From voxel to complex network

Data integration in medical imaging

Marco Diego Dominietto

Biomaterials Science Center, University of Basel
Department of Surgery and Orthopedics, Hospitals Schaffhausen, Switzerland

Traitement d'Images en Physique Médicale

Port-Bourgenay , October 7-9, 2015

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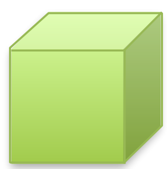
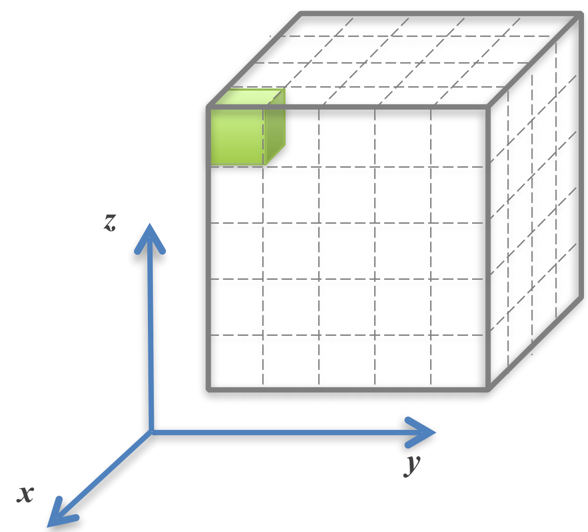
Voxel

Def: In 3D images, a voxel is a unit of graphic information that defines a point in three-dimensional space. For a given image modality, a voxel is the minimum measurable volume.

$$v = v(x, y, z)$$

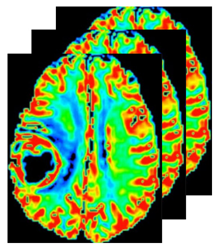
Spatial domain $\Re^3$

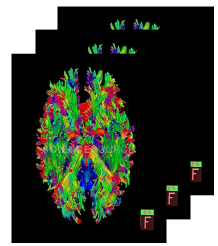




Multi-modalities approach allows to have more information about anatomical details and physiological properties of the same tissue. For each modality we can extract one or more **features**.

- perfusion
- glucose metabolism
- oxygen distribution
- vascular structure
- permeability
- CA uptake
- blood velocity
- etc.





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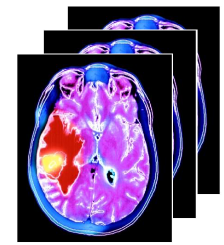

Introduction

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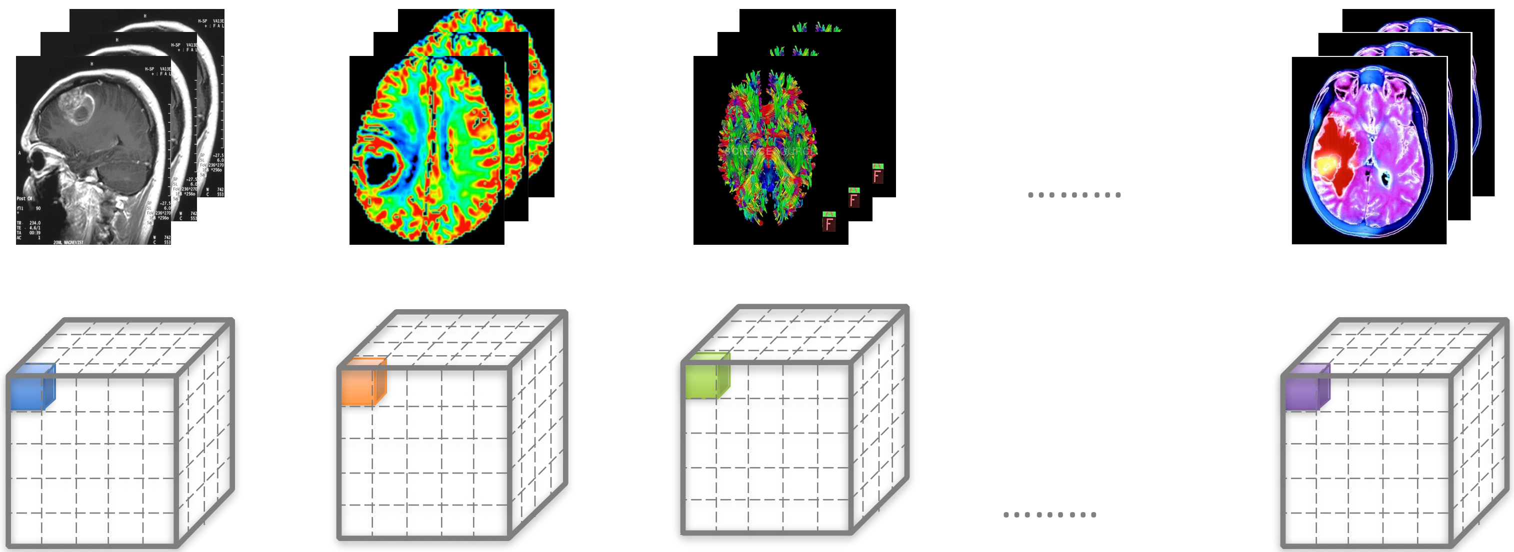

Feature F_1 F_2 F_3 F_N

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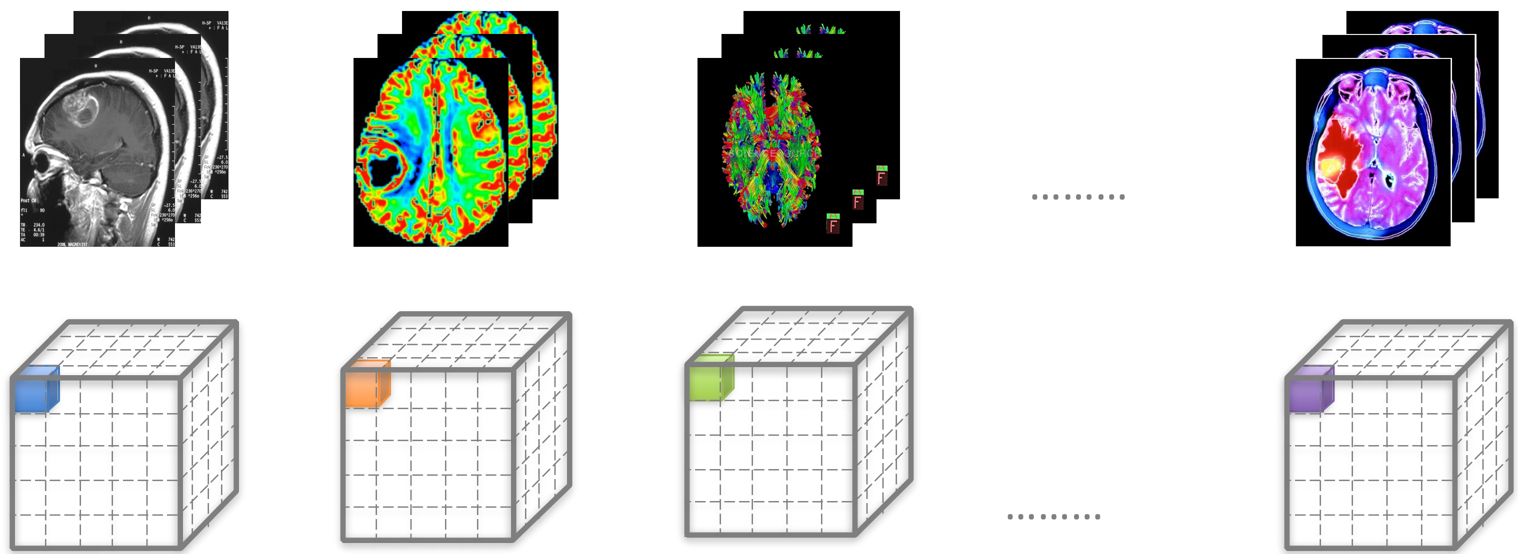

Feature F$_1$ F$_2$ F$_3$ F$_N$

$$v = v(x, y, z)$$

Spatial domain $\Re^3$

$$v = v(F_1, F_2, F_3, \ldots F_N)$$

Features domain $\Re^N$

$$v = v(F_1(t), F_2(t), F_3(t), \ldots F_N(t))$$

Time domain $\Re^1$

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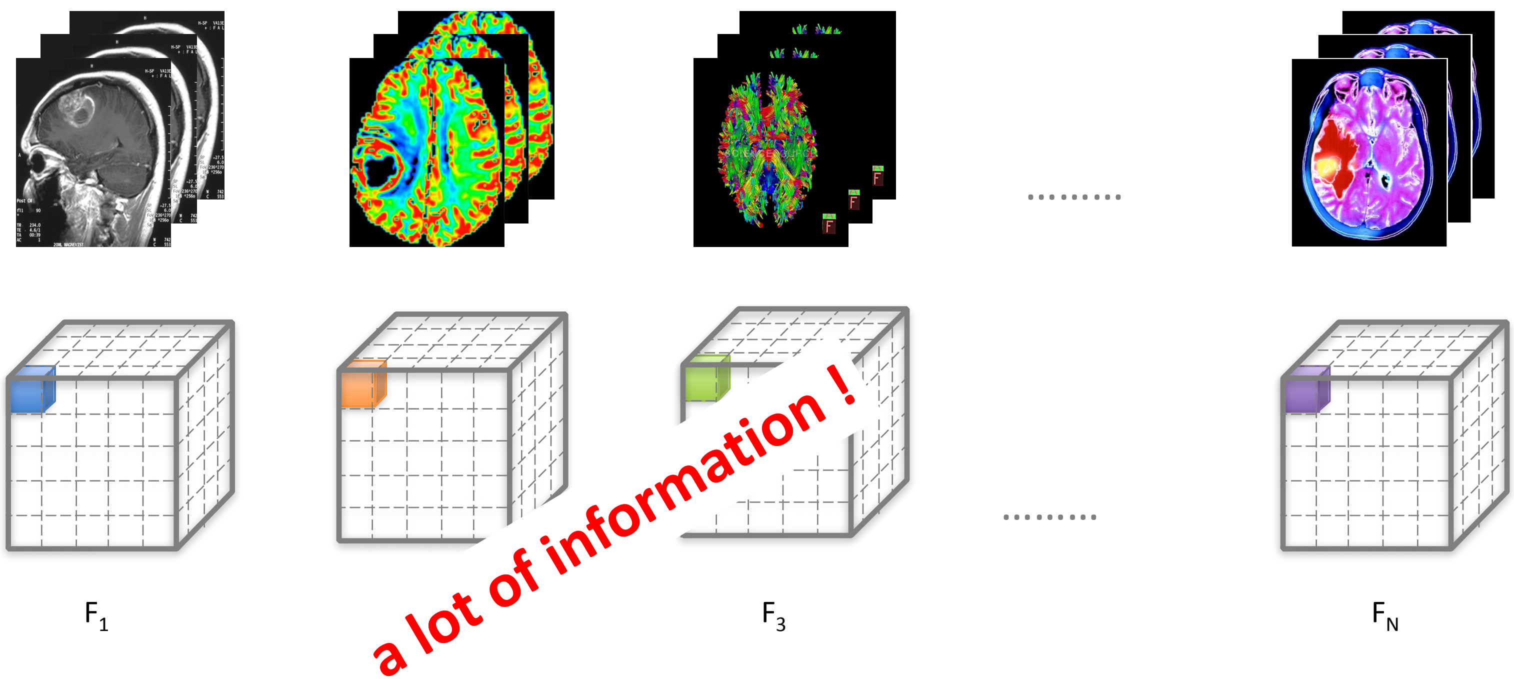

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Features domain $\Re^N$

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Time domain $\Re^1$

How to keep into account all these information?

…it isn't a co-registration problem!

Data Integration

complexity

Spatial domain $\mathfrak{R}^3$

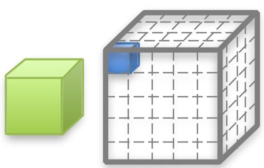
Spatial domain $\mathfrak{R}^3$

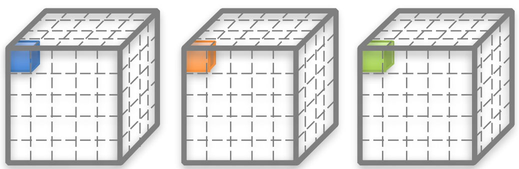
Features domain $\mathfrak{R}^N$

Spatial domain $\mathfrak{R}^3$

Features domain $\mathfrak{R}^N$

Time domain $\mathfrak{R}^1$





Shape analysis

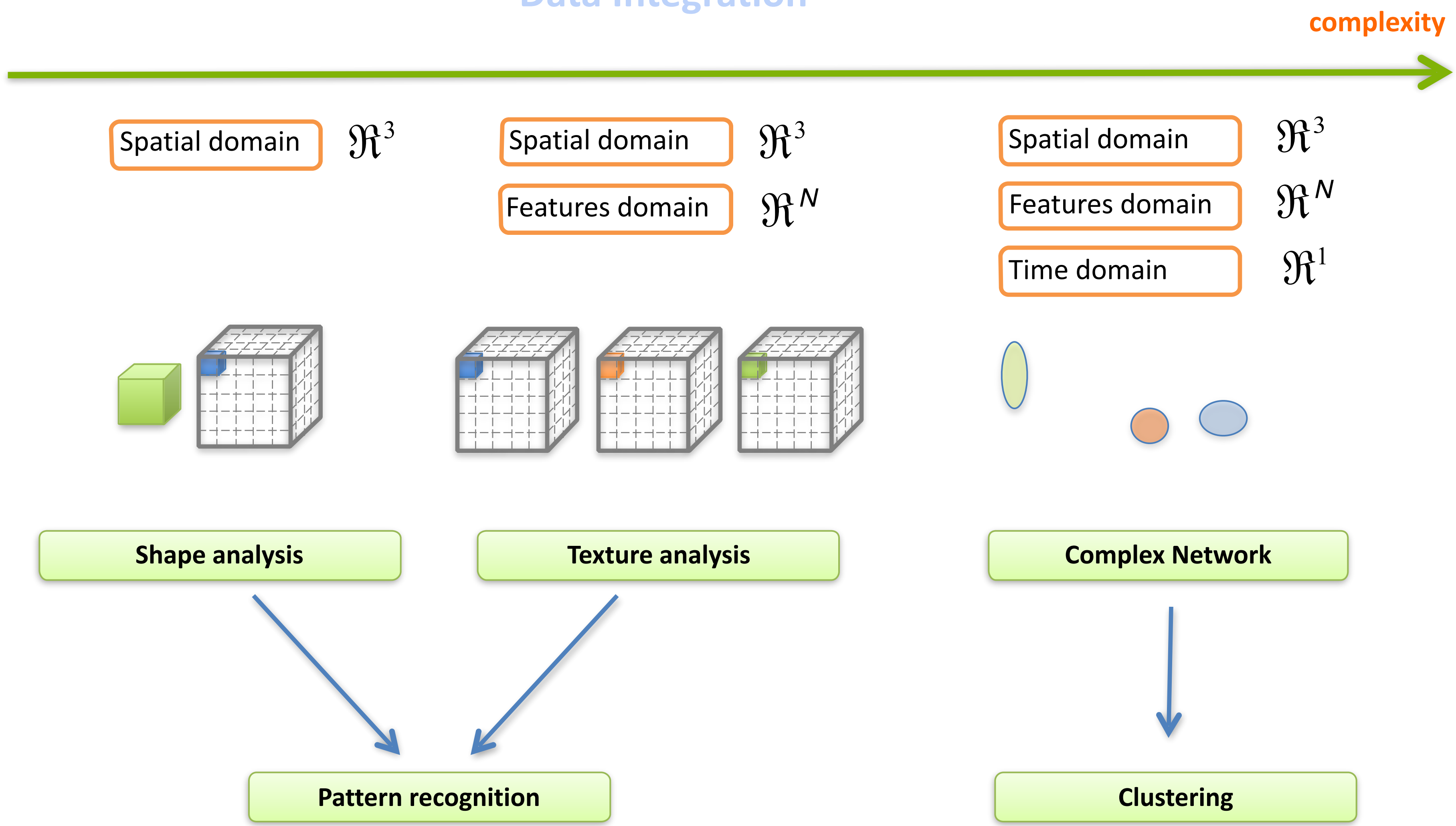
Texture analysis

Complex Network

Pattern recognition

Clustering

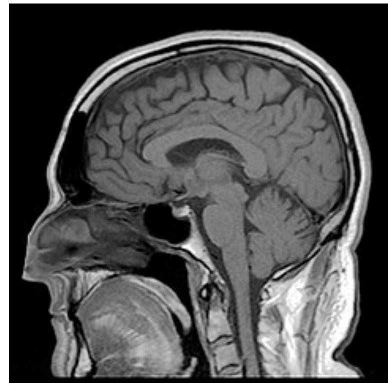
Data Integration



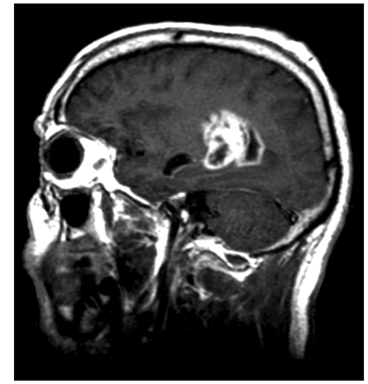
What is our goal?

