Short Thesis for the degree of doctor of philosophy (PhD)

Investigation and application of 3D printed phantoms in medical imaging diagnostics

by János Kiss

Supervisor: Dr. László Balkay

University of Debrecen
Doctoral School of Molecular Medicine

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Head of the **Defense Committee**:	György Panyi, PhD, DSc
Reviewers:	Csaba Cserháti, PhD, DSc
	Ákos Szlávecz, PhD
Members of the Defense Committee:	György Panyi, PhD, DSc
	Csaba Cserháti, PhD, DSc
	Dávid Légrády, PhD
	Mihály Simon, PhD
	Ákos Szlávecz, PhD

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, 26 April 2024.

1. Background and objectives of the doctoral thesis

Physical phantoms used alongside medical imaging devices allow comprehensive analysis of the imaging capabilities of each modality and their specific calibration. In addition, they can be used to great advantage in the development and testing of new imaging techniques and algorithms without the need to involve real patients in the process. This will help improve diagnostic accuracy and the quality of therapy planning. A distinct advantage of their use is that they allow repeatable and comparable tests under the same conditions.

The materials used to make phantoms need to retain their mechanical integrity over a long period of time, up to several years. In most cases, this is achieved by using plastic, glass and plexiglass solutions, which are objects that can be filled with a liquid medium and divided into separate segments. Their common characteristic is that they are built up from simple shapes (spheres, rods, cylinders) with reproducible geometric accuracy.

In the field of MRI, solutions of biological origin (vegetables and fruits) are also used, given their relaxation properties similar to human tissues. The tissue equivalent properties of artificial MR phantoms are mainly solved by using aqueous solutions of nickel chloride, copper sulphate or manganese. The potential of plants in nuclear medicine modalities (PET, SPECT) is not appropriate because objects of biological origin that do not show vital functions cannot be used, nor are they widely used in CT techniques because the image does not show the contrast or pixel value difference despite to the presence of the parts (fibres, seeds, etc.) that make up the plant phantoms that would allow their use as phantoms.

Generally speaking, measurements using simple phantom constructs do not always allow to investigate image deviations, such as noise or possible imaging errors, which may be observed during patient examinations.

3D printing is a set of automated, additive manufacturing solutions capable of producing complex and purpose-driven products at relatively low operating costs, and the rapid development and versatility of this technology has created new opportunities in the field of medical imaging. With a well-maintained printer, objects equivalent to injection moulded variants can be created by applying layer upon layer of a material that can withstand mechanical stress while maintaining surface quality to meet aesthetic criteria. In recent years, a number of publications have shown that for certain imaging modalities and specific diagnostic questions, 3D printing technologies offer a suitable method for the efficient design and fabrication of phantoms. However, far from realising the full potential of this method, it appears that for every specific imaging problem, 3D printed phantoms can be found or developed that can provide a relevant answer to the clinical question.

The phantoms created using this technology can be customised to match the unique, complex anatomical structure of the patient, allowing the creation of an accurate and reproducible examination environment, but also simulating rare or pathology-specific conditions. Manufacturing 3D printed phantoms is a complex process that is not without its challenges. The process takes into account many aspects, including the mechanical properties and morphology of living tissue. The creation of anthropomorphic models requires precise measurement and calculation methods. In addition, the correct choice of materials and setting of printing parameters are key to producing realistic phantoms. The resulting models can be so detailed and accurate that they can even faithfully reproduce the texture of the tissue, thus allowing systematic analysis of different textures and patterns and the use of the information gained from them.

In the field of nuclear cardiology, there are a number of diagnostic challenges that are not effectively addressed by the

current procedures using simplified geometry phantom constructs, and the need for anatomically correct, easily produced and efficiently applied image quality phantoms has arisen. One such challenge is the systematic investigation of image artefacts resulting from inhomogeneity in heart wall thickness, which is hampered by the unavailability of anthropomorphic heart phantoms, as this cannot be achieved by conventional fabrication methods.

The visualisation provided by imaging techniques does not always provide sufficient information on the complex anatomical and histological relationships and their prognostic value. Texture analysis, which is the subject of radiomics, can be used to quantitatively characterize patterns and features that are not always or only qualitatively detectable by the human eye. In recent years, texture analysis has become an active area of research to investigate the reliability and clinical relevance of the method. However, the rapid increase in the number and variety of texture indices (TI), which represent the quantitative results of analyses, has posed a challenge in characterising individual pathologies and evaluating the clinical relevance of their use.

