Lecture 28
Segmentation: Biomarker Development and Radiomics

MP574: Applications

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Learning Objectives

- Introduce common texture measures and shape-measures used to generate features
- Introduce generalized approach to biomarker development - “radiomics”
  - Strategy is to extend the data-driven approach to expand the dimensionality of the data
  - Multiple image contrast and quantitative measures
  - Almost totally data-driven after curation by expert readers

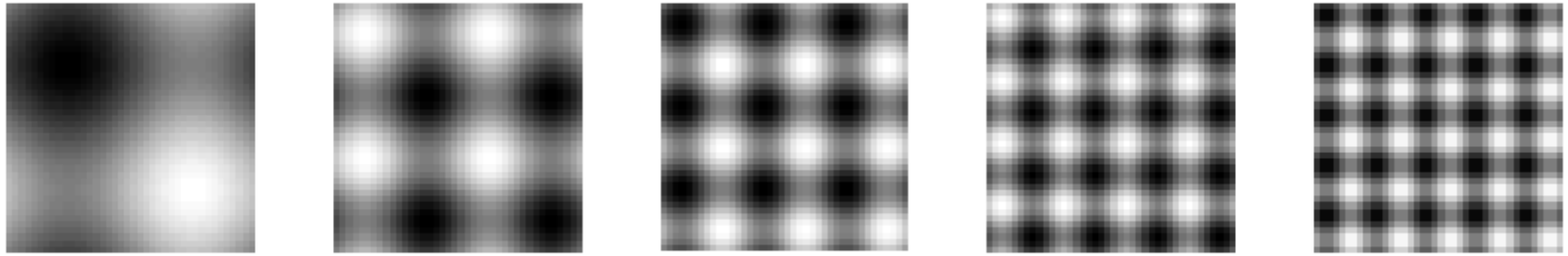
Features and Patterns

- Patterns are ordered sequences of measurements (e.g. shape and texture measures. Could also be functional perfusion etc…)
- Example pattern matrix:

$object$	$feature\,1$	$\cdots$	$feature\,n$	
1	i	$i+1$	i_n	Pattern x_1
$\vdots$	.	.	.	Pattern x_2
n	.	.	.	Pattern x_n

Characterization

How can we characterize these images?



CV = 0.05 **CV = 0.05** **CV = 0.05** **CV = 0.05** **CV = 0.05**

CV (Coefficient of Variation) = STD/mean

Textural features

- **First order** texture measures are statistics calculated from the original image values, like variance, and do not consider pixel neighbor relationships.

- **Second order** measures consider the relationship between groups of two (usually neighboring) pixels in the original image.
  - Gray Level Co-occurrence Matrix (GLCM)
  - Run Length Matrix (RLM)

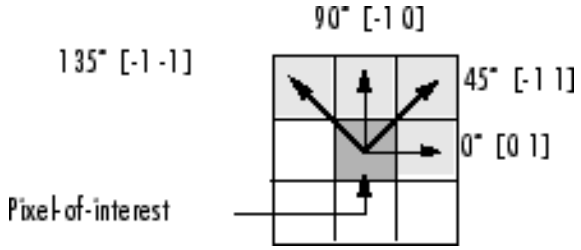
- **Higher order** textures (considering the relationships among three or more pixels) are theoretically possible but not commonly implemented due to calculation time and interpretation difficulty. There has been some recent development of a more efficient way to calculate third-order textures.
  - Neighborhood Gray-Tone-Difference Matrix (NGTDM)

Gray Level Co-occurrence Matrix

A gray level co-occurrence matrix (GLCM) contains information about the positions of pixels having similar gray level values. The GLCM is defined by:

$$P_{ij}(d,\theta) = n_{ij}$$

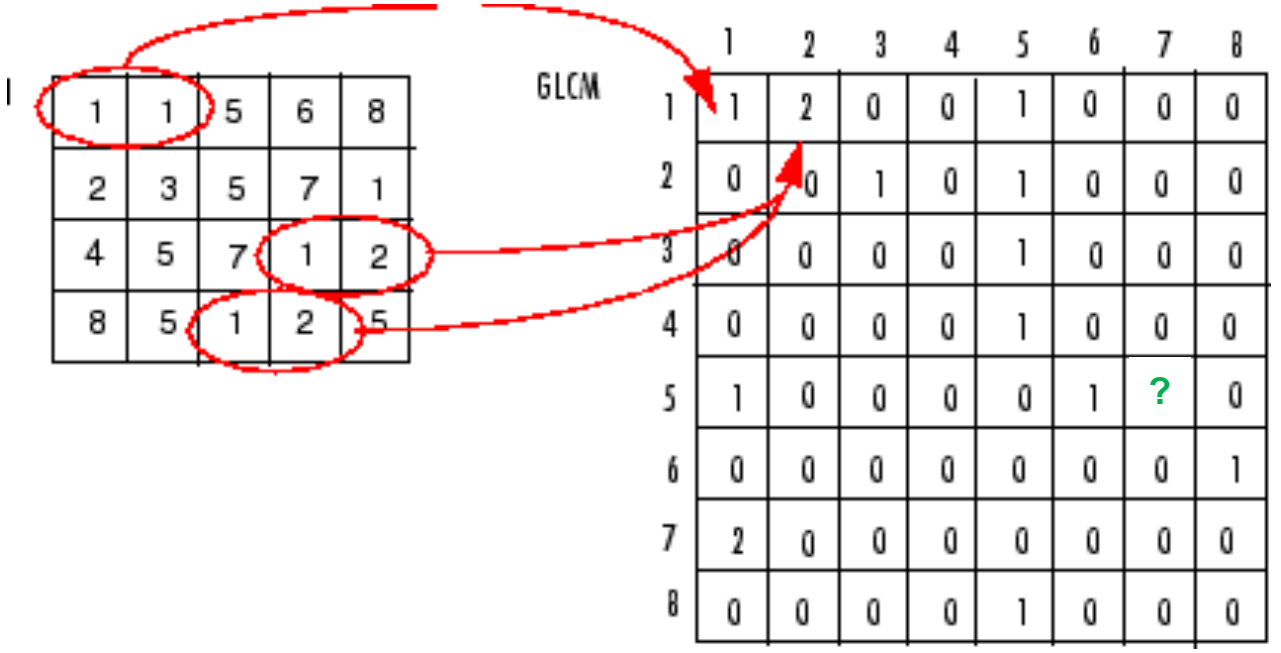
$$[alternatively, P(i,j|d,\theta)]$$



where n_{ij} is the number of occurrences of the pixel values (i,j) lying at distance d in the direction θ.

