

**Short Thesis for the Degree of Doctor of Philosophy (PhD)**

**Texture Analysis in  $^{18}\text{F}$ -FDG Human PET/CT images**

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**UNIVERSITY OF DEBRECEN**

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# **Texture Analysis in $^{18}\text{F}$ -FDG Human PET/CT images**

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The Examination takes place at the library of the Department of Physiology, Faculty of Medicine, University of Debrecen at 11:00 am, 28th of May, 2019.

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen at 13:00, 28th of May, 2019.

## **1. Background and objectives**

Positron Emission Tomography (PET) a non-invasive imaging technique has become an indispensable method in medical diagnostics over the past 20 years. Molecules taking part in transport or metabolic processes are conjugated with positron decaying nuclides and injected as tracer molecules (called often radiopharmaceuticals) into the living organism. The distribution of these molecules depends on the intensity and local distribution of the involved transport or metabolic processes. Detection of the decay of the radiolabel allows the 3-dimensional mapping of the distribution of the radiopharmaceutical. Accordingly, the equilibrium distribution of the radiopharmaceuticals indicates the intensity and tissue distribution of the appropriate functional features. As to the measurement techniques the detection of the 511 keV annihilation gamma particles is independent of the tracer molecule and the positron decaying radionuclid used.

Recently hybrid systems comprising PET and computer tomography (CT) devices are used almost exclusively. CT-imaging allows the anatomical localization of the accumulation with submillimeter accuracy and at the same time, it makes possible to carry out corrections completed during the reconstruction of the PET images. One of the most common tracers is the glucose analogue Fluorodeoxyglucose ( $^{18}\text{F}$ -FDG or FDG). The cellular uptake of the FDG is identical with that of the physiological glucose thus the equilibrium distribution of the intravenously injected FDG can be regarded as a 3-dimensional glucose metabolic map of the organism. The

currently accepted idea that tumorous tissue carry out more intensive carbohydrate metabolism relative to normal tissue originates from Otto Heinrich Warburg (1924 Nobel Prize). Accordingly, higher accumulation of the FDG tracer indicates higher glucose metabolic activity, thus it may refer to tumour manifestation.

In addition to the  $^{18}\text{F}$ -FDG PET tracer the most frequently used radiopharmaceuticals are:  $^{11}\text{C}$ -Choline,  $^{11}\text{C}$ -Methionine;  $^{18}\text{F}$ -Fallypride,  $^{18}\text{F}$ -FET,  $^{18}\text{F}$ -Dopa;  $^{18}\text{F}$ -NaF;  $^{68}\text{Ga}$ -PSMA; and  $^{18}\text{F}$ - $\beta$ -Amyloid, which allow the diagnosis of primary brain tumor dopamine receptor levels, bone lesions, prostate cancer and Alzheimer's disease. Every newly developed tracer may measure additional feature providing a more complete characterization of the particular lesion. Recently the research and development of PET radiopharmaceuticals is steadily progressing, and the number of communications reporting synthesis of new radiopharmaceuticals has increased significantly. The primary aim of diagnostic PET imaging is to indicate and characterize any accumulation different from the standard physiological one. Appropriate and effective tumour-treatment is absolutely dependent on the accuracy of the carbohydrate metabolic map. Repeated PET scanning between the successive treatment cycles or after the completion of the treatment may indicate the necessity of a change in the therapy or confirm the efficacy of the treatment. PET imaging has an impact in the planning of the radiotherapeutic protocol, the planning of the target area and the appropriate dose map. It helps targeted biopsy sampling facilitating sampling from the region of the lesion having the highest glucose metabolic activity. PET images provide accurate information about FDG accumulations higher or lower relative to the healthy control. The possibly most complete description of such lesions is

substantial to an accurate diagnosis comprising volume of the lesion with diameter maximum. In addition, the SUV (standard uptake value) or the highest SUV value of the lesion is also recorded in the report. Diagnosis containing numerical data may have prognostic value and support better estimation of the course of a particular disease and the expected survival time. Such prognostic factor for particular diseases can be the tumour volume, the SUVmax, or the tumour lesion glycolysis (TLG) defined as the product of the last two parameters.