The diagnosis of a suspected lesion faces two basic problems:

1 **detection** of the suspected lesion



healthy brain

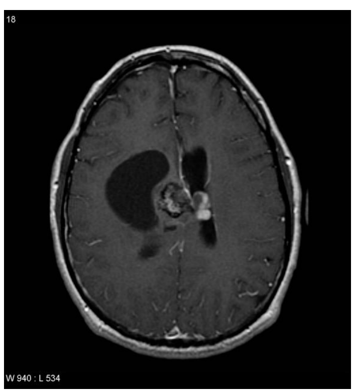


glioma

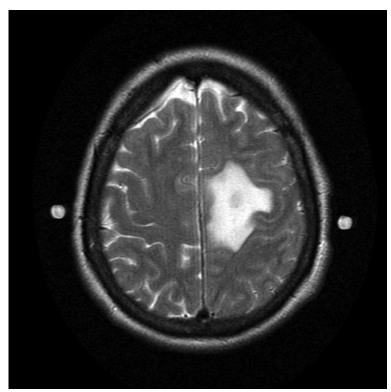
disease

yes no

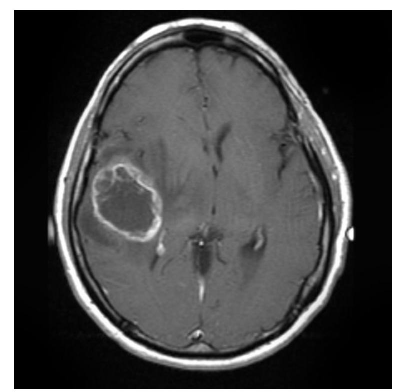
2 **classification** of the lesion



Pilocytic astrocytoma



anaplastic astrocytoma



glioblastoma multiforme

disease

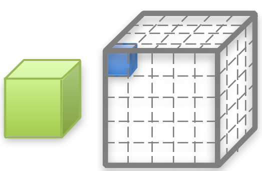
grade

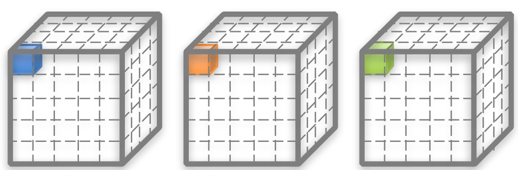
Data Integration

Spatial domain $\Re^3$

Spatial domain $\Re^3$

Features domain $\Re^N$



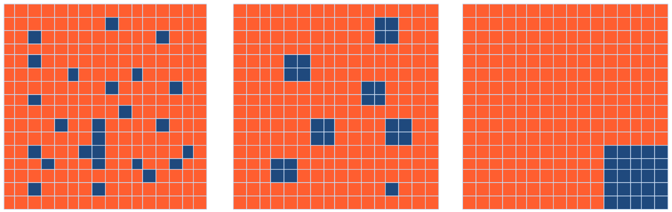


Shape analysis

- perimeter
- volume
- surface area
- compactness

Texture analysis

- histogram → 6 moments of the normal distribution: mean, st.dev., etc.
- fractal dimension
- lacunarity →
- Fourier transf.



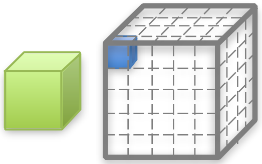
Same number of lacunas (25) but three different values of Λ ($\Lambda_1 > \Lambda_2 > \Lambda_3$)

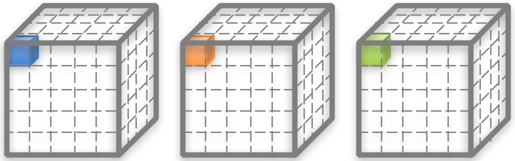
Data Integration

Spatial domain $\Re^3$

Spatial domain $\Re^3$

Features domain $\Re^N$





Shape analysis

Texture analysis

perimeter

volume

surface area

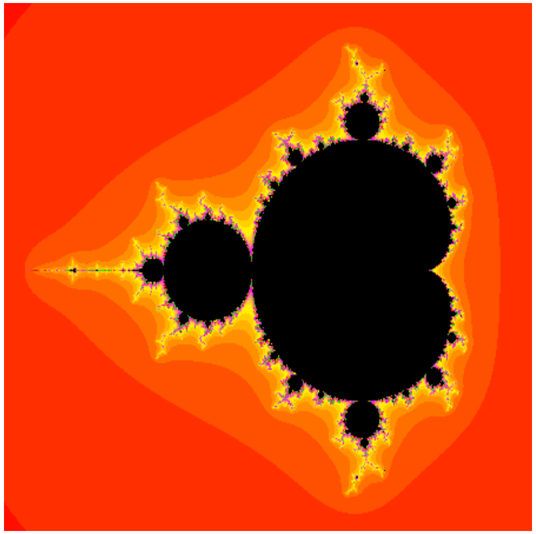
compactness

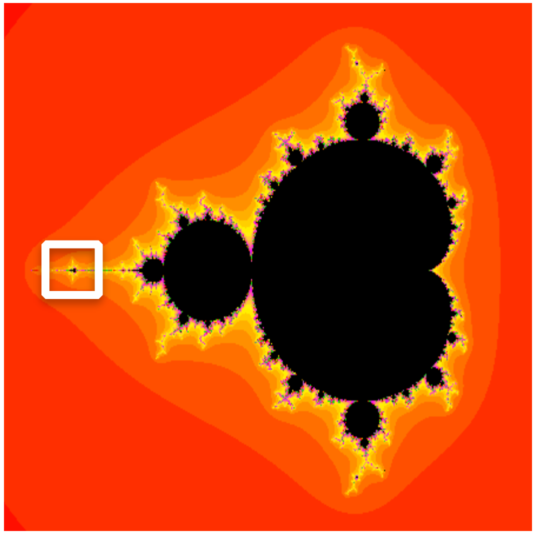
histogram

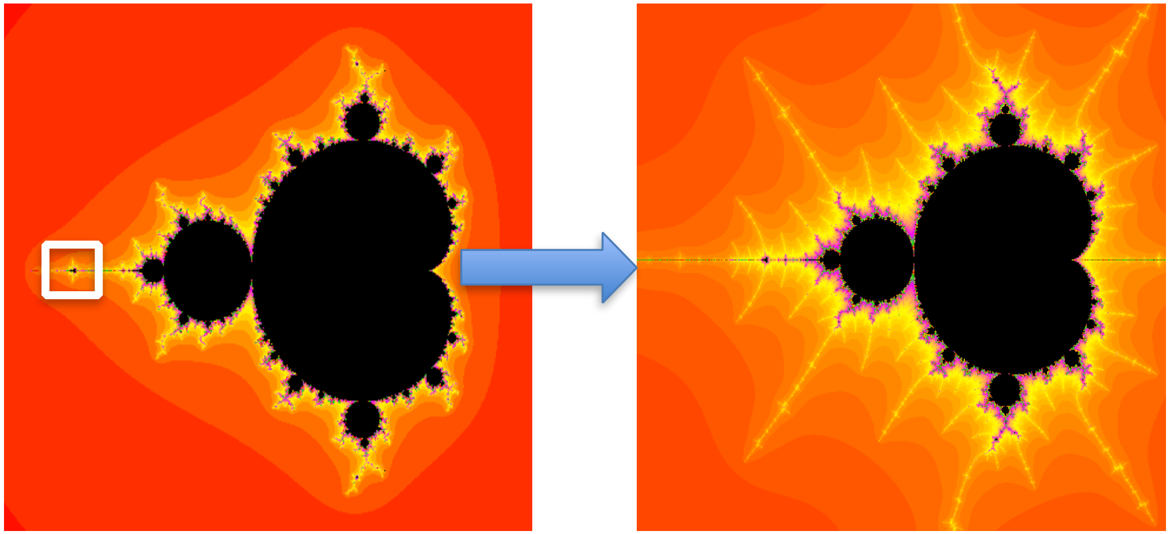
fractal dimension

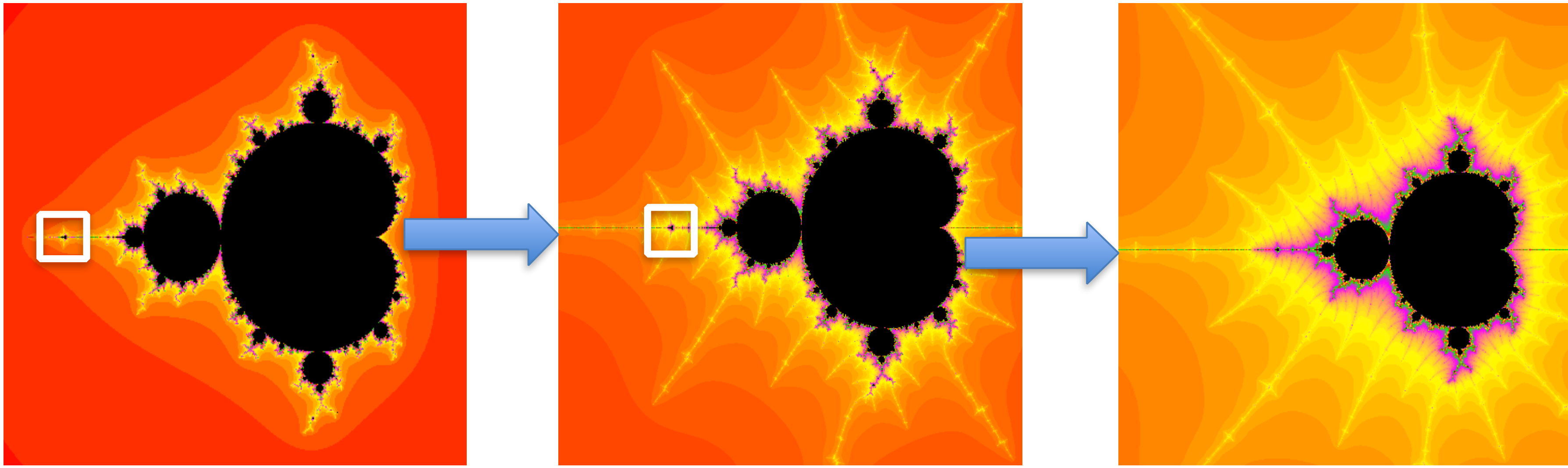
lacunarity

Fourier transf.