The co-occurrence matrix P_{ij} has dimension $n \times n$, where n is the number of gray levels in the image.

Gray Level Co-occurrence Matrix



$P_{ij}(d=1,\theta=0^o)$

GLCM = graycomatrix(I, 'GrayLimits', [1 8], 'Offset', [0 1]);

Statistics derived from GLCM

- Energy: $f_1 = \sum_i \sum_j p_{ij}^2$
- Entropy: $f_2 = -\sum_i \sum_j p_{ij} \ln p_{ij}$
- Homogeneity: $f_3 = \sum_i \sum_j \frac{p_{ij}}{1+(i-j)^2}$
- Contrast: $f_4 = \sum_i \sum_j p_{ij}(i-j)^2$
- Dissimilarity: $f_5 = \sum_i \sum_j p_{ij}|i-j|$
- Correlation: $f_6 = \sum_i \sum_j \frac{(i-\mu_i)(j-\mu_j)}{\delta_i \delta_j}$

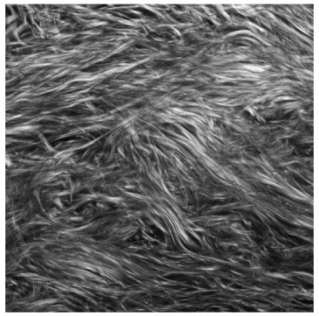
$$\begin{cases} \mu_i = \sum_i \sum_j i p_{ij} \\ \delta_i^2 = \sum_i \sum_j i^2 p_{ij} - \mu_i^2 \end{cases}$$

- …

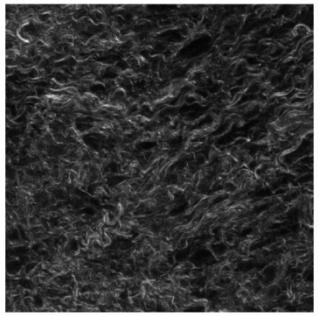
Typically d=1, averaged over all four directions in 2D

