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Review of the doctoral thesis

of MSc. Eng. Mateusz Mesek

Title: „The noninvasive technique of determining local stiffness of human arteries"

prepared under the scientific Supervisors

DSc. PhD. Eng. Ziemowit Ostrowski and prof. Leif Rune Hellevik

in the discipline Biomedical Engineering

1. Formal basis for the preparation of the review

The formal basis for the preparation of this review is Decision No. 104/2024 of the Discipline Council of Biomedical Engineering of the Silesian University of Technology of 21 November 2024 (document: RDIB.0211.104.2024) on the nomination as reviewer, for the doctoral thesis of Mateusz Mesek, M.Sc. Eng. The review was based on the submitted doctoral thesis.

2. Actuality of topic choices and positioning of research

Many studies are being conducted worldwide by scientists from various research centers on aspects related to the circulatory system, especially arteries. The research includes the search for new techniques and methods supporting diagnostics, the development of more precise models describing physical phenomena occurring in arteries, research into material properties, as well as the development of numerical models and analyses with their use.

Research works related to the use of numerical models (e.g. using the finite element method) with an accurate description of the mechanical properties of materials and the interactions between them is very promising.

That is the reason why new, extended models are being developed to describe and analyze arterial phenomena and their influence on blood flow parameters and organs (e.g. the heart) more precisely. This is important for the diagnosis of cardiovascular diseases, the assessment of the disease progression and the planning of treatment.

Regarding the environment in which arteries are located (soft tissue), very specific working conditions related to blood flow, the elastic structure of artery walls (requiring the use of non-linear material descriptions), as well as the fact that blood shows the characteristics of a non-Newtonian fluid (in the view of the latest research), most of the models obtained do not fully reflect the complexity of the phenomena occurring in arteries, therefore new solutions are still being developed.

Therefore, the research problem of developing a methodology for non-invasive determination of arterial stiffness is a very complex topic and fits in with current research trends in the field of biomedical engineering, in especially those related to research in the field of modeling cardiovascular system components.

3. Formal characteristics of a doctoral thesis

The dissertation submitted for review is a scientific study of a methodological and experimental nature, which proposes and presents a methodology for measuring arterial stiffness using ultrasound to measure arterial wall displacement and an applanation tonometer to measure arterial waveforms, together with a solution to the inverse problem of estimating Young's modulus. In the experimental part, the methodology proposed in the dissertation was validated using an artificial artery with known mechanical properties, and the developed tool was applied to medical data (measurements of carotid artery parameters of patients).

The assessed doctoral thesis is written in English, has 114 pages and contains 97 bibliographical references, 32 figures and 22 tables in the main text and 4 figures in the appendix. The thesis consists of 8 numbered chapters and an unnumbered bibliography, a summary in English and a summary in Polish.

4. Evaluation of the content of the work

In Chapter 1, entitled "Introduction" (12 pages long and divided into several sub-sections), the Doctoral Candidate presented an introduction to the subject in terms of arterial elasticity and its impact on the risk of cardiovascular disease. The Author also formulated the aim of the dissertation, which is to develop a non-invasive procedure for estimating the Young's modulus of the left common carotid artery (LCCA) based on ultrasound measurement of arterial wall displacement and intra-arterial pressure measurement using applanation tonometry. The presented objective of the work is ambitious and has application features, especially in the case of the development of goal-oriented software, which would then be validated on a full group of patients. According to the reviewer, a certain lack in the dissertation seems to be the absence of research hypotheses that the Candidate would confirm or reject during the research and then put up for discussion at the end of the dissertation.