The potential benefits of texture analysis are becoming more pronounced in clinical investigations, such as improving imaging techniques, evaluating findings and the patient's subsequent pathway. However, a problem with texture indices provided by analyses is that the parameters that prove useful in each modality, or their mathematical abstractions, are not treated consensually in the literature. This leaves the question of the emergence of consistent, sufficiently heterogeneous, durable and easy-to-use phantoms for the given modalities as an open issue.

Phantoms intended for the analysis of radiomics parameters do not generally represent anatomically correct organs, but rather a single geometric object with a concrete but complex texture. These phantoms are predefined in shape, giving the

possibility to highlight or suppress even small geometric details in the structure. However, there is no consensus in the literature on the feasibility of generically creating a radiomics phantom whose data can be used to actually infer the same texture parameter of living tissue.

3D printing technology is also increasingly emerging in the field of MR radiomics. However, there are currently very few publications on such phantom constructs, as it is particularly difficult to create phantoms that are sufficiently heterogeneous in both time and complexity for texture computations, and to produce them in a reproducible way.

The creation of new, structurally heterogeneous, printed phantoms is motivated by this gap in the field, as quantifiable radiomic evaluation is particularly important for otherwise unquantifiable MR imaging. By creating a phantom that is structurally stable, easy to produce in a timely manner, and reliably reproducible for certain parameters of texture analysis, many previously unanswered questions can be investigated.

During the research underlying the dissertation, we analyzed the broader applicability of patient-specific anthropomorphic and mathematical abstract phantoms produced using specific fused deposition modeling (FDM) 3D printing technology with polylactic acid (PLA) and polyethylene terephthalate glycol (PETG) filament materials in the fields of nuclear cardiology and MRI imaging. In one part of our investigations, we explored whether a printed anthropomorphic heart phantom could be created for SPECT/CT diagnostic applications in cardiology to efficiently analyze the imaging characteristics of the procedure. Additionally, we examined the methods, results, and reliability of texture analysis for two different types of 3D printed phantom constructions with abstract textures in MRI images.

2. Objectives

In our research, we focused on two areas in which the primary idea was to answer clinically relevant, still open questions. Accordingly, we set the following objectives in the work leading to this thesis, taking into account the different imaging equipment and examination methods.

1. We wanted to answer the question whether it is possible to reproducibly create a segmented, hollow and thus fillable left ventricular myocardial phantom from real patient data, which retains its clinical anthropomorphic character after fabrication using FDM 3D printing technology.

2. We hypothesized that once a myocardial phantom model has been generated from a healthy patient dataset, it can be modified to simulate ischemic lesions. And we wanted to demonstrate that the resulting normal and defect-containing phantoms could be used to test nuclear cardiology SPECT/CT procedures.

3. We aimed to investigate the reliability and reproducibility of texture calculations in MR diagnostics by creating structurally heterogeneous, fillable, 3D printed abstract radiomics phantoms using FDM technology.

4. The printed abstract phantom constructs were designed to be examined on two different MRI machines, with several collection protocols. Furthermore, we planned to compare the results of the resulting radiomic analyses with data from plant-based biological systems measured on the same equipment.

3. Materials and methods

3.1 Designing a myocardial phantom

One of our goals was to create an anatomically as accurate as possible myocardial phantom from real images. For this purpose, we used anonymized whole-body ^{18}F-FDG (fluorodeoxyglucose) PET/CT images of a healthy adult male (age: 67 years, weight: 63 kg). We used the 3D Slicer software (version 4.10.2 r28257) for both the scanning and pre-processing of the original image and the segmentation process. We segmented the left ventricular myocardial volume of interest from the images and then cavitated the virtual myocardial volume in the resulting model. The entire model was equipped with a pedestal in which a bubble trap was designed to facilitate volume filling. For each modeling phase, we used Autodesk Meshmixer (Autodesk Inc., San Rafael, California, USA, version 3.5.474) and Trimble SketchUp Pro 2020 (Trimble Inc., Sunnyvale, California, USA, version 20.0.373) software. Two left ventricular myocardial phantoms (LVm) were created. The normal LVm phantom corresponded to the original segmented cardiac volume and had an infusible volume of 190 ± 1 ml, whereas the defected type mimicked a transmural perfusion defect in the infusible volume by incorporating a 20 × 30 mm oval solid plastic, resulting in an infusible volume of 165 ± 1 ml.