SHG images of breast tissues

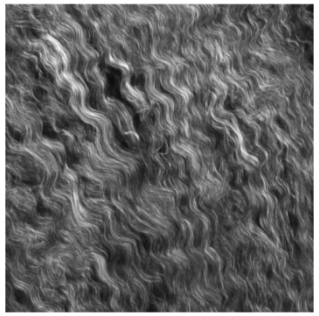
Normal



High risk



Cancer

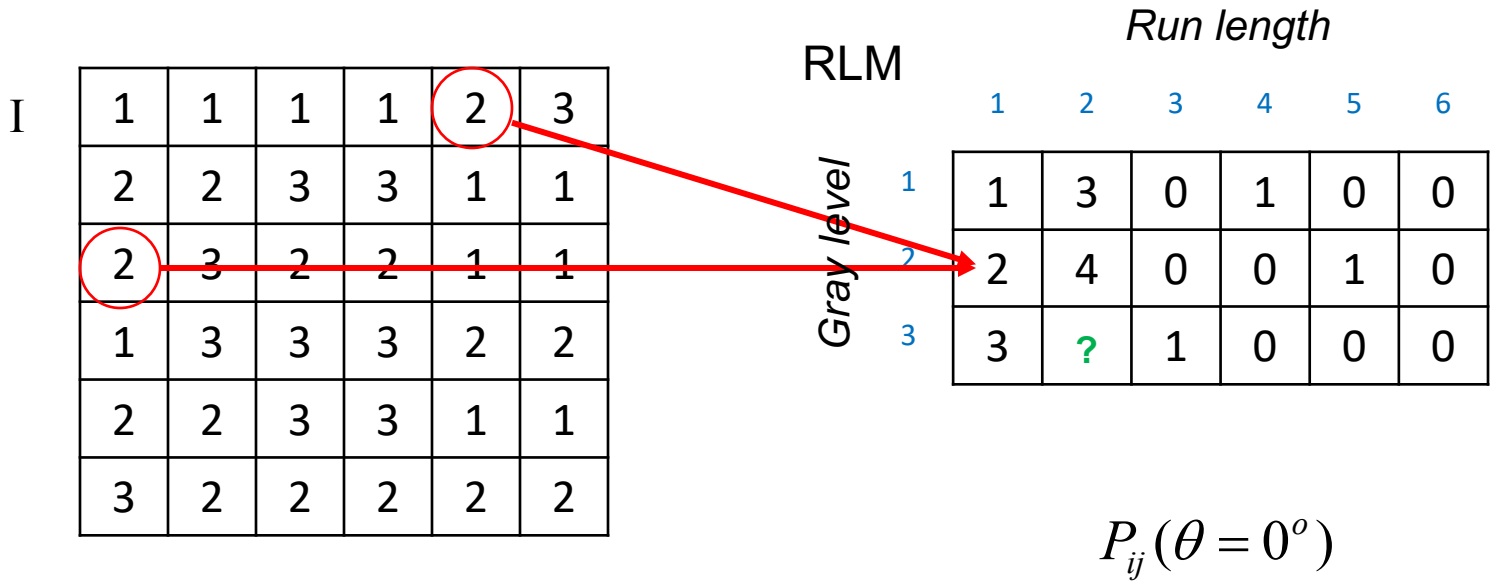


Textures

	Normal	High Risk	Cancer
autocorrelation	13.55	5.39	13.22
contrast	0.59	0.35	0.47
correlation	0.89	0.76	0.86
cluster prominence	81.94	18.18	42.16
cluster shade	7.32	2.34	3.88
dissimilarity	0.48	0.32	0.42
energy	0.14	0.30	0.19
entropy	2.58	1.82	2.29
homogeneity	0.86	0.88	0.88
maximum probability	0.27	0.51	0.34
sum of squares	13.59	5.45	13.24
sum average	7.03	4.47	7.05
sum variance	29.64	10.47	30.34
sum entropy	2.13	1.56	1.93
difference variance	0.59	0.35	0.47
difference entropy	0.84	0.67	0.76

Texture analysis can be performed after wavelet or curvelet transformation

Run Length Matrix



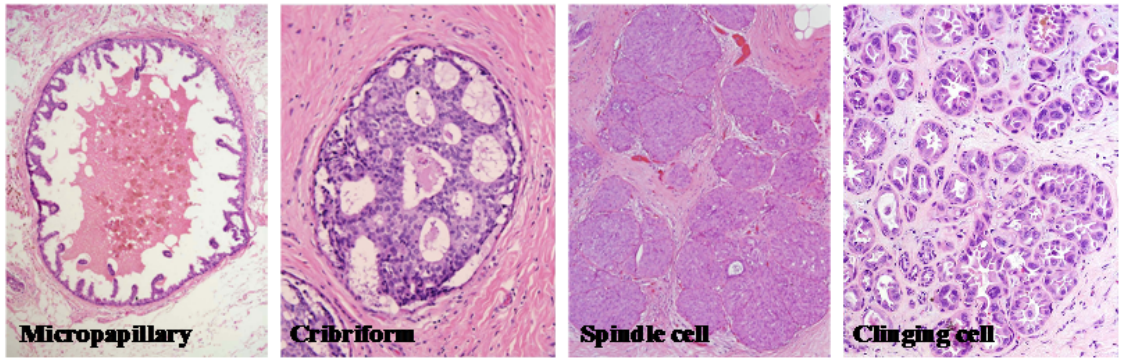
$$P_{ij}(\theta = 0^{o})$$

Statistics derived from RLM

- Short Run Emphasis: $$SRE = \sum_i \sum_j \frac{p_{ij}^2}{j^2}$$
- Long Run Emphasis: $$LRE = \sum_i \sum_j p_{ij} j^2$$
- Low Gray-Level Run Emphasis: $$LGRE = \sum_i \sum_j \frac{p_{ij}}{i^2}$$
- High Gray-Level Run Emphasis : $$HGRE = \sum_i \sum_j p_{ij} i^2$$
- Short Run Low Gray-Level Emphasis: $$SRLGE = \sum_i \sum_j \frac{p_{ij}}{i^2 j^2}$$
- Short Run High Gray-Level Emphasis: $$SRHGE = \sum_i \sum_j \frac{p_{ij} i^2}{j^2}$$
- …

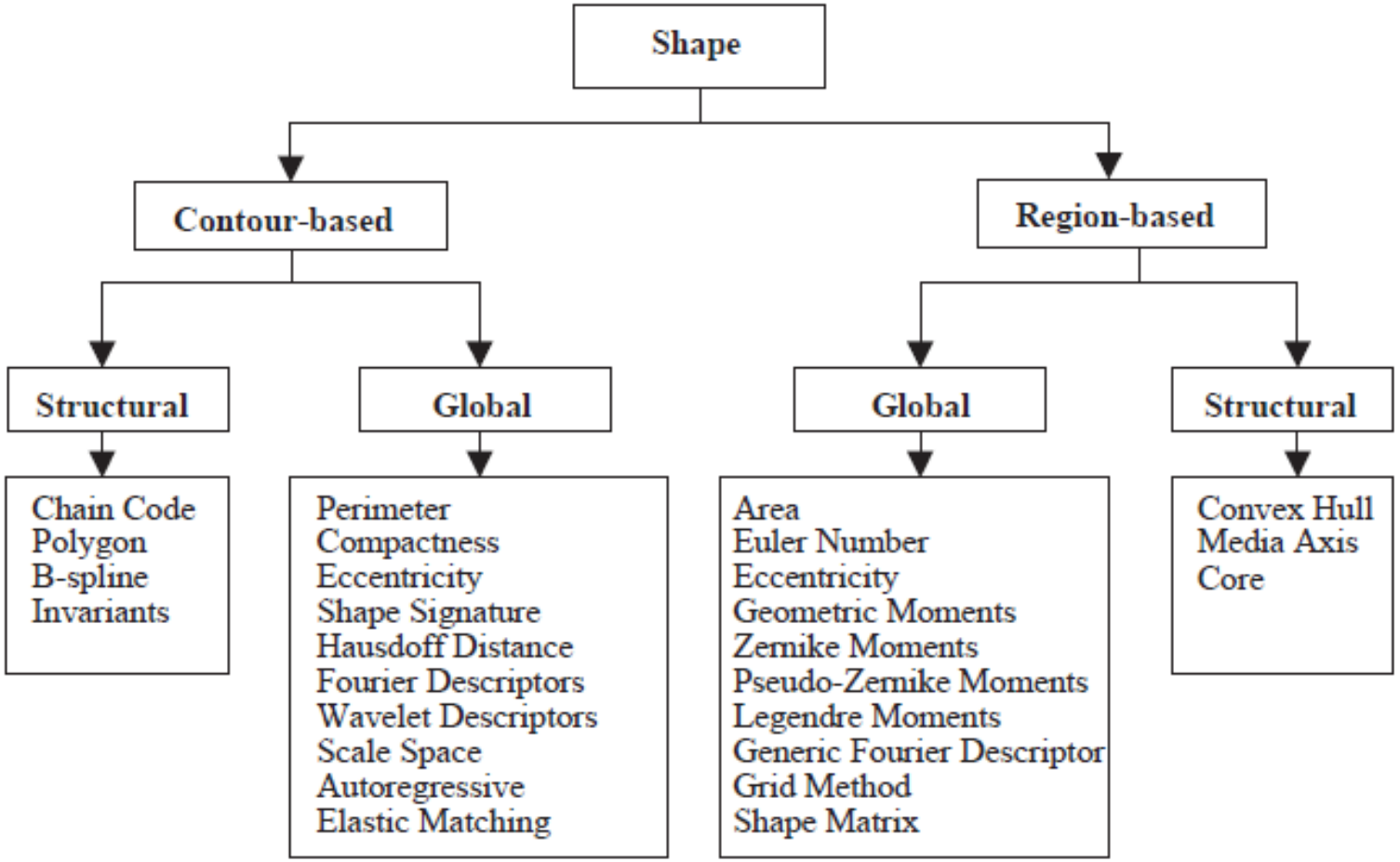
Morphological classification of human breast cancer

