Thesis for the Degree of doctor of philosophy (Ph.D.)

Monte-Carlo simulation based analysis of performance parameters in the MiniPET scanner, developed for preclinical studies

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1. Introduction

Positron emission tomography is a relatively new approach in medical imaging, which was introduced into the clinical diagnostic protocols two decades ago and it is applicable widely in medicine. The sensitive tools of PET technology enable the non-invasive study of biochemical processes in tissues, the examination of neurological or psychological diseases, cardiological lesions and cancer. The information acquired by this reliable and efficient diagnostic method usually can not be replaced from other sources. In the last decades the significance of in-vivo models in biological research has increased, implying the demand for the in-vivo examination of small animals using imaging techniques. The resolution of human PET-cameras (about 4mm) can not provide the appropriate spatial resolution (less than 1 mm) for small animal studies. To overcome this problem several programs have started in the late 90s to develop high resolution PET instruments dedicated to small animal experiments. These developments resulted the first experimental, later commercial instruments in the early 2000s. During the decade the development of small animal PET-cameras has become a widely researched area and several research groups have presented own devices. Meanwhile it became desired to work out general methodologies for the characterization of small animal cameras (spatial resolution, field of view, sensitivity), and the NEMA NU 4-2008 collection of measurement and evaluation protocols were developed as standard. Nowadays almost solely this standard is used to determine the parameters of small animal PET cameras.

In PET-technology, especially in the development of small animal PET instruments, the simulation of data acquisition processes has become a general. In the development of PET mini-cameras simulation is a crucial tool to analyse data acquisition and determine the most appropriate geometry, the ideal crystal material, the optimal electronics and various further components of the system, thus the imaging capabilities and performance parameters of the developed camera can be studied without building it in the various configurations.

In Debrecen the PET-program started in the early 90s and beside the participation of the PET Center, experts from the MTA-ATOMKI actively took part in the development. Being the first project in the region, the developement of a high resolution small animal PET camera (MiniPET-I) was started in 2001. The project was founded by a NKFP tender and was realized with the participation of the PET Center. The MiniPET-I still does not have full detector ring therefore the projections for reconstruction were produced by rotating 4 detector modules (each of them containing 20 x 20 pin crystals) ordered into the geometry with 90 degrees between neighbouring the detectors. The resolution of the system was 2 mm. The development of the full-ringed MiniPET-II instrument was started

in 2006 with the support of another NKFP tender, which has been finished recently, and the first biological projects have already been started using the developed device.

2. Aims of the research

My work aimed to solve the following issues related to the development of the MiniPET-I and MiniPET-II scanners:

1. Development of a software (VPET: Virtual PET Scanner) for the analytical and statistical (Monte-Carlo) simulation based modelling of data acquisition in human and small animal PET scanners. This development includes the embedding of the software into the M3I (MultiModal Medical Imaging) framework, developed earlier in our institute.

2. Determination of technical characteristics and performance parameters of the MiniPET-I scanner through measurements and simulations. The fitting of the previously developed VPET software to the special data acquisition protocol of the instrument. The validation of VPET by real acquisitions and the comparison of the measured and functional parameters of the scanner.

3. Determination of performance parameters and imaging characteristics of MiniPET-II according to the NEMA NU 4-2008 collection of standards. Implementing the required methodological developments in the M3I framework.

4. Proofing the usability of the MiniPET-II scanner through real biological studies. Development of biological measurement protocols.

3. Materials and Methods

3.1. The developed software system for multimodal medical imaging

To fulfil the aimed developments we have used the MultiModal Medical Imaging framework, which was worked out with the support of successive tenders, started by the experts of the PET Center and continued by the Institute of Nuclear Medicine. The aim of the framework is to provide software libraries for imaging, into which the developed software components can be embedded and used in further projects, instead of constituting standalone, independent solutions. Therefore, the M3I package become a continuously developing software system covering all the areas of medical imaging. After developing the multimodal imaging methods, the use and extension of the libraries became a crucial part of the MiniPET project.