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In the further subsections of Chapter 1, the dissertation Author presented a literature review of existing techniques for non-invasive estimation methods and the proposed method for solving the inverse problem. He presented in detail the method of searching for and selecting specified literature items, which is very positive. The literature description presented allows for a very clear and easy search for the right pieces of literature. The Author then summarized the most important information contained in the articles that are relevant to the topic of the doctoral thesis. The reviewer found it unclear why the table captions were placed below the tables, as this space is usually reserved for captions under the figures. In the case of tables, it is usually assumed that the corresponding description is placed above the table to which it refers. The current formula for table descriptions, adopted by the Candidate, makes it somewhat difficult to find the right table when analyzing the text. An additional weakness of this chapter is the confusion in the brief description of the individual chapters of the dissertation, sub-section 1.2. 'Outline', on page 9. The descriptions of Chapter 3 and Chapter 4 have been switched, which is listed before Chapter 3. Moreover, the description of Chapter 5 has been placed at the end of the previous subsection, i.e. Subsection 1.1. At the beginning of the work, this situation makes the reader feel that the Author has not taken control of the editorial side of the work.

In Chapter 2, entitled 'Theory' (18 pages), the doctoral Candidate presented the basic elements and equations of continuum mechanics necessary to understand the formulation of constitutive models of linear elastic as well as hyperelastic materials. In addition, it discusses inverse problems and the most commonly used techniques for solving them, regularization, and Kalman filtering algorithms together with the equations that describe them. All equations are properly numbered except for the equation on page 30 – between the equations labelled (2.53) and (2.54). In this case, the equation does not have its own unique identification.

In Chapter 3, entitled 'Experiments' (8 pages), the PhD thesis Author presented a description of the research platform and the parameters of the individual hardware components necessary to conduct the experiment in order to collect appropriate data to test the proposed method of non-invasive assessment of the stiffness of the left common carotid artery (LCCA). The test station was developed as part of the ENTHRAL project (funded by the Norwegian Financial Mechanism 2014-2021). In general, this chapter is a shortened version of the article 'Evaluating the precision and reproducibility of non-invasive deformation measurements in an arterial phantom' published in Measurement in 2023, of which the Doctoral Candidate is a co-author and which is referred to in the literature as dissertation item [77]. Most of the figures in this chapter (except for figures 3.5, 3.6 and 3.7) are also taken from article [77]. In addition, the Author indicated that the ultrasound measurements and the processing of the ultrasound data were carried out by PhD. Eng. Jan Juszczyk (Department of Medical Informatics and Artificial Intelligence, Faculty of Biomedical Engineering, Silesian University of Technology).

In the reviewer's opinion, it seems that the name of this chapter is not fully accurate and should be closer to 'Materials and methods' rather than 'Experiments' as it is currently written. To supplement this chapter, there could be a description of the tasks and their area of work in which the researcher directly participated in relation to the described article [77]. The article includes a section entitled 'CRediT authorship contribution statement'. However, in the case of the description of the Candidate PhD student's authorship contribution, it is quite limited and does not provide a full view of the work involved in creating the article. The missing information in section 3.3. Medical data is the number of patients, especially since on page 44 there is a description under the figures where the term 'Patient3' appears. It is also not explained why the 'Patient3' data were chosen to present a comparison of the pressure course (Figure 3.6 and Figure 3.7). This consequently brings up the question whether the graphs would have been different for other patients. Are the graphs shown in figures 3.6 and 3.7 representative or are they just examples?

In figure 3.6, the values shown on the individual axes are difficult to read – it would be a good idea to enlarge the size of the graph or improve the quality (resolution) of the descriptions of the individual axes.

In Chapter 4, entitled 'Proposed approach' (12 pages long), in individual subsections, the Candidate discussed issues related to the sensitivity analysis of the finite element mesh for two types of mesh (coarse and fine), and the comparison of static and dynamic finite element analysis. The Author also presented details of the geometry and mechanical properties of the material used and described the algorithm used to process the data obtained from the system of cameras and sensors built into the experimental station. Tests using FEBio software for FEM analysis and Kalman filtering are also described. In the final part of the chapter, the Author presents experimental data obtained from an artificial artery phantom and describes the algorithm used to process this data. One of the critical remarks in this chapter is the incorrect placement of Figure 4.1 (currently at the top of page 46), while the description relating to it is only at the very bottom of the page. A similar situation concerns Figure 4.2. on page 47, which not only precedes the footnote and text referring to it, but is also located in the wrong subsection, i.e. 4.1.1 Geometries, Boundary conditions, material constants and mesh sensitivity, instead of in subsection 4.1.2 Mesh sensitivity, in which paragraph the correct reference is Figure 4.2.