#	Morphological classification	#	Morphological classification
1	Inflammatory	11	Clear cell
2	Pregnancy-associated	12	Medullary
3	Comedo	13	Secretory
4	Micropapillary	14	Signet ring cell
5	Papillary	15	Mucinous
6	Cribriform	16	Tubular
7	Solid	17	Lobular neoplasia
8	Clinging	18	Mixed cell types
9	Spindle cell	19	Apocrine
10	Neuroendocrine	20	Malignant myoepithelioma



Hsiao *et al* (2010)

Shape Descriptors



Zhang & Lu (2004)

Chain Code

A chain code is a lossless compression algorithm for monochrome images

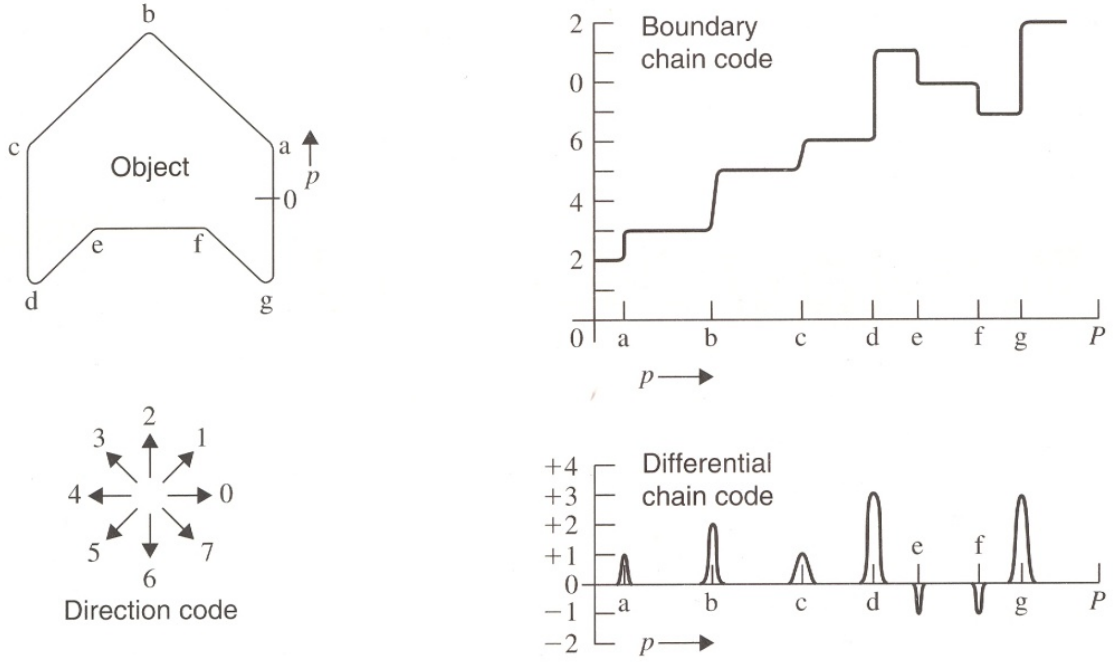
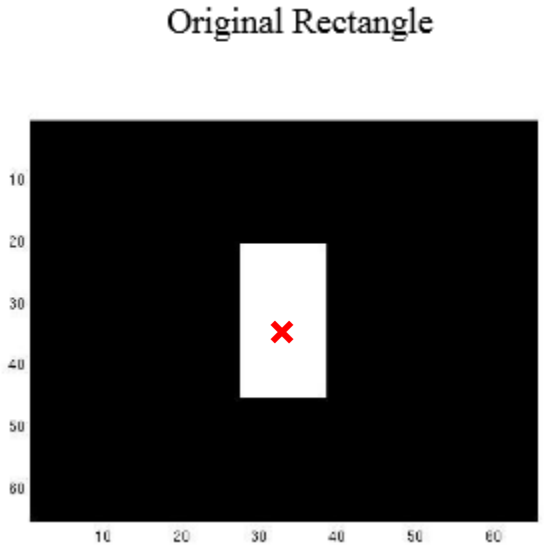
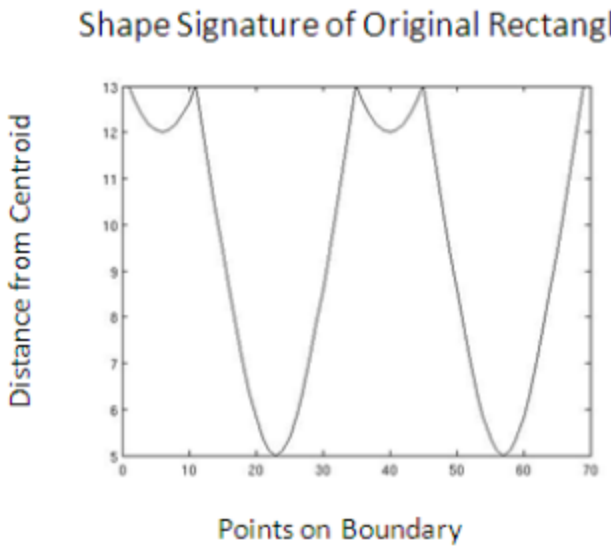


Figure 19–6 The chain code and its derivative

Shape Signature

The 1D functional representation of the 2D shape boundary is called **shape signature**.