3.2. Monte-Carlo simulation software and hardware system

Monte-Carlo based simulation is an indispensable tool in modern detector engineering, depending on the available computing capacity it can be applied more-or-less efficiently. In the case of the MiniPET project the size of the crystals and the structure of the crystal matrix in the detector are primarily determined by the size of the photoelectron-multiplier, therefore simulation can not be used in this part of the development. However, the parallelly started hardware and software developments required the simulation system, since PET-software can not be developed without measured data, it was replaced by simulations until the hardware was finished. Due to these reasons the first version of the software system became ready before finishing the detector ring. The used Monte-Carlo simulation system is based on the GATE (*Geant4 Application for Tomographic Emission*) software, which is built upon the Geant4 software from CERN.

3.3. The MiniPET-I scanner

The detector system of the MiniPET-I scanner contains 4 arrays of detectors, fixed to a gantry with the radius of 93.6 mm, rotatable around its axial axis. Each of the detector blocks consists of 64 pieces of LSO (lutetium oxyorthosilicate polluted by cerium) pin crystals with size of 2 x 2 x 10 mm3, ordered into 8 x 8 shaped matrices. The light impulses of the crystal blocks are converted to electric signals by Hamamatsu position-sensitive photo-electron multipliers. These signals are digitalized by the integrated electronics of the

detector modules and then signal processing algorithms running on XILINX Virtex FPGA cards convert the digitalized signal to the form appropriate for network transmitting. The event packages are forwarded to the data acquisition server by a Microchip PIC 18F452 micro-controller. The scanner consists of 4 detector blocks, 4 acquisitions (with the difference of 22.5 degrees in rotation around the axial axis) are required to collect enough events for image reconstruction. Since rotation is required for reconstruction and the 17mm of axial field of view is relatively small, the scanner is primeraly used for demonstrational purposes and to study the issues of PET-data acquisition. Altough some biological measurements were performed for demonstration, the instrument have never been used in complex biological projects

3.4. The MiniPET-II scanner

The detector system of the scanner consists of 12 detector blocks, in a ring with a diameter of 211mm. In the detector blocks the gamma emission is detected by LYSO (Cerium-doped Lutetium Yttrium Orthosilicate) scintillator crystal matrices and the optically attached Hamamatsu H9500 position sensitive photo-electron multipliers. Each of the crystal arrays contains 35 x 35 crystals, with the size of 1.27 x 1.27 x 12 mm3, glued by the provider using highly photoreflexive material. The detector signals are digitalized with 0.156 ns time resolution by the four channel data acquisition cards developed by the Department of Electronics, ATOMKI. During the processing of the signals the Xilinx Virtex-4 FX12 FPGA modules perform the generation of timestamps, computation of energy, position discrimination, the identification of the signal form and verification of status. The developers have embedded a PPC based Linux environment into the FPGA chips. This operating system provides the availability of the detectors as complete computers on the network accessible through standard networkig protocols. Furthermore, the detector modules can run the own data acquisition and communication programs.

3.5. MiniPET software system

The software of the MiniPET has been developed using the M3I software system which contains several special applications beyond the library components. These applications can be used for data acquisition, rebinning, image reconstruction and to perform various corrections related to PET technology.

3.6. The measurements performed along the standard NEMA NU 2008-4

The performance parameters of the MiniPET-II scanner were determined according to the NEMA NU-4 standard (2008) declaring the protocol of performance measurements for small animal PET scanners. The prescribed measurements have been performed and the acquired data have been processed with the proprietary software. Four groups of performance parameters can be distinguished: the quantitative characteristics of spatial resolution of the instrument, loadability of the scanner, sensitivity and imaging capabilities. In the former three cases the standard Single Slice Rebinning (SSRB) method was used for rebinning and for sinogram generation and Filtered Backprojection for analytic reconstruction (with Ramlak filter a 0.9 cutoff frequency), respectively. Processing the measurements of the image quality phantom, SSRB rebinning and 20 iterations of the ML-EM methods were used for reconstruction.