3.1.1 3D printing of LVm phantoms

Repetier-Host software (Hot-World GmbH & Co. KG, Willich, Germany, version 2.1.6) was used to create the 3D printing plans. The phantoms were created using an Anet A8 (Anet Technology Co., Ltd., Shenzhen, China) FDM type 3D printer and 3DJAKE transparent PETG filament. Multiple copies (N=6) of the two models were printed. In some cases (N=2), separate print

layers were visible on the outer tips of the finished phantoms, which were fused afterwards. To prevent possible leakage, Prisma Color acrylic spray was applied to the outer surface of the phantoms, and M5 screws were 3D printed to ensure a tight fit.

3.1.2 Print reproducibility, leakage test

The reproducibility of phantom production was tested with three separate print runs. To check for leakage, in each case, at least two water fillings were performed with a 50 ml syringe, and the phantoms were then rotated and stored for a few hours. To determine the production accuracy, spiral CT scans were performed on the water-filled normal LVm phantoms on a Mediso AnyScan® DUO FLEX SPECT/CT system (Mediso Medical Imaging Systems Ltd., Budapest) and the images were coregistered using Mediso's InterView™ FUSION (version 3.08.0008) image processing software package to visualize any discrepancies.

3.1.3 Phantom fill-ups, SPECT/CT measurements

An aqueous solution of the isotope ^{99m}Tc was used for the imaging, with red food colouring mixed in to improve visual detection of possible bubbles and leakage. SPECT/CT measurements were performed on both normal and defective LVm phantoms without the use of additional Compton scattering medium or a phantom containing background activity. These measurements are referred to as "in air" measurements. Only the normal LVm phantom was placed in the environment with background activity (Anthropomorphic Torso Phantom™). Hereafter, we refer to this measurement as the "in torso" measurement. All imaging acquisitions were performed with identical parameters on an AnyScan® DUO FLEX SPECT/CT system equipped with a low energy, high

resolution (LEHR) collimator. CT images were also acquired for attenuation correction and fusion visualization.

3.1.4 Data processing

The measured data were processed using Mediso InterView™ XP (version 3.06.006) and Tera-Tomo™ 3D SPECT-Q iterative CT-based image reconstruction with scatter and attenuation correction. The 17-segment polar map technique was chosen for quantitative evaluation. Measurements of normal and defective myocardial phantoms "in air" were compared to explore the effect of the presence of the defect alone on the radioactive distribution. To investigate the effect of the presence of a scattering medium, measurements of normal LVm phantoms "in torso" and "in air" were compared. The calculated percentage differences of the comparisons were used to construct and analyse additional quasi-virtual polar maps.

3.2 Adaptation of radiomics phantoms and MR testing methods

3.2.1 Biological phantoms

For biological phantoms, it is important that they are structurally water-rich, heterogeneous, stable over time, relatively compact, taking into account their plant properties, and of a size suitable for MR studies. On this basis, we used 4 kiwis, 3 tomatoes and 3 onions in our studies. For each MR image, all 10 biological phantoms were inserted into the field of view. One of the four pre-selected kiwis ($kiwi_{rot}$) was rotated perpendicular to its primary axes between the three repeated MR scans to investigate the possible effect of orientation on the calculated texture indices.

3.2.2 3D printed phantoms

3.2.2.1 QR code based phantom construction

The initial Quick Response (QR) code was encoded with the textual information "UNIDEB MRI TEXTURE ANALYSIS PHANTOM" with an error correction setting of M (15%). This was then converted into a 3D model using Trimble SketchUp Pro 2020 (Trimble Inc., Sunnyvale, CA, USA, version 20.0.373) by forming the code components into columns and placing this into an enclosing brick body open from above. This created a spatial QR code with a 5 × 5 cm square base with a 4 cm high wall, in which the columns of the code project 3 cm. This model will be referred to as the "large QR code", while a smaller version was also created with dimensions of 4 × 4 × 3 cm^3. The latter is referred to as the "small QR code", with a code height of 2 cm. The containers were filled with an aqueous solution of $NiCl_2$ at a concentration of 10 mM.

3.2.2.2 Hilbert-cube based phantom construction

For the second 3D-printed phantom model, the goal was to create a tube in a 5 × 5 × 5 cm Hilbert cube model that could be filled with a 10 mM aqueous solution of $NiCl_2$. To create the tube, we used Autodesk Meshmixer (Autodesk Inc., San Rafael, California, USA, version 3.5.474) with a wall thickness of 1 mm. In addition, for the original model, we used Trimble SketchUp Pro 2020 software to create a checkerboard-like external pattern in three dimensions, which achieved a more robust shape and extra spatial heterogeneity with the alternating plastic shape. The phantom, hereafter called a Hilbert cube, was given a fractal-like Menger sponge shape on the outside and a pipe system following the second-order Hilbert cube on the inside.

