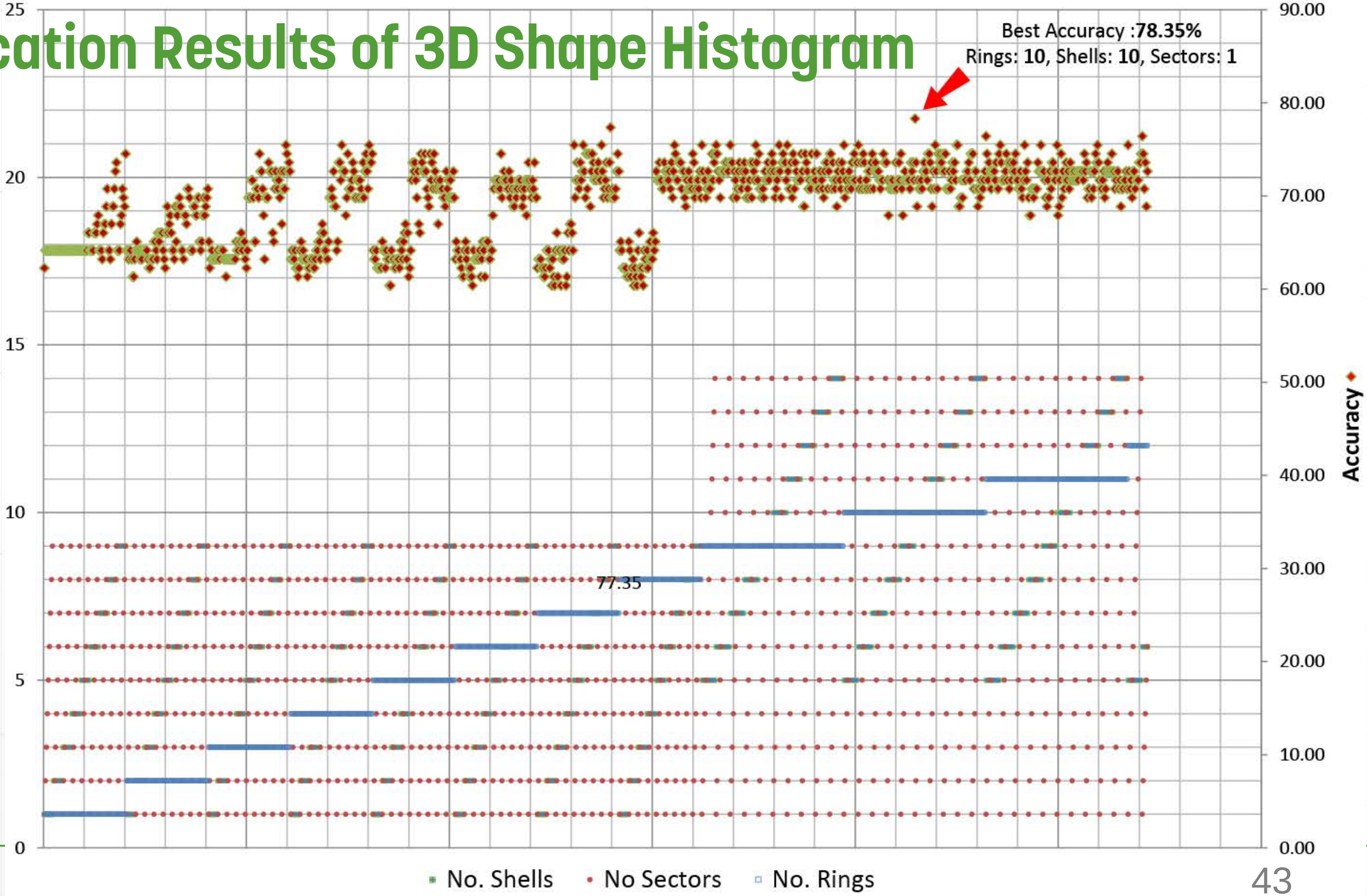
Evaluation results of all features using Random Forest classifier

Measure	value for all the features
Accuracy	**89.92**
Precision	**89.7**
AUC	**0.9**