3.7. Biological studies

3.7.1. Measurement protocols

The performance parameters declared in the NEMA-standard certify the usefulness of the MiniPET-II scanner in biological research. Furthermore, we have developed special data acquisition and image reconstruction protocols for the measurements. In the protocol set up some parameters were fixed (3 ns of coincidence window, 350 – 650 keV energy discrimination, 50 ns random time window translation, 3-to-1 coincidence relation among the detectors) but the duration of acquisition, the number of measurements in the mapping regions and the bed movements between two measurements were changed within reasonable limits. The primer data is stored and archived in list mode lr5 file form. These primer data files are converted to 3D-LOR data files, after performing energy and position discrimination, random and uniformity correction. From the 3D-LOR data 2D-LOR files are generated with the SSRB method followed by the application of 20 iterations of 2D ML-EM reconstruction algorithm. The voxel size of the reconstructed volume is 0.22 x 0.22 x 1.34 mm3 and the radius of reconstruction is 21.5 mm for the mouse phantom and 30 mm for the rat phantom, respectively.

3.7.2. Testing the MiniPET-II on animal models

Comparison of images from PET and auto-radiographic studies. ^{18}F-Fallypride (D2 dopamine antagonist) tracer was injected into the tail vein of a healthy rat, with

activity of 25.6 MBq. The PET measurement was started in the 60th minute after the injection of the radio-pharmacon. After the acquisition whole-body auto-radiographic studies were performed: the over-anaesthetized rat was frozen in liquid air, and 60 μm thick sections were cut along the striatum. In some sections the distribution of the radio-pharmacon was determined using the PhosphorImager instrument provided by the vendor Molecular Dynamics.

Beside the standardized methods, several further parameters and common algorithms have been applied for the reconstruction of the PET images. The rebinning was performed by SSRB and MSRB, generating sinograms with 180 and 210 projections, respectively, followed by analytic (FBP) and iterative (ML-EM) reconstruction algorithms. In FBP the Ramlak and Hamming filters were used while the number of iterations were changed from 10 to 40 in the ML-EM method. The ratio of the average activity in the striatum and in the surrounding tissue were analysed as the function of the reconstruction methods and parameters. We used the BrainCAD software to manually segment the striatum and other tissue regions in some representative slices of the reconstructed images.

Determination of the optimal exposition time in dynamic PET studies. The acquisition time dependence of dynamic measurements was determined using tumorous mouse models. ^{18}F-FDG radio-pharmacon with 4.9 Bq activity was injected into tumorous mice. The acquisition was performed from the 3rd until the 53th minute after the injection. Five dynamic sequences were acquired with exposition times of 0.5, 1, 2, 5 and 10 minutes. To manually select the 2.68 m (two times the distance of neighbouring slices) thick VOI region two slices of the images with 10 minutes of exposition were used since these images have the best statistical properties. For all the images for each of the dynamic sequences the activity of the chosen 3D region was determined.

Animal experiments with the analysis of tumorous mouse and rat models. Several demonstrative studies documented the suitability of the MiniPET-I tomograph for the analysis of biological systems. In these studies the available radio-pharamcons and tumorous mouse and rat models were used. The studies were performed in 1-3 weeks after the implantation of the tumour. The radio-pharamcon was injected intravenously, the animals were anaesthetized and after reaching the state of equilibrium the acquisition was performed according to one of the static, dynamic or whole-body protocols.

4. Results

4.1. Development of virtual PET software system

The development of the VPET software system is a dominant part of my dissertation. VPET offers two kinds of methods to generate primer data sets for some possible measurements: the simulation software based on GATE and the proprietary analytic methods. To emulate the physics of PET data acquisition, the idle time and pile up phenomenon in signal generation the most common Monte-Carlo based PET simulator, namely the GATE software was chosen. To appropriately model the network based transmission of the digitalized signals a special, event based simulation module was developed (DAQS – *DAQ Simulation Module*) to adjust the data generated by GATE. The DAQS emulates the timing characteristics of the tools (buffers, FIFO-s, network transmission devices, data acquisition servers) used in the MiniPET project.