The clear endeavour of all post-reconstruction image processing is to retrieve new numerical information of prognostic significance and stored in the picture (Radiomics). This means finding and defining quantitative parameters whose prognostic value can be demonstrated. These data are increasing the diagnostic value of the test. The number of reports dealing with the characterization of the tumour texture and its diagnostic value has exploded during the last 5 years. Reviewing a large number of communications on the analysis and the prognostic value of the texture of PET images at the early phase of my PhD activity we realized the importance of studying the necessity, possibility and reliability of research in this special line. Published results of the research were controversial as algorithms of the calculation of texture parameters were not clearly defined and the software were not validated. In addition, it is not clear how noise and resolution affect reliability of the texture analysis and the related statistical errors committed during investigation of prognostic value are not known.

## Aims

Considering that the role and importance of the texture analysis is increasing in PET imaging as well as the fact that

many conceptual and methodological questions have been raised in the literature regarding the analysis of the texture, the following questions were addressed in the doctoral thesis:

- 1) Investigation of the volume dependence of nearly 30 parameters used for the numerical characterization of the texture: Determination (if it is possible) the minimum size (primarily on an empirical basis), below which the heterogeneity test is not relevant due to the constraints of the PET imaging.
- 2) Examination of the reproducibility of heterogeneity parameters for different reconstruction algorithms and data acquisition times.
- 3) Sensitivity examination of the individual texture parameters applying time-dependent pattern.
- 4) Investigation of the relationship and correlation between the visual qualitative classification and the calculated texture parameters in the case of specific human lesions. This task is planned for three different re-sampling (discretization, binning) scenarios.
- 5) Development of a new phantom measuring technics allowing the creation of arbitrary activity distribution (texture) with reproducibility higher compared to earlier methods. The method should be fast (<1 hour preparation and PET testing time).

## 2. Materials and Methods

### Investigated textural features

A total of 26 heterogeneity parameters (HePs) proposed during the last years have been tested: Homogeneity (HOM), Correlation (COR), Entropy (ENT), Contrast (CON), Intensity Variability (IV), Zone Percentage (ZP), Size-Zone Variability (SZV), Short Zones Emphasis (SZE), Long Zones Emphasis (LZE), Grey-Level Non-Uniformity (GLNU), Low Grey-Level Zone Emphasis (LGLZE), High Grey-Level Zone Emphasis (HGLZE); Short Zone Low Grey Level Emphasis (SZLGLZE); Short Zone High Grey-Level Emphasis (SZHGLE); Long Zone Low Grey Level Emphasis (LZLGLZE), Long Zone High Grey-Level Emphasis (LZHGLE), Run Percentage (RP), Short Run Emphasis (SRE), Long Run Emphasis (LRE), Grey-Level Non-Uniformity (GLNU), Low Grey Level Run Emphasis (LGLRE), High Grey Level Run Emphasis (HGLRE), Short Run Low Grey-Level Emphasis (SRLGLE), Short Run High Grey-Level Emphasis (SRHGLE), Long Run Low Grey-Level Emphasis (LRLGLE), Long Run High Grey-Level Emphasis (LRHGLE).

In addition to the listed parameters, the coefficient of variation of the voxel values (CV) were also examined. This parameter does not belong by definition to texture parameters because the determination of its numerical value does not take into account the spatial arrangement of the voxels. When calculating the texture parameters, the intensities of the voxels within the selected region of interest are always rescaled. Three types of re-sampling were used and tested: lesion relative resampling (LRR), lesion absolute resampling (LAR) and absolute resampling (AR).

### Volume dependency

We have developed a simple but very informative procedure for volume dependency testing. All PET/CT equipment are delivered with a homogeneous cylindrical phantom for routine calibration and image quality testing. As the upload of this phantom is fast and simple it was used in our investigations to test the volume dependence of the texture parameters. Carrying out phantom measurements with three human PET/CT scanners, VOIs of different size (0.5-1000 ml) were defined on the reconstructed images and the pattern analysis was performed on the respective voxels. The calculated values of the individual texture parameters were plotted against the volume of the VOI. As the phantom was filled by a homogeneous water solution of the radiopharmaceutical (5kBq/ml  $^{18}\text{F}$ -FDG solution), it is reasonable to assume that a given parameter for a given (homogeneous) pattern has to have the same numerical value regardless of VOI volume. In case the numerical value of a parameter shows volume dependence this parameter is not suitable for pattern characterization.

