Laboratory Instruction: Hello AI Summer School (June 2020)

The purpose of this lab is to analyze cancer images and perform a survival prediction task.

The task will start with tumor segmentation.

From the shared repository, download the provided data set:

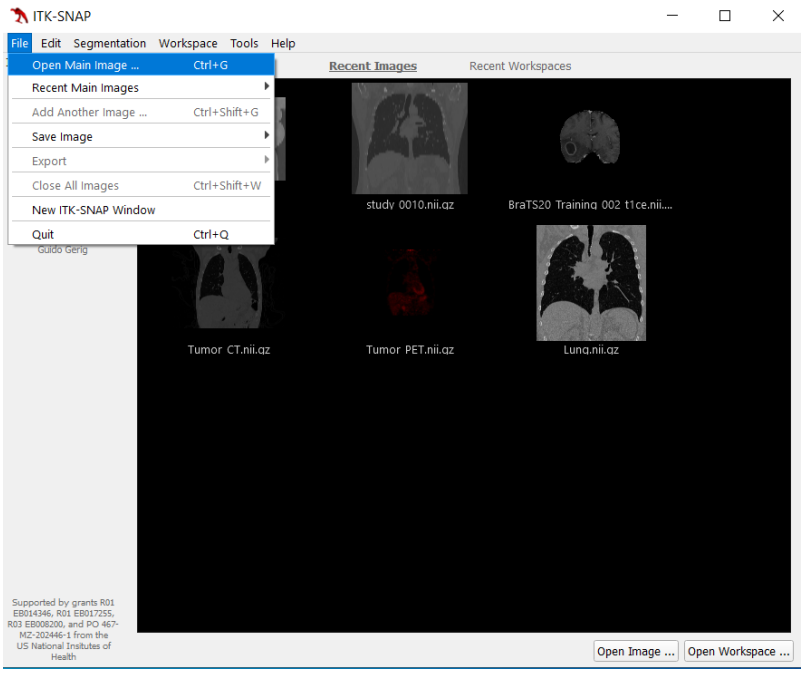
It contains one CT scan from a non-cancer subject and another PET-CT scan from a subject diagnosed with Non-Small Cell Lung Cancer. You can download the data from:

Part I: Image Visualization

The first step is to visualize the volumetric data. You can download and install ITK-Snap for visualization.

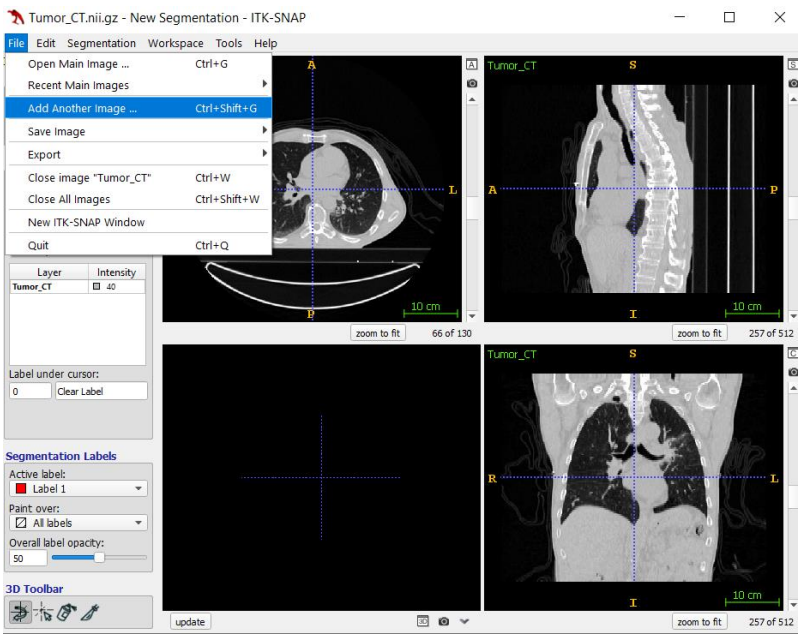
Start with "Lung Tumor" detection via multi-modal imaging:

1) Open the software ITK-Snap and click on File/Open Main Image.



2) Browse the path to the data directory where you already downloaded and saved the "Example_PET_CT" on your machine. In this directory, there are two files representing the same subject with aligned CT and PET images.
3) Open the CT file "Tumor_CT.nii" and click next.