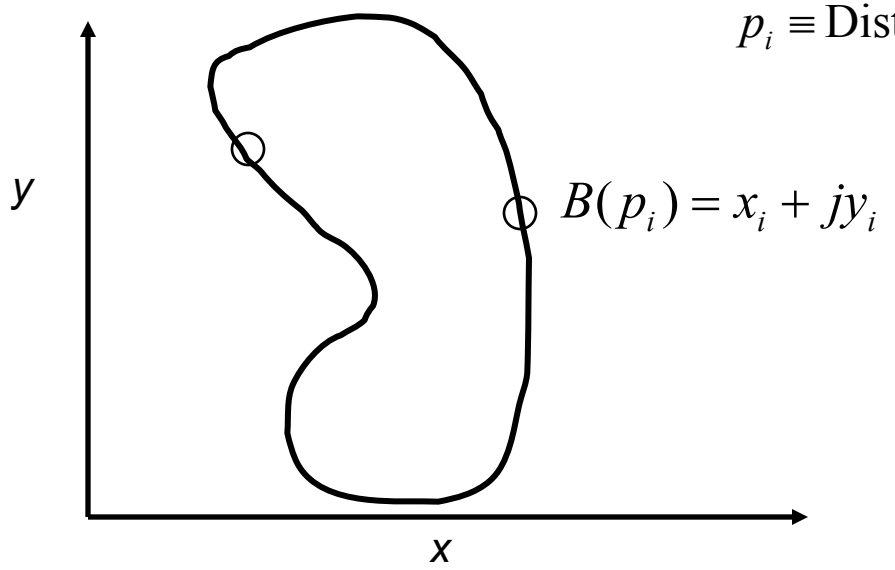


Translation invariant

Fourier Descriptors

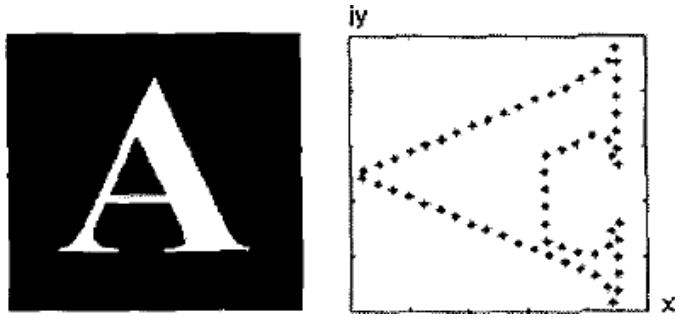
Fourier descriptors are **invariant** to translation, rotation, scaling, and change of starting point

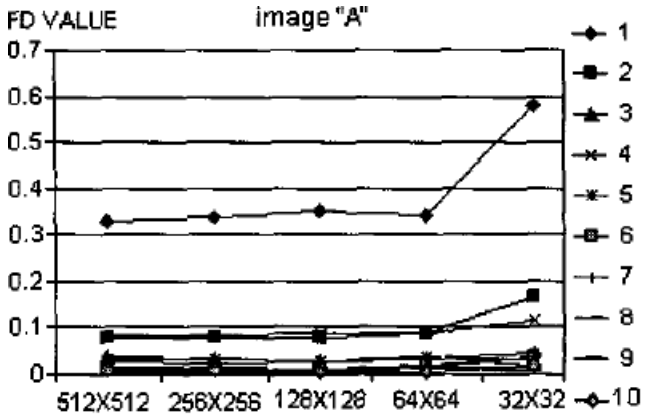
$$p_i \equiv \text{Distance along the boundary}, i = 1, \cdots, N_b.$$



Fourier transform of $B(p_i)$ results in a periodic function with coefficients characteristic of object shape.

Example of Fourier Shape Descriptor





$$s(n) = x(n) + iy(n), \qquad n = 0, 1, 2, \dots, N-1$$

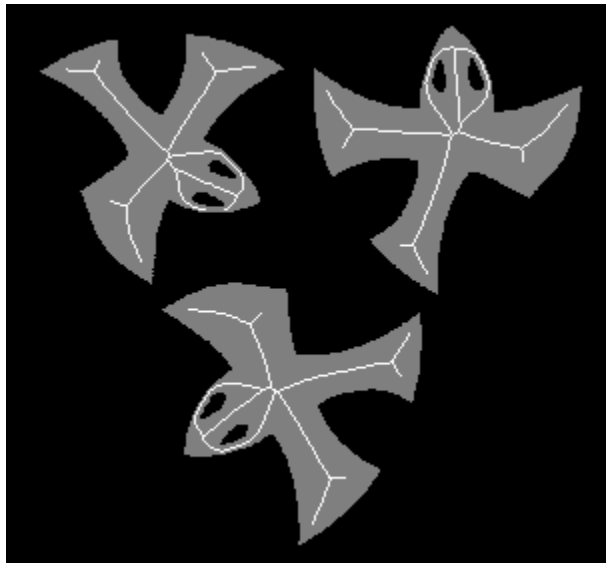
$$z(k) = \frac{1}{N}\sum_{n=0}^{N-1} s(n)e^{-i2\pi kn/N}, \qquad k = 0, 1, \dots, K-1$$