### Reproducibility

A self-made 7-compartment revolver phantom was constructed for our reproducibility investigations and mounted to the standard NEMA IEC phantom. The background of the revolver phantom was filled with 5kBq/ml and the syringes with 20 kBq/ml, 40 kBq/ml and 80 kBq/ml activity aqueous solution and the composite phantom was scanned with a Siemens Biograph mCT choosing 240 sec/bed position. After list-mode acquisition, 60, 120, 180 and 240 second reconstructions were made under different conditions (with and without TOF and PVE corrections). The phantom measurement was repeated three times resulting in 3 parallel sets of images each with 24



reconstructed items. During the evaluation of the reconstructed images, a 40% SUV threshold was used for volume determination in each case. The average and the standard deviation of the texture parameter was calculated from the 3 measurements belonging to the given acquisition time and reconstruction method, from which data the coefficient of variation (standard deviation / average) was also calculated.

### Sensitivity

In our sensitivity studies we investigated to what extent the value of a particular parameter changes with the change of the pattern. For this purpose, the revolver phantom mounted to the NEMA IEC phantom was used again. The change in the pattern was achieved by using  $^{11}\text{C}$  and  $^{18}\text{F}$  radionuclides with 20 minutes and 110 minutes half-lives, respectively in the aqueous solutions filling into the phantom. In the initial phase of the measurement, the activity of the syringes filled with  $^{11}\text{C}$  dominated, and because of the different half-lives, identical activity concentration of the syringes appears over time, and later the syringes containing the  $^{18}\text{F}$  nuclide dominate. During the evaluation of the reconstructed images, a 40% threshold based segmentation was applied reflecting the homogeneous activity distribution, and the value of the texture parameters for the VOI thus obtained was plotted against time.

### Visual evaluation

In addition to analysing the numerical behaviour of heterogeneity parameters in different phantom environments, we were wondering whether the values of the parameters obtained correlated with the visual perception of the radiologist/nuclear medicine experts. Three different resampling methods were used to calculate the parameters. In a Matlab environment a program and a graphical interface (GUI) was created that randomly displayed the slices of human

lesions. The GUI allowed the specialist to score from 1 to 5 the heterogeneity of the displayed lesion. The scoring was performed independently by three nuclear medicine experts and stored for each lesion in csv format for statistical analysis. After averaging the scores, a Spearman correlation analysis was performed using the IBM SPSS statistical program.

### **Preparing and setting up a heterogeneous phantom based on 3D linear movement**

A phantom measuring method was developed with a  $^{22}\text{Na}$  calibration point source continually moved in the field of view of the PET camera completing a static scan. Thus, the moving point source resulted in a 3-dimensional activity distribution in the reconstructed image. The point source was moved by orthogonally fixed high-precision robot arms, controlled by a program running in a Matlab environment. The minimum step in the movement of the robot necessary to a continuous activity distribution was determined first. In case the distance between successive stopping of the 3D linear stages is larger than the spatial resolution the result of the procedure will not imitate a homogeneous activity distribution. In case of too small steps the time required by the measurement is too long. The first thing to do is the determination of the largest moving step still resulting in a continuous activity distribution with the point source residing for identical length of time in each grid point. To do this, the source was moved along a line with different steps and a line profile was drawn after each move. Then, with the step found to be optimal, homogeneous activity distribution was imitated within a cube of  $48 \times 48 \times 48 \text{ mm}^3$  and the standard deviation and CV values of the voxel intensities were examined. The measurement was performed on a Mediso AnyScan PETCT camera. The reproducibility of the activity distribution patterns

obtained by using the 3D linear stage phantom was also investigated. Homogeneous activity distribution was imitated within a sphere of 36 mm diameter in 5 successive runs on the Mediso AnyScan PC. The sphere and background intensity ratio were set to 3:1. Reproducibility was characterized by the standard deviation/average, calculated for the mean, minimum and maximum values (for both background and sphere), and a coefficient of variation was calculated also for the time required to complete these measurements. To study the interdependence between the reconstructed activity concentration and the length of time the point source spends in the grid points this time was varied between 0 and 6 sec. Having completed the move an intensity profile was created on the reconstructed image. The slope of the fitting straight line provided the required proportionality factor between the waiting time and the reconstructed activity concentration.