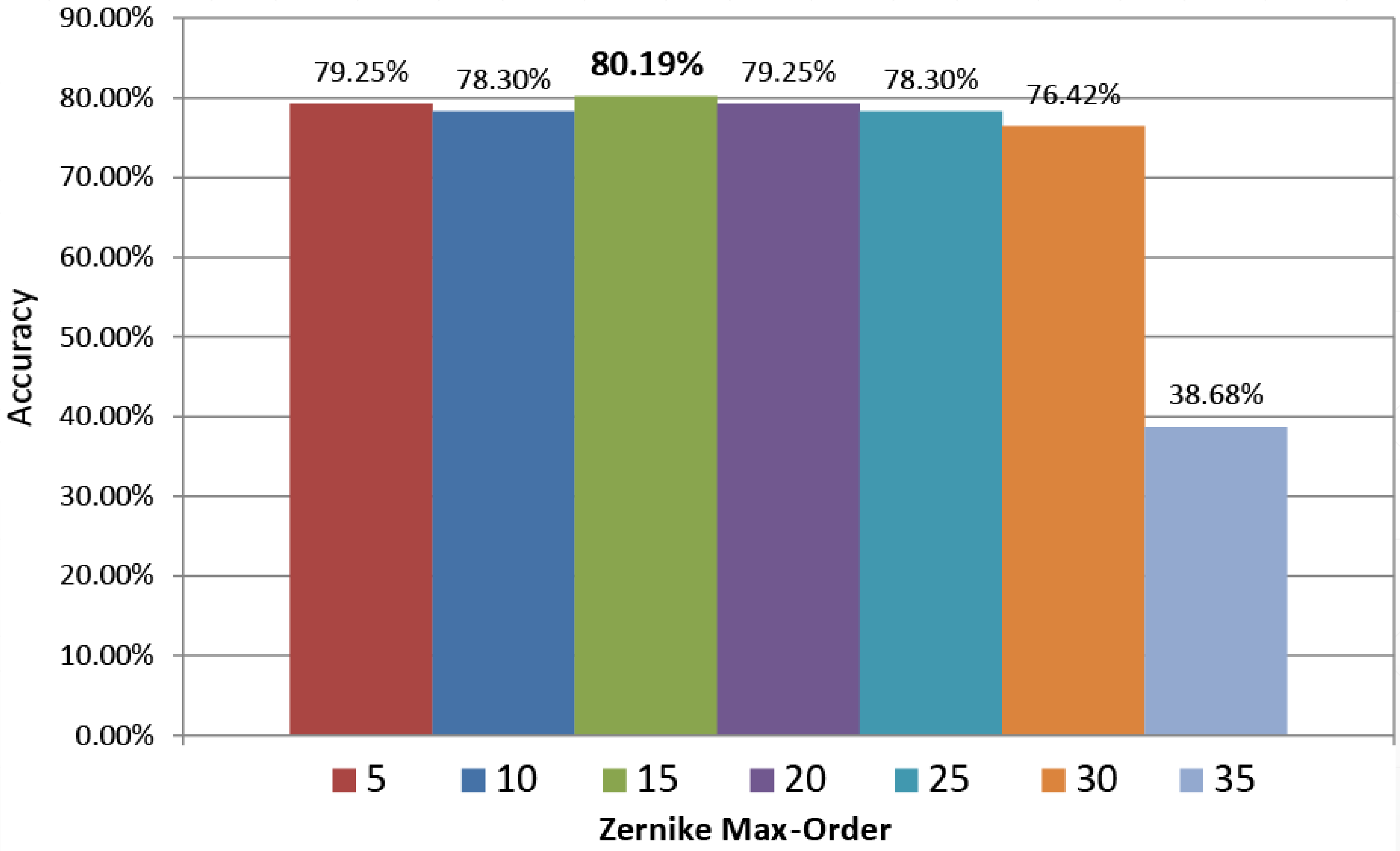
Classification accuracy only based on volume-radius histogram