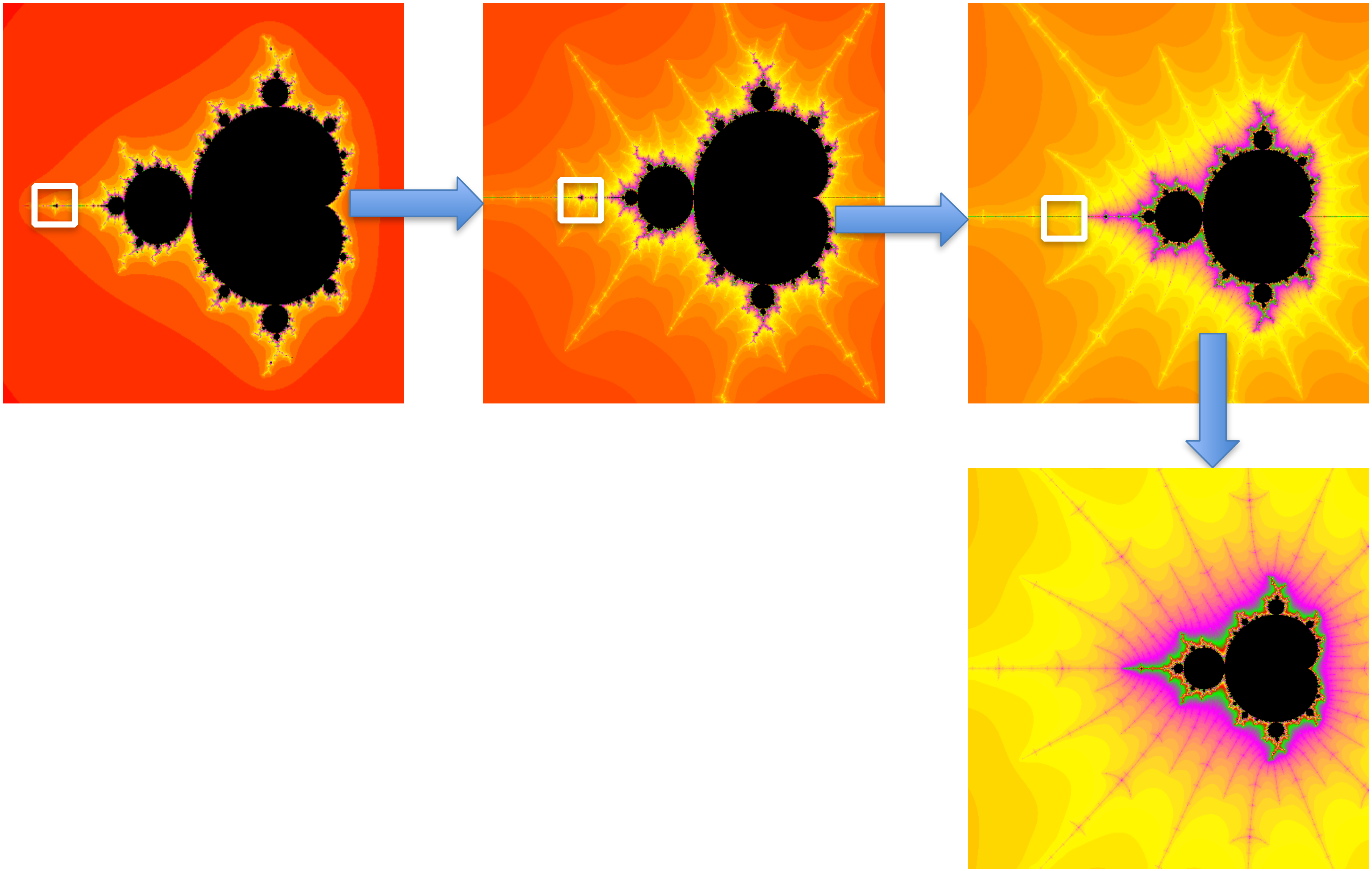








Fractal Dimension



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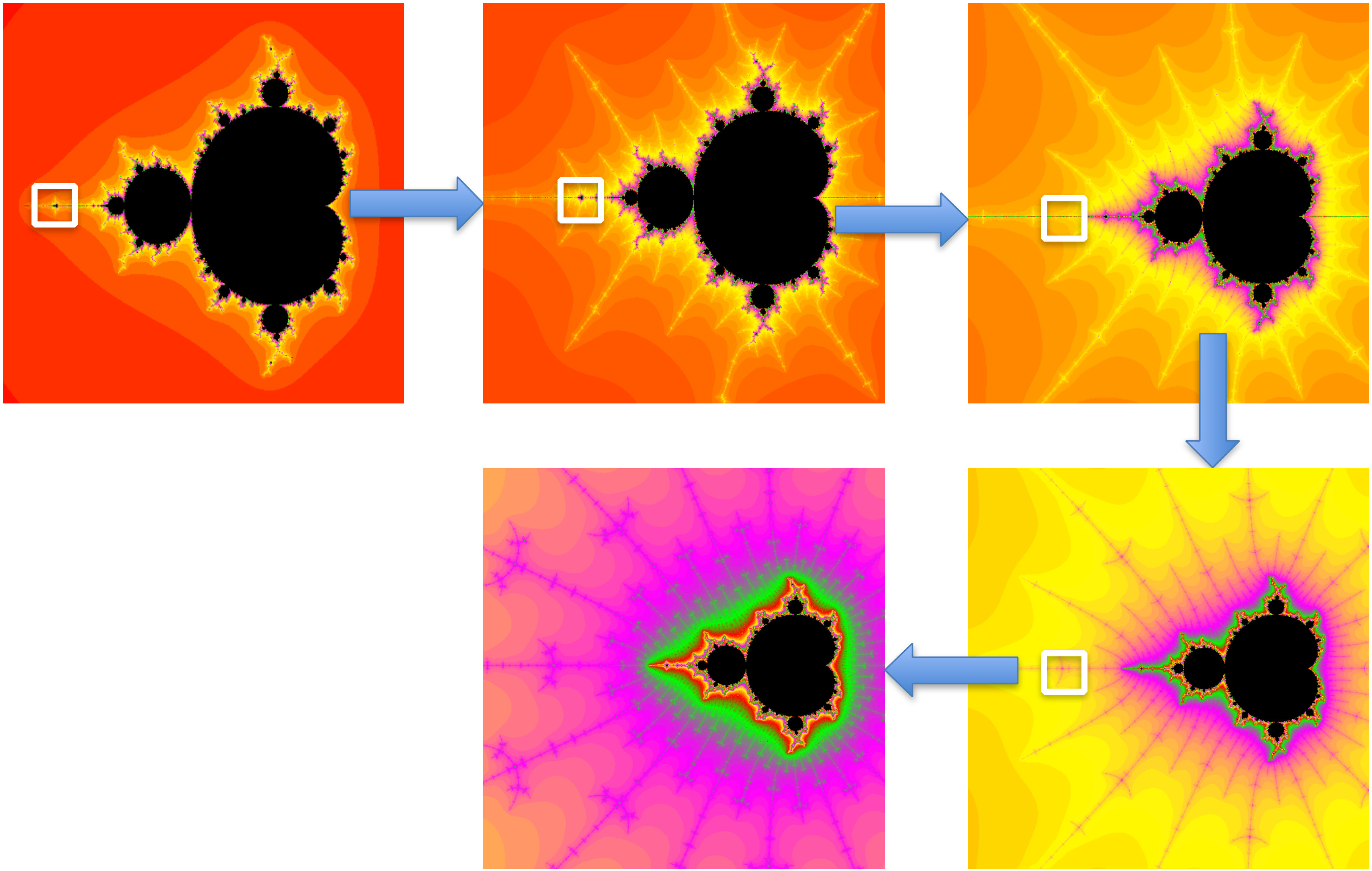
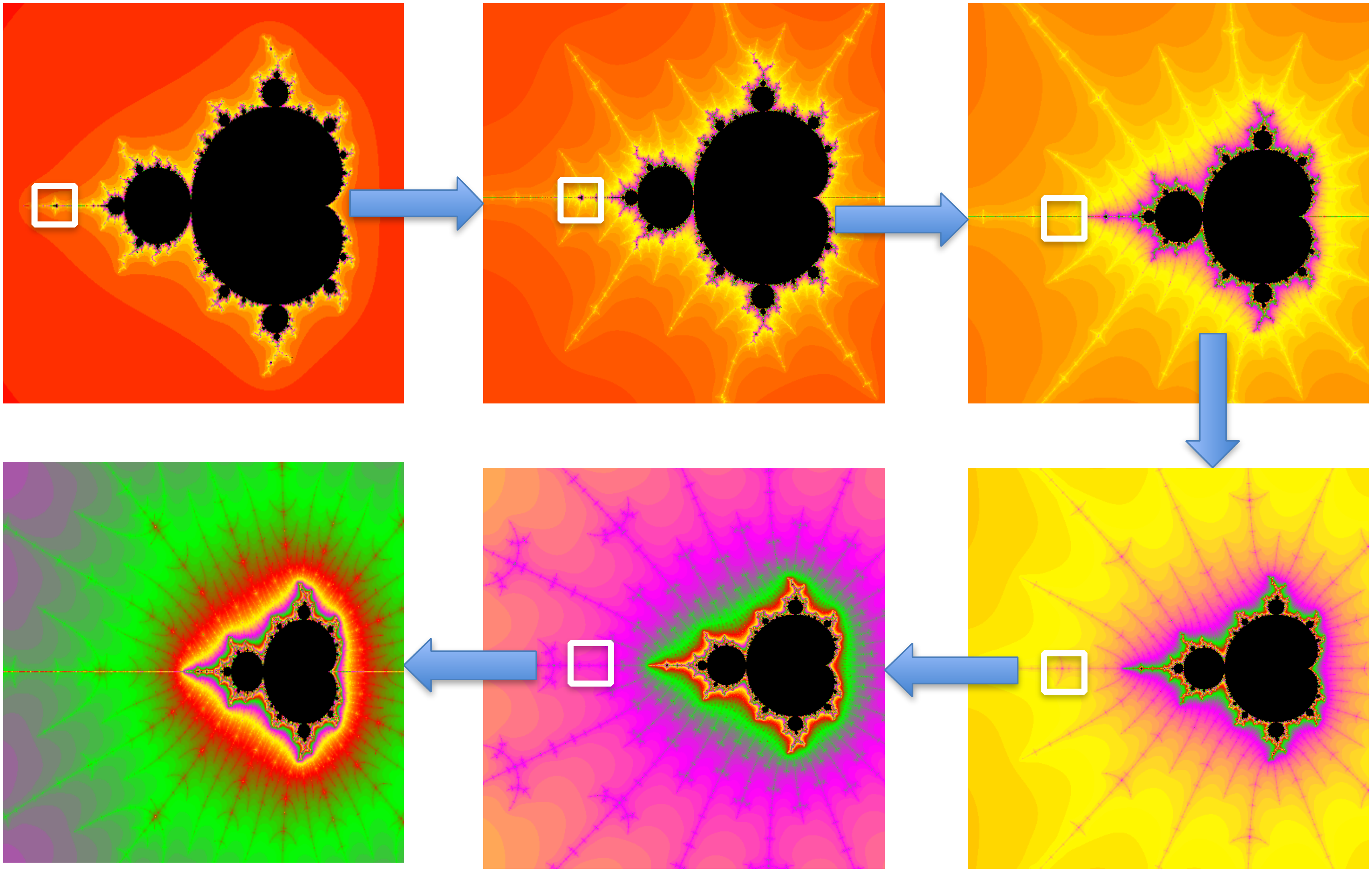
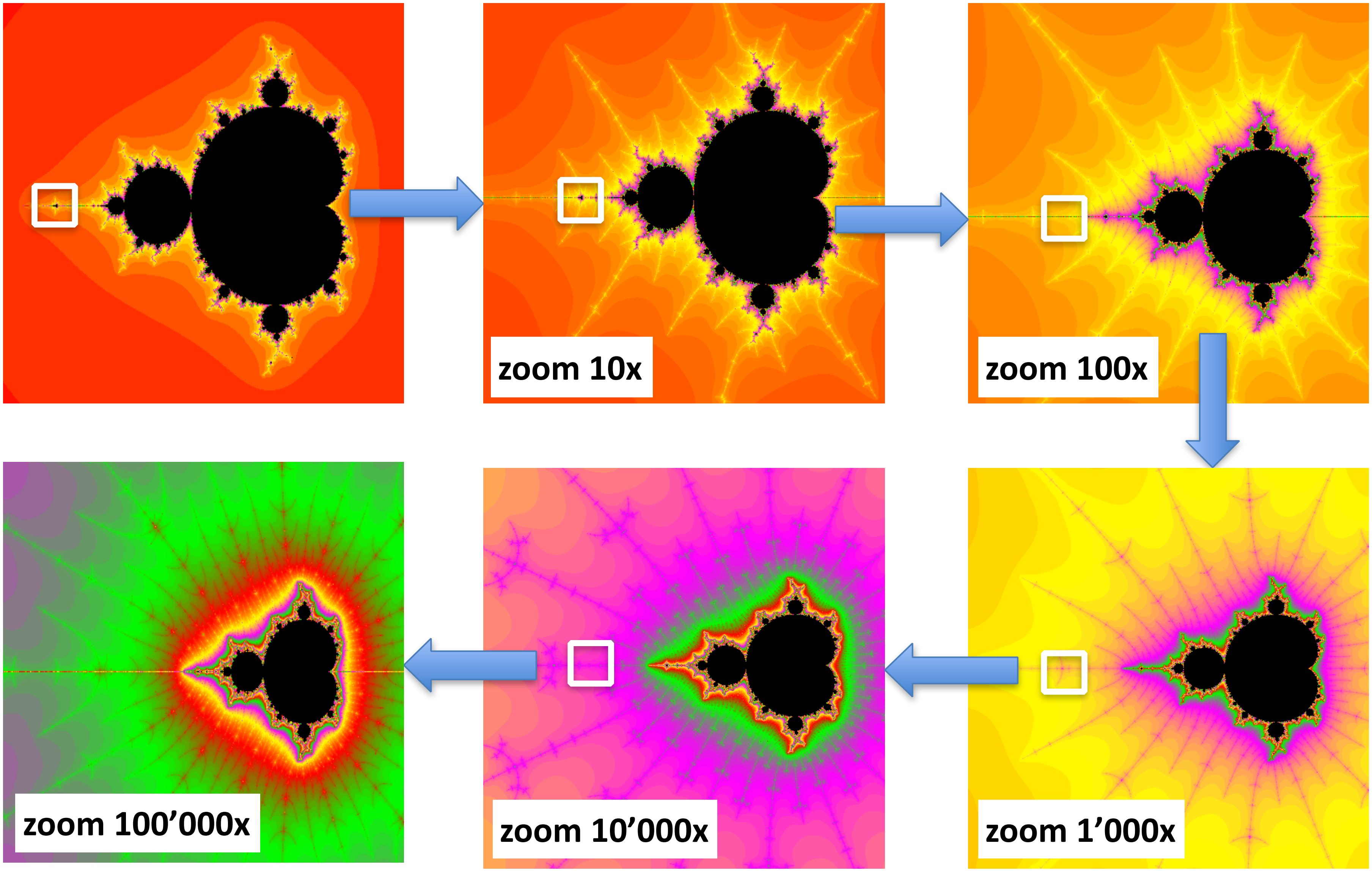
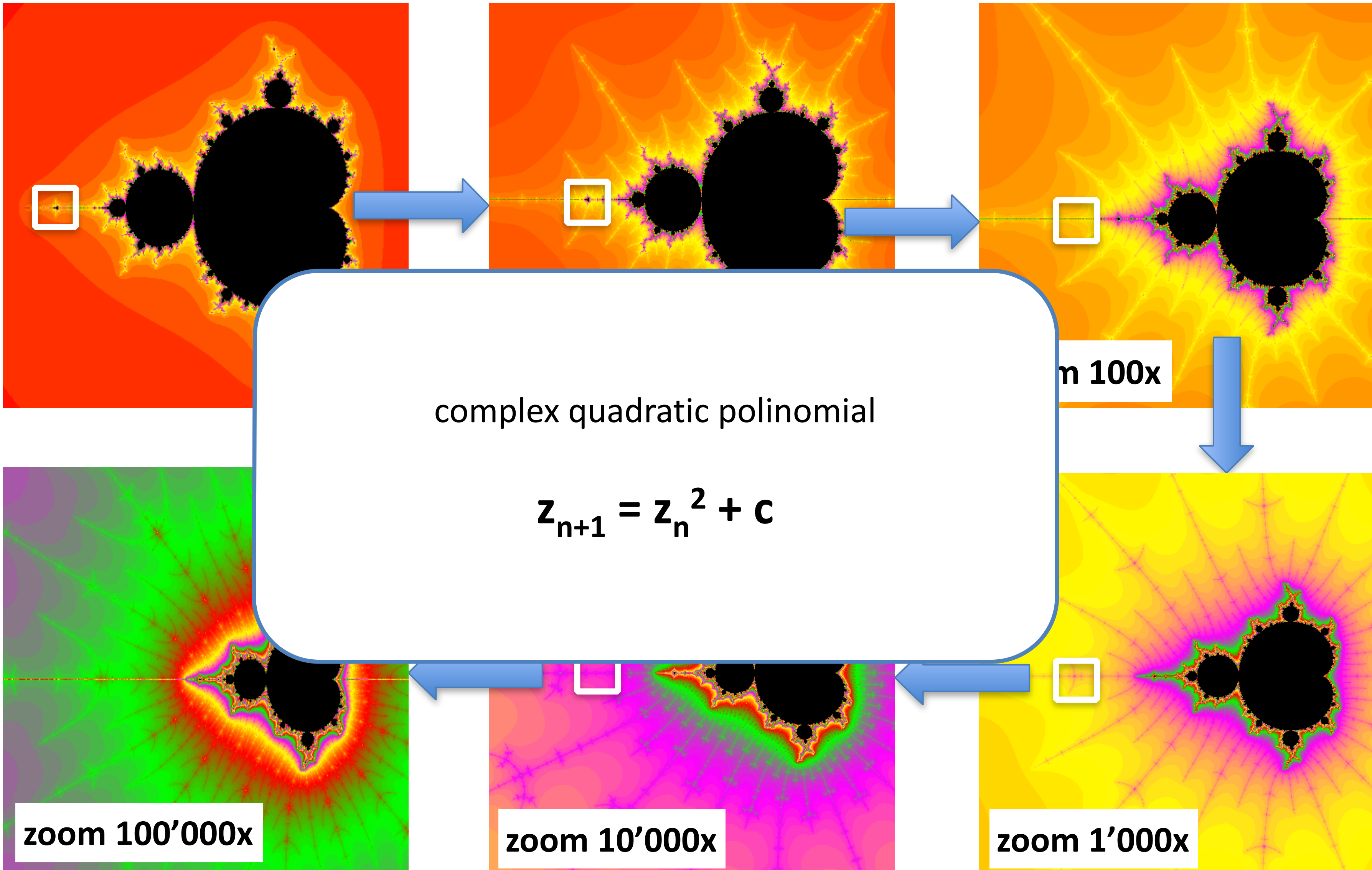


Fractal Dimension



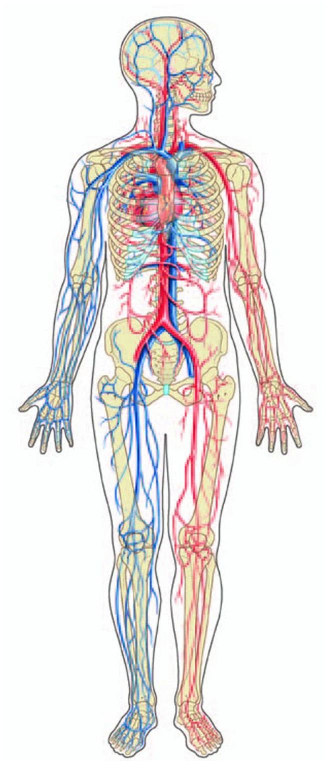

zoom 10x
zoom 100x
zoom 1'000x
zoom 10'000x
zoom 100'000x



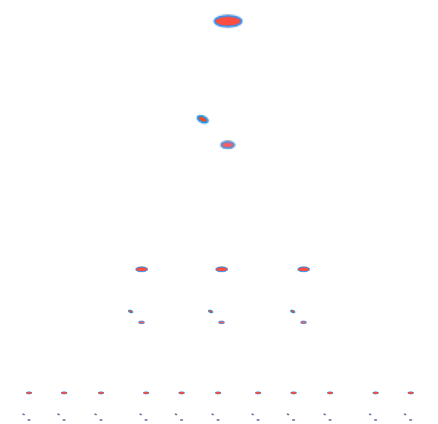
complex quadratic polinomial

$$z_{n+1} = z_n^{\,2} + c$$

This **self-similar fractal structure** is the optimal model developed by Nature to accomplish those tasks



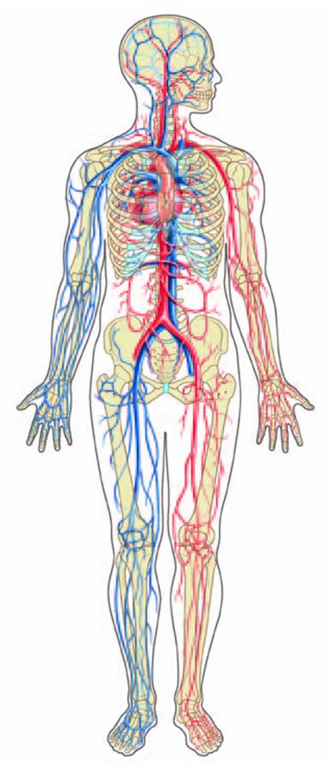
- Distribute the blood to **several organs**
- Delivery **different quantity** of blood
- Transform the blood flow from pulsed to **continuous**
- **Remove the waste** (metabolites, CO_2,...)
- It should **work continuously** for 80 years, longer is better!