In several phases of the PET development an essentially faster method is required, namely the analytic simulation. For this purpose the **lr5sim** software was developed. Although this kind of simulation does not emulate the physical phenomenon of PET data acquisition the noisy results of the emulated mapping can be used to evaluate the reconstruction algorithms. In the development of VPET the libraries of the M3I system were used. This package offers complex, Monte-Carlo based and analytic simulation methods fitting the multimodal medical imaging software system developed previously in the institute. Accordingly, the same software can be used to reconstruct, view and analyse the simulated data and the real PET acquisitions, as well.

VPET runs in Linux operating system on computer cluster controlled by the SUN Grid Engine task scheduler. However the current version of the GATE is not suitable to run in parallel environment, therefore the simulation is divided into time intervals of the same length, and each CPU emulates the events of a dedicated time period controlled by the scheduler. Using VPET the data acquisition of an arbitrary PET scanner can be modelled. The simulation process is presented in the followings.

In each case the input of the simulation consists of the digital phantom and the descriptor file, containing the parameters of the scanner and the acquisition. Both of them contain geometrical and technical information to carry out the Monte-Carlo or analytic simulation. GATE models the PET acquisition by following individual $\beta+$ decays. The digital phantom represents the 3D stationary distribution of a PET-isotope by placing the distribution in the field of view of the virtual scanner. With this phantom the frequency of $\beta+$ decays can be determined in each position of the field of view. The lr5from program can convert the result of the simulation into the lr5 format of real data acquisitions.

The developed data-transmission-effect modelling algorithm (DAQS) can be used, as well. From this conversion the result of the GATE simulation is a list mode sequence of events stored in the same way as if it was real measurement. Using the **lr5gen** application one can convert the list mode file to 3D-LOR file, which is the general input format for image reconstruction. In this case, instead of Monte-Carlo simulation, the estimated counts of the coincidence lines are determined by summing the coincidence events along the appropriate LORs going through the radioactive distribution represented by the phantom. This can be computed by line integrals using the **lr5sim** application. The result of this kind of simulation is stored in 3D-LOR format which can be used directly in reconstruction.

4.2. Application of the Virtual PET: modelling the MiniPET-I scanner

The Virtual PET software system was evaluated using the MiniPET-I scanner: several simulations were carried out to measure loadability, time and energy resolution and the results were compared to the results of real acquisitions. In this work we have chosed GATE based simulation, modelling the physical phenomenon of real acquisitions and the data transmission protocol of the MiniPET-I scanner, as well. The following parameters were analysed: event counting speed, distribution of time differences of coincidence event pairs, energy spectrum and coincidence-event counting speed.

4.2.1. Simulation of event counting speed

The event counting speed of the MiniPET-I scanner increases monotonously as the function of the activity in the field of view and after reaching 7 MBq it converges to 60kcps. This phenomena can not be modelled in GATE simulations, only the simulations extended by the tools of the DAQS package can emulate it. The loadability curve of the simulation fits well the loadability of real measurements confirming the reliability and necessity of the combined (GATE-DAQS) simulation.

4.2.2. Simulation of the distribution of time differences of coincidence event pairs

The distribution of time differences of coincidence event pairs was measured and simulated up to 6 MBq activity. Using GATE+DAQS simulation the distributions fit each other well confirming the usability of the combined simulation.

4.2.3. Simulation of the energy spectrum

The energy resolution of the instrument is defined as the quotient of the half-value-width and energy of photo peaks in the amplitude distribution of detector signals. The mean energy resolution is 19.1% with a variance of 0.7%. These values are similar to the simulated results, namely 21.5% mean resolution and 0.2% variance.

4.2.4. Speed of coincidence event counting and scanner sensitivity

The practicability of VPET was confirmed by the comparative analysis of activity dependent simulated and measured coincidence event counting speeds. Since the maximum of countrate in measurements and simulations fit each other well (1.28 and 1.3 kcps) and the results are obtained using similar activities (6.0 and 6.1 MBq). For the sensitivity of the MiniPET-I scanner the linear part of the loadability curve was simulated and the result 305 +- 15 cps/MBq value fits the measured 285 +- 19 cps/MBq sensitivity well.