3.2.2.3 3D printing of radiomics phantoms

All three phantoms were 3D printed from a white ecoPLA material manufactured and distributed by 3DJake using a Creality Ender 3, FDM type machine. For this, the printing design was implemented using Repetier-Host (Hot-World GmbH and Co. KG, Willich, Germany, version 2.1.6) software.

3.2.3 Acquisition of MR images

The measurements were performed on a Philips Achieva 3.0T (TX) with a field strength of 3 Tesla and a Siemens Magnetom Essenza 1.5T MRI machine. A single 6-channel head coil was available for the 1.5T equipment, while an 8-channel head coil and a 32-channel neurovascular coil were available for the 3T case. For both devices, we used isotropic 1 × 1 × 1 mm^3 and 2 × 2 × 2 mm^3 voxel resolutions with 3D T1- and T2-weighted sequences in routine clinical protocols. Each phantom measurement was repeated three times with the same parameter, positioning and geometric setup.

3.2.4 Image visualisation and segmentation

Segmentation of the images was performed semi-automatically using 3D Slicer (version 4.10.2 r28257). For the 3D printed phantoms, virtual masks in the shape of cubes and cylinders of different sizes were defined and placed on all relevant shots. For the biological phantoms, we used 3D Slicer's "Grow from Seeds" algorithm to make the masks as close as possible to the objects, and then manually corrected them for the boundary zones between the fruit/vegetable and the surrounding air.

3.2.5 Normalisation and discretisation

Due to the different parameters of the different MRI machines and the non-quantitative nature of the imaging technique, it was necessary to normalise the data. For this procedure, the $\mu \pm 3\sigma$ normalization technique was used, where μ is the mean of the image and σ is the standard deviation of the image. After normalization, two different discretization methods were used, the Fixed Bin Number (FBN) and the Fixed Bin Size (FBS) technique. For FBN the fixed bin parameter chosen was 64, while when using FBS the bin width used was 0.15 for normalized images and 50 for non-normalized images.

3.2.6 Calculation of texture indices

A total of 40 predefined TI functions were implemented in the radiomics evaluation using MATLAB (2020, The MathWorks Inc., Natick, MA, USA) framework software. Following the chosen discretization, 18 GLCM (Gray Level Co-Occurrence Matrix), 11 GLSZM (Gray Level Size Zone Matrix) and 11 GLRLM (Gray Level Run Length Matrix) TI were extracted from the VOIs defined by the segmentations during the analyses. With the

normalization, the simpler statistical characteristics of each segment were also made comparable, so that the calculated parameters were complemented with 5 histogram-based statistical characteristics for VOIs globally.

However, 11 out of the 45 features obtained were already inconclusive in the first test analyses, and therefore we drew conclusions from the results of 34 radiomics parameters.

3.2.7 Statistical analysis

To assess the variability, coefficients of variation (CV) were calculated from the mean and standard deviation of the texture indices of the measurement triplets, which shows how consistent the parameters calculated from the matched measurements are.

The inter class correlation coefficient (ICC) is a widely used reliability indicator in the literature. For the ICC calculations examining the reproducibility of each TI, the "2-way mixed effect" model was used in addition to the "single rater/measurement" type and the "absolute agreement" definition. Calculations were performed for 14 different pairs of data sets, comparing results (averages of repeated measures) from two different measurement designs and using all phantoms.

Both the CV and ICC calculations were performed using MATLAB (2020, The MathWorks Inc., Natick, MA, USA) and Microsoft Office Excel 2016 software.

3.2.8 QR code readability test

The QR code phantoms were also subjected to what we call a QR code readability test. Using two different methods, we tried to read back the encoded textual information for MR recordings of QR codes. Due to the nature of the phantoms, they contain

readable structure only in the coronal planar direction, so this was used for the evaluations.

For decoding, we used a script we wrote in a Python framework, which determined whether a successful decoding was performed on each coronal slice of the MR record containing all QR codes. On the other hand, we displayed on a monitor a single central coronal slice of the same "original" recordings and tested the success of successful readouts using different types of smartphones from several manufacturers.

The "original" images had a relatively low pixel count, so we also rescaled them to 1024 × 1024 pixel resolution using an interpolation method to improve the hoped-for readout yield. These will be referred to hereafter as "interpolated images". The value of successful decodes was expressed as a percentage of the number of coronal images, and this parameter was defined as the readout rate. Finally, we took the average of the matched measurement triplets as the readout rate to be presented.