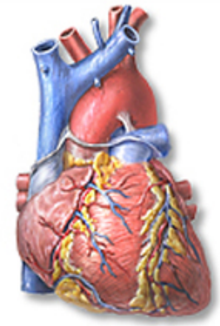


$$D = \lim_{r \to \infty} \frac{\log N(r)}{-\log\left(\frac{1}{r}\right)}$$

D = dimension
N = number of self similarity (3)
r = reduction factor (2)

Vascular system





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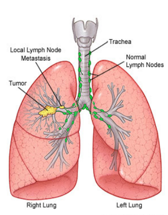
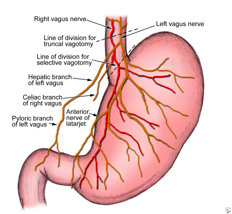
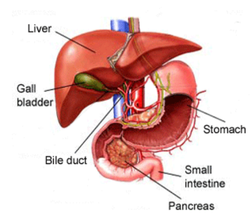
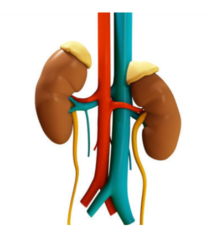






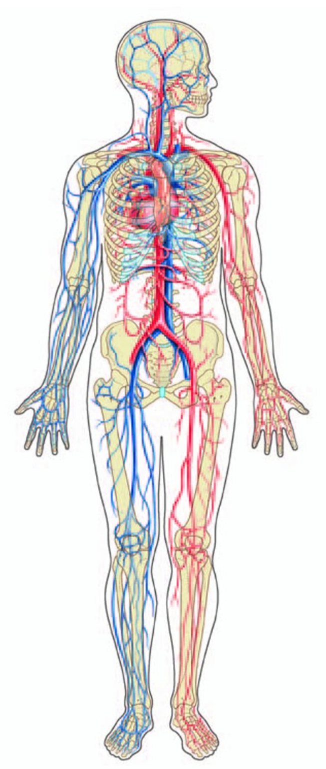


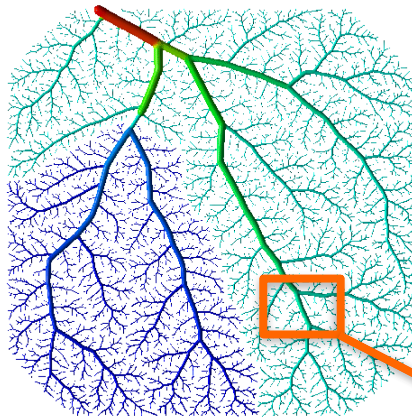
…

Perfusion and Fractals

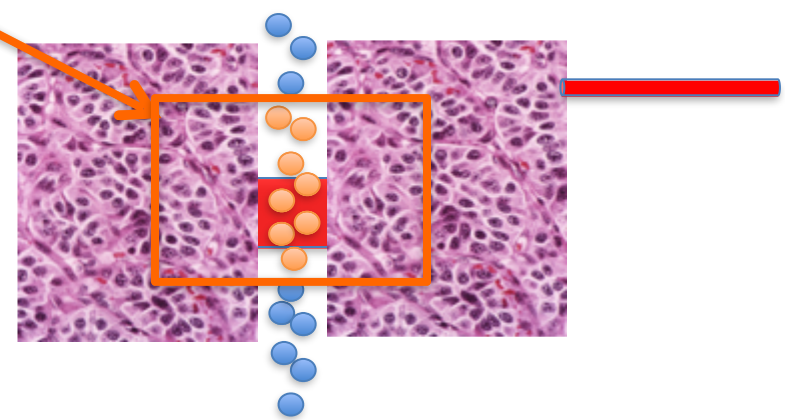
Vascular system

vessel tree





Blood stream
(blood-pool agent,
radiotracer,
contrast agent,…)



non-permeable healthy vessel

perfusion

BF

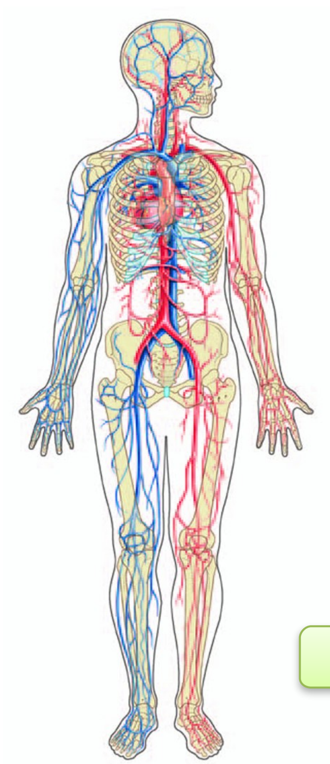
volume of blood in the voxel (BV)

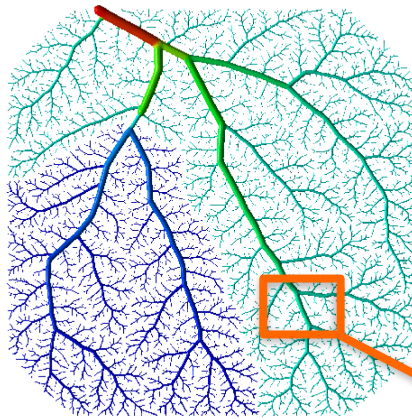
velocity of the blood in the voxel

Perfusion and Fractals

Vascular system

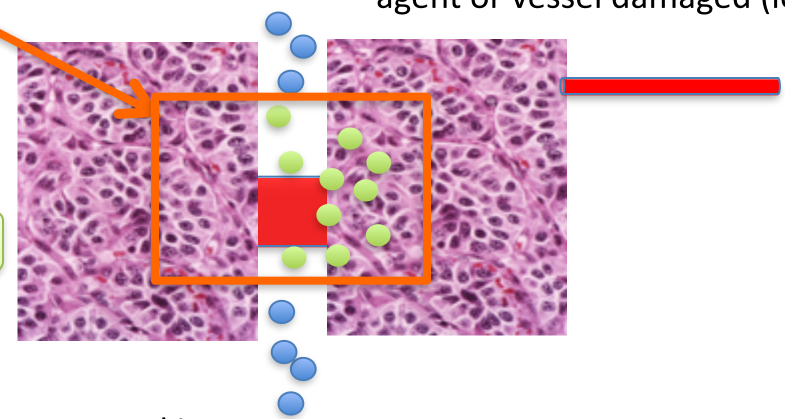
vessel tree





Blood stream
(blood-pool agent,
radiotracer,
contrast agent,…)

extravasation:
vessel permeable to contrast-agent or vessel damaged (leaky)



permeable non healthy vessel

permeability → blood transfer constant from vascular compartment to extracellular space

extravasation → volume of blood extravasated into extracellular space

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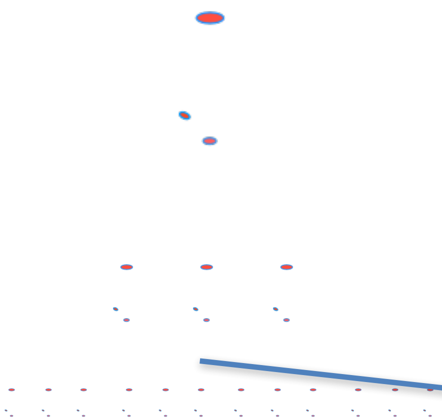
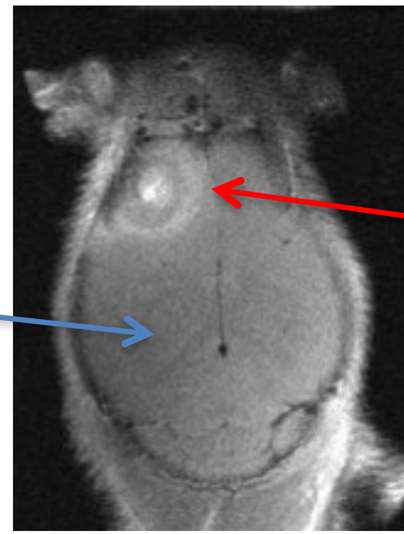
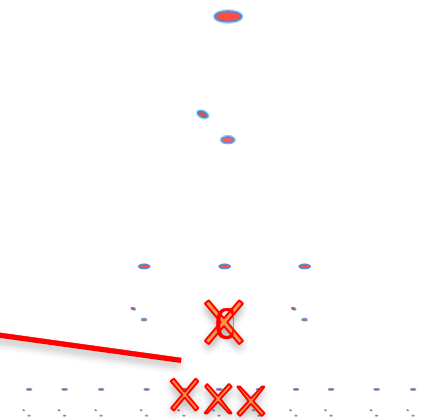
Tumor vs healthy tissue

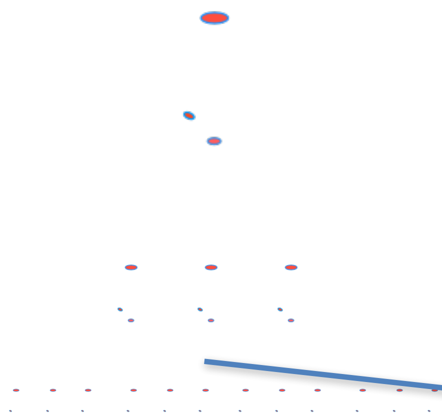


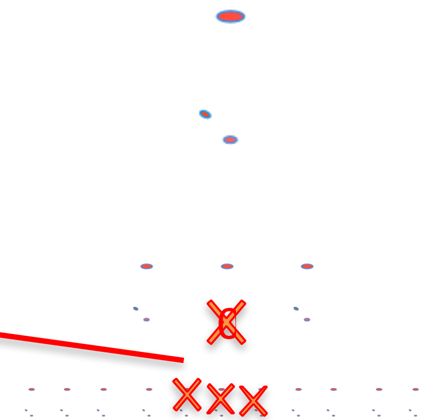




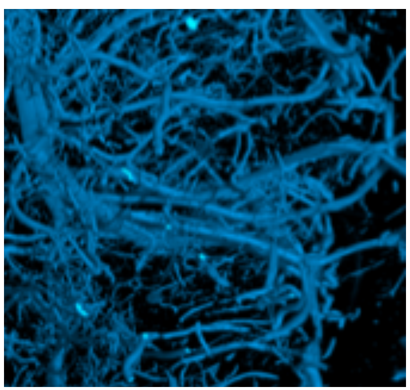
Murine glioma GL261
T1-w MRI – CA: Gd-Dota

Tumor vs healthy tissue

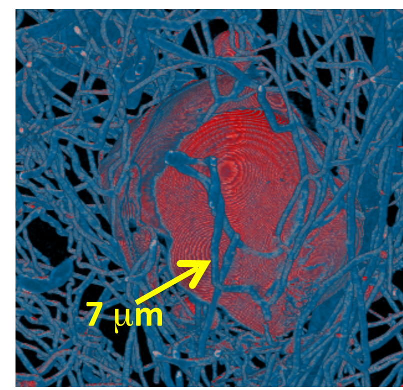




Murine glioma GL261
T1-w MRI – CA: Gd-Dota



SRμCT (absorption contrast)
Brain sample casted with **PU4ii**

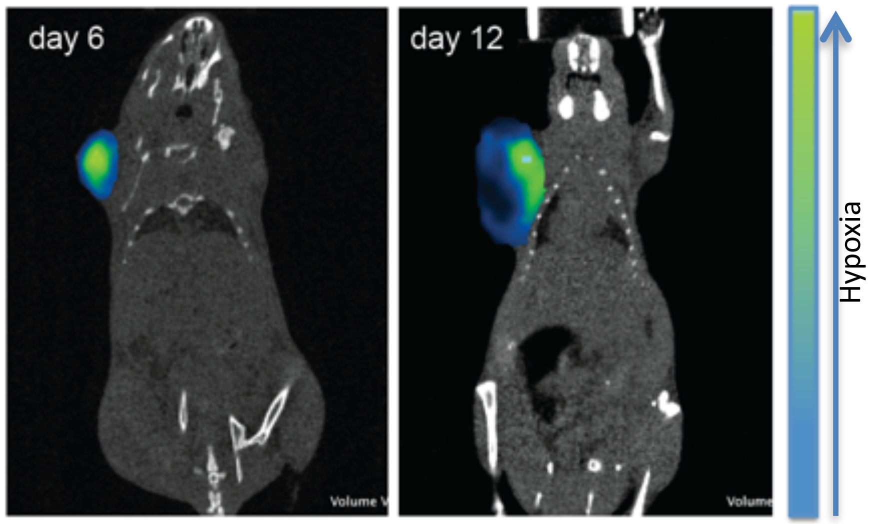


SRμCT (absorption contrast)
Tumor sample casted with **PU4ii**

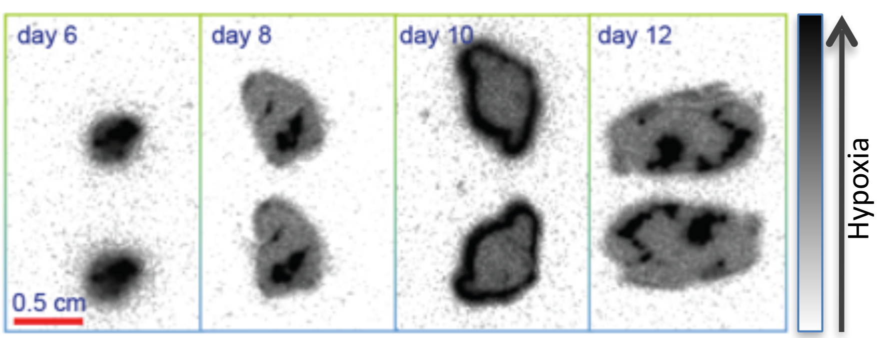
More **organized** structure of vessel network
Fractal Dimension = 2.23 ± 0.02

Chaotic structure of vessel network
Fractal Dimension = 2.78 ± 0.03

Hypoxia evaluation



18F-MISO PET/CT C51 murine tumor



Autoradiography

Collaboration with: *Steffi Lehmann (IBT, ETHZ), Michael Höner (AIC-PET, ETHZ)*

Hypoxia

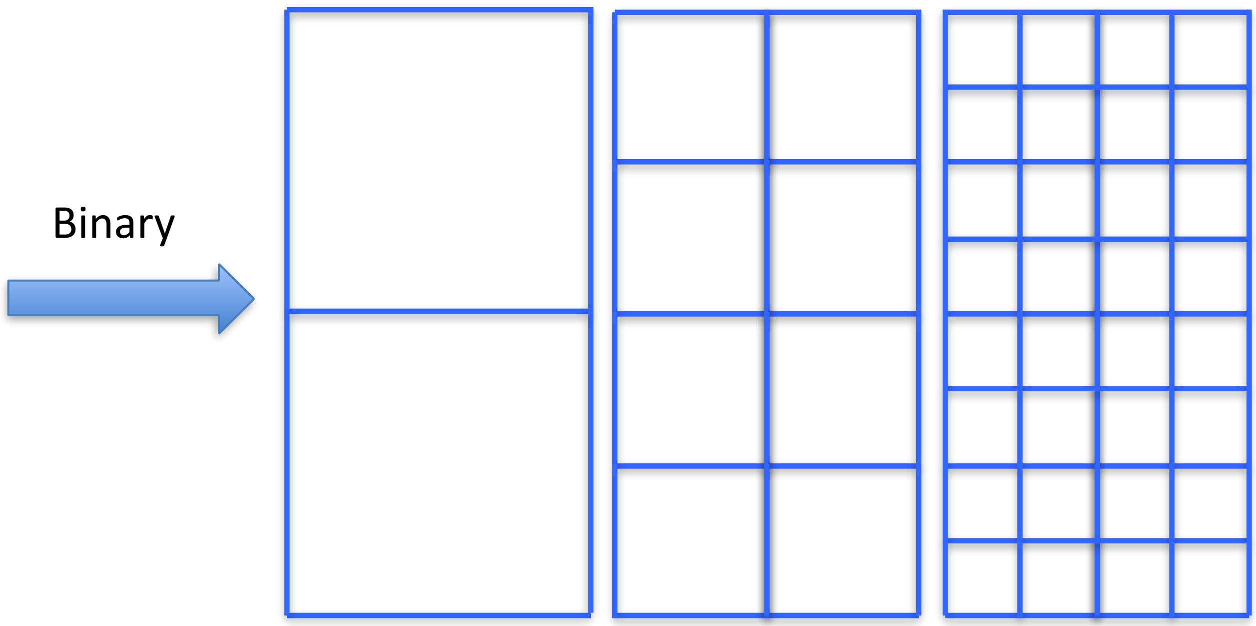
Hypoxia level is a **trigger** of the angiogenesis

^{18}F-MISO diffuse into the cells:

- **aerobic condition**: the radical compound is reoxidized and diffuse out of the cells
- **hypoxic condition**: it is bind to intracellular macro-molecules and accumulate inside the cell.