In order to demonstrate the possibilities of the phantom measurement, further distributions of different geometry were imitated: spherical shell, heart shape and real human lesion, obtained from an anonymised patient record. The change in the texture as a function of the position within the FOV was studied by changing the localization of the same (imitated) lesion within the FOV. The lesion was located at the center of the FOV or 30, 50, 100 mm from it in a Mediso AnyScan PC camera. Records were reconstructed with PSF correction and without correction. The texture parameters were calculated after segmentation with a 40% threshold value. The most exciting option out of those this phantom concept allows is the comparison of the imaging features of the various PET/CT cameras. A human lesion pattern was scanned using the Mediso AnyScan PC and a GE Discovery MI digital PET / CT camera, and a nanPET/MR

device (Mediso nanoScan PM) with altered pattern size. The reconstructed images were analyzed visually and numerically.

### **3. New scientific results**

#### **HeP volume dependency**

To determine the volume dependence of the selected 27 texture parameters, a simple and easy-to-do method was developed requiring only a single homogeneous cylindrical phantom measurement. The simple procedure resulted in a remarkable amount of information. During the evaluation of the phantom spherical VOIs of different volume were defined and evaluated using the LAR method, and the discretization value (bin number) was set to 64. Examining the volume dependence of the 27 possible texture parameters, basically four different behaviours were observed. It was clearly demonstrated that the numerical value of 18 parameters showed extensive changes with the alteration of the size of the segmented volumes. In addition to the volume dependence of 5 further parameters their numerical value showed large fluctuations even in case of a noise-bearing but otherwise homogeneous pattern. Based on the literature the metabolically active tumour volume may have prognostic significance in some clinical cases, therefore this prognostic value may be inherited in the characteristic texture parameters of the pattern. Thus, a texture parameter strongly correlated with the tumour volume may have prognostic value, but in this case the given heterogeneity parameter cannot be called a texture parameter.

In the following, we focused on volume independent texture parameters. Based on the visual judgment of the curves, an approximately 25-30 ml is the minimum volume below which

texture analysis does not make sense using the currently available PET cameras. It is interesting that with this protocol there was not found any significant difference between the clinical PET devices. In addition to the results of homogenous phantom measurements, we also performed a texture analysis of lesions from human studies on the Philips Gemini TF 64. The observed volume dependence also confirms the relevance of phantom measurements, as the results showed a very similar tendency. Fanny Orlhac and coworkers also received similar results in the study of human lesions. Out of 31 parameters 10 and 19 showed correlation with the volume with  $|r| > 0.8$  and  $|r| > 0.6$ , respectively. Using 18F-FDG PET images and probability calculation considerations, Frank J. Brooks in a recent communication estimated a minimum volume of 45 ml, which is very close to the 25-30 ml volume provided by our phantom measurement. The method described by Frank J. Brooks requires a more complex mathematical evaluation compared to our method using the homogeneous cylinder phantom measurement. In addition, our real phantom measurement reflects the imaging capability of the given PET scanner and the effect of the applied reconstruction algorithm, the reconstructed voxel size and the evaluation algorithm. It has to be also mentioned that in the case of a hand drawn VOI and the InterView Fusion software we use, the segmentation algorithm assigns each voxel touched by the contour of the VOI at the slightest measure to the VOI. In case a small volume VOI is contoured its volume can be significantly overestimated by this approach. As a result of the completed tests the following parameters proved to be volume independent: ENT, COR, HOM, CON, SZE, LGLZE, SZHGLE, HGLRE, COV.

### HeP reproducibility

Reproducibility study was performed on the 9 volume independent heterogeneity parameters. For these tests, a phantom with a heterogeneous pattern was put together from everyday laboratory syringes available anywhere and relatively easy to fill. Entropy, Homogeneity, and Correlation parameters appeared highly reproducible with an error below 5% regardless of the reconstruction method and PET data acquisition time. Using appropriate data acquisition and reconstruction protocols, the reproducibility error can be kept below 10% for the variation coefficient and the Contrast parameters. Due to high ( $> 10\%$ ) reproducibility error, parameters SZE, HGLRE, SZHGLE and LGLZE were also excluded from the acceptable heterogeneity parameters.

