# REVIEW

by Prof. Jenia Nachkova Vassileva, PhD,
Member of the Scientific Jury for the procedure for acquiring the scientific and educational degree "Doctor" by Yanka Ivanova Baneva,
according to the Order No P-109-338/ 05.08.2022 of the
Rector of the Medical University – Varna

**Theme of the dissertation:** Innovative phantoms for image quality research in modern mammography techniques
**Area of higher education** 4.1 Physical Sciences
**Doctoral program in the specialty: Medical physics**

The thesis of the PhD candidate Yanka Ivanova Baneva, who is a medical physicist and an assistant professor in the Department of Physics and Biophysics of the Medical University in Varna is on a topic of high importance. Breast imaging plays a major role in the early detection and successful treatment of breast cancer. The incidence rate of this socially significant disease is growing both globally and nationally in Bulgaria, with survival significantly increasing when tumor formations are detected at an early stage, when they are localized and have a small size. The specifics of the tissue structure of the mammary gland and its pathological formations pose a challenge for the imaging hence putting high requirements for the image quality, imaging equipment, as well as the conditions for interpretation of the images. This determines the rapid technological development of imaging methods and the interest in the introduction of new methods and techniques with higher sensitivity. In clinical practice, along with traditional methods such as X-ray mammography and ultrasound imaging (US), newer methods have been rapidly introducing such as magnetic resonance imaging (MRI), three-dimensional mammogram (tomosynthesis), contrast enhanced spectral mammography, computed tomography (CT), and molecular methods such as scintimamography and positron emission tomography (PET). A well-established method for population screening is the X-ray mammography, and with the latest Recommendation 2022/0290 (NLE) of 20 September 2022, the European Commission approved also tomosynthesis as a screening method. In five of these imaging modalities ionising radiation is used, which is associated with a certain radiation risk from the exposure of the mammary gland tissues, and especially the glandular tissue which has a higher radiation sensitivity. This defines the important of the optimisation task in these methods, meaning to acquire breast images of needed diagnostic quality with the minimum possible dose commensurate with the diagnostic purpose. This optimization task is particularly relevant in the methods used for screening, which requires detection of early signs of malignancy such as microcalcifications sized 50-150 μm, soft tissue tumor formations with small differences of densities between the adipose and glandular tissues and the subtle structural changes. Optimisation is a complex task that starts with the selection of imaging equipment, its setup and maintenance, the introduction of a quality control program including acceptance, commissioning and periodic tests, as well as the optimal performance of the image acquisition by good patient positioning and immobilization, compression of the breast, selection of exposure parameters and, finally, optimal viewing conditions. In this process, which must be subject to a comprehensive quality assurance (QA) programme, the medical physicist plays an important role. The phantoms, physical or computational, are the most important part of the medical physics tools. These describes the importance for the clinical practice and the actuality of the topic of the PhD work of the medical physicist Yanka Baneva.

The dissertation has a total volume of 105 pages and includes 49 figures and 19 tables. I note the lack in the bibliography of Bulgarian publications in the field of quality control and dosimetry in X-ray mammography, such as the PhD thesis of Simona Avramova-Cholakova and the attachment with guidelines for quality control in X-ray mammography, as well as publications on the topic by the medical physics team from the National Center for Radiobiology and Radiation Protection. A brief overview of the Bulgarian experience in the field would add arguments about the value of the PhD student's research for the practice in Bulgaria.

The dissertation is structured logically in nine chapters, The first and second chapters introduce into the subject and define objectives of the research; the third and fourth chapters describe respectively the materials and methods of the study, the following three chapters present the results of the research on three different tasks with specific objectives, and the following two chapters summarize the results and contributions of the dissertation.

The research topic is well defined and very important: to create, validate and use innovative computer phantoms for studying the image quality in the modern modalities for imaging of the mammary gland, such as digital mammography, tomosynthesis and contrast enhanced spectral mammography. This goal fits perfectly into the modern field of virtual clinical trials for development and validation of new imaging techniques, or for optimisation of the existing imaging system, which saves time and money to create many physical phantoms, as well as unnecessary exposure of patients in the clinical validation of the methods. In order to achieve this objective, six specific tasks are formulate, the implementation and the results of which are detailed in the dissertation.