Can be made “invariant” to rigid transformations by normalizing to low frequency terms:

$$c(k-2) = \frac{|z(k)|}{|z(1)|}, k = 2, 3, \dots, K-1$$

Skeleton Descriptors

Skeleton is an important topological descriptor of a 2D binary object



BW2 = bwmorph(BW,'skel',Inf);

- Average length of the skeleton of the object
- Ratio of number of points on the skeleton to number of points inside the object
- Ratio of number of points on the skeleton to number of points on the boundary of the object
- Ratio of number of branch points to number of points on the skeleton

Moments

Recall that the set of moments of a bounded function $f(x,y)$

$$M_{jk} = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} x^j y^k f(x,y)\,dx\,dy \qquad \mu_{jk} = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} (x-\bar{x})^j (y-\bar{y})^k f(x,y)\,dx\,dy$$

$$M_{00} = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(x,y)\,dx\,dy$$

Central Moments

$$\bar{x} = \frac{M_{10}}{M_{00}}, \qquad \bar{y} = \frac{M_{01}}{M_{00}}$$

Center of gravity of the object

Normalized Moments for Multi-scale Object Recognition

- Central moments are computed using the centroid of the image object
  - Equivalent to an image whose center has been shifted to coincide with the object centroid
  - Implies invariant to translations
- Consider scaling by:
- $\begin{bmatrix} x' \\ y' \end{bmatrix} = \begin{bmatrix} S_x & 0 \\ 0 & S_y \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix}, S_x = S_y = \alpha$

- Consider moments under scaling:

$$f(x', y') = f(\alpha x, \alpha y); x' = \alpha x,\ y' = \alpha y$$

$$\mu'_{pq} = \iint (\alpha x - \alpha \bar{x})^p (\alpha y - \alpha \bar{y})^q f(x', y') dx' dy'$$

$$\mu'_{pq} = \alpha^{p+q+2} \mu_{pq}$$

$$\mu'_{00} = \alpha^2 \mu_{00}$$

- Normalized central moments:

$$\eta_{pq} = \frac{\mu_{pq}}{\mu'^{\gamma}_{00}}, \text{where } \gamma = (p+q+2)/2; p+q = 2, 3, \ldots$$

Invariant Moment Descriptors

A set of 7 **invariant moments** (IM) which are invariant to rotation, scaling and translation are given by Hu

$$\phi_1 = \eta_{20} + \eta_{02}$$

$$\phi_2 = (\eta_{20} - \eta_{02})^2 + 4\eta_{11}^2$$

$$\phi_3 = (\eta_{30} - 3\eta_{12})^2 + (3\eta_{21} - \eta_{03})^2$$

$$\phi_4 = (\eta_{30} + \eta_{12})^2 + (\eta_{21} + \eta_{03})^2$$

$$\phi_5 = (\eta_{30} - 3\eta_{12})(\eta_{30} + \eta_{12})\left[(\eta_{30} + \eta_{12})^2 - 3(\eta_{21} + \eta_{03})^2\right] + (3\eta_{21} - \eta_{03})(\eta_{21} + \eta_{03})\left[3(\eta_{30} + \eta_{12})^2 - (\eta_{21} + \eta_{03})^2\right]$$

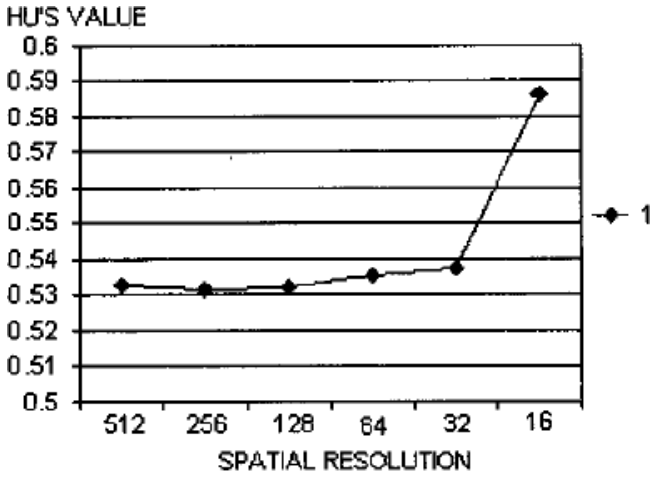
$$\phi_6 = (\eta_{20} - \eta_{02})\left[(\eta_{30} + \eta_{12})^2 - (\eta_{21} + \eta_{03})^2\right] + 4\eta_{11}^2(\eta_{30} + \eta_{12})(\eta_{21} + \eta_{03})$$

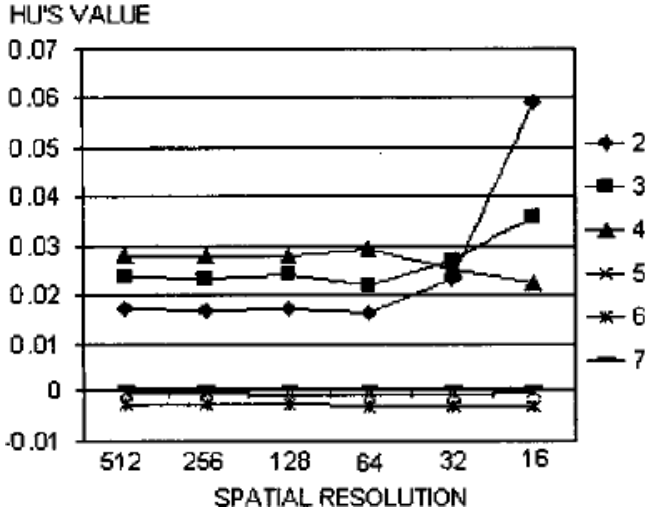
$$\phi_7 = (3\eta_{21} - \eta_{03})(\eta_{30} + \eta_{12})\left[(\eta_{30} + \eta_{12})^2 - 3(\eta_{21} + \eta_{03})^2\right] + (3\eta_{12} - \eta_{30})(\eta_{21} + \eta_{03})\left[3(\eta_{30} + \eta_{12})^2 - (\eta_{21} + \eta_{03})^2\right]$$

where $\eta_{pq} = \mu_{pq}/\mu_{00}^{\gamma}$ and $\gamma = 1 + (p+q)/2$ for $p + q = 2, 3, \ldots$