### HeP sensitivity

Sensitivity testing of the remaining (ENT, HOM, COR, COV) parameter candidates was performed using the double-isotope revolver phantom. The obtained results provided interesting results not yet documented in the literature. In the case of the variation coefficient the corresponding time-dependent curves belonging to the two extreme patterns imitated showed a difference with a minimum in the homogeneous state. The time dependence of Entropy, Correlation, and Contrast parameters is described by a step function, meaning that different parameter values are assigned to (remarkably) different pattern. The continuously changing intensity and contrast of the pattern surprisingly does not result in a continuous change in the numerical value of these parameters. This strange phenomenon is explained by the algorithm of the re-sampling procedure discussed later. The Homogeneity parameter was not sensitive to the pattern, so this parameter is not considered to be suitable for texture analysis. As a result of the investigations specified in

points 1 to 3 of the chapter Aims, out of the of the examined 27 texture parameters, only 3 heterogeneity parameters (Entropy, Correlation, Contrast) and a descriptive statistical (COV) parameter corresponded to the volume independency expectations. Accordingly, these parameters may have prognostic value.

### Visual assessment

In the next phase of my doctoral thesis, we sought to answer the question of whether there is a correlation between the visual perception of a lesion and the value of the calculated texture. This is a very critical issue, and even preliminary results are hardly found in the literature. The main motivation was the explanation of the sensitivity measurement previously discussed. We did not understand why the texture parameters (Entropy, Correlation, Contrast) that were finally found to be compliant did not follow the degree of intensity change. In analysing the trends, we have assumed that the difference between the voxel values in the calculation of the texture is distorted. By reviewing the relevant literature data, we have implemented 3 different re-sampling algorithms. They were similar from the point of view that the values of lesion activity distributions of arbitrary but different SUV values are retained differently.

Processing experimental data related to questions listed in Aims No 1-3, the LRR re-sampling method was used, since at the time of the relevant experiments this discretization was typically used. However, this method re-samples each lesion by redistributing the lesion intensities according to the given bin between the lowest and highest values. Thus, after re-sampling, the minimum and maximum intensities will not be retained. In fact, the nature of the pattern may also become distorted (as if

we applied a filter) when significant changes occur in the intensity data. This explains the stepwise behaviour in the sensitivity test of the 5 accepted texture parameters. This experience also raises the question of what heterogeneous pattern means. The question can be divided into two parts, namely what is the definition of the pattern and when is it regarded heterogeneous. Patterns are basically characterized by two distinct features: the intensity values present in the image and the spatial distribution of the intensity values. In order to better approximate the heterogeneity of a pattern, in our further studies we have asked three experienced nuclear medicine specialists to scale the heterogeneity of real lesions on a one to five scale without clarification the meaning of the pattern and heterogeneity.

According to our analysis there was no correlation between the visual scale values of the lesion homogeneity and the HeP data as calculated by using the LRR method ( $p > 0.05$ ). This finding is in accord with the facts observed evaluating results of sensitivity investigations. Heterogeneity parameter values obtained using lesion absolute resampling and absolute resampling re-sampling showed significant correlation with visual perception grading, except for Correlation. The correlation coefficients and significance levels of these resampling methods were practically identical. In addition to the rescaling, the AR and LAR transformations retain the activity (or SUV) of the lesions. It is basically due to the fact that the calculated heterogeneity parameters correlate really close with the visual qualification of the nuclear medicine specialists.

### Heterogeneous phantom robot

Keeping in mind the results of the experiments with the homogeneous and revolver phantoms including relevant