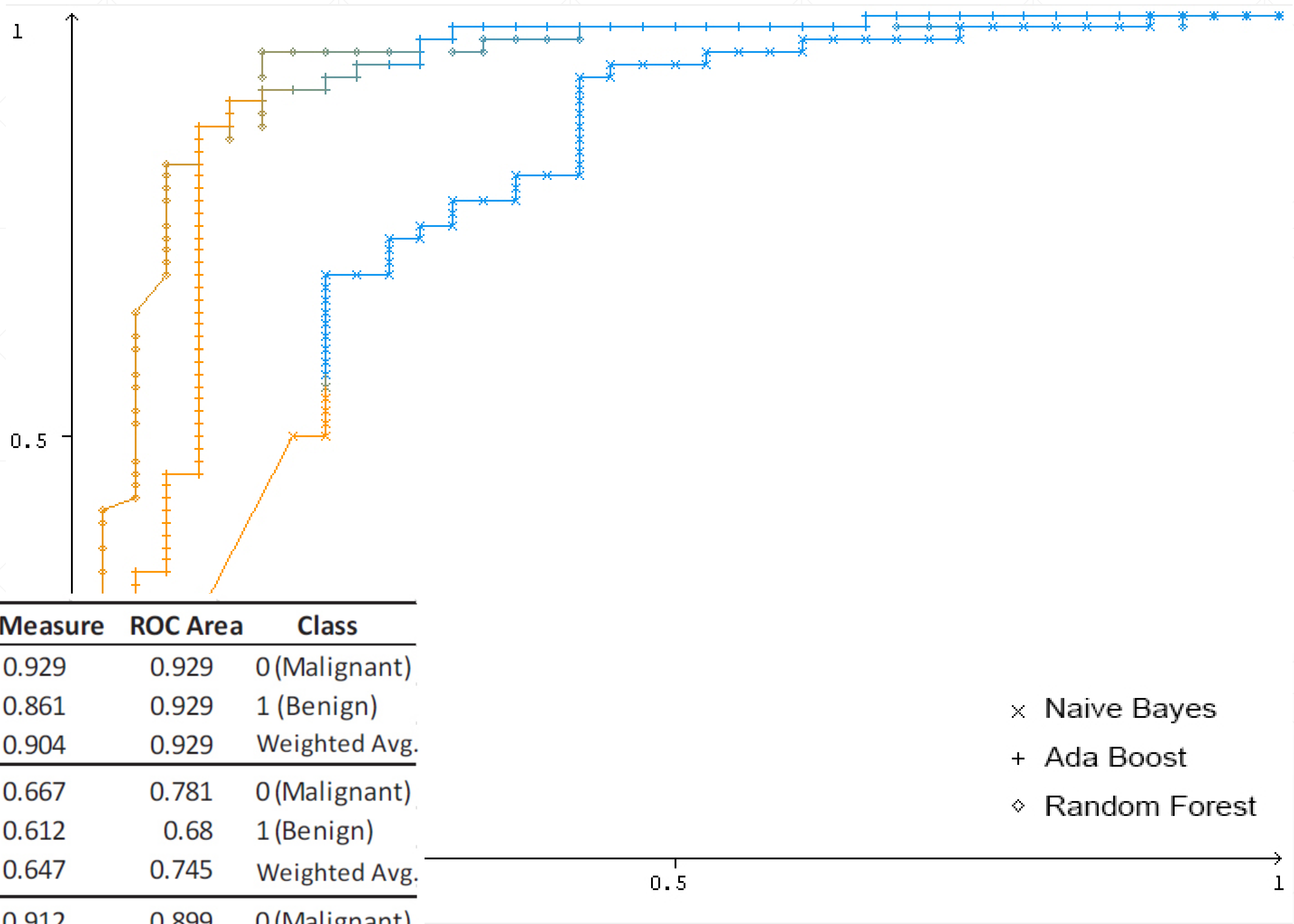
Classification Results of 3D Shape Histogram



Classification accuracy only from Zernike features with different orders



Choosing classifier



ML Algorithm	TP Rate	FP Rate	Precision	Recall	F-Measure	ROC Area	Class
Ranodom Forest	0.956	0.184	0.903	0.956	0.929	0.929	0 (Malignant)
	0.816	0.044	0.912	0.816	0.861	0.929	1 (Benign)
	0.906	0.134	0.906	0.906	0.904	0.929	Weighted Avg.
NaiveBayes	0.559	0.211	0.826	0.559	0.667	0.781	0 (Malignant)
	0.789	0.441	0.5	0.789	0.612	0.68	1 (Benign)
	0.642	0.293	0.709	0.642	0.647	0.745	Weighted Avg.
AdaBoost	0.912	0.158	0.912	0.912	0.912	0.899	0 (Malignant)
	0.842	0.088	0.842	0.842	0.842	0.899	1 (Benign)
	0.887	0.133	0.887	0.887	0.887	0.899	Weighted Avg.