Heterogeneous distribution of ^{18}F-MISO during tumor growth

Box Counting - BC



..... $s \rightarrow p$

FD = Fractal Dimension

N(s) = number of box needed to cover the image

s = size of the box

p = pixel dimension

$$D = \lim_{s \to p} \frac{\log N(s)}{-\log(s)}$$

Russel, D., Hanson, J., Ott, E., 1980. ***Dimension of strange attractors***. Physical Review Letters 45 (14), 1175–1178

Benoit B. Mandelbrot , ***The Fractal Geometry of Nature***, Spektrum Akademischer Verlag; 1990

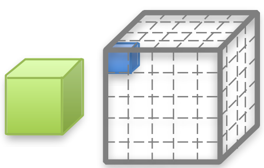
Data Integration

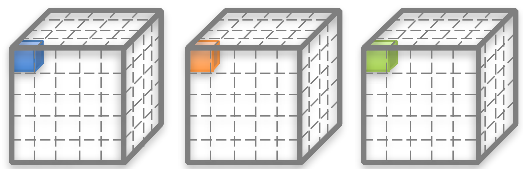
complexity

Spatial domain $\Re^3$

Spatial domain $\Re^3$

Features domain $\Re^N$

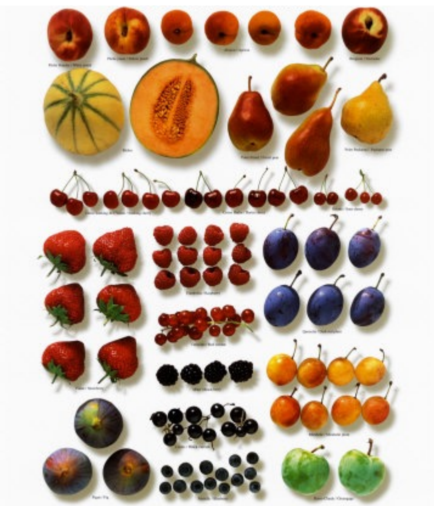




Shape analysis

Texture analysis

Pattern recognition



Black BOX

 peach

 prune

 melon

 apple

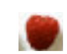
 sliced melon

 cassis

 pear

 strawberry

 fig

 raspberry

 apricot

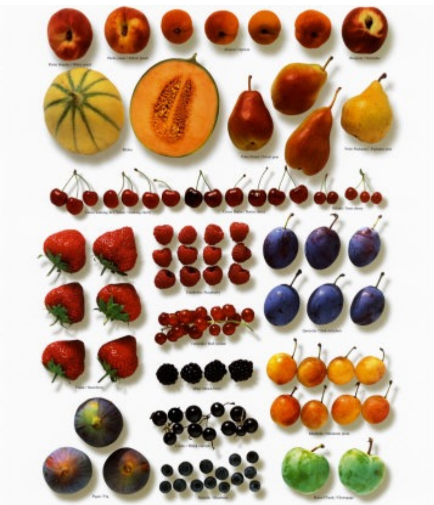
 blueberry

 cherries

 blackberry

 red currant

input



2D image

Pattern recognition process

Feature extraction → Feature analysis → Pattern classification

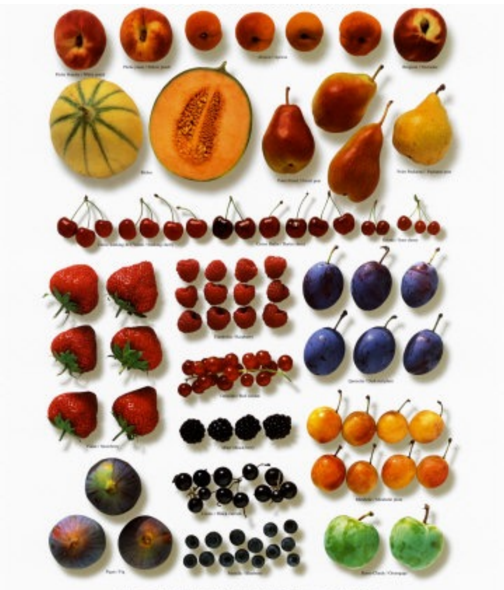
Application-specific feedback

Feature extraction

Goal 1: **individuate** the objects **inside** the image

Shape analysis

Original image



D(x,y,z)

Objects: A, B, ….N

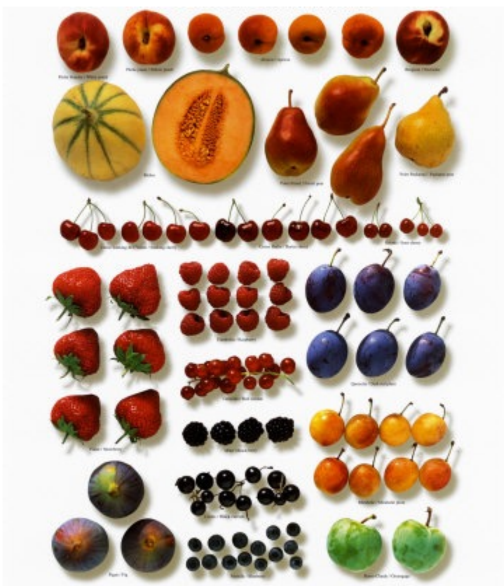
Feature extraction

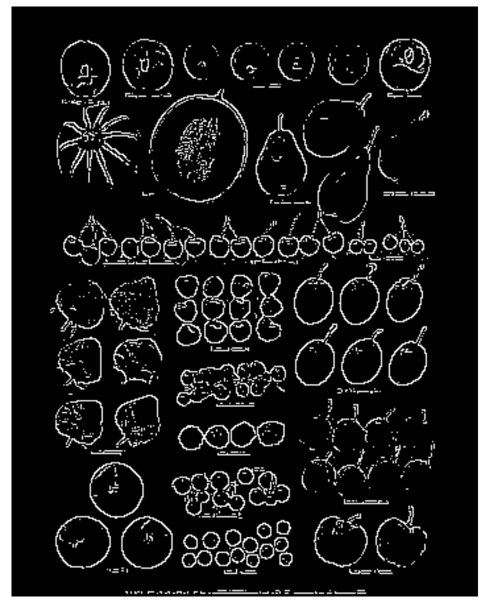
Goal 1: **individuate** the objects **inside** the image → **Shape analysis**

Original image

Contours

Mask





D(x,y,z)

C(x,y,z)

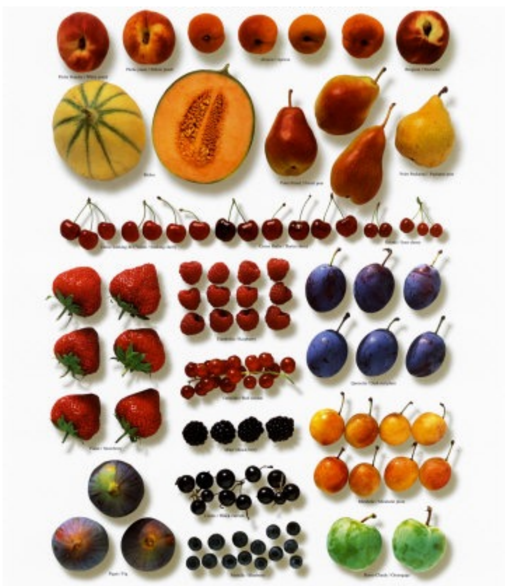
M(x,y,z)

Objects: A, B, ….N

Feature extraction

Goal 1: **individuate** the objects **inside** the image → **Shape analysis**

Original image

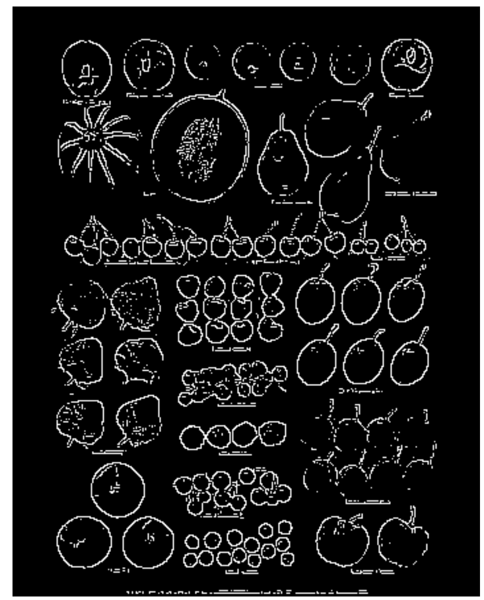


D(x,y,z)

Feature extraction operators

F_C, F_M, …

Contours



C(x,y,z)

Contour = F_C (D)

Mask

M(x,y,z)

Mask = F_M (D)

Objects: A, B, ….N

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Feature analysis

Goal 2: evaluate **morphological parameters** of each extracted objects (A, B ,..N)

SHAPE

- perimeter
- volume
- surface area
- compactness
- ....

TEXTURE

- histogram
- fractal dimension
- lacunarity
- Fourier transf.
- ....

Objects with different shapes.

Objects with similar shapes but different texture

morphological parameters matrix

$\mathbf{A}(S_A, V_A, C_A, (m_1\ m_2\ \dots\ m_6)_A, FD_A, \Lambda_A, \dots)$

$\mathbf{B}(S_B, V_B, C_B, (m_1\ m_2\ \dots\ m_6)_B, FD_B, \Lambda_B, \dots)$

...

$\mathbf{N}(S_n, V_n, C_n, (m_1\ m_2\ \dots\ m_6)_n, FD_n, \Lambda_n, \dots)$

$\downarrow$

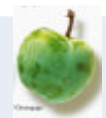
feature space IR^n

n = number of evaluated features

Pattern classification

Goal 3: **automatically classify** the extracted objects on the basis of their features information.

At this level we have extracted those objects in the features space. At this stage we can **only say** that the **object are different**.

			...	**N**
surface	S_A	S_B		S_n
volume	V_A	V_B		V_n
compactness	C_A	C_B		C_n
histogram moments	$(m_1\ m_2\ \dots\ m_6)_A$	$(m_1\ m_2\ \dots\ m_6)_B$		$(m_1\ m_2\ \dots\ m_6)_n$
fractal dimension	FD_A	FD_B		FD_n
lacunarity	Λ_A	Λ_B		Λ_n
….				

Clustering measures

Distance measures

Similarity measures

Find if:

- **A, B, …N** are statistically **identical**
- **A, B, …N** are statistically **different**

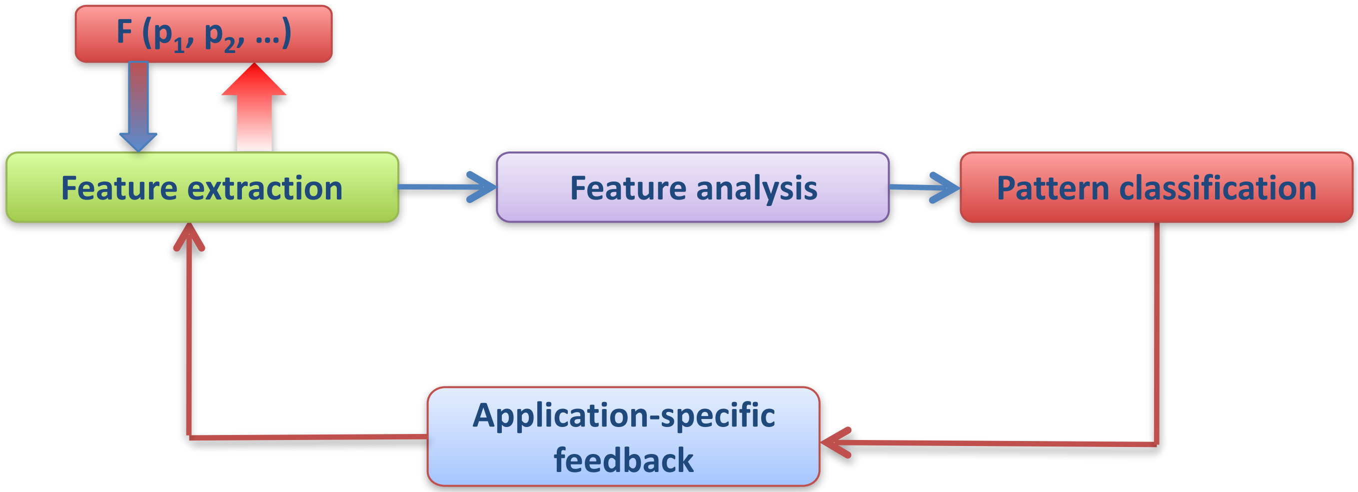
and **quantify** the difference.

Pattern recognition process

F (p_1, p_2, …)

Feature extraction → Feature analysis → Pattern classification

Pattern recognition process

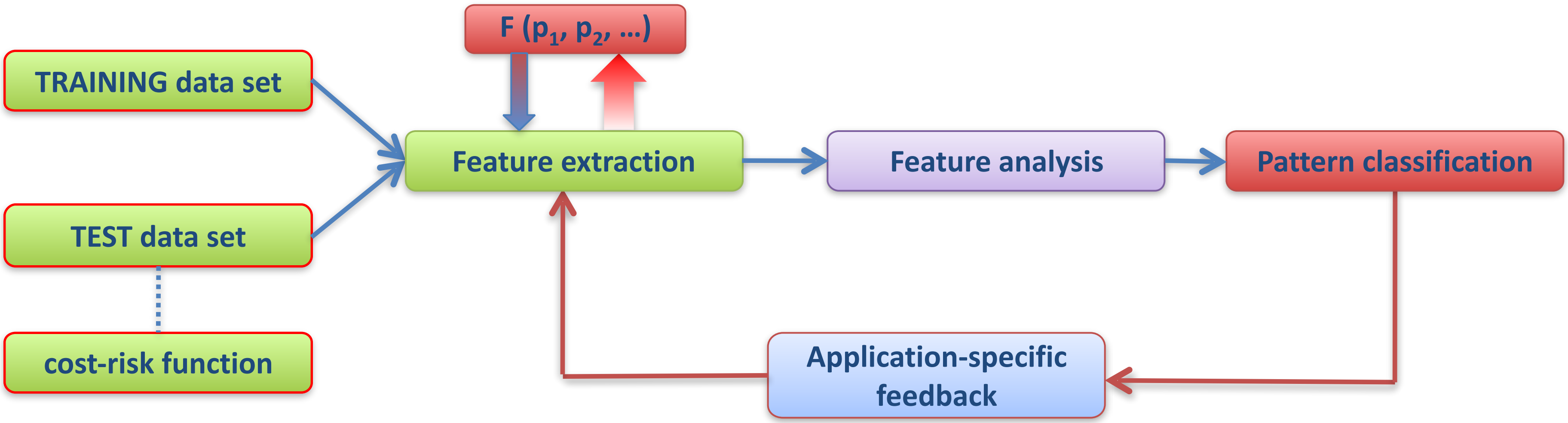


The final **results** from pattern recognition can be used **as input** to **automatically re-define the parameters p_i** of feature extraction operators.

This procedure can be **iteratively repeated** to improve the feature extraction process.

MACHINE LEARNING

Pattern recognition process



The final **results** from pattern recognition can be used **as input** to **automatically re-define the parameters p_i** of feature extraction operators.