positive and negative experiences we decided to develop a phantom construction. After the results of the homogenous and revolver phantom examinations, and the positive and negative experiences, we decided to develop a phantom construction allowing imitation of arbitrary activity pattern practicably without restriction. A method based on robot technology was found as a good solution, the detailed and satisfactory construction of which was part of the PhD program. The developed technique allowed to move a point source from gridpoint to gridpoint within a cube of  $5 \times 5 \times 5 \text{ cm}^3$  size. Having determined the required grid size, i.e. the step used to move the source and the waiting time in the individual grid points, we managed to create a homogeneous activity distribution on the reconstructed image. The variation coefficient of the voxels of the reconstructed cube was 2.34%, which reports on a very good homogeneity. This result also proves the idea that a moving point source can result in an extensive 3-dimensional activity on a reconstructed image. Homogeneous sphere, spherical shell and heart shape were also imitated to prove the flexibility of the method. Although these geometries may at first glance seem very elementary and simple, the production of some of them (e.g. heart shaped distribution) would be very complex applying traditional Plexiglas phantoms. A special experiment was carried out using the developed phantom with residence time the point source spends in the gridpoints continuously changing between 0 and 6 seconds. It was shown that with these residence times and using the given (0.8 MBq)  $^{22}\text{Na}$  point source activity concentrations between 0 and 14 kBq/ml can be achieved. This is a range of activity concentration identical to that experienced in  $^{18}\text{F}$ -FDG clinical PET investigations. Using higher activity point source allow maintaining higher accumulations with the same waiting times.

The reproducibility of the shapes and textures produced by the robot phantom was also examined. A sphere was imaged in a cube volume with 3:1 activity ratio and the scan was repeated 5 times with a Mediso AnyScan PET camera. The coefficient of variation of the minimum, maximum and average values of the corresponding segmented VOIs was calculated for both the sphere and the background cube from the reconstructed images. The very small (0.038%) coefficient of variation of the total movement time demonstrates the reliability of the method. The coefficient of variation of the measured heterogeneity parameters on the reconstructed images of the proposed PET patterns made with robot technology was below 5%. Taking into account the high accuracy of the robot arm movements ( $<0.05$  mm), this figure characterizes basically the uncertainties in the radioactive decomposition and the PET equipment sampling.

The first clinically relevant problem studied and cleared using the robot phantom was how the mapping of a particular pattern is distorted depending on its location within the field of view of the PET camera. Texture parameters were calculated with and without PSF correction for images of the same simulated lesion located in 4 different locations. No effect of the PSF correction was found on the results obtained, and the change in the numerical value of most of the heterogeneity parameters was below 5% when the localization of the lesion was changed. The Contrast Texture parameter was the only exception out of the 5 HePs tested showing changes in its numerical value between 15,5%-to 18% with changes in the localization of the lesion. Although this HeP performed well in the volume dependence, reproducibility, sensitivity tests, the present result casts doubt on its reliability.

The most exciting option offered by the phantom technique is the comparison of texture qualification of the same pattern by different PET/CT cameras. According to our current knowledge, there is no other phantom method capable to reproducibly imitate arbitrary patterns in the field of view of PET scanners. The same distribution was imitated on 3 different PET/CT cameras (Mediso AnyScan PC, GE Discovery MI, Mediso nanoScan PM). The efficiency of the of our robot phantom is demonstrated by the fact that simply reducing the 4 mm moving step used with clinical cameras to 1 mm, we succeeded to imitate the same lesion on a nanoPET device.

Images of the same pattern by the two clinical scanners got very similar visual grading what is surprising as the performance of the two devices is significantly different. With the GE Discovery MI somewhat more contrastive images were obtained visually, although one of the reasons for this may be the difference between the voxel sizes. The reconstruction by the Discovery MI camera occurs with default  $2.73 \times 2.73 \times 2.73 \text{ mm}^3$  voxel size while Mediso AnyScan PC uses  $4 \times 4 \times 4 \text{ mm}^3$  voxels. For Mediso nanoScan PM, the recording shows that the voxel size used ( $0.4 \times 0.4 \times 0.4 \text{ mm}^3$ ) is too small because a voxel size pattern appears on the recording. The difference between the numerical values of the texture parameters of the images obtained by the two clinical PET cameras from the same lesion was  $> 15\%$  with the exception of the Entropy. In case of the Contrast parameter the ratio of the two numerical value is about 2. These results underline the necessity to harmonize the PET/CT imaging in a multi-center clinical trials comprising also pattern analysis. The degrees of freedom involved in the harmonization are primarily in the reconstruction, as the data acquiring capability of PET devices cannot be modified by the user.