- High degree of information redundancy.
- Higher-order moments are very sensitive to noise

Example of Fourier Shape Descriptors vs. Moments for Multi-scale Object Recognition





Chen, Petriu and Yang,
https://ieeexplore.ieee.org/document/1344967/figures#figures

Biomarker Development Process

1. Develop curated dataset

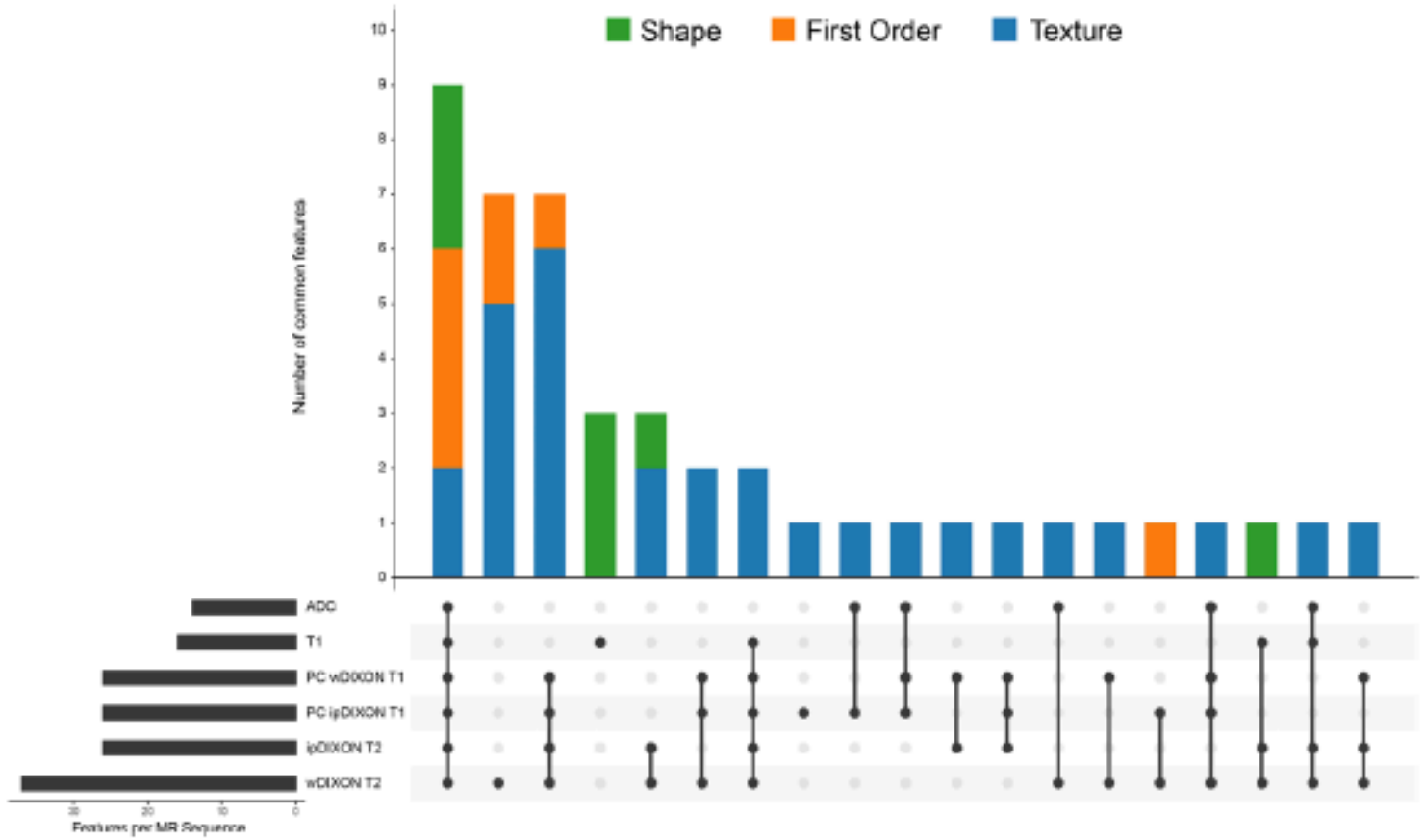
- Expert readers manually delineate disease features
- Preferably multi-parametric datasets (MRI contrasts)

2. Identify features

- Large number of candidate features
- Use statistical criteria to identify reproducible features (ICC, CCC)

3. Identify non-redundant (un-correlated) features clusters

- Step-wise regression models
- Spearman correlation matrix



(2019) 9:2068 | https://doi.org/10.1038/s41598-018-37984-8

Intra-Class and Cross-Correlation Coefficients

- Used to identify thresholds for feature and cluster selection
- Intra-class correlation coefficient:

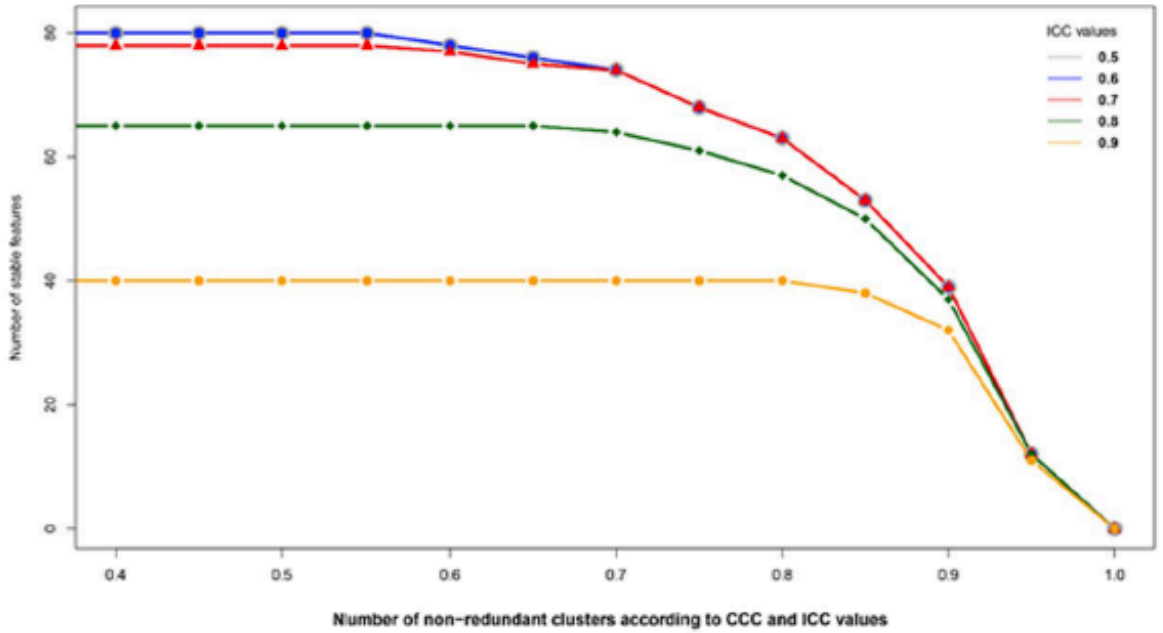
$$\mathrm{ICC} = \frac{Cov(x_1, x_2)}{{\sigma_{x_1}}^2 + {\sigma_{x_2}}^2}$$

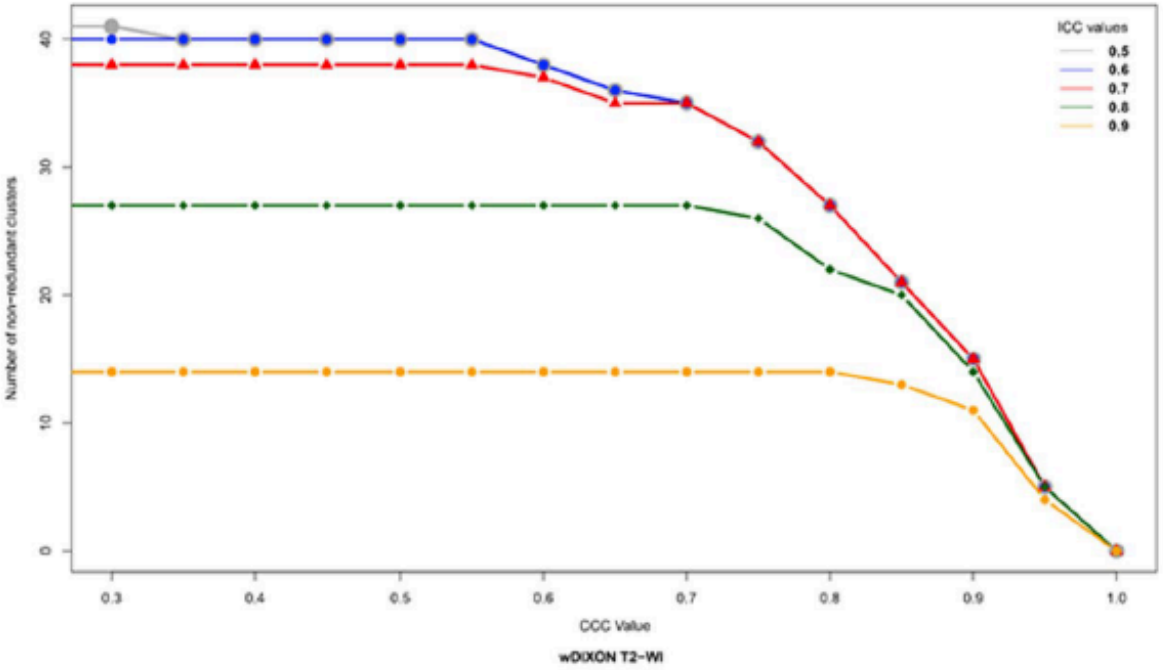
  - Proportion of total variance that is "between groups."
  - Reproducibility

- Cross-correlation coefficient:

$$\rho = \frac{Cov(x_1, x_2)}{\sigma_{x_1}\sigma_{x_2}}$$

  - Pearson correlation coefficient
  - Redundancy





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Feature Selection and Hierarchical Clustering

Deciding on the variables that provide the best prediction

1. Best model: search for all possible models and take the one with the highest R^2 (lowest Mallows' C_p)

2. Stepwise regression: useful when the number of predictor variables is large.
   a. Backward elimination: start with all variables, test them one by one and remove any that are not significant.
   b. Forward selection: start with no variable in the model and try out one by one and include them if they are statistically significant.

stepwise(), stepwisefit()

Summary

- Biomarker Development and Radiomics (Data-Mining)
- Strengths
  - Expands dimensionality of the data set to improve diagnostic power
  - Agnostic, data-driven reduced subjective bias imposed by more deterministic approaches
- Limitations
  - Features drawn from the data are typically highly correlated
  - Statistical clustering approaches to improve conditioning and optimize classification
  - Requires large amounts of high quality training data to improve accuracy