4) You can scroll up and down in each of the three orthogonal views of Axial, Coronal and Sagittal.
5) You can change the image contrast to visualize the details with the best possible intensity. To do so, click on "tools/Image Contrast/Contrast Adjustment" and through the histogram you can change the level of contrast.
6) Scroll up and down through the slices. Can you find the abnormality within the lung?
7) Now, on the same opened window, click on "File/Add another image/":

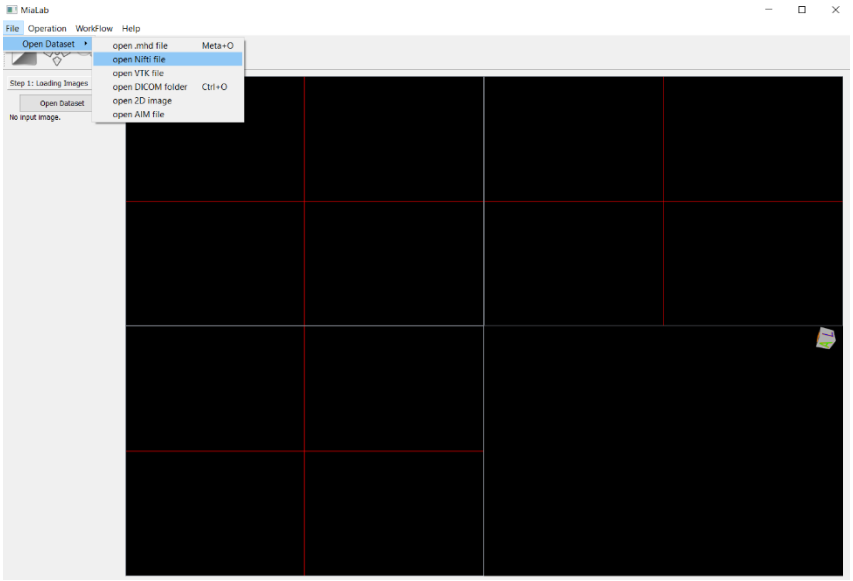


8) Browse the path to the same data directory and select "Tumor_PET.nii", then click next.

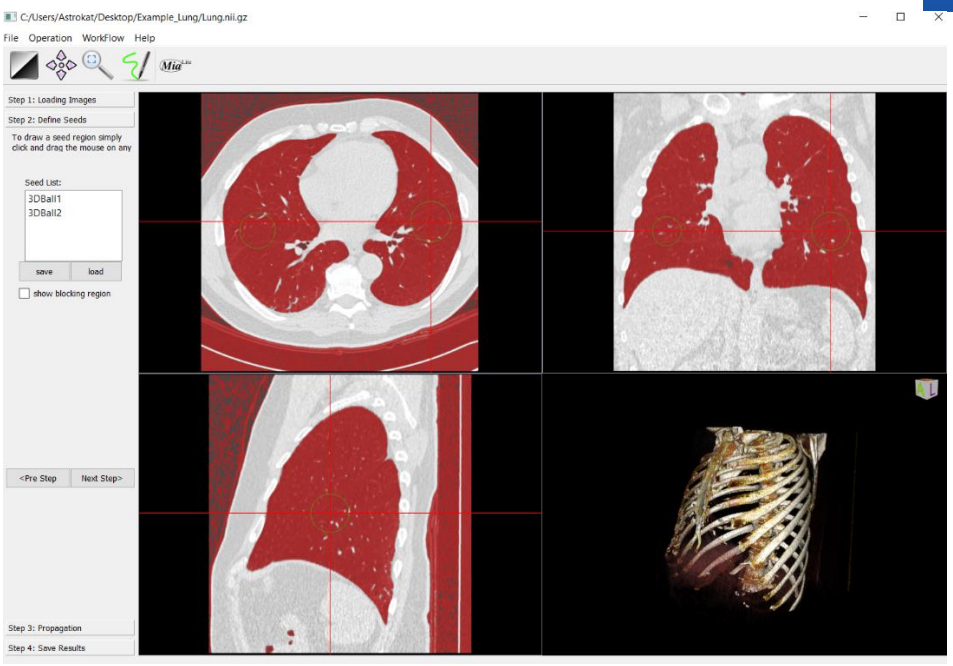
9) Mark the option “as a semi-transparent” and set the colormap as “Jet”. By this setting, both of the CT and PET images will be displayed simultaneously on the same window.
10) Go through different slices again and try to detect the abnormalities.
11) What was the effect of adding PET images? How many regions within the PET image, represent the abnormal metabolic activity? Which organ/tissue is illustrated with hyperintensity in the fused image?