4.3. Determining the performance parameters of MiniPET-II

4.3.1. Spatial resolution

The spatial resolution of the scanner is 1.3 mm in the centre of the field of view and increases to 2.3 mm toward the radial margin (25 mm from the centre). The central resolution is commensurable to the crystal size of the MiniPET-II scanner (1.35 mm) similarly to other instruments with analogous structure, published so far. The central resolution is less then 1mm when the reconstruction is carried out by the commonly used iterative ML-EM method instead of the FBP specified in the standard.

4.3.2. Analysis of the loadability curve and determination of the coincidence event rate originated from the scattering of 511 keV photons

Analysis of loadability curves, measured with mouse phantom. The event counting speed of the system in real measurements reaches the maximal 65.5 kcps which corresponds to 39.4 Mbq activity in the phantom. The NEC curve reaches the maximum (65.5 kcps) at somewhat less activity (38.8 MBq). The ratio of coincidences from scattering is 12.3 % in mouse phantom measurements. The maximum places of the curves are determined by fitting curves on the measured points.

Analysis of loadability curves measured with rat phantom. Similar measurements were carried out with rat phantom to determine the countrate curves. Accordingly, without energy discrimination the maximal real event countrate is 22 kcps when 42.6 Mbq of activity is present in the FOV. The maximum (15.8 kcps) of the NEC curve arises at almost the same phantom activity (41.8 Mbq). The ratio of events from scattering is 16.2 % in this case. Using wider energy window (with decreased lower bound) the measured NEC values (and real counts) increase in the case of the mouse and rat, as well: 14%, 22% and 32% with 450 keV, 350 keV and 250 keV lower energy thresholds. In practice the use of the energy window 350keV - 650keV seems to be a good compromise.

4.3.3. Determination of the sensitivity of MiniPET-II scanner

The sensitivity of a PET-scanner is the percentage relation of the detected events and the activity in the field of view expressed in decays/second. In the central position 6.3 cps/kBq (0.63 %) is the sensitivity of one crystal ring while the sensitivity of the full system (according to the standard) is 11.4 %.

4.3.4. Image quality analysis

The image quality phantom is reconstructed using SSRB rebinning followed by 20 iterations of the ML-EM reconstruction method. The uniformity of the scanner is 7.8 %, the Recovery Coefficient (RC) indicating the insensitivity of the system to subvolume effects is 0.11 in the rod of 1mm diameter and 0.96 in the rod of 5 mm diameter. In the water filled cylinder the Spill Over Ratio (SOR) is 24 % while it is 13 % in the empty cylinder, respectively.

4.4. The analysis of the spatial resolution and uniformity of MiniPET-II through simulation

4.4.1. Comparison of the spatial resolution and the simulated results

In the simulations of point source, similarly to the real measurements, we have used the digital model of a glass pipette containing a drop of liquid ^{18}F-FDG instead of the 11Na point source declared in the NEMA MSZ. The modelled activity and acquisition time were the standardized values. The simulated data were processed by the Virtual PET package and the images were reconstructed using the same parameters we had used with the real measurements. The resolution of the MiniPET-II scanner arose better through Monte-Carlo simulation than in measurements: in the centre of the field of view 0.95 mm, in

5 mm radial distance the resolution is 1.1 mm, respectively. The difference comes from the lack of uniformity correction compensating the different sensitivity of pin crystals. The GATE software does not considers this discrepancy, therefore the behaviour of the crystals is simulated with identical physical parameters. With uniformity correction algorithm, being developed later, the real spatial resolution must equal the simulated values.

4.4.2. Comparison of the measured and GATE simulated image quality parameters

The simulated scanner uniformity (5.6 %) is better than the measured parameter (7.8 %). The simulated RC parameters are also better than the measured ones and by increasing the diameter of the hot rods the simulated values converge faster to the theoretical maximum. The simulated and measured SOR parameters do not differ. The difference of the simulated and measured parameters arises from the lack of correction compensating the different sensitivity of crystals. After performing this correction, the measured and simulated values are expected to be the same.