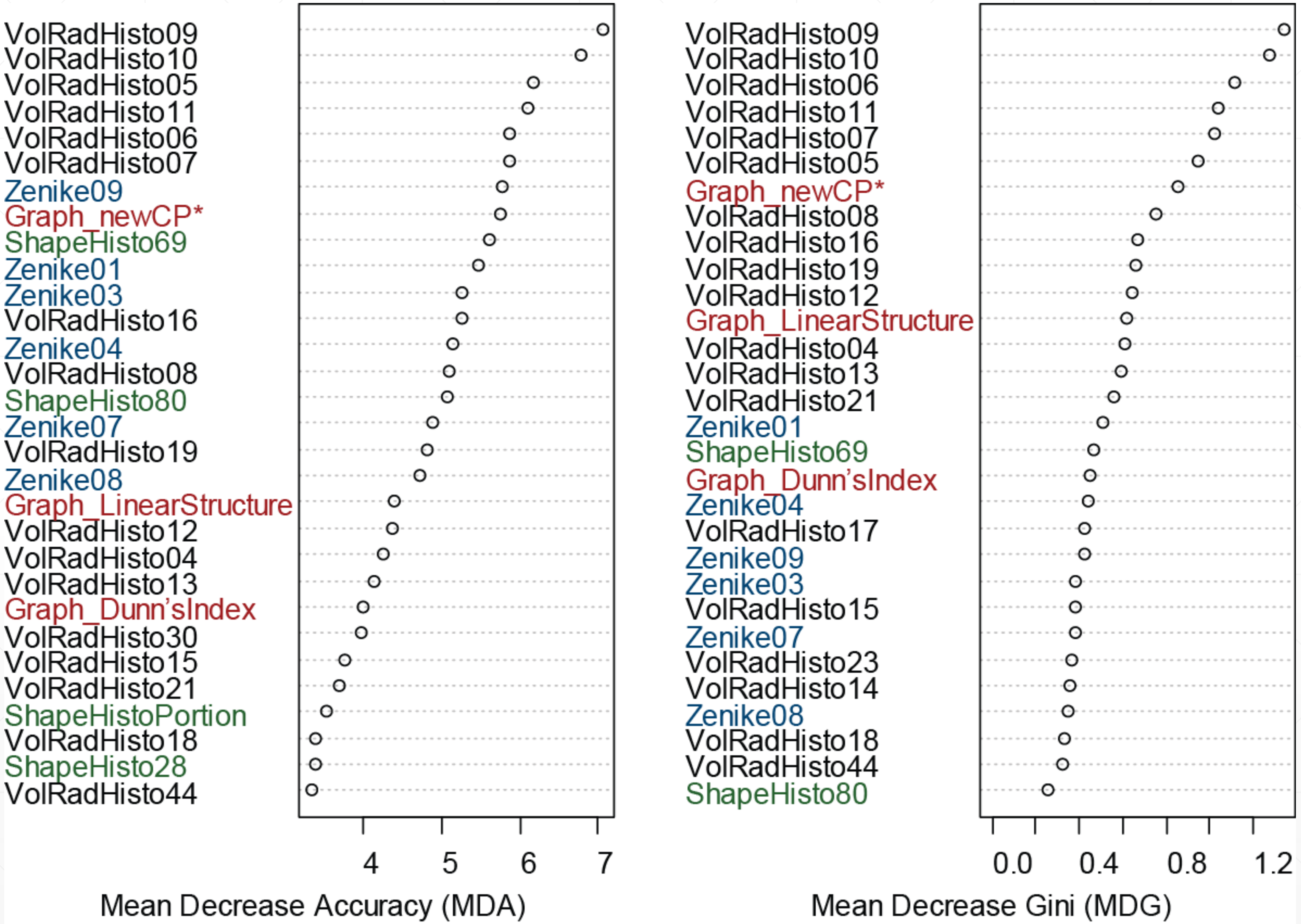
Feature Selection in Random Forest (Top 30)

- Mean Decrease Accuracy
  - How well the model actually predicts
- Mean Decrease Gini
  - Reflects the overall goodness of fit.