Part IIa: Lung Segmentation Task

1) The software you are going to use for segmentation is called “MiaLab”.
2) After downloading the MiaLab, go to “File/Open Dataset/Open NIFTI file” and browse the path to the “Example_Lung” data directory and open the “Lung.nii”



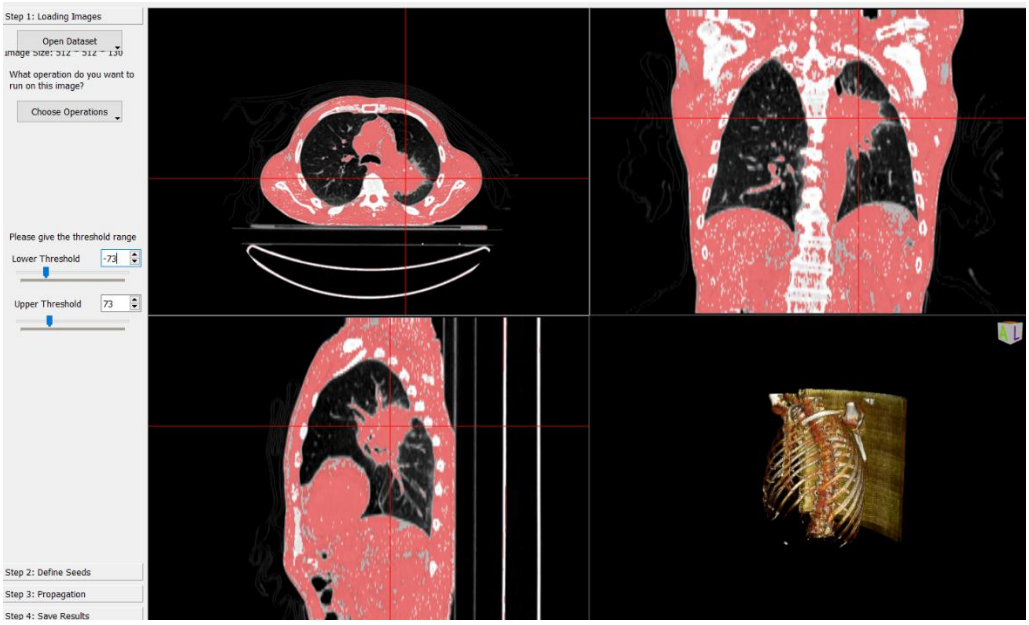
3) By scrolling up and down you can go through different slices. Moreover, by holding the right-key button on your mouse and move it toward left and right and up and down, you can change the level image contrast.
4) From the menu “Choose operations” on the left side, choose “Threshold based segmentation”. If the intensity contrast has changed, you can use your right click on your mouse to reset the contrast to your favorite level.
5) Set the “Lower Threshold” to -1000 and “Upper Threshold” equals to -500. And then click on “Define Seeds” and draw a circle on the tumor. From this step, you have restricted the region of interest to those organ and tissues that lie in the same intensity range.
6) This is a semi-automatic segmentation method which means it requires some user-interactions. The restricted region of interest is highlighted in Red color and as you can observe, it contains even the image background. Therefore, it is essential to initial the segmentation regions by defining “seed points”. Click on “Define seeds” and draw two (or more) circles over the left and right lungs (the green circles in the following screenshot).



7) The interaction part is over. Click on “next step”, set the “smoothing factor” as 0.1 and Start the algorithm. As you can see, the initial seeds evolve toward to the boundaries of the region of interest.
8) Is this an accurate segmentation result? If not, click on the previous step and fine-tune your settings including the upper/lower threshold as well as smoothing factor, then try again.

