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The review of the PhD thesis
"*Feasibility study of lesion detection by means of Total-Body Jagiellonian Positron Emission Tomography scanner*"
performed and prepared by Meysam Dadgar
at Faculty of Physics, Astronomy and Applied Computer Science
of Jagiellonian University

Cancer is the second leading cause of death for people in the world. These diseases are characterized by abnormal growth of cells that divide uncontrollably. Cancer cells can destroy normal body tissue and spread throughout the human body. The overall survival rate of many patients with neoplastic diseases increases thanks to the use of modern methods of diagnostics and therapy. Large neoplastic lesions can be diagnosed based on visible symptoms or with the use of non-invasive diagnostic techniques, such as MRI, CT or PET.

Among the diagnostic techniques used in oncology, PET is distinguished, as it enables the detection of neoplastic functional changes throughout the body. Here, during one examination, it is possible to simultaneously visualize the primary cancer lesions and existing metastases to distant locations. The continuous development of this technique is aimed at improving the sensitivity and spatial resolution of the equipment to register small functional changes in patients' bodies. The location of these changes allows to implement a personalized treatment plan and monitor its effects during treatment.

Due to patients' radiological protection and the duration of the examination, equipment manufacturers are constantly striving to increase the axial field of view (FOV) of various PET scanners. Modern commercial solutions, which are most often found in most hospitals, are characterized by a FOV in the range of 20 - 30 cm. In this case, the examination of the patient's whole body is based on sequential measurements, during which the bed with the patient moves step by step or continuously in relation to the gantry, allowing the registration of signals from the whole body.

Increasing FOV entails an increase in the value of such a PET scanner parameter as its sensitivity. The state-of-the-art 200 cm total-body scanner developed at California State University has sensitivity approximately 40 times greater than commercial PET scanners. The use of such a generation of scanners allows for a thorough examination of the patient's body in one step. The diagnostic results obtained here enable a more accurate and personalized diagnosis, which is a necessary step in an effective therapy. The main limitation of commercial/laboratory PET scanners for total body examinations (TB PET) is their cost which limits their availability for general use.

Since 2013, research has been carried out on a new type of PET scanner called Jagiellonian Positron Emission Tomography (J-PET), the design of which is based on long plastic scintillators supplemented with SiPM semiconductor photomultipliers. The innovation of this solution is the arrangement of SiPM and electronic readings from "arbitrarily" long plastic scintillators. This allows to enlarge the axial field of view, as needed, without adding any detection or electronic modules. The main purpose of the reviewed work is therefore to demonstrate the usefulness for oncological examinations and estimate the parameters of Total-Body J-PET with an axial FOV of 2 m.

The author also set himself the goal of assessing the detectability of cancer lesions with this innovative and inexpensive TB J-PET scanner based on plastic scintillators. In the reviewed dissertation, the author makes an effort to:

- assess the detectability of lesions with the cost-effective TB J-PET scanner based on plastic scintillators,
- perform a series of MC simulations using the GATE software to assess the detectability of designed changes in TB J-PET using anthropomorphic XCAT phantoms,
- use new software for image reconstruction (called QETIR) due to the specific arrangement of the detector with multilayer geometry in the TB J-PET scanner.

The reviewed work contains 101 pages. The content is divided into 8 separate chapters with Bibliography and Appendix giving additional comparison of existing total body scanners. The work is illustrated with 67 figures and 3 tables with numerical values.

At the beginning of the thesis, the author presents the most modern PET technology, especially in the aspect of total body examination and presents the need to conduct MC simulations using GATE software in order to assess the detectability of designed changes in Total-Body J-PET.

In Chapter 2, the author describes the basics of cancer diseases and their classification. The chapter also contains the characteristics of anatomy and physiology of the liver as a "test organ", its oncological abnormalities and diagnostic methods.

The basic principles of J-PET technology and its advantages as a promising alternative to conventional tomographs are presented in Chapters 3 and 4. Sets of various simulation tools, selection criteria for different case detection events and the characteristics of the XCAT phantoms used are described in Chapter 5. The results of the simulations are presented in Chapter 6. Conclusions resulting from the carried out simulation tests of cancer lesions in the Total-Body J-PET examination are described in Chapters 7 and 8.