4.5. Biological measurements

4.5.1. Comparison of PET images and autoradiographic examinations

The PET-measured data were evaluated by analysing of the ratio of radiopharmacon accumulated in the striatum and in the surrounding tissues, as the function of iterations in the commonly used ML-EM reconstruction algorithm. The tissue ratio is defined as the ratio of the mean activity in the ROI manually drawn on the striatum and the ROI representing the tissue background. The increase of this parameter indicates better mapping, since the decreasing background or increasing striatum accumulation increases the ratio. The comparative analysis of images with different number of iterations shows the same tendency: by increasing the number of iterations the accumulation in the striatum increases, reaches the maximum at the 20th iteration and then slowly decreases.

4.5.2. Analysis of the time characteristics of dynamic PET studies

We have analysed the dependence of the time-depending tissue accumulation curve on the timing order of the dynamic studies. The list mode storage of the acquired data enables the posterior adjustment of the acquisition periods. According to this feature 5 different dynamic PET image sequences were generated with exposition times of 0.5, 1, 2, 5 and 10 minutes.

Using the ROI extracted from the image with 10 minutes of acquisition we have determined the tissue accumulation curves corresponding to the various exposition times and found that by using MiniPET-II it is possible to perform dynamic studies with 30 seconds of acquisition time since the accumulation curve fits the curves of the statistically better mappings with 5-10 minutes of exposition. This result proves that even the fast pharmocinetic processes can be studied dynamically with exposition time less than 1 minute.

4.5.3. Demonstrative animal experiments on tumorous mouse and rat models

We have showed so far that the measured technical parameters of the MiniPET-II instrument optimized by the developed simulation software fit the parameters determined by simulation. The results of the small animal studies performed with the developed scanner document that the sensitivity and resolution capabilities of the MiniPET-II make the device appropriate to perform in- vivo studies of in-tissue biochemical processes in laboratorial small animals.

Using MiniPET-II we have studied leuchemic rats injected with ^{18}F-FDG and ^{11}C-methionine tracers. The detected radiopharmacon accumulations enabled the in-vivo identification of the anatomically digested tissue lesions and the numerical characterization of the the primer and metastatic lesions. Since the PET images are used to analyse functional features the amount of anatomical information is slight, implying that the lesions can be mapped to predefined structures only approximately. To overcome this drawback MRI and CT images can be acquired using the same geometry and the PET images are fused with those generated by anatomical imaging techniques. In this case ^{18}F-FDG and MRI acquisitions were performed on a rat with hepatocellular carinomy demonstrating the potentials of PET-MRI registration. The practicability of PET-CT registration was presented through the fused axial sections of ^{18}F-FDG PET and CT-images of the skull of a healthy rat.

5. Discussion

The aim of the MiniPET project was to develop a small animal PET scanner appropriate for biological studies. The aims of my PhD work related to the project was to develop a complex PET-simulation system and to determine the operating parameters and mapping characteristics of the MiniPET-II instrument according to the methodology described in the NEMA NU 4-2008 standard, furthermore to compare these parameters with the simulated ones. Another aim was to work out measurement and reconstruction protocols for biological studies.

During the project the Virtual PET software has been developed containing analytic and Monte-Carlo simulation methods. The software was validated using the MiniPET-I scanner and successfully applied in the developments of MiniPET-II. We have found that the widely used GATE simulation software can not be used to model the network based data acquisition of the MiniPET-project since GATE does not contain tools to appropriately emulate the asynchronous data transmission. To overcome this drawback the DAQS software module has been developed. This software processes the event packages generated by GATE and models the event loss caused by the network based data acquisition.

The simulation performed by the GATE+DAQS system approximates well the countrate curve determined by measurements however the larger (significantly larger than the activities in biological studies) the activity in the field of view is, the more difference in the curves arise. This difference is interpreted as some weak dependence on the load (events to process) of data transmission speed among the FPGA system and the PIC microcontroller parts of the detector modules. The simulated and measured data differ only in the single event counting rate. However the distribution of time stamp differences and the energy spectrums fit well. Accordingly, in the real measurement region the simulation models well the dependence of the coincidence countrate on the activity in the field of view.