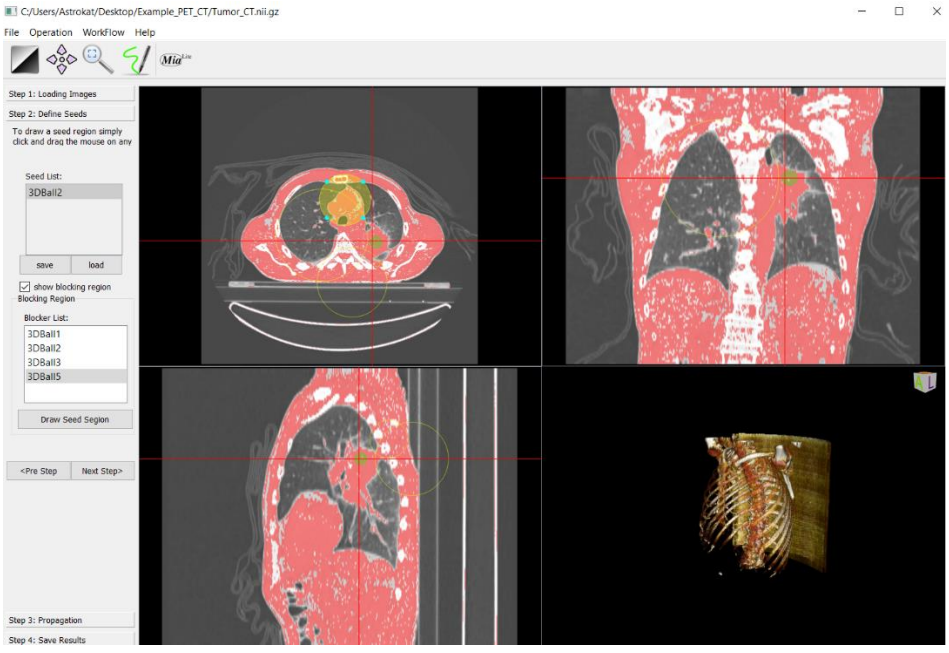
Part IIb: Lung Tumor Segmentation Task

In this exercise, you are going to segment lung tumor within the chest CT scan that you already detected in part1. If you try to repeat the same steps of part IIa, immediately you will find that the intensity characteristics of the tumor is quite similar to its nearby healthy tissues. Therefore, it is quite challenging to set lower/upper threshold values that only cover the tumor region.



One solution to address such problem is to add "blocking regions" to prevent the initial seeds from evolving and leaking toward certain regions.

1) Repeat the same steps as part IIa to load the "Tumor_CT.nii", find the proper intensity range and set the initial seed over the target tumor. Then click on "show blocking region" and draw the blocking regions wherever the target tumor is connected to the nearby healthy tissues. Please note you can use all the 3 orthogonal views in different slices to set the blocking regions.



Please note, the blocking regions are illustrated with yellow color. Press next step and start the model. Was adding "blocked regions" helpful for tumor segmentation?

Part III: Feature Extraction and Learning Algorithms

The exercises within this part of the lab are prepared as Jupyter Notebook files.

Supplementary Material

Deformable Image Segmentation

Deformable models are a famous class of image segmentation methods which are very useful for medical image segmentation. These methods combine different source of information including geometric, physic and estimation theory [3].
The fundamental approach of these methods is as follows:

First, we have to define an energy functional. This energy term should reflect some information about image data which is either related to image statistics (region-based) or edges of the image (edge-based). This term is called $E_{external}$. The energy should include a regularization term to make the segmented boundaries smooth; this term called $E_{internal}$. Sometimes, based on the problem, some constraints would be added to the energy functional such as shape constraint ($E_{constraint}$) [4].

$$E_{external} + E_{internal} + E_{constraint}$$

Then, we set an initial contour (surface or even seeds) on image plane and set this initialization as an argument of the energy functional. By using the concept of variational calculus, we minimize the energy functional with respect to the argument and this process leads the contour to evolve on the image domain.

In a general view, we can divide these methods into two major categories: parametric and non-parametric. In parametric methods, we parameterize the contour (surface) e.g. with B-splines.

$$E_{snake} = \int_{s=0}^{1} \{E_{ext}(V(s)) + E_{int}(V(s)) + E_{const}(V(s))\} ds$$

However, there exist some difficulties with this approach. They are very sensitive to initialization; they cannot follow the topological changes such as merging and splitting; and different parametric methods lead to different results. To solve the mentioned problems, some methods were introduced such as Gradient Vector Flow and Dynamic Directional Gradient Vector Flow.