- The MDA is thought to be a better measure

Evaluation results using Random Forest classifier

Measure	MDA	MDG
Accuracy	89.6	89.6
Precision	89.6	90.6
AUC	0.957	0.963

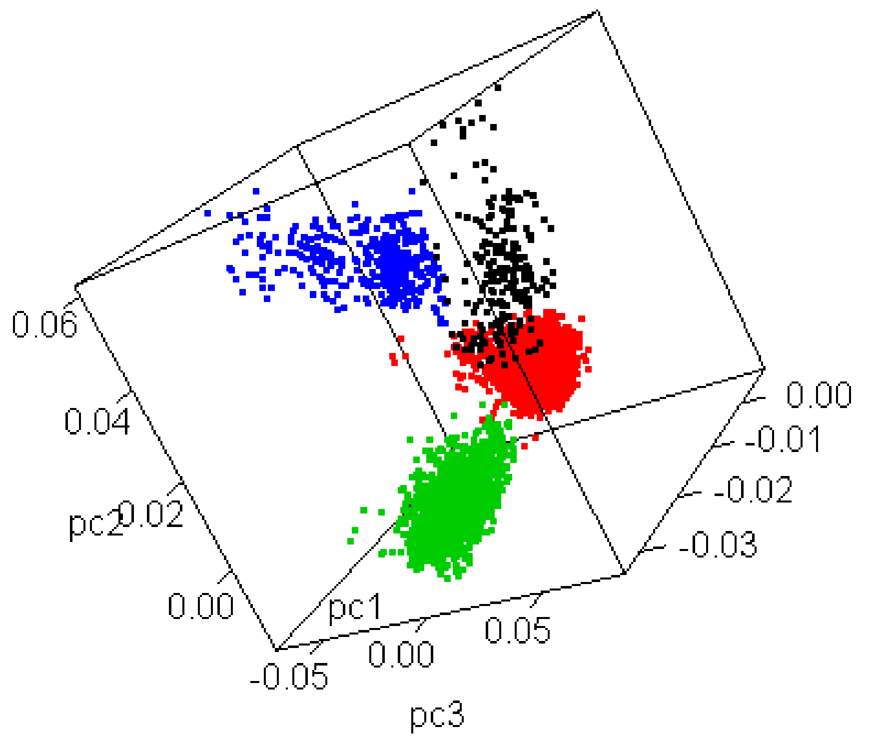


Principal component analysis (PCA)