We have determined the operating parameters of the MiniPET-II scanner according to the NEMA NU 4-2008 standard and found that the developed scanner has almost the same parameters as the commercial systems (microPET Focus 120, Explore Vista DR, Inveon DPET) with similar structure. Some parameters (homogeneity, maximum of NEC and the ratio of the scattered and true coincidence events) do not depend directly on the geometric parameters of the scanner. The numeric value of these parameters depend determinatively on the characteristics of the detector blocks (material of crystals, optical attachment, loadability of PMT), the quality of signal processing electronics and the parameters of reconstruction. Besides, the homogeneity sensitively reflects the possible imperfections and defects of the correction algorithms.

The homogeneity of the MiniPET-II and the microPET Focus is commensurable. Considering the ratio of scattered and real events none of the commercial instruments perform better than the MiniPET-II, except the Inveon instrument. Considering the maximum of the NEC curve (NEC_{max}) and the corresponding activity, the higher the activity, the higher maximal counts can be measured. Due to the relatively small speed of the Xilinx Virtex-4 FX12 FPGA chip (performing the primary processing on the digitalized PMT corner signals), the MiniPET-II scanner is only the forth among the compared devices in the sense of loadibility. Although the maximal loadability of the MiniPET-II scanner is low when comparing to similar commercial devices, the value still significantly exceeds the counting speed required for the routinely applied activities in biological experiments. Based on these results it can be stated that the small loadability does not limit the applicability of the instrument.

The resolution and sensitivity have direct dependence on the geometry of the scintellational crystal matrix. The spatial resolution (SR) of the reconstructed image of PET-acquired and corrected data depends on several factors (the average range of positrons in tissues, the size of the source, the diameter of the detector ring, etc.). Knowing the parameters of the ^{18}F point source, used in the experiments to determine the spatial resolution, the error of the position relaxation can be estimated. In the case of the MiniPET-II, the microPet Focus 120, the Explore Vista DR and the Inveon DPET scanners this parameter is 0.43, 0.17, 0.37 and 0.33 mm. Obviously the position resolving algorithm of the still developing MiniPET-II scanner works with the most error. This is compensated by the smallest crystal size providing almost the same spatial resolution in the centre of the field of view. Apropos of spatial resolution, note that according to the standard, all the values are extracted from images reconstructed by FBP. Applying the ML-EM iterative method, which is routinely used in small animal studies, the spatial resolution of the MiniPET-II is found to be less than 1 mm. The radial corruption of the spatial resolution can be decreased only by applying further correction methods (namely resolution recovery). The implementation of these algorithms is still in progress.

When comparing the operating parameters of various instruments, we have to consider that the measurement and computation of the parameters differ. Only the parameters of the MiniPET-II and the Inveon scanner and the homogeneity of the microPET Focus 120 were determined according to the means of the NEMA NU 4-2008 standard. The sensitivity parameters showed the highest variance since the measuring protocols differ the most. Probably this is the reason why the sensitivity of the MiniPET-II scanner seems to exceed all the mentioned instruments however other scanners have better geometrical efficiency with the similar crystal size.

Based on the parameters extracted from the reconstructions of the measured image quality

phantom the laboratorial small animal studies could have been started in that phase of the development, even though the correction methods were only partly developed. The determined uniformity, RC and SOR values will be enhanced by further developments on the image reconstruction and correction methods using the spatial resolution and image quality parameters determined by the Virtual PET as reference values.

Through small animal measurements we have confirmed that the reconstruction protocol, worked out on phantom measurements, provides high quality images in real biological studies, as well. The qualitative comparison of the images from in-vivo and autoradiographic measurements performed using ^{18}F-Fallypride proved the competency of the instrument for biological measurements. With the same measurements we have demonstrated that the developed image reconstruction protocol satisfies the demands of biological studies related to spatial resolution and small noise level. Using tumorous rat model we have analysed the influence of the sensitivity on the time schedule of dynamic studies. We have found that MiniPET-II is appropriate to perform measurements with 30 seconds of exposition time, nevertheless properly reflecting the variance of tracer-accumulation in time.