4. New scientific results of the thesis

4.1 SPECT/CT examination of 3D printed LVm phantoms

4.1.1 Compliance of the finished LVm phantoms

The 3D-printed LVm phantoms were found to be easily refillable several times, and the screws of the filling holes closed properly during the measurements, thus no air bubbles or leakage was observed. The average return volume of the three syringe fillings was 189.4 ml ± 1.4 ml, including the volume of the bubble trap, which allowed the full use of the established test volumes. An important finding is that often even the manufacturer's commercial heart phantoms do not have a bubble trap, as its design would be challenging using conventional manufacturing techniques. A further result is that no leakage or evaporation was observed from a fully filled volume of a normal and a defective phantom, even after three months of storage.

Based on the coregistration obtained by InterView™ FUSION software of the three times repeated high-resolution CT images, the image of the phantoms showed a good agreement in terms of both shape and fillable volume, thus our method allows reproducible production from imaging perspective.

The phantom design process created offers a high degree of flexibility by allowing the models to be scaled in size and to accommodate different numbers and shapes of perfusion defects within the volume to be filled. Realistic shape accuracy is of great importance when testing the optimal settings of image reconstruction algorithms and to eliminate artifacts caused by geometric variation. Moreover, our phantom reconstruction can help to find optimal iteration settings for a given image reconstruction for geometrically simpler LV phantoms. Our method also provides the possibility to print up to two small hearts based on standard gated patient image

sequences, thus testing the ejection fraction measurement accuracy of different reconstruction methods. The anatomically correct design of the LV myocardium may also be important when comparing the effect of hybrid or ellipsoidal sampling to generate polar maps.

4.1.2 SPECT/CT measurements of LVm phantoms

In the reconstructed images of the "in air" SPECT measurements, the activity distribution of the phantoms followed the anthropomorphic shape very well and was nicely depicted in the usual clinical routine myocardium shape. The differences between the images of the defective and normal phantoms gave a well-detected difference in the projected volume. The signal dropout boundaries had a fine structure and followed the shape and size of the planned defect.

Each of the printed phantoms was compatible with the standard anthropomorphic torso phantom, with both phantom realizations fitting in both suspension and size in place of the original heart insert. The reconstructed SPECT images clearly demonstrated that the activity distribution of the standard LVm phantom was well represented despite the background activity of the torso phantom. This is particularly pronounced in view of the fact that the normal phantom was placed in the torso phantom after the "in air" measurement, so that its own activity was already reduced compared to the initial measurements. The phantoms remained intact throughout the experiments, and the loaded ^{99m}Tc-containing radioactive solution did not dissolved in the volume of the core phantom.

4.1.3 Polar map analyses

Using 17-segment polar map analysis, we found that the two types of measurements of the normal LVm phantom differ only slightly, while the edge of the defect phantom is significant only

in the defect regions compared to the normal. For the "in air" measurements of normal and defective LVm, the basal anterolateral region was the most significant of the 17 segments. Comparing the initially high-signal mid-inferior region of the normal LVm model with the same segment of the defective LVm model, we observed a significant decrease due to the artificial defect.

The apparent differences in polar map segments between measurements of the normal LVm phantom in two configurations ("in air" and "in torso") can be attributed to at least two sources. The activity of the radiopharmaceutical was measured in the "torso" with a reduced value (59.8 kBq/ml) compared to the "in air" case (72.74 kBq/ml). In addition, the liver and background compartments loaded in the torso phantom (62.45 kBq/ml and 20.15 kBq/ml, respectively) represented significant ratios that were realistic for real human SPECT measurements. Thus, as expected, the signal-to-noise ratio of the image was also altered and lower, which occurred primarily in the basal anterolateral and apex regions. In general, however, all three polar maps showed similar peak and apical region values.

For each of the three measurements, detailed comparisons of the relative perfusion values for each region, characterized by relative percentage difference, were presented using differential polar maps, where the basis for comparison was the "in air" measurements of the normal LVm phantom. For relative % differences, a negative value represented a deterioration, while a positive value represented a region with better stacking. The normal LVm "in torso" segment values were typically smaller in the basal region compared to the "in air" data.