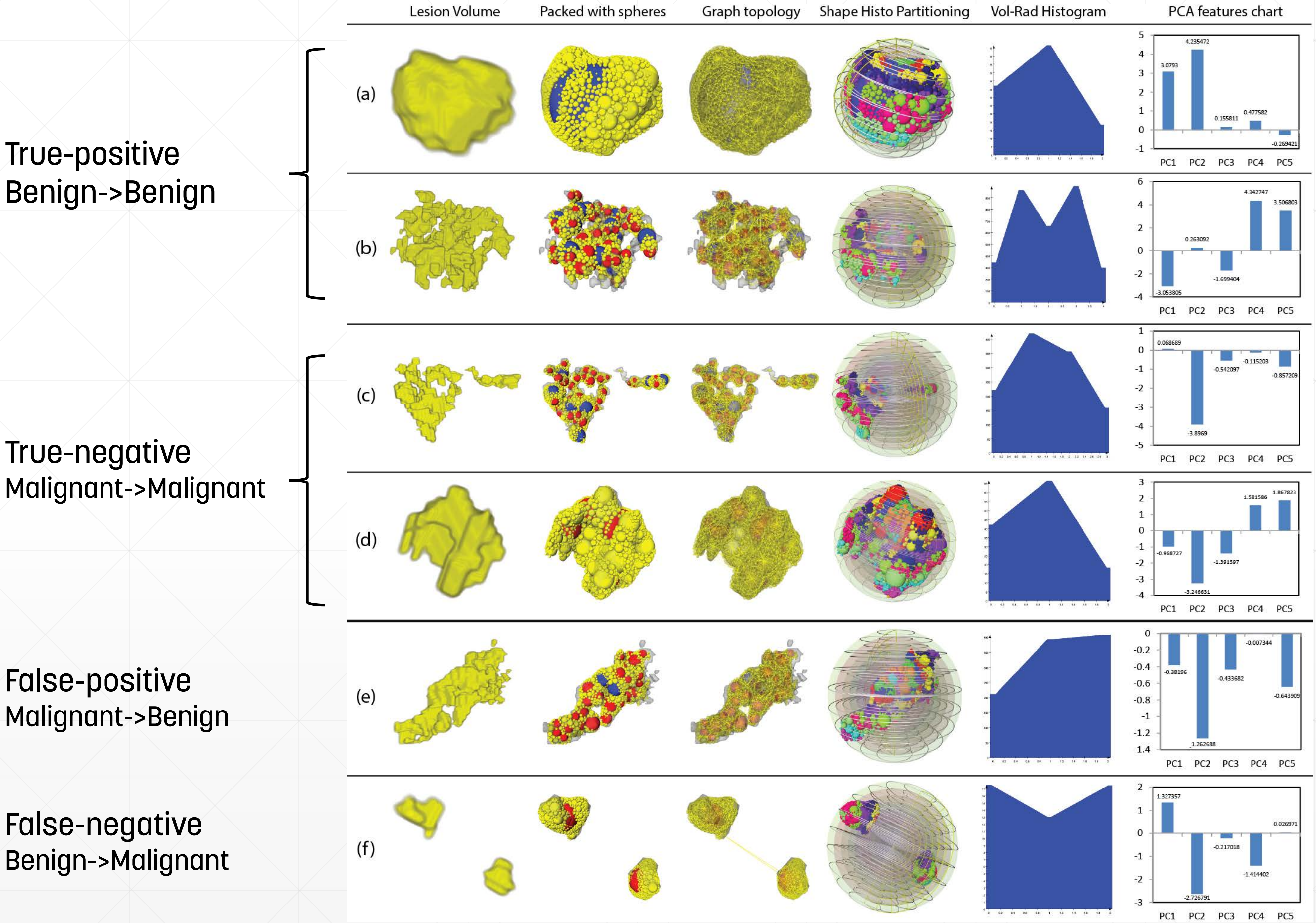
- Linearly transforms a high-dimensional input vector into a low-dimensional
  - by calculating the eigenvectors of the covariance matrix
- Eventually, only 5 principal components are left

Evaluation results using RF classifier

Measure	PCA on MDA	PCA on MDG
Accuracy	89.6	**89.6**
Precision	89.6	**89.6**
AUC	0.965	**0.972**



r-bloggers.com



Lesion Volume
Packed with spheres
Graph topology
Shape Histo Partitioning
Vol-Rad Histogram
PCA features chart
True-positive
Benign->Benign
True-negative
Malignant->Malignant
False-positive
Malignant->Benign
False-negative
Benign->Malignant
(a)
(b)
(c)
(d)
(e)
(f)
3.0793
4.235472
0.155811
0.477582
-0.269421
-3.053805
0.263092
-1.699404
4.342747
3.506803
0.068689
-3.8969
-0.542097
-0.115203
-0.857209
-0.968727
-3.246631
-1.391597
1.581586
1.867823
-0.38196
-1.262688
-0.433682
-0.007344
-0.643909
1.327357
-2.726791
-0.217018
-1.414402
0.026971
PC1 PC2 PC3 PC4 PC5

Summary

Summary & conclusion

- The goal:
  - Classification of the non-mass lesions using only morphological features
- Approaches:
  - Using sphere packing
  - Evaluating the performance real clinical breast MRI data.
- Results:
  - Accuracy of 89.6%, Precision of 89.6%, AUC of 0.972
  - Using RF, MDA, PCA and 10-fold cross validation
  - Morphological features can be used for classification

Future work

- Combination with kinetic and textural features
- More advanced segmentation algorithms
- Normalization of volumetric data
- 3D shape histogram step:
  - Volume enclosed by partition
  - Wireframe sphere orientation
- Evaluation:
  - More advanced ML techniques
    - ANN and deep learning

Questions