Several small animal PET-studies have been performed with various radiopharmacons available in our institute, in some cases extended by autoradiographic, CT and MRI studies. With the produced demonstrative documents we have presented that the MiniPET-II instrument is a general tool in both PET-technology related R+D projects and biological studies.

With similar demonstrative purposes, several studies were performed to prove the applicability of the MiniPET-II. These results also reflect the lack and demand of CT studies parallel with the PET acquisitions. The demand can be partly satisfied by the CT and MRI tomographs used in human diagnostics but requires extra costs, more experimental work and complex organization and logistics.

6. Summary

The purpose of the MiniPET project was to develop a small animal PET-scanner competent for biological studies. In my PhD work, related to this project, we have aimed the development of a complex PET-simulation system, the determination of operative parameters of the MiniPET-II scanner according to the standard, the development of measurement and image reconstruction protocols for biological studies. In the meanwhile we have developed the Virtual PET software containing methods for the analytic and Monte-Carlo based simulation. The software was validated using the MiniPET-I scanner and was successfully used in the development of the MiniPET-II complex software system.

The operating and mapping parameters of the MiniPET-II scanner were determined according to the means of the NEMA NU 4-2008 standard. We have found that the developed instrument has almost the same properties as the commercial devices with similar structure.

Performing small animal measurements with MiniPET-II we have confirmed that the optimal image processing protocols, determined by phantom measurements, provide high quality images in real studies, as well. Through dynamic PET-studies we have showed that MiniPET-II has appropriate time resolution to follow even cinetic changes.

We have performed small animal PET measurements with various radiopharamcons available in our institute, in some cases followed by autoradiographic CT and MRI studies. The composed demonstrative documents show that the MiniPET-II scanner is an efficient, competitive device for R+D projects in PET technology and biological studies, as well.

6.1. Highlighting own results

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7. Publications

7.1. Publications used in the dissertation

1. Kis SA, Emri M, Opposits G, Tron L, Balkay L. (2007) Comparison of Monte Carlo simulated and measured performance parameters of miniPET scanner. Nuclear Instruments and Methods in Physics Research Section A.; 571: 449-452 IF: **1.220 (2007)**

2. Hegyesi G, Imrek J, Kalinka G, Molnar J, Vegh J,Balkay L, Emri M, Kis SA., Tron L, Kerek A. (2006) Ethernet based distribution data acquisition system for a Small Animal PET. IEEE Transaction on Nuclear Science; 53: 2112-2117 IF: **1.497 (2006)**

7.2. Posters related to the dissertation

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7.3. Other posters

1. Opposits G, Balkay L, Kis SA, Mudrony L, Galuska L, Tron L, Banfalvi G, Valastyan I, Imrek J, Molnar J, Novk D, Kerek A , Emri M. (2006) miniPET: a versatile software development framework for small animal PET scanners. 3rd International Conference on Imaging Techniques in Subatomic Physics, Astrophysics, Medicine, Biology and Industry; Svédország, Stockholm, Június 27 – 30.

2. Kis SA, Balkay L, Emri M, Tron L. (2005) A miniPET kamera detector-paraméterit analzáló program fejlesztése. Magyar Orvostudományi Nukleáris Társaság XIV Kongresszusa; Várgesztes, Május 26-28.

3. Imrek J, Hegyesi Gy, Kalinka G, Molnár J, Novák D, Valastyán I, Balkay L, Emri M, Opposits G, Kis SA, Trón L, Bükki T, Szabó Zs, Kerek A. (2007) Internals and evaluation of the miniPET-II detector module. IEEE Nuclear Science Symposium and Medical Imaging Conference; Honolulu, USA, Október 27 – November 3.

4. Valastyán I, Imrek J, Kis SA, Molnár J, Novák D, Balkay L, Emri M, Trón L, Bükki T, Kerek A. (2006) Full 3-D cluster-based iterative image reconstruction tool for a small animal PET camera. 1st European Conference on Molecular Imaging Technology; Marseille, Franciaország, Május 9 - 12.

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