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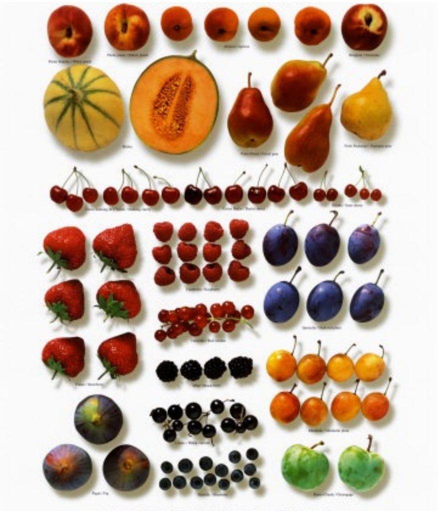
MACHINE LEARNING



Pattern recognition process

 peach

 prune

 melon

 apple

 sliced melon

 cassis

 pear

 strawberry

 fig

 raspberry

 apricot

 blueberry

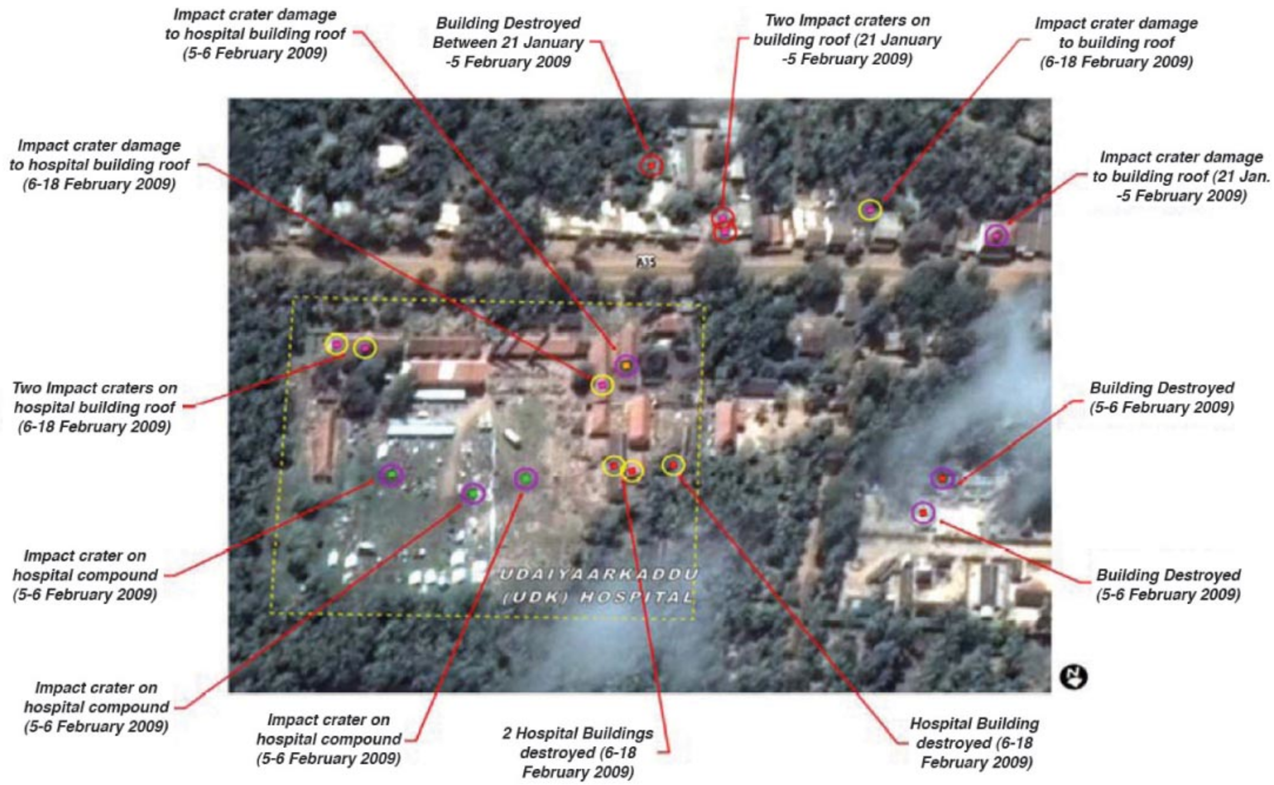
 cherries

 blackberry

 red currant

Military applications

Used to discover enemy targets over satellite maps or check the air raids and bombing

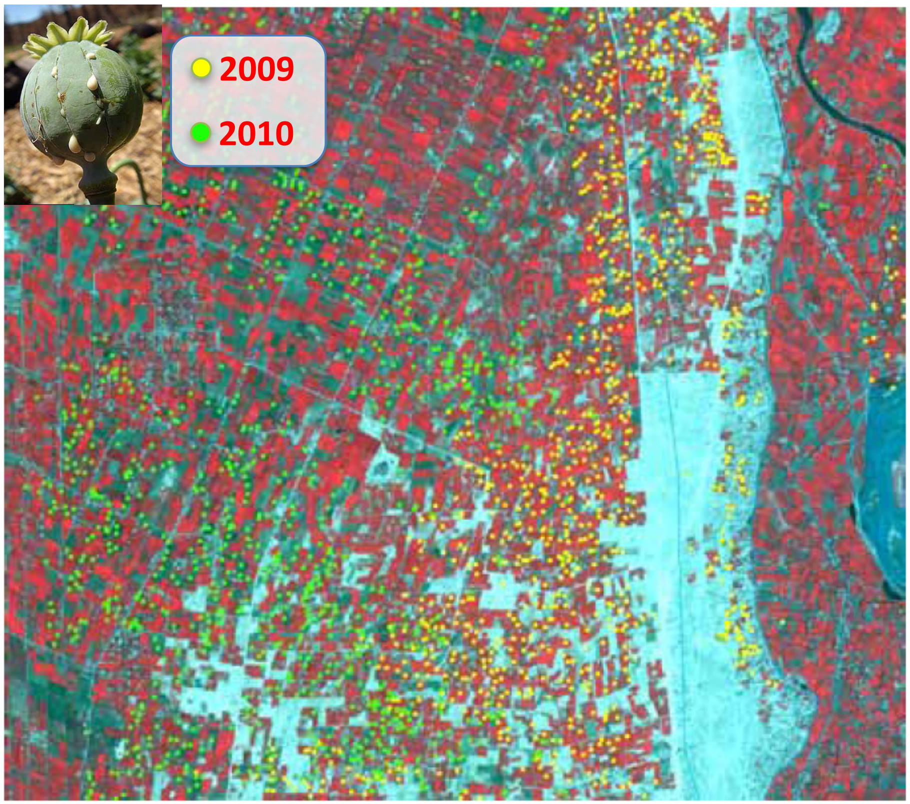


Darusman Report commissioned by UN, Sri Lanka

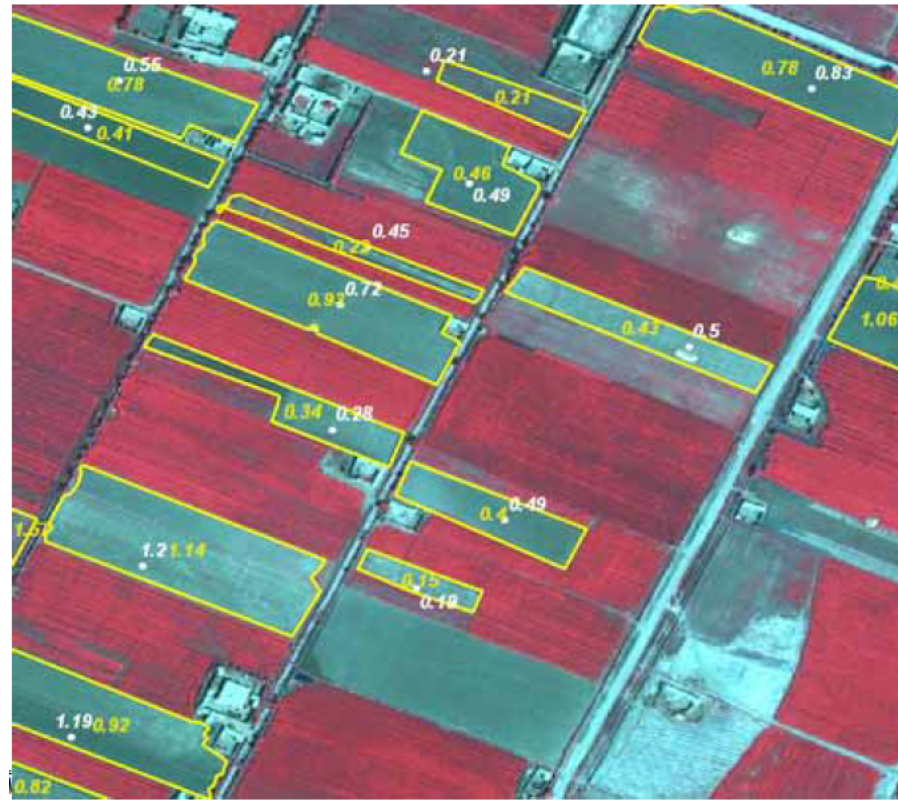
http://www.thesundayleader.lk/wp-content/uploads/2011/04/map.jpg

Opium cultivated areas

Nad Ali district, Hilmand province, Afghanistan



Satellite image with pattern recognition of opium cultivated areas



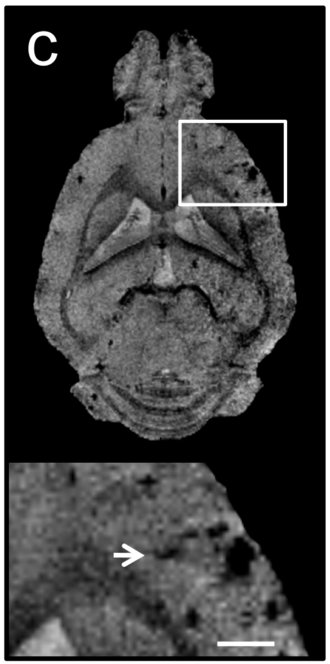
Satellite image with pattern classification (areas in ha) of opium cultivated/eradicated areas

UNODC
United Nations Office on Drugs and Crime

Angela Me,
Afghanistan Opium Survey 2010

Medical applications

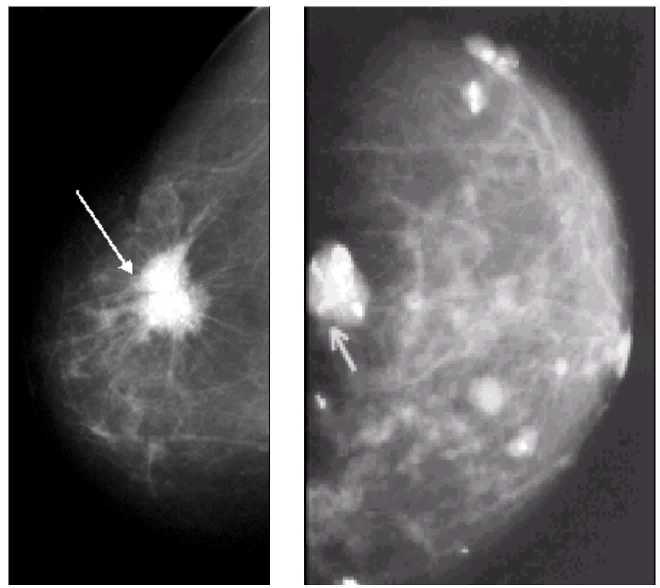
Alzheimer disease



Jan Klohs et al.,
J Cereb Blood Flow Metab. 2011
Aug 17;

Stefan KloÅsppel, et al.,
Brain (2008), 131, 6810689

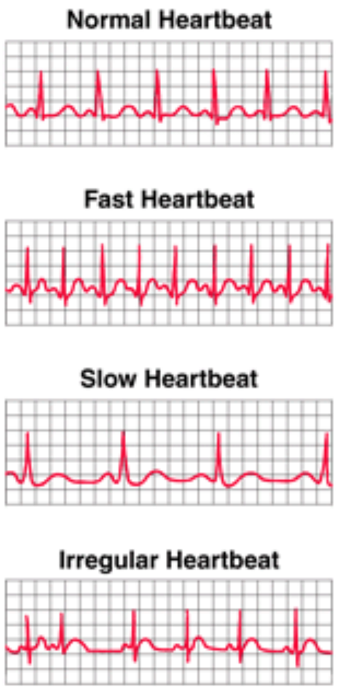
Breast cancer



http://www.szote.u-szeged.hu/radio/emlo/aemlo6a.htm

Gebrim LH, Sao Paulo Med J. 2000 Mar 2;118(2):46-8.

ECG pattern



Desok Kim et al.,
2008 International Conference on
BioMedical Engineering and Informatics

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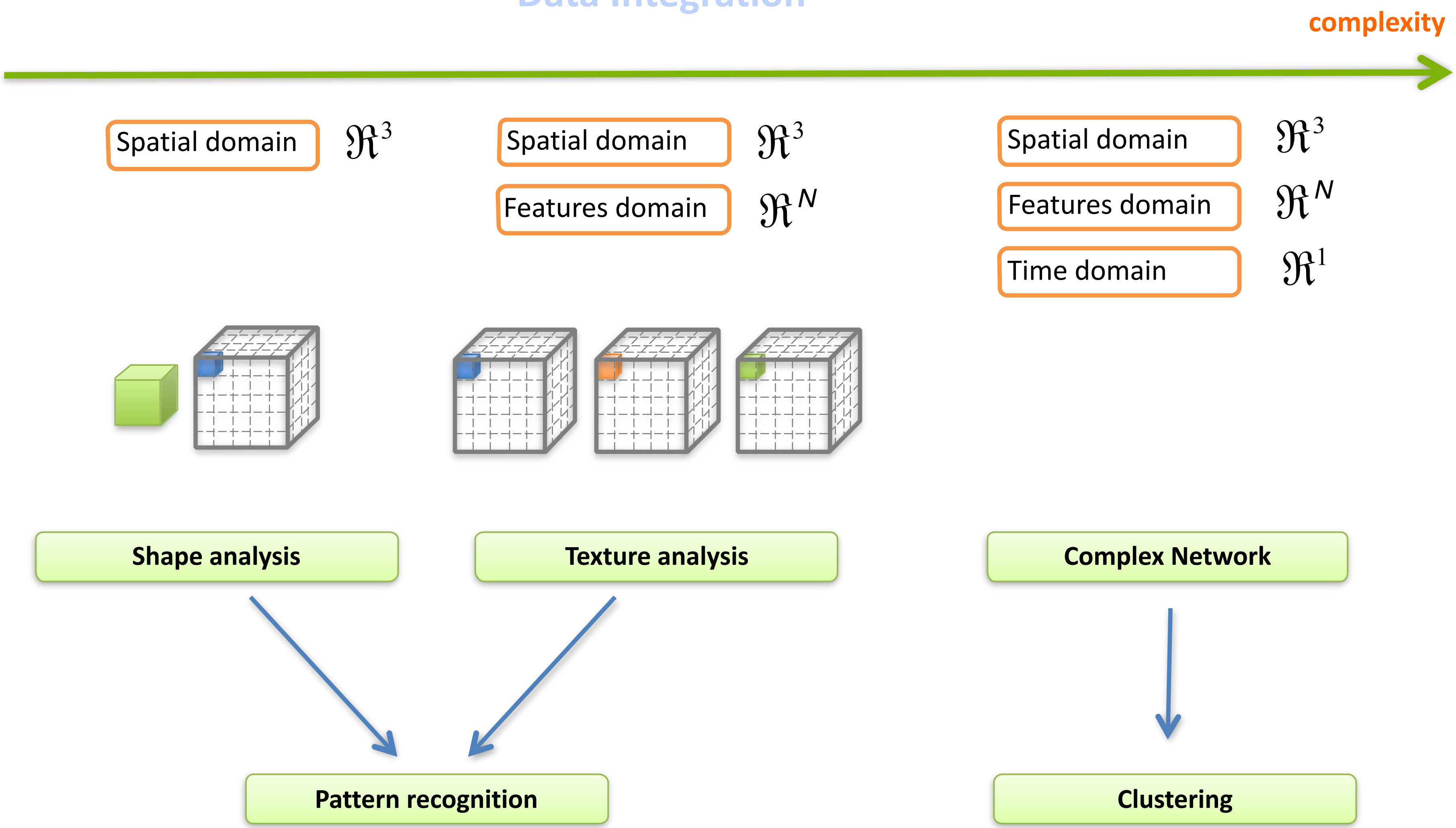
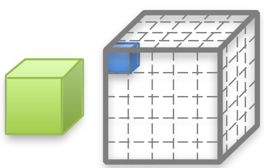
Data Integration