In the non-parametric methods, the concept of "Level Set" function is utilized. In this method, we map the information from image plane to a smooth function (Level Set). When we set the initial contour on

the image, we can consider that we divided the image into two parts: outside of the contour and inside of the contour. Also, the contour itself will be the edge between inside and outside regions. Therefore, we map the image in a way which the inside part represented by negative values, the outside by positive values and the zero-level set is related to the contour boundary.

$$\begin{cases} \varphi(x,t) < 0;\ x \in \Omega \\ \varphi(x,t) > 0; x \in\ \overline{\Omega} \\ \varphi(x,t) = 0; x \in \partial\Omega \end{cases}$$

By this function, we can follow the contour evolution by only finding the zero values of the level set function.

As we look at the whole process more carefully, we can find that the level set based method is exactly a PDE equation, because we try to evolve a function through the time on an image (we have to variable, spatial and temporal). The whole evolution function can be written as:

$$\frac{\partial\varphi}{\partial t} + V.\nabla\varphi = 0$$

This equation can be read as: level set function (φ) will be changed though the time spatially with the speed (energy) of V.

Regarding this formula, there are some notation:

- Normal vectors can be calculated as: N = $\frac{\nabla\varphi}{|\nabla\varphi|}$
- The evolution should be done only toward normal vector of each point: $v_n = V.\frac{\nabla\varphi}{|\nabla\varphi|}$
- Curvature of the contour (surface) can be calculated as: $\kappa = -\nabla(\frac{\nabla\varphi}{|\nabla\varphi|})$
- The boundaries of the level set function can be obtained by: $\delta(\varphi)|\nabla\varphi|$ where δ is Dirac delta function.
- We can use Heaviside function to find inside and outside of the function:
$$\begin{cases} H(x) = 1\ if\ x > 0 \\ H(x) = 0\ if\ x < 0 \end{cases}$$
- Integral over the contour (surface) for a quantity like $P(x,t)$ is presented by:
$$\int_{R^n} p(x,t)\delta(\varphi)|\nabla\varphi|dx$$
- "Reinitialization" process helps the contour to hold its zero level after each iteration and prevent it from being too flat or too sharp.
- Level set function $\varphi(x,t)$ defines over the whole image but in order to speed up the evolution process, the computation will often be done in a narrowband around the zero-level set.

MiaLab software contains variety of energy functionals; however, for this lab you will use a threshold based level set method. The external energy of this method forces the initial seeds to evolve toward

other voxels in the image which have the same intensity range. This intensity range is modified by the user. As an internal energy, a regularization energy is employed to make the evolving contour as smooth as possible [5].

Features Definition [6]

Two types of features were extracted from the segmented tumors.

A. Geometric features:

These features describe the size and shape of the segmented tumors. For the following definition let name the volume of the tumor as V and its surface area as A. $X = \{\vec{X}_1, \vec{X}_2, \dots, \vec{X}_n\}$ represents spatial coordination of n voxel within the tumor region and $I = \{I_1, I_2, \dots, I_n\}$ is their corresponding intensities.

A1) Volume:

Number of the voxel within the tumor region multiplied by the voxel volume. Please note, the voxel volume depends of the imaging modality and can be changed from one patient to other,

$$\text{Volume} = n.v$$

A2) Surface area:

By dividing the tumor surface into connected triangles, surface area is calculated as:

$$\sum_{i=1}^{N} \frac{1}{2} |a_i b_i \times a_i c_i|$$

A3) Surface to volume:

The ration of surface area to volume.

N is the total number of triangles used to cover the tumor surface and a,b, and c are edge vectors of the triangle.

A4) Solidity:

This features defines as $Area/_{Convex\ hall\ area}$

For instance, since a rectangle is convex thus its area is the equal to its convex area and therefore it has a solidity of 1.

A5) Major Axis Length:

For each tumor, eigenvalues of all voxel toward x,y, and z direction is calculated and sorted and the major axis length will be the largest eigenvalue.

A6) Minor Axis Length:

Similar to major axis length, but the second largest eigenvalue.

A7) Least Axis Length:

Similar to major axis length, but the smallest eigenvalue.

A8) Elongation:

The ratio of Minor Axis Length to Major Axis Length.

A9) Flatness:

The ratio of Least Axis Length to Major Axis Length.

A10) Sphericity:

This measure shows how much a tumor is similar to a sphere.

$$\frac{(36\pi V^2)^{\frac{1}{3}}}{A}$$

A11) Spherical Disproportion:

Another sphericity measure defined as $\frac{A}{4\pi R^2}$ where R is the radius of sphere which have the same volume as the tumor.