Furthermore, in the reviewer's opinion, figures 4.4, 4.5 and 4.6 containing graphs could be enlarged to use the full available width of the page. This would make the diagrams presented in them simpler to read, and it would be easier to assess the accuracy of the measurement data overlaps. Furthermore, in subsection 4.2.1 Patients data, the number of patients examined is not given again. Only from tables 4.7 and 4.8 can it be deduced that the number of patients is 3 (one woman and two men). Moreover, in both of these tables, the patient numbering descriptions are used, sometimes written with a small letter and sometimes with a capital letter. In section 4.2 Experimental data - phantom, the Candidate indicated that the measurements of the mechanical properties of the samples were carried out by DSc. PhD. eng. Grzegorz Kokot, Department of Mechanics and Computational Engineering, Faculty of Mechanical Technology, Silesian University of Technology, as part of the ENTHRAL project. The average material thickness measurements were determined by means of X-ray radiation as part of the ENTHRAL project, carried out by PhD. Eng. Łukasz Krzemiński (Research and Teaching Laboratory of Nanotechnology and Materials Technology, Faculty of Mechanical Engineering and Computer Science, Silesian University of Technology).

Chapter 5, entitled 'Model validation' (14 pages long), presents issues related to model validation, simulation results using linear-elastic material description and Neo-Hookean material description, which were then compared with experimental data obtained for four variants of artery phantoms: b2, b3, b4, b5. The load parameters of the artery phantoms corresponded to four physiological states categorised as operating parameters: A - optimal, B - normal, C - high normal and D - grade 1 hypertension. As a result of the conducted considerations, the most suitable model was selected for further analysis in the next chapters of the dissertation. In the case of the records describing individual samples (b3, b4, b5, b6), the question is raised as to why the results for samples b1 and b2 were not presented, or at least an explanation as to why this sample numbering was adopted, omitting the designations b1, b2?

Furthermore, some editorial reservations can be made regarding the presentation of the drawings and tables contained in subsections 5.1 Sample b3 (p. 58), 5.2 Sample b4 (p. 62), 5.3 Sample b5 (p. 65), 5.4 Sample b6 (p. 68) describing the results obtained for individual samples of artificial artery. In the subchapters presented, there are no descriptions or text comments to the figures and data tables. In addition, there are no references to the items mentioned in the text.

Chapter 6, entitled 'Numerical examples and results' (10 pages long), it presents topics related to examples of numerical analyses based on semi-empirical data, enabling verification of the proposed method using the extended Kalman filter and double extended Kalman filter based on phantoms of arteries with known physical parameters. In addition, the Author of the dissertation presented Kalman filtering tests designed to estimate the displacement of artery walls and determine the Young's modulus. The results obtained on the basis of the experiment and on a group of three patients were presented and described. The question that appears is, what is the reason for such a limited group of patients? What conditions were responsible for this?

In Chapter 7, entitled 'Discussion and Conclusions' (4 pages), the Doctoral Candidate discussed the results and presented the final conclusions, demonstrating that the objective of the thesis had been achieved, which was supported by the results of the research described in the previous chapters. This part of the thesis is supplemented by the PhD student's comments on the possibility of improving the approach proposed in the thesis,

in order to implement it in clinical practice as a tool with the potential to work in real time, which should definitely be counted as a plus. The discussion leaves something to be desired due to the fact that there is practically no reference to the work of other authors and no comparison of the results obtained with the results obtained by other researchers. This gives the reader the impression that less attention was paid to this part of the dissertation.

In Chapter 8, entitled 'Appendix' (26 pages long), the doctoral Candidate presented additional materials in the form of a detailed principle of operation of the Kalman filter used in the proposed approach and code written in Python for processing measurement (input) data and implementing the Kalman filter.

In addition to the 8 chapters mentioned above, the dissertation contains unnumbered chapters such as