When comparing the defect and normal LVm measurements, significant differences in the area of contiguity were specifically found only at the defect site. A difference of around ten percent, but only for a specific segment, was observed at a single site in the two comparisons: 10.2% in the apical lateral and 10.6% in

the basal anteroseptal segment. As these were only local in nature, they are more likely to be due to statistical error in measurement and processing (e.g. reorientation). The values of the normal LVm - defective LVm comparison ranged from [-24.7% to 10.6%], and in 11 of the 17 segments the value was less than 5%. And the values for the normal LVm phantom "in air" - "in torso" comparison ranged from [- 12.4% to 10.2%], and 10 segments had values less than 5%.

When comparing measurements of the normal LVm phantom "in air" vs "in torso", the increase or decrease in each region was not due to the nature of our phantom but was presumably caused by the manual heart reorientation performed in a given step of the software evaluation and its uncertainty, since a significant part of the variation was observed in the basal peripheral regions, whereas the values of the other regions, except for the basal anterolateral region, were around 5%.

To complement the work, we also prepared a portable LVm phantom kit, which included a copy of each of the two types of phantoms, as well as the necessary locking and suspension screws and phantom holders to facilitate filling. Once we were convinced that our design could be used effectively, we used this cardio-phantom set to provide other working groups with the opportunity to investigate phantoms and nuclear cardiology procedures. We have sent such a set to three universities abroad, Manchester University NHS FT, Nuklearmedizinische Klinik und Poliklinik, Technischen Universität München and Klinik und Poliklinik für Nuklearmedizin, Universitätsklinikum Leipzig, to investigate further possible applications.

4.2 Texture analysis of MRI scans using 3D printed phantoms

4.2.1 Visual comparison

The robust texture of the Hilbert cube was not affected by the applied T1 and T2 weighted contrast and different acquisition resolutions (1 mm, 2 mm), in all cases it was well represented in the images. In contrast, for QR code frames, pattern recognition varied significantly as a function of image resolution, with the visibility of finer patterns deteriorating when using 2 mm resolution for both the small and large variants.

After a preliminary visual inspection of high (1 mm) and low (2 mm) resolution images, we found that both the textures observed on the biological phantoms and the 3D printed variants heterogeneity correspond to real clinical situations. However, the finer textures (high frequency features) of the phantoms were often blurred, but this did not compromise the identifiability of the biological phantoms, so that the objects in the images could be clearly identified as representing the phantom. These results emphasise that the reliability of texture indices can depend to a large extent on the spatial resolution of the input images and thus on the information content on which the analysis is based.

4.2.2 Reproducibility of radiomic indices

To test radiometric reproducibility, the CV values calculated from three identical measurements were further averaged for each object. Our results clearly showed that the calculated reproducibility of the normalized images was better for most of the phantom constructs, but this trend was reversed for two kiwis. Our observation proved to be true not only for each object considered separately, but also for each radiomics group as a

whole, so that, except for the histogram-based group, normalization is advantageous in terms of reproducibility.

The significant variation in the histogram-based indices was to be expected, as this parameter set primarily provides a global measure of image texture, so averaging over significantly different objects clearly leads to biased results. As described, the use of normalization improves repeatability in most cases, so all further radiomics results presented in this thesis were for the normalized case, which results are presented as color maps.

Of the 45 texture indices initially included in the evaluation, 11 were eliminated from further analyses based on CV data greater than 10%. These TI's were JMax, JVar, Energy, ClusterShade, ClusterProm, HGRE, SRHGE, LRHGE, LZE, LZLGE and LZHGE. Accordingly, only 34 texture index data were used for further inference.

The comparison of the $kiwi_{rot}$ and the other three kiwi phantoms showed that the reproducibility of the data of the $kiwi_{rot}$ rotated between acquisitions is lower, as its CV values are globally higher. The histogram-based CV value was definitely higher for the kiwis compared to the other objects. However, this phenomenon was not observed for the $kiwi_{rot}$. The evaluation of the $kiwi_{rot}$ rotated between measurements clearly shows that if one wants to use the image material of a repeated MR scan for texture analysis, it is advisable to scan the tissue or organ in the same position, since the texture resolution of kiwifruit or other tissues with similar character is finer than the spatial resolution of the MRI device involved in the scan. However, apart from the kiwis's histogram data, it can be generally stated that there was no characteristic difference in reproducibility data obtained with biological and 3D printed phantoms.