A12) Asphericty:

$$\left(\frac{A^3}{36\pi V^2}\right)^{\frac{1}{3}} - 1$$

A13) Compactness1:

Another measure represents how much a tumor volume resembles a sphere.

$$\frac{V}{\sqrt{\pi}\, A^{\frac{2}{3}}}$$

A14) Compactness2:

$$36\pi \frac{V^2}{A^3}$$

A15) Compactness3:

$$\frac{V}{\sqrt{\pi}\, A^{\frac{3}{2}}}$$

A16) Centroid distance:

Euclidean distance between the geometric centroid (C_g) and the centroid weighing each voxel by its intensity value (C_i).

$$\|C_g - C_i\|$$

B) Textural Features

Textural features cover a wide range of characteristics which are employed to capture heterogeneity inside the tumor volume.

Gray Level Co-occurrence Matrix features:

It is a matrix with the size of $(N_g \times N_g)$ describing the second order joint probability function of an image. For simplifying the formula let:

P(i,j): normalized co-occurrence matrix,

$p_x(i)$: marginal probability with respect to x

$p_y(j)$: marginal probability with respect to y

μ_x: mean of p_x

μ_y: mean of p_y

σ_x: standard deviation of p_x

σ_y: standard deviation of p_y

$$p_{x+y}(k) = \sum_i \sum_j P(i,j), i + j = k; k = 2,3, \dots, 2\, N_g$$

$$p_{x-y}(k) = \sum_i \sum_j P(i,j), |i - j| = k; k = 2,3, \dots, N_g - 1$$

HX = $\sum p_x \ln(p_x)$

HY = $\sum p_y \ln(p_y)$

HXY1 = $-\sum_i \sum_j P(i,j) \ln(p_x(i)p_y(j))$

HXY2 = $-\sum_i \sum_j p_x(i)p_y(j) \ln(p_x(i)p_y(j))$

B1) Autocorrelation:

$$\sum_i \sum_j ij\, P(i,j)$$

B2) Cluster Prominence:

$$\sum_i \sum_j \left[i + j - \mu_x - \mu_y\right]^4 P(i,j)$$

B3) Cluster shade:

$$\sum_i \sum_j \left[i + j - \mu_x - \mu_y\right]^3 P(i,j)$$

B4) Contrast:

$$\sum_i \sum_j [i-j]^2 P(i,j)$$

B5) Correlation:

$$\frac{\sum\sum ijP(i,j) - \mu_x \mu_y}{\sigma_x \sigma_y}$$

B6) Difference Entropy:

$$-\sum_{i=0}^{N_g-1} P_{x-y}(i) log_2\left[P_{x-y}(i)\right]$$

B7) Difference Variance:

$$\sum_{i=0}^{N_g-1} (i - \mu_{x-y})^2 P_{x-y}(i)$$

B8) Dissimilarity:

$$\sum_i \sum_j |i-j| P(i,j)$$

B9) Energy:

$$\sum_i \sum_j [P(i,j)]^2$$

B10) Entropy:

$$-\sum_i \sum_j P(i,j)\, log_2(P(i,j))$$

B11) Homogeneity:

$$\sum_i \sum_j \frac{P(i,j)}{1 + |i-j|}$$

B12) Information measure of correlation1:

$$\frac{H - HXY1}{\max\{HX, Hy\}}$$

B13) Information measure of correlation2:

$$\sqrt{1 - e^{-2(HXY2 - H)}}$$

B14) Inverse difference moment normalized:

$$\sum_i \sum_j \frac{P(i,j)}{1 + (\frac{|i-j|}{N_g{}^2})}$$

B15) Inverse difference normalized:

$$\sum_i \sum_j \frac{P(i,j)}{1 + (\frac{|i-j|}{N_g})}$$

B16) Maximum probability:

$$\max\left(P(i,j)\right)$$

B17) Sum average:

$$\sum_{i=2}^{2N_g} \left[iP_{x+y}(i)\right]$$

B18) Sum Entropy:

$$-\sum_{i=2}^{2N_g} P_{x+y}(i) log_2[P_{x+y}(i)]$$

B19) Sum of squares:

$$\sum_i \sum_j (i-\mu)^2 P(i,j)$$

Gray Level Run Length Matrix

Gray level run represents length of the number of the consecutive pixels which have similar intensity values. Gray level matrix $p(i,j|\theta)$ show the number of times (j), an intensity value (i) appears consecutively in a certain direction (θ). For simplifying let:

N_g: Number of intensity values in an image
N_r: Maximum run length
$N_s = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} p(i,j)$: total number of runs
$p_r(j) = \sum_{i=1}^{N_g} p(i,j)$: the sum distribution of the number of runs with run length j
$p_g(j) = \sum_{j=1}^{N_r} p(i,j)$: the sum distribution of the number of runs with intensity value i
$N_p = \sum_{j=1}^{N_r} jp_r$: Number of voxels in the image
$p_n(i,j) = \frac{p(i,j)}{N_s}$: Normalized run length matrix
$\mu_r = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} jp_n(i,j)$: the mean run length
$\mu_g = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} ip_n(i,j)$: the mean intensity values

B20) Short run emphasis:

$$\frac{1}{N_s} \sum_{j=1}^{N_r} \frac{p_r}{j^2}$$

B21) Long run emphasis:

$$\frac{1}{N_s}\sum_{j=1}^{N_r} j^2 p_r$$

B22) Gray level non uniformity:

$$\frac{1}{N_s}\sum_{j=1}^{N_r} p_g^2$$

B23) Run length non uniformity:

$$\frac{1}{N_s}\sum_{j=1}^{N_r} p_r^2$$

B24) Run percentage:

$$\frac{N_s}{N_p}$$

B25) Low gray level run emphasis:

$$\frac{1}{N_s}\sum_{i=1}^{N_g} \frac{p_g}{i^2}$$

B26) High gray level run emphasis:

$$\frac{1}{N_s}\sum_{i=1}^{N_g} i^2 p_g$$

B27) Short run low gray level emphasis:

$$\frac{1}{N_s}\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} \frac{p(i,j)}{i^2 j^2}$$

B28) Short run high gray level emphasis:

$$\frac{1}{N_s}\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} \frac{p(i,j)i^2}{j^2}$$

B29) Long run low gray level emphasis:

$$\frac{1}{N_s}\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} \frac{p(i,j)j^2}{i^2}$$

B30) Long run high gray level emphasis:

$$\frac{1}{N_s}\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} p(i,j)i^2 j^2$$

B31) Gray level variance:

$$\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} \left(i-\mu_g\right)^2 p_n(i,j)$$

B32) Run length variance:

$$\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}(j-\mu_r)^2 p_n(i,j)$$

Gray Level Size Zone Matrix

This matrix represents the amount of homogeneous connected areas within a volume with certain size and intensity. P(i,j) shows the number of connected zones with intensity value of i and size of j. Briefly, it would present the heterogeneity within tumor volume. For simplifying let:

N_g: The number of intensity values inside an image

N_z: The size of the largest homogeneous region

$N_s = \sum_{i=1}^{N_g}\sum_{j=1}^{N_z} p(i,j)$: total number of homogeneous zones

$p_z(j) = \sum_{i=1}^{N_g} p(i,j)$: Sum distribution of the number of zones with size j.

$p_g(i) = \sum_{j=1}^{N_z} p(i,j)$: Sum distribution of the number of zones with intensity value i.

$N_p = \sum_{j=1}^{N_z} jp_z$: Number of the voxels in the image

$p_n(i,j) = \frac{p(i,j)}{N_s}$: normalized size zone matrix

$\mu_z = \sum_{i=1}^{N_g}\sum_{j=1}^{N_z} jp_n(i,j|\theta)$: the mean zone size.

$\mu_g = \sum_{i=1}^{N_g}\sum_{j=1}^{N_z} ip_n(i,j|\theta)$: the mean gray level.

B33) Small zone emphasis:

$$\frac{1}{N_s}\sum_{j=1}^{N_s}\frac{p_z}{j^2}$$

B34) Large zone emphasis:

$$\frac{1}{N_s}\sum_{j=1}^{N_s} j^2 p_z$$

B35) Gray Level Non Uniformity:

$$\frac{1}{N_s}\sum_{j=1}^{N_s} {P_g}^2$$

B36) Zone size non uniformity:

$$\frac{1}{N_s}\sum_{j=1}^{N_z} p_z^2$$

B37) Zone percentage:

$$ZP = \frac{N_s}{N_p}$$

B38) Low gray level small zone emphasis:

$$\frac{1}{N_s}\sum_{i=1}^{N_g}\sum_{j=1}^{N_s}\frac{p(i,j)}{i^2 j^2}$$

B39) High gray level small zone emphasis:

$$\frac{1}{N_s}\sum_{i=1}^{N_g}\sum_{j=1}^{N_s}\frac{p(i,j)i^2}{j^2}$$

B40) Low gray level large zone emphasis:

$$\frac{1}{N_s}\sum_{i=1}^{N_g}\sum_{j=1}^{N_s}\frac{p(i,j)i^2}{i^2}$$

B41) High gray level large zone emphasis:

$$\frac{1}{N_s}\sum_{i=1}^{N_g}\sum_{j=1}^{N_s}p(i,j)i^2j^2$$

B42) Gray level variance:

$$\sum_{i=1}^{N_g}\sum_{j=1}^{N_s}\left(i-\mu_g\right)^2 p_n(i,j)$$

B43) Zone Size Variance:

$$\sum_{i=1}^{N_g}\sum_{j=1}^{N_s}(i-\mu_z)^2\, p_n(i,j)$$

B44) Zone Entropy:

$$\sum_{i=1}^{N_g}\sum_{j=1}^{N_s}p_n(i,j)log_2(p_n(i,j))$$

Neighborhood Gray Tone Difference Matrix

The ith entry of this matrix, $s(i|d)$represent the sum of intensity differences of the voxels with intensity value of I and the average intensity of A_i of their neighboring voxels within a distance d. For simplifying let:

n_i: number of voxels with grey level i

$N_v = \sum n_i$: total number of the voxels

N_g: Maximum intensity level in the image

N_p: Total number of intensity in the image

$p(i) = \frac{n_i}{N_v}$: probability of intensity i

B45) Coarseness:

$$\frac{1}{\varepsilon + \sum_{i=1}^{N_g} p(i)s(i)}$$

ε is a small number to prevent from dividing by zero.

B46) Contrast:

$$\left(\frac{1}{N_p\left(1-N_p\right)}\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}p(i)p(j)(i-j)^2\right)\left(\frac{1}{N_v}\sum_{i=1}^{N_g}s(i)\right)$$

B47) Busyness:

$$\frac{\sum_{i=1}^{N_g} p(i)s(i)}{\sum_{i=i}^{N_g}\sum_{j=i}^{N_g}|ip(i)-jp(j)|}, p(i)\neq 0, p(j)\neq 0$$

B48) Complexity:

$$\frac{1}{N_v}\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}|i-j|\frac{p(i)s(i)+p(j)s(j)}{p(i)+p(j)}, p(i)\neq 0, p(j)\neq 0$$

B49) Strength:

$$\frac{\sum_{i=i}^{N_g}\sum_{j=i}^{N_g}[p(i)+p(j)]\,(i-j)^2}{\varepsilon+\sum_{i=i}^{N_g}s(i)}, p(i)\neq 0, p(j)\neq 0$$

References

[1] Martin Vallières, Emily Kay-Rivest, Léo Jean Perrin, Xavier Liem, Christophe Furstoss, Nader Khaouam, Phuc Félix Nguyen-Tan, Chang-Shu Wang, Khalil Sultanem. (2017). Data from Head-Neck-PET-CT. The Cancer Imaging Archive. doi: 10.7937/K9/TCIA.2017.8oje5q00

[2] O. Grove, A. Berglund, M. Schabath, H. Aerts, A. Dekker and et.al., "Quantitative Computed Tomographic Descriptors Associate Tumor Shape Complexity and Intratumor Heterogeneity with Prognosis in Lung Adenocarcinoma," *PLOS One,* 2015.

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[5] C. Wang, H. Frimmel and Ö. Smedby, "Fast level-set based image segmentation using coherent propagation," *Medical Physics,* 2016.

[6] J. E. Timmeren, R. Leijenaar, W. Elmpt and et.al., "survival prediction of non-small cell lung cancer patients unsing radiomics analyses of cone-beam CT images," *Radiotherapy and Oncology,* vol. 123, no. 3, pp. 363-369, 2017.

Links to the materials:

MiaLab software: https://www.dropbox.com/s/xmqbrmhgjbztdy9/MiaLab.zip?dl=0

Dataset: https://drive.google.com/file/d/17p4ck6WKUB7SOLT6gTnDa2ORK9qOb3SL/view?usp=sharing

Or https://1drv.ms/u/s!AqGtg0tHeNzDbIF2tCWRlQs2g1g

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