The introduction covers 38 pages and provides an overview of the current state of the research in the field, as an introduction and motivation for the research study. It reviews the increasing morbidity from breast cancer, the types of pathology formations in the breast and the types of techniques (which would be more accurately called "imaging methods"), comparison of the existing modalities, and three more short sections describe the image acquisition in mammography and the radiological description of the findings. Despite the presence of these basic logical elements in the introduction, they lack sufficient clarity and logic, especially considering that the dissertation is in the field of medical physics and the student is a medical physicist. There is no systematic introduction of the main characteristics of the image quality (such as the fundamental contrast, unsharpness and noise, and their combination into more complex quantities such as signal to noise ratio (SNR), quantum detection efficiency (DQE)). I would expect to see a better description of the interactions of photon with matter, which defines the differences in the X-rays attenuation as a result of absorption and scattering when passing through tissues in the mammary gland. I do not find definitions of the dosimetric quantities used for the study such as the measurable incident and entrance air kerma, as well as the estimated risk quantity average dose in the glandular tissue of the mammary gland, also called average (mean) glandular dose. There is no description why low-energy X-ray beam is used for breast imaging, neither an adequate description of the mammography system and its essential components and characteristics. And most importantly for the optimization task – what are the factors influencing the mammography image quality and mean glandular dose, the most important of which are the X-ray spectrum (depending on the material of the anode of the X-ray tube, the tube voltage and the added filtration of the X-ray tube), the compression of the breast, and the type of image receptor. Although the introduction contains some of these concepts, the text is quite chaotic and illogically arranged and suffers factual and terminological inaccuracies. Some examples: On page 12, the author wrongly claims that a screening program was introduced in Bulgaria in 2013, although no national screening program (population screening) exists in the country, and only a pilot project was run for a short time, which can hardly explain the decline in mortality. It seems that the author does not distinguish between screening and diagnosis, as on page 20 it is stated that for the purposes of the screening mammography ACR introduced the BI-RADS system. Precisely, BI-RADS system was introduced to standardise the description of findings in the breast images acquired in mammography, US imaging and MRI. Section 1.4 deals with the types of tumour formations in the mammary gland but lacks a clear categorisation in terms of visualisation requirement and image quality characteristics (soft tissue tumour formations are sensitive to contast and noise, and microcalcifications - to the image unsharpness determining the resolution. On page17, there is a wrong statement that "the expected attenuation of X-ray beam when passing through pathology is called density". Perhaps the author means that the difference in the X-ray beam attenuation when passing through a soft tissue tumor formation and the surrounding breast tissues forms a difference between the optical densities in the image, which is called contrast. Page 21 wrongly states that 'the breast is exposed due to differences in the acoustic impedance of the two types of tissues it passes through, the US is partially reflected'. There is no adequate and correct explanation of the MRI method, which is also incorrectly called "nuclear magnetic resonance", which is the physical phenomenon forming the bases of MRI. CT image formation is also not well explained. In section 1.5.4, dedicated to the mammography method, there are a number of inaccuracies and a vague classification of the types of the three main mammography techniques based on the image receptor – screen-film mammography, computed radiography (CR) and digital radiography with flat-panel detectors (DR). There is a wrong statement that "the study in two projections reduces the possibility of image rejection due to occurring artifacts", in fact the two projections are used to more accurately locate pathologies in the mammary gland. Incomplete and physically inaccurate is the description of the modality "tomosynthesis". For example, the X-ray source (and not the source of ionizing radiation) does not rotate around the object at a certain angle, but moves following a circular trajectory, within an arch with angles between 15 and 60°. On page 25, it is not clear in what dose quantities are given the numbers for the dose in tomosynthesis. In section 1.5.7 dedicated to the contrast-enhanced spectral mammography, there are also a number of inaccuracies. On page 28, there is discussion on the "quality of rays", possibly referring to "quality of X-ray beam", a term that is not defined anywhere in the work. It is unclear what the term "image precision" means,°  as well as what is meant by "enhanced quality control". Section 1.6 talks about a "denser glandular tissue in women under the age of 25, possibly meaning that in younger women the mammary gland is denser due to the predominant presence of glandular tissue. The text currently presented in the section 1.7 titled "Image acquisition in X-ray mammography" would better fit into the previous section 1.5.4 where the method is discussed. This short text has many inaccurate phrases such as "different breast structures have small absorption differences in X-ray examination", or "due to absorption of the beam in the tube walls, reducing the anode voltage will not result in an image being acquired'. The author quotes a historical publication for the focal spot size of 0.6 mm and the focus to image receptor distance of 45 mm, while missing to mention about the current requirements for the focal spot size of 0.3 mm (large focus) and 0.1 mm (fine focus), and the minimum focus-to image receptor distance of 55 mm, which are needed for acquiring images of high spatial resolution. There are also numerous terminological inaccuracies such as: "X-ray penetration coefficient" instead of the correct "X-ra absorption coefficient"; "source of ionizing radiation" instead of "X-ray source ", or even better "tube focus"; "contrast resolution" instead of "contrast"; "blurring" instead of "unsharpness", "mamogram" or "X-ray picture" instead of "mammography image"; "placement of a contrast agent" instead of "injection" or "administration", "dose load" instead of "dose", and some others with inaccurate terms in Bulgarian. These inaccuracies are also seen throughout the whole dissertation, plus some in the following chapters: "X-ray device" instead of "X-ray system", "anode filter" on 59 instead of "anode and filter combination", which along with the tube voltage determines the quality of the X-ray beam spectrum. Some of these inaccuracies might be explained with the translation from English to Bulgarian, however, their abundance shows a lack of knowledge of the terminology in Bulgarian, which is quite a problem as the author is a lecturer in medical physics for medical students.