It was observed that the repeatability of most texture features was better at 1.5 T (CV_{mean} =1.94%) than at 3 T (CV_{mean} =2.11%) and T1 weighting. In addition, there was no significant difference between FBN and FBS discretization, either when

considering the objects individually or when considering all objects data averaged together. In the latter case, CV_{mean} = 2.04 % and 2.06 % for FBN and FBS rebinning, respectively. The reproducibility of biological object measurements was dramatically improved when using 1 mm isotropic resolution compared to 2 mm collections. This is also true for the small QR code phantom, but the trend is interestingly reversed for the Hilbert cube and the large QR code. However, it is true for all 3D printed phantoms that T2 weighted sequences provide better reproducibility.

4.2.3 Reliability of radiomic indices interpreted from MRI images

The ICC calculation of the 14 possible protocol comparison scenarios showed that the worst correlation is between the two studies performed on different MR systems. In some cases, negative values appeared between the data of these four correlation pairs studied, which means that they are practically unvaluable. The remaining 10 pairs of MRI protocols had good or excellent correlations for almost all TI groups. Outstanding is the case of the 3T_T1_8ch-32ch_1mm and 3T_T1_8ch-32ch_2mm comparisons.

One of the main findings of our studies was that 3D printed phantoms are similarly robust and provide reproducible TI metrics as biological phantoms, and thus may be beneficial in determining optimal radiomic MR imaging protocols. This is very relevant as the texture indices that result from the analyses are fundamentally dependent on the MR field strength and the setup parameters of the protocols, so harmonization of MRI systems would be important, but this is an insurmountable challenge with biological phantoms as they suffer structural degradation over time. Our 3D printed phantom constructs eliminate this problem. Their physical properties have not changed since the presented measurements were performed

(~2 years), while plant phantoms were considered structurally stable for only one to two weeks.

4.2.4 Readability tests of QR codes on MR images

The image quality of the texture information stored in the phantoms was also assessed by the readout yield of QR codes, which showed how the stored deep-level information is degraded by MR imaging. We hypothesized that successful decoding of the QR code would demonstrate that the MR image sequence preserved most of the physical properties of the original texture.

The readability results of the QR code recordings showed a fundamental dependence on the acquisition settings used, such as the coils used, the field strength applied or even the acquisition resolution, all of which can affect the degree of information loss. This was true for both Python-based and mobile phone-based decoding. None of the methods used could detect information from images with a resolution of 2 × 2 × 2 mm^3. Clearly, the interpolation applied to the images did not have a significant corrective effect on the recovery of the image information content. However, for the high-resolution MR images (1x1x1 mm^3 isotropic volume), the textual information stored in the phantoms was recovered in many cases under different readout procedures.

This result showed that the image quality is good enough to preserve the information content. The QR code reading algorithms have a predefined error correction function that gives an exact measure of the possible degradation. In our case, the texture information that can be read out with an error tolerance chosen to 15% at optimal settings indicates that the information content of the object in the MR device and the image formed by the acquisition does not change significantly at the texture level. This is very significant, as this phenomenon is analogous to the clinical situation, where the detection of a

lesion may depend on the experience of the radiologist in a particular tumour lesion, where we can only assume that the imaging preserves all the information that is important to us. To our knowledge, such distortion of information (the content of the QR code) at a deeper level in the texture, and its investigation, has not yet been reported in the literature. The metric of the degradation of embedded information can be used as a useful new parameter in addition to the existing radiomics features.

5. Summary

We have demonstrated that it is possible to create a 3D-printed, fillable, anthropomorphic left ventricular myocardial phantom, constructed from FDG PET/CT images of a real subject. We sought to implement two scenarios that are common in the clinical setting, creating both a normal and an anthropomorphic cardiac phantom with a defect. Using two phantom constructs loaded with ^{99m}Tc activity, we acquired SPECT/CT images under different study protocols and performed 17-segment polar map analysis to demonstrate the nuclear cardiological reliability and utility of the printed phantoms. The 3D design and printing process presented in this thesis is flexible and allows the production of anthropomorphic cardiac phantoms of different sizes (mimicking different adult and pediatric scans) and with specific defects and stacking, making it specifically suited for the investigation and improvement of SPECT imaging and image quality.