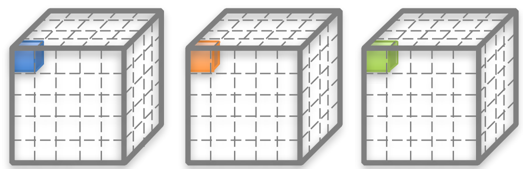


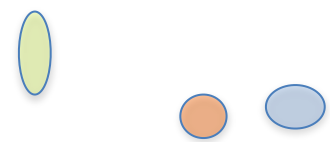
Data Integration

complexity

Shape analysis		Texture analysis		Complex Network	
Spatial domain	$\Re^3$	Spatial domain	$\Re^3$	Spatial domain	$\Re^3$
		Features domain	$\Re^N$	Features domain	$\Re^N$
				Time domain	$\Re^1$







Shape analysis

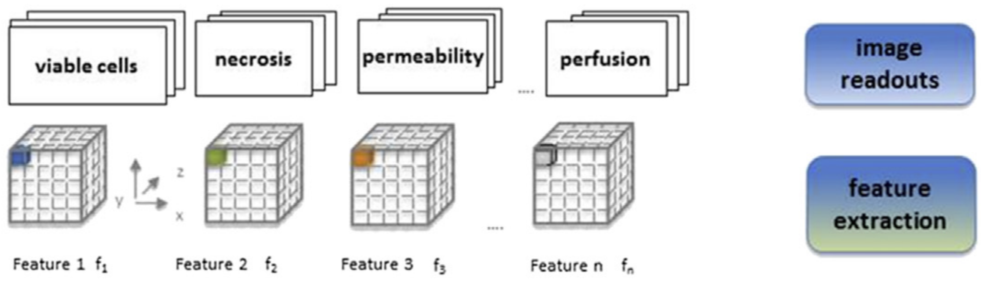
Texture analysis

Complex Network

Pattern recognition

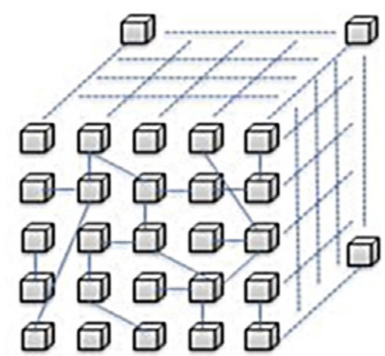
Clustering

Imaging to Network



The **nodes** are identify by the voxel and described by the features F_1 F_2 $F_{3\ldots}$ F_M

$$n_{x,y,z} \equiv v(F_1, F_2, F_3, \ldots F_M)_{x,y,z}$$



The **edges** (links) between the nodes are determined on the basis of **similarit** between the nodes

$$E_{n_i,n_k} \equiv \Theta\left[C_{N_T,2}^{\substack{i=1\to N_T \\ k=1\to N_T}}(n_i, n_k)\right]$$

All the edges form the **adjacency matrix**

$$M \equiv E_{n_i,n_k}\Big|_{\substack{i=1\to N_T \\ k=1\to N_T}}$$

Integrative analysis of cancer imaging readouts by networks
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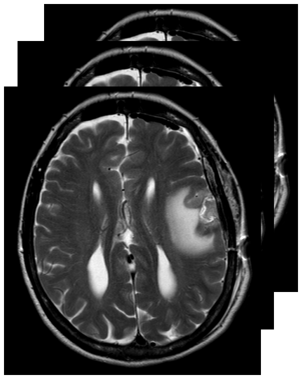
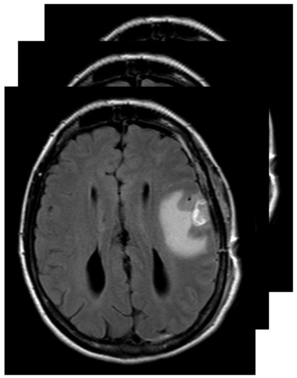
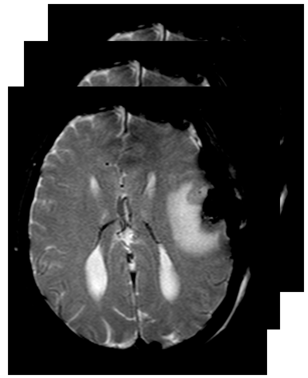
Molecular Oncology, Volume 9, Issue 1, January 2015, Pages 1–16



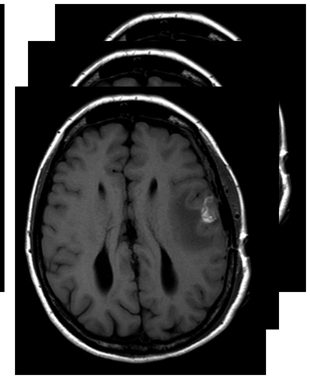
sT2-TSET-sense
Feature 1



sT2w-FLAIR
Feature 2

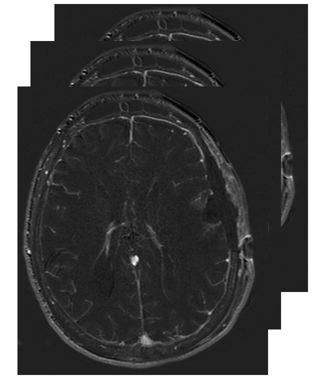


T2w- FE-EPI
Feature 3



T-SE-pre Gadolinium
Feature 4

.....

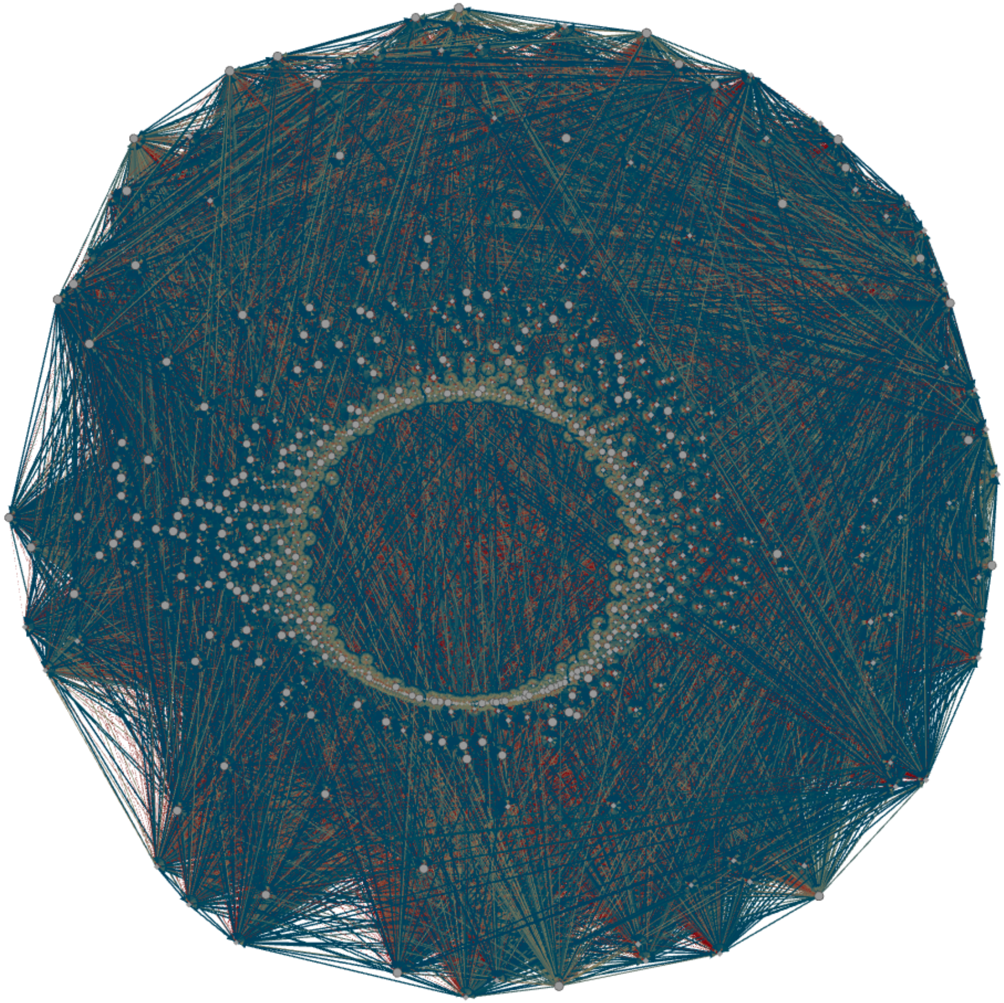


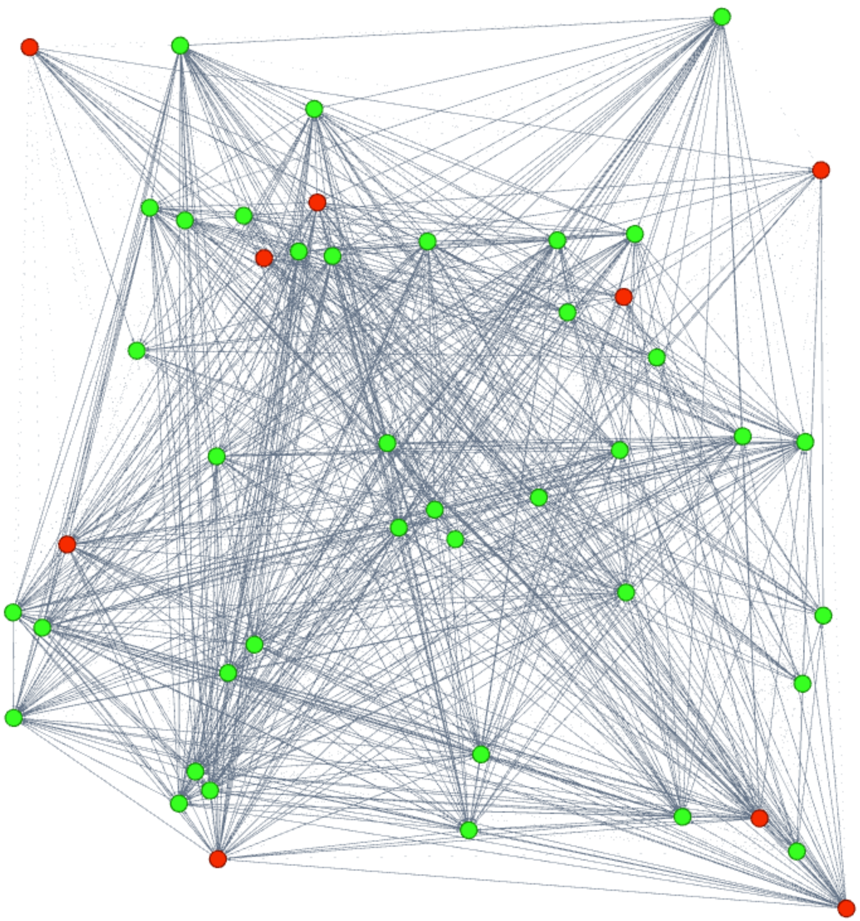
Sous-angiography
Feature 7

3D Regions of interest including:

- Tumor tissue
- Healthy tissue 1cm

BRAINX dataset from Osirix database



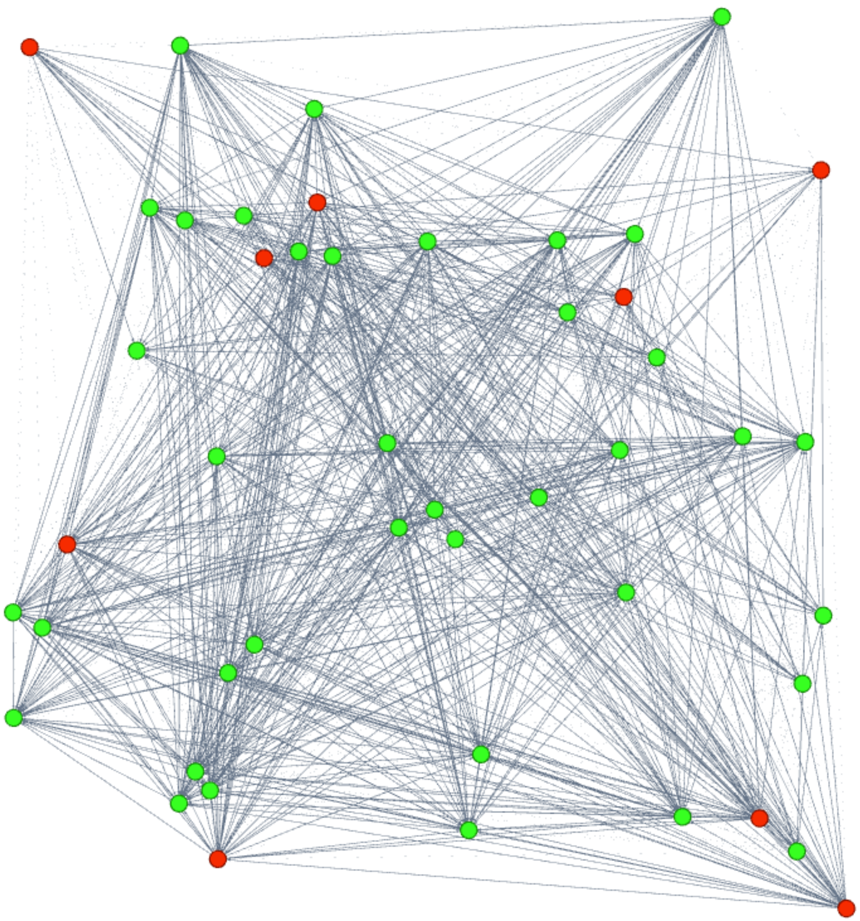


Nodes: 47
Edges: 1081
Directed Graph

Tumor

Healthy tissue

Small 3D ROI subset



Nodes: 47

Edges: 1081

Directed Graph

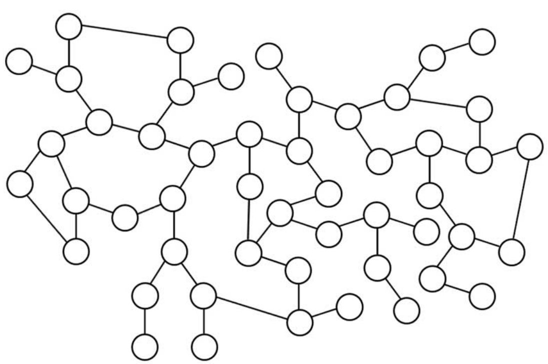
Tumor

Healthy tissue

Small 3D ROI subset

What is the information behind nodes and edges in clinical terms?

Random network



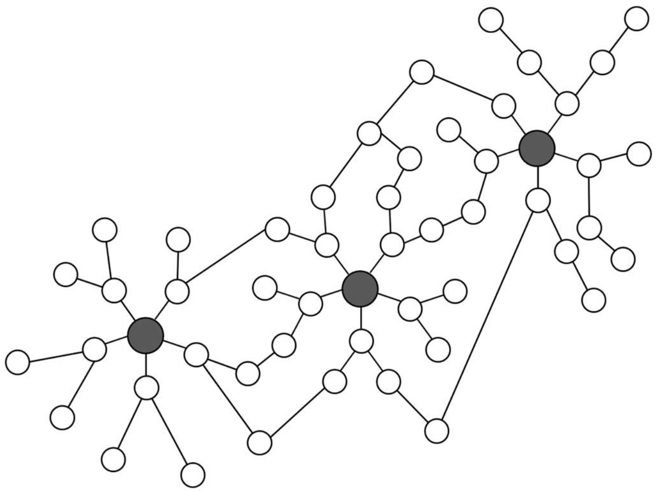
Follow **Poisson** distribution

Homogeneous structure

Nodes have almost the same number of edges

Examples: secondary roads networks

Scale-free network



Follow **Power Law** distribution

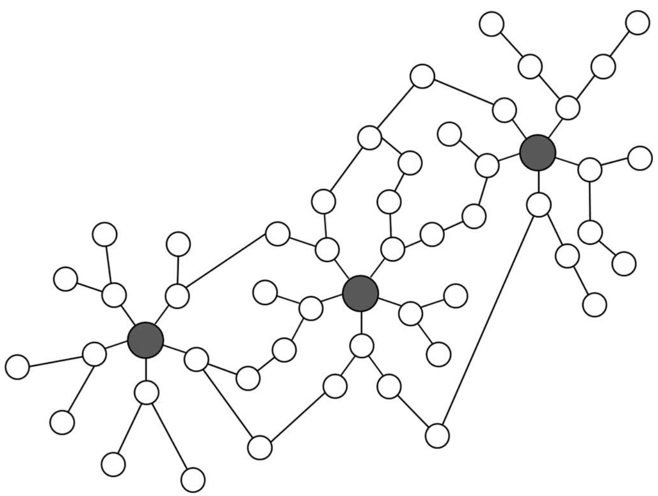
Inhomogeneous structure

Nodes have different number of edges

Example: airlines networks, social networks, biological networks, etc.