Chapter 3 is focused on the physical and computational models of the mammary gland for X-ray examinations, with a focus on anthropomorphic phantoms. An overview of some available physical phantoms is presented, including those obtained with a 3D printer based on computational phantoms. Two of the most popular anthropomorphic computer phantoms, created by researchers from the University of Pennsylvania, USA and the University of Patras, Greece, as well as the BreastSimulator software application, developed and used by the team of Assoc. Prof. Bliznakova for a variety of research tasks, including those included in the thesis. This chapter would benefit of inclusion of the definition of the terms -"tissue-equivalent material" and "effective atomic number" which defines the tissue-equivalent materials, as well as including in Table 5.3 in Chapter 5 the calculated values of the atomic number of the different types of tissues in the mammary gland and those of tissue-equivalent materials such as PMMA, water, polyethylene.

Chapter 4 presents the methods used in the thesis, including five software applications: LUCMFRGen to create three-dimensional computer models of compressed mammary glands of different sizes and volumes; BreastSimulator to generate a computer model of uncompressed breast, containing all the main components with the option to vary their dimensions; XRAYImagingSimulator to simulate the system for obtaining 2D and 3D images using the Monte Carlo method; FDKR for reconstructing tomographic images generated by tomosynthesis or CT scans and filtering them, and QualityPlatform for calculating descriptive characteristic derived from X-ray images, such as fractal size, frequency analysis characteristics, first and second line statistics.

Chapter 5 presents the results of the study aimed at generating computer models of compressed mammary gland that simulate existing anthropomorphic physical phantoms, and their validation for use in planar mammography and tomosynthesis. For this purpose, the phantom of Cockmartin *et* al. was chosen as the starting point, and with the software application *LUCMFRGen* four models with different compositions have been created, two of which are computer versions of the physical phantom, and the other two are its variations with substances closer to the composition of tissues in the mammary gland. The X-ray spectrum of a modern X-ray systems for digital mammography and tomosynthesis with a tungsten target and a rhodium filter is simulated, and virtual planar and three-dimensional images were obtained, the latter reconstructed with two versions of the back projection algorithm. Using statistical methods, the resulting virtual images were compared with each other and with those of the images of the two physical phantoms, using 193 regions of interest in each image. *LucMFRGen* software has been shown to be a reliable tool for creating complex computer models of the mammary gland that can be used as a basis for creating realistic anthropomorphic physical phantoms.