The author has a very good knowledge of the problem and specialist literature on the subject. The large number of latest references reflects the author's excellent preparation for conducting investigation in medical imaging techniques. The author cites 93 titles of specialist literature in his bibliography, including only 7 articles published before 2000 and 61 titles published since 2015.

The revived PhD thesis is based on the author's 14 main articles published since 2020. The author declares that he has simulated the operation of the scanner, image reconstructions, and processing and presented the results in 6 articles.

The PhD thesis by Meysam Dadgar contains several inventive suggestions concerning methods of PET examinations using TB scanner. In conclusion, I think that the results of the dissertation clearly show that for such a scanner it is necessary to determine the optimal acceptance angle of the recorded events, which results in a significant improvement of the system's axial resolution (here by a factor of 2). The last important conclusion obtained after reading the thesis is the demonstration of the ability of the Total-Body J-PET scanner to detect changes in the early stages of disease for patients with different BMI parameters. This feature, combined with the exact localization of tumors, allows for the necessary assessment of the disease state in order to plan the treatment precisely.

Meysam Dadgars's research achievements being well-presented, extensive, and engaging make me assess his PhD thesis very well.

My duty as a reviewer, however, is to point out some inaccuracies and obtain additional information the lack of which made it slightly difficult for me to understand some fragments of the reviewed dissertation. In this part of my review, I will refer to the individual fragments of the evaluated manuscript and the physical results obtained for the J-PET scanner, and thus:

1. In the PET image reconstruction, the absorption and the Compton scatter corrections have a significant impact on the final result. Have these two effects been taken into account in the simulations performed? How would the measurement of these values look like in a real TB J-PET scanner?
2. It says on page 22 - "*The conventional PET scanners, with the best achievable nominal spatial resolution (~ 3.6 mm) are not a suitable option to detect small lesions in the sub-centimeter grades* ***due to their limited AFOV***" - I don't understand how FOV affects the ability to detect small lesions
3. The simulated sensitivity map of the J-PET system is shown graphically on pages 42 and 43 in Figures 35 and 36. Due to the symmetry of the system, it would be very helpful to include a cross-section plot showing numerically relative changes in sensitivity as a function of location.
4. Graphs 40 and 41 on page 47 show that the sensitivity of J-PET is negligible (only a few cps / kBq), which makes using such a configuration in routine clinical trials difficult. This result shows that we have a long way to fulfill the dream written on page 24 of this work, eg. "*Due to the large AFOV, total body pet scanners have more sensitivity compared to conventional*

tomographs, which enhances the possibility of detecting smaller lesions [72]. Total-Body PET scanners extended the applicability of molecular imaging to a wider range of fields such as cardiovascular disease, multi-organ imaging, physiological study, treatment monitoring, whole-body dynamic imaging, etc., which are not possible with current tomographs due to their limited AFOV."

5. On page 48 in the chapter Spatial Resolution it says "*A point source inside of a hot background air-filled phantom with a ratio of 10:1 has been utilized to investigate the effect of the applying AA cut on the spatial resolution of the Total-Body J-PET.*" - how to physically build an air-filled phantom providing the quoted TBR ratio? I understand that anything is possible in the simulation process.
6. At the end of thesis in Fig. 66 and Fig. 67 we find the sensitivity of the TB J-PET system at a maximum of about 70 cps/kBq, while at no point in the dissertation we find such a value. What is the difference between the J-PET scanner presented in these figures and the scanner simulated in this dissertation.

Finally, I would like to mention one more problem that has not been explained in the PhD thesis. In chapters 6.5 and 6.6 the author presents the results of the MC simulation for various combinations of cancer changes in the liver of the anthropomorphic phantom. These results are extremely valuable and show the possibilities of clinical application of such a solution. However, there is no single important information about the statistics of registered cases in any simulation and a comparison of the statistics amount to a typical clinical measurement, which would illustrate the usefulness of conducting the study.

The inaccuracies mentioned above do not change my very positive assessment of the PhD thesis by Meysam Dadgar. I consider it my duty to inform that the PhD student mastered very well both technical skills and ability of correct analysis of MC simulated data and their detailed interpretation based on theoretical background and knowledge of the latest literature.

Concluding, I state that the reviewed PhD thesis by Meysam Dadgar fulfills all the requirements necessary for such a type of monographs in Poland. I put forward a motion to allow Mr Meysam Dadgar for further procedure of a doctoral degree.