Scale-free network

Network dynamic is governed by **physiological rules**.



Authorities

Authorities are nodes that contains useful information on the network behavior

Example: web pages

Hubs

Hubs are nodes that tell us where the best authorities are to be found

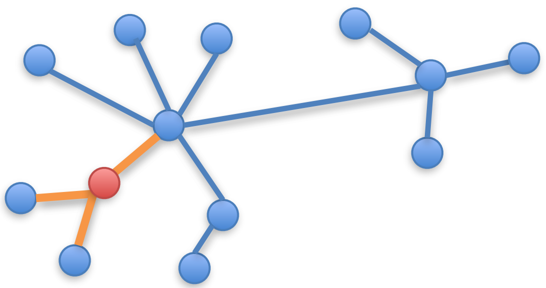
Example: google search results

Metrics/statistics

Centrality

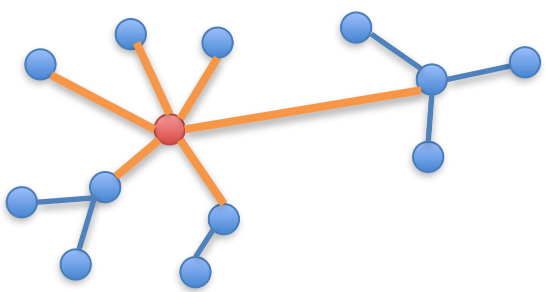
For a given node, centrality measures the number of nodes connected to it

- centrality degree
- eigenvecor centrality
- katz centrality
- Page Rank



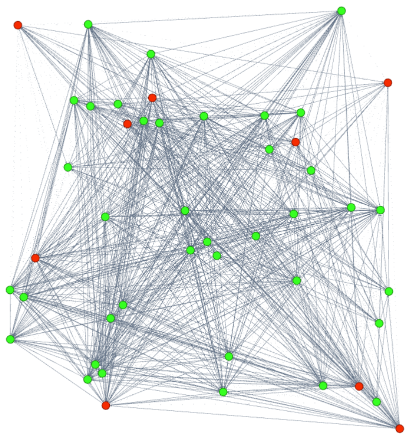
Closeness centrality

For a given node, closeness centrality measures the mean distance with the other nodes (based on feature similarity).



Goal: evaluate **nodes hierarchy**

Results: microscopic level



higher centrality degree

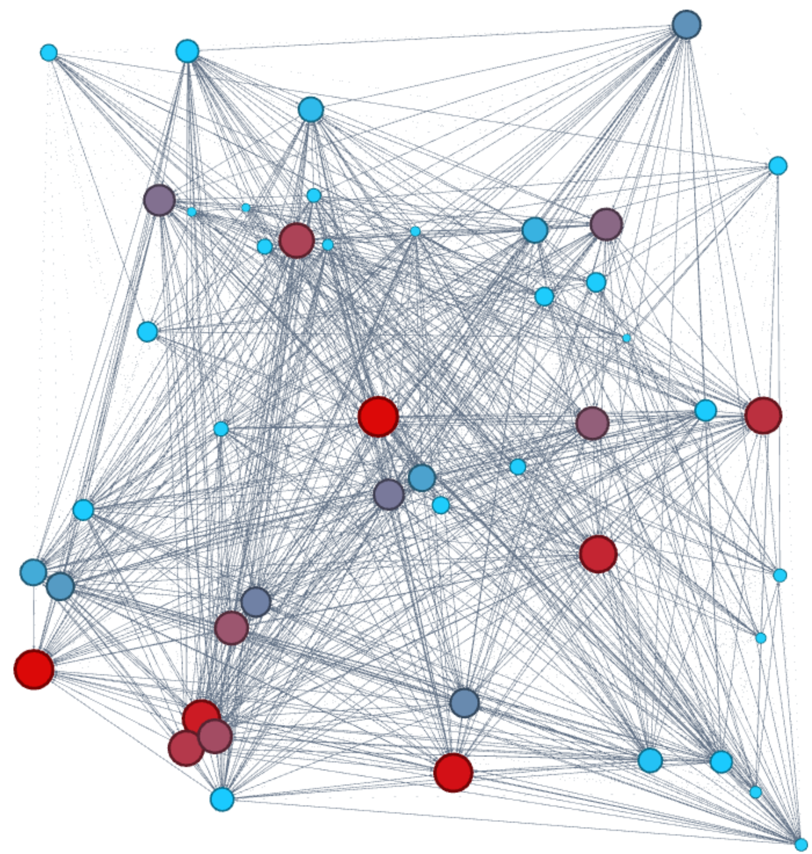
lower centrality degree

Nodes higher number of edges/connections have higher importance

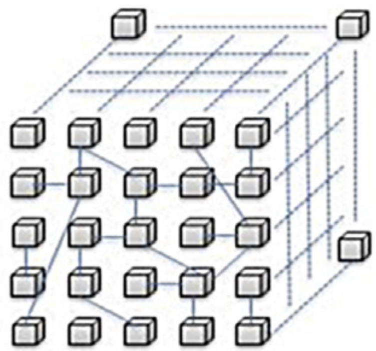
They control the majority of the other nodes

target for therapy

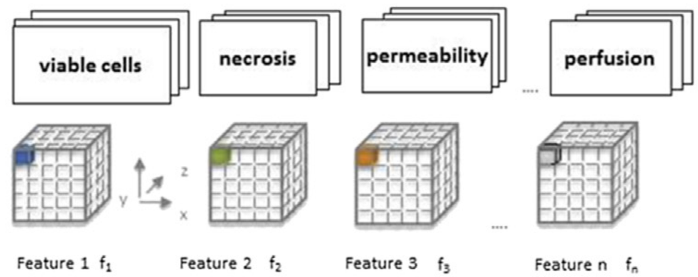
Nodes hierarchy



State



Based on features value, for each nodes is possible to define a **state**



$$state(v(x,y,z)) = \mathrm{V}\ (\mathrm{f}_1, \mathrm{f}_2, \mathrm{f}_3 \ldots, \mathrm{f}_n)_{x,y,z}\Big|_{ANGIOGENIC}$$

$$state(v(x,y,z)) = \mathrm{V}\ (\mathrm{f}_1, \mathrm{f}_2, \mathrm{f}_3 \ldots, \mathrm{f}_n)_{x,y,z}\Big|_{NON-ANGIOGENIC}$$

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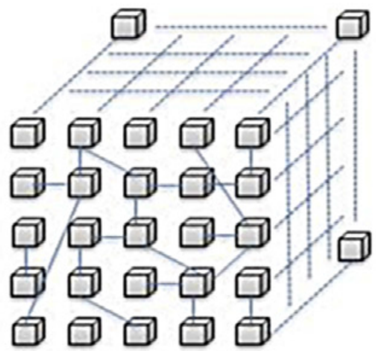
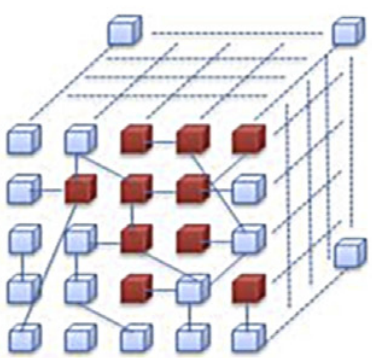
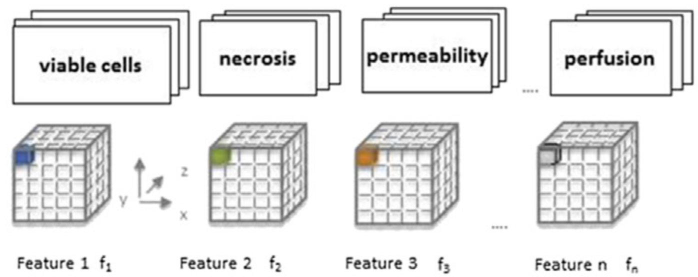
State



Voxel Clustering



Based on features value, for each nodes is possible to define a **state**



$$state(v(x,y,z)) = \mathrm{V}\ (\mathrm{f}_1, \mathrm{f}_2, \mathrm{f}_3 \ldots, \mathrm{f}_n)_{x,y,z}\Big|_{ANGIOGENIC}$$

$$state(v(x,y,z)) = \mathrm{V}\ (\mathrm{f}_1, \mathrm{f}_2, \mathrm{f}_3 \ldots, \mathrm{f}_n)_{x,y,z}\Big|_{NON-ANGIOGENIC}$$

Nodes in the same state can be grouped in **clusters**

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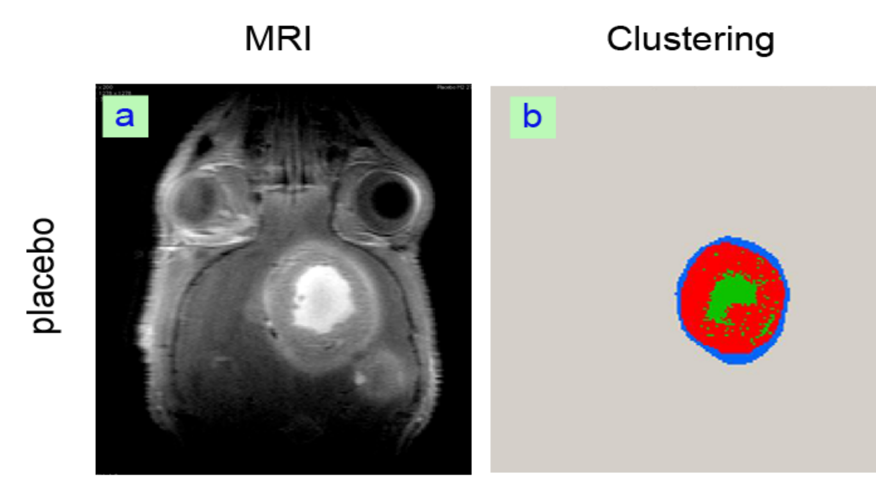
Results: macroscopic level

Table 1 – List of features characterizing tumor tissues (left), and corresponding MI modality through which feature measurements are obtained (middle). References are reported for each example.

Features	MI modality	Reference
Morphology:		
shape	MRI (T_1, T_2, ρ), CT	(Young, 2007)
solid vs liquid regions	MRI (T_1, T_2, ρ), CT	(Young, 2007)
necrotic regions	MRI (T_1, T_2, ρ), CT	(Berry et al., 2008)
viable regions	MRI (T_1, T_2, ρ)	(Berry et al., 2008)
alteration in cellularity	MRI – ADC	(Drevelegas, 2011; Haacke, 1999)
apoptosis	PET (^{124}I-annexin V)	(Blankenberg, 2008)
Inflammatory status		
edema formation	MRI (T_1, T_2, FLAIR), CT	(Young, 2007)
infiltration of immune cells	MRI (cell tracking SPIO)	(Bulte, 2009; Ahrens and Bulte, 2013)
Physiology		
angiogenesis	MRI (DCE)	(Barrett et al., 2007)
vascular architecture	CT (angiography), MRI (angiography)	(Matsumotoa et al., 2007; Hartung et al., 2011)
vessel density	MRI (VSI)	
hemodynamic response	MRI (DSC)	
vascular permeability	MRI (DCE)	
tumor oxygenation	PET (^{18}F-MISO), MRI (BOLD, ^{17}O)	
acidosis	MRI, MRS	
Tumor metabolism		
glucose consumption	^{18}FDG PET	
metabolites concentration	MRS	



Three types of tissue in a different state

- S1 --> highly angiogenic
- S2 --> proliferating tissue
- S3 --> necrotic tissue

Quantification of antiangiogenic treatment effects on tissue heterogeneity in glioma tumor model
Marco Dominietto, Sandra Bürgi, Michael Dobosz, Anja Renner, Gudrun Zahlmann, Werner Scheuer and Markus Rudin
Submitted manuscript

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Pattern Recognition

ImageJ
Image Processing and Analysis in Java

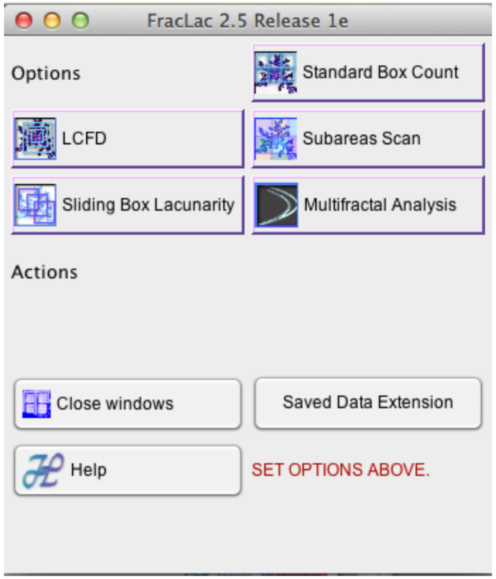
+

FracLac for ImageJ
Morphological Digital Image Analysis Tools

MATLAB
The Language of Technical Computing

+

Boxcount toolbox



Complex Network

MATLAB
The Language of Technical Computing

C++ Java

+

Gephi

Cytoscape

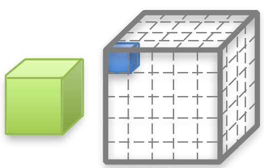
MATHEMATICA 5

IDL

Data Integration

complexity

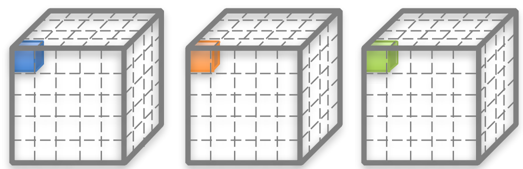
Spatial domain $\Re^3$



Shape analysis

Spatial domain $\Re^3$

Features domain $\Re^N$



Texture analysis

Pattern recognition

Spatial domain $\Re^3$

Features domain $\Re^N$

Time domain $\Re^1$

Complex Network

Clustering

Data Integration

complexity

Spatial domain $\Re^3$

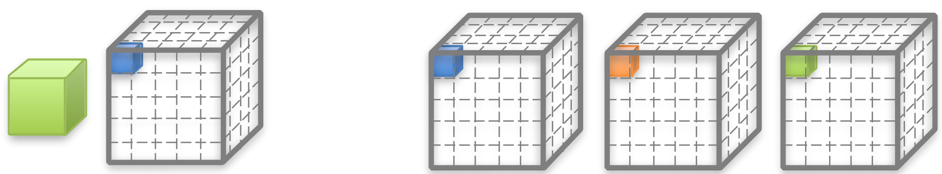
Spatial domain $\Re^3$

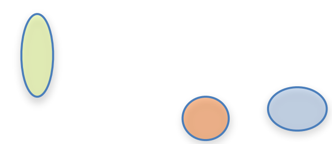
Features domain $\Re^N$

Spatial domain $\Re^3$

Features domain $\Re^N$

Time domain $\Re^1$





Shape analysis

Texture analysis

Complex Network

Pattern recognition

Clustering

The end !

"…In the era of internet, the real knowledge does not come from the amount of information we are able to process, but from the number of connections we are able to establish among them".

Somewhere in the web

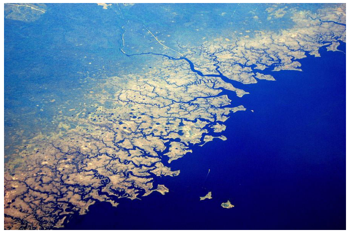
People from:
Biomaterial Science Center, University of Basel (Switzerland)
Department of Surgery and Orthopedics, Hospitals Schaffhausen

Enrico Capobianco
Center for Computational Science, University of Miami,
Miami, FL, (USA)

Giulio Magrin
MedAustron, Wiener Neustadt (Austria)

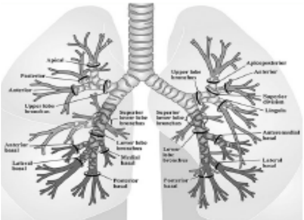
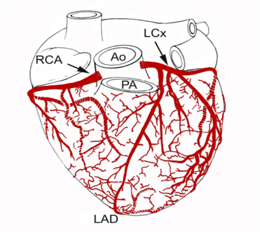
Several example in nature:

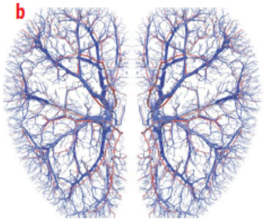




Several example in living organism:

Several example in human body:



Several example in human "constructions":

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