As the next step, we made the simplest possible harmonization, the improved voxel size of the GE Discovery MI device with better performance was changed from  $2.73 \times 2.73 \times 2.73 \text{ mm}^3$  to  $4 \times 4 \times 4 \text{ mm}^3$  used by the Mediso AnyScan PC, and  $1.2 \times 1.2 \times 1$  for nanoScan. We used  $2 \text{ mm}^3$  voxel size. After harmonization and in the case of interpolation, there is already a minimal visual difference between the three very different devices. Interestingly, after the harmonization of voxel sizes only, the differences in the HeP data between clinical devices dropped below 10%, and the Contrast parameter instead of the previous multiplier 2 only showed a 15% difference. This result predicts that heterogeneity values provided by various PET devices can be harmonized by a comprehensive optimization process. The contrast and shape distortion of various PET equipment is well known in the art, which makes it difficult to achieve the goals set by Radiomics. Distortion caused by the imaging properties of the different devices, as well as the distortions caused by the different collection and reconstruction protocols, can hide the true biological effect in a multi-centered study. In connection with this, recent publications have already appeared that seek to reveal these differences. Since there is no suitable phantom available on the basis of previous publications, the effect of different PET devices has been simulated by changing the reconstruction parameters and collection times. Orlhac et al., Reported a process (ComBat) for harmonizing the values provided by various PET imaging agents. A method for harmonizing DNA microarray measurements was implemented for harmonization. Since there was not enough phantom available until the publication, the article was based on patient data that were identified on 2 PET/CT cameras and a third PET/CT device was simulated with a post-filter reconstruction. However, harmonization based on real human measurements is

questionable due to the low biological reproducibility of the pattern.

Considering that in the new method proposed by us, the point source was moved in the air without activity outside the spreading, weakening medium and field of vision, no weakening or scattering correction was necessary during the reconstruction. For this reason, imaging does not exactly match the conditions of real human measurements. In the present paper we have proved the principle of a new method, that by moving a point source we can create arbitrary activity distribution using reconstructed images using real PET measurements. The above-mentioned drawbacks are likely to be overcome if the point source is moved in water with a given activity concentration to provide more complex conditions for human studies.

## 4. Summary

During my doctoral thesis I have discovered the theoretical significance of the analysis of the lesions pattern and the limitations of the current measurement technology. We believe that the texture of the PET image holds clinically relevant information. However, faced with the complexity of pattern measurement, we have tried to grasp, examine and clarify the most fundamental and methodologically important issues. Understanding and further developing the process of PET imaging is a phenomenon that, in some cases, is only an approximation to real human testing conditions. The results in my thesis are basically derived from phantom measurements. Phantoms, but also their method of measurement and evaluation, came from their own ideas, always keeping in mind that the results from them are relevant to solving a real clinical question. Volume dependence of potential heterogeneity parameters, dependent reproducibility and sensitivity of reconstruction and collection protocol were investigated. Based on the results obtained, the parameter was considered suitable to quantify the pattern appearing on the reconstructed image. In fact, we have developed a minimum condition system, which requires a possible, volatile, independent and sensitive parameter against a possible texture parameter. The requirements for heterogeneity parameters were tested for phantom measurements. The significance of my results lies not in the parameters that appear to be appropriate, but in the effort to validate the parameters through phantom measurements. For further parameters worth investigating, a correlation study was also performed to try to find out if there is any correlation between the visually appearing pattern and the numerical value of the given parameter. The results show that re-sampling in the calculation of the texture parameters plays a very important

role in working with visually interpretable numerical values. Finally, we have created a phantom measurement methodology that uniquely enables the simulation of arbitrary activity distribution with high reproducibility. As a result, it opens the way for the harmonization of various PET/CT equipment, which is a prerequisite for multi-center clinical research in a large patient population.



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Candidate: Attila Forgács  
Neptun ID: F9L736  
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### List of publications related to the dissertation

1. **Forgács, A.**, Kallós-Balogh, P., Nagy, F., Krizsán, Á. K., Garai, I., Trón, L., Dahlbom, M., Balkay, L.: Activity Painting: PET images of freely defined activity distributions applying a novel phantom technique.  
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### List of other publications

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*J. Nucl. Cardiol.* 25 (5), 1645-1654, 2018.  
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4. Garai, I., Barna, S., Nagy, G., **Forgács, A.**: Limitations and pitfalls of 99mTc-EDDA/HYNIC-TOC (Tektrótyd) scintigraphy.  
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