In the second part of our work on abstract, fillable, 3D printed phantoms we have developed in the field of MR imaging, we have demonstrated that they offer a unique opportunity to analyse the reliability and challenges of radiomics analysis. Two different types of printed models in triplicate (small and large QR code cubes and a Hilbert cube) and, for comparison, three types of biological phantoms (kiwifruit, tomato and onion) were examined on two different MR machines under a range of setup parameters. Through the radiomic analyses performed, we found a good agreement between the applicability of biological and 3D-printed phantoms. We further determined that the most robust radiomics features are provided by 3D T1 weighted imaging, with lower field strength (1.5 T) and better spatial data acquisition (1 mm^3). We find that the large QR code cube phantom is more useful for identifying our chosen texture indices than the smaller variant or Hilbert cube phantom. We observed that, as expected, QR codes also allow for a finer

analysis of texture distortion by checking the readability of textual information stored in the codes. In turn, the more robust texture of the Hilbert cube allows for the rapid filtering of underperforming, less useful texture parameters. Based on our results, the flexibility of 3D printing may be a favourable method for producing phantoms for the analysis of radiomics features, and even for comparing the radiomics performance of MR devices. Moreover, unlike biological phantoms, this type of phantom remains stable over time, even after several months or even years. In view of this, they have the potential to answer a number of questions that are still open today in diagnostic radiomics analysis.

6. Publications on which the thesis is based

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Registry number: DEENK/485/2023.PL
Subject: PhD Publication List

Candidate: János Kiss
Doctoral School: Doctoral School of Molecular Medicine
MTMT ID: 10054246

List of publications related to the dissertation

1. **Kiss, J.**, Balkay, L., Kukuts, K., Mikó, M., Forgács, A., Trencsényi, G., Krizsán, Á. K.: 3D printed anthropomorphic left ventricular myocardial phantom for nuclear medicine imaging applications.
   EJNMMI Phys. 9 (1), 34, 2022.
   DOI: http://dx.doi.org/10.1186/s40658-022-00461-3
   IF: 4

2. Veres, G.*, **Kiss, J.***, Vas, N. F., Kallos-Balogh, P., Máthé, N. B., Lassen, M. L., Berényi, E., Balkay, L.: Phantom Study on the Robustness of MR Radiomics Features: comparing the Applicability of 3D Printed and Biological Phantoms.
   Diagnostics. 12 (9), 1-24, 2022.
   DOI: http://dx.doi.org/10.3390/diagnostics12092196
   * Theese authors contributed equally to this work.
   IF: 3.6

List of other publications

3. Krizsán, Á. K., Kukuts, K., Al-Muhanna, W., Szoboszlai, Z., Balázs, L., Szabó, B., **Kiss, J.**, Nekolla, S., Barna, S., Garai, I., Bükki, T., Forgács, A.: Performance evaluation of a novel multi-pinhole collimator on triple-NaI-detector SPECT/CT for dedicated myocardial imaging.
   EJNMMI Phys. 10 (1), 1-16, 2023.
   DOI: http://dx.doi.org/10.1186/s40658-023-00541-y
   IF: 4 (2022)

4. Botár, R., Molnár, E., Garda, Z., Madarasi, E., Trencsényi, G., **Kiss, J.**, Kálmán, F. K., Tircsó, G.: Synthesis and characterization of a stable and inert Mn-II-based Zn-II responsive MRI probe for molecular imaging of glucose stimulated zinc secretion (GSZS).
   Inorg. Chem. Front. 9 (3), 577-583, 2022.
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5. Abad Galán, L., Hamon, N., Nguyen, C., Molnár, E., **Kiss, J.**, Mendy, J., Hadj-Kaddour, K., Onofre, M., Trencsényi, G., Monnereau, C., Beyler, M., Tircsó, G., Gary-Bobo, M., Maury, O., Tripier, R.: Design of polyazamacrocyclic Gd3+ theranostic agents combining magnetic resonance imaging and two-photon photodynamic therapy.
Inorg. Chem. Front. 8 (9), 2213-2224, 2021.
DOI: http://dx.doi.org/10.1039/D0QI01519A
IF: 7.779

6. Kálmán, F. K., Nagy, V., Váradi, B., Garda, Z., Molnár, E., Trencsényi, G., **Kiss, J.**, Même, S., Même, W., Tóth, É., Tircsó, G.: Mn(II)-based MRI contrast agent candidate for vascular imaging.
J. Med. Chem. 63 (11), 6057-6065, 2020.
DOI: http://dx.doi.org/10.1021/acs.jmedchem.0c00197
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7. Botár, R., Molnár, E., Trencsényi, G., **Kiss, J.**, Kálmán, F. K., Tircsó, G.: Stable and inert Mn(II)-based and pH responsive contrast agents.
J. Am. Chem. Soc. 142 (4), 1662-1666, 2020.
DOI: http://dx.doi.org/10.1021/jacs.9b09407
IF: 15.419

Total IF of journals (all publications): 49,244
Total IF of journals (publications related to the dissertation): 7,6

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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