Chapter 6 studies the influence of the X-ray spectrum and the phantom thickness on the image quality. Four complex computational phantoms were created with realist modelling of mammary glands with different ration of adipose and glandular tissues. Virtual images were acquired using eight different spectra generated by varying the target material (molybdenum and rhodium), additional filter (molybdenum and rhodium) and tube voltage (from 25 to 31 kV). The quantitative descriptors of image quality demonstrate the feasibility of the developed methods and their potential for virtual research studies and algorithms based on artificial intelligence. The contributions of this study are indisputable, but their presentation suffers terminological inaccuracies and technical errors. On page 72 the outdated dose quantity Entrance surface exposure (ESE) based on the "exposure" quantity in the unit Roentgen (R), instead of the correct "incident air kerma" measured in gray (Gy).

Chapter 7 present the application of the computer models for research studies in contrast-enhanced spectral mammography with two energies. Three models of varying heterogeneity of the structures were developed, to which objects simulating tumor masses of different size and density were added, to which an iodine-based contrast agent can be also added. The images were obtained with two X-ray spectra with mean energy of 20 keV and 34 keV respectively. Then, the algorithm for contrast enhancement is simulated which is based on the different physical contrast between normal tissues and lesions with accumulated contrast agent. The results demonstrate the working capacity of the modelling method, which will be further validated by comparison with experimental data.

The ambitious objective of this research study is fully met; the contributions of the dissertation are well identified and follow logically from the results. Scientific achievements can be synthesized in three directions – 1) innovative computer models of the mammary gland with varying heterogeneity and simulated lesions of different composition and size were created, including the possibility of adding a contrast agent; 2) a script was developed to generate X-ray spectra of different beam qualities, which was used to study the influence of the spectrum on the image quality; (3) the applicability of the *LUCMFRGen* software was validated for virtual X-ray mammography, tomosynthesis and contrast enhanced spectral mammography, which can precede experiments with physical phantoms and clinical trials with patients. These methods can be used to design physical phantoms for research and quality control purposes.

The work on the dissertation was carried out in a multidisciplinary team of researchers with different professional qualifications as evidenced by the four publications on the subject. The one published in the journal Physica Medica, European Journal of Medical Physics results from a successful international collaboration with other leading groups in the field of breast imaging. Two of the presented publications are just abstracts presented at scientific conferences and cannot be accepted as full publications. The candidate had presented topics of her research in five scientific conferences. The scientific publications are sufficient in number with a decisive contribution of the PhD candidate. In three of the scientific publications the candidate is the first author.

The value of the research results and its scientific and practical contributions are indisputable. However, their presentation in the thesis is disappointing. In addition to the previously mentioned factual and terminological inaccuracies, some technical errors are present, such as formatting of tables and certain figures, lack of titles of axis in figures (e.g. figures 6.4, 6.5 and 6.6) or inaccuracies in the units (e.g. EkV in Table 6.2) as well as poor formatting of the list of references. The names of the authors are missed in the list of own publications. I strongly recommend the candidate to pay attention for more accurately using the terminology in the physics of medical imaging, especially because of her responsible role as a lecturer in medical physics for medical students.

Despite my critical remarks, which I hope will benefit the PhD candidate, I believe that the dissertation makes significant scientific contribution to one of the most important areas of medical imaging. The results also have an indirect contribution to improving the quality assurance system in X-ray mammography. Based on these arguments, I give an overall positive assessment of the dissertation and a positive vote for awarding Yanka Ivanova Baneva the scientific and educational degree "Doctor".

28. 09.2022 Signature:

Prof. Jenia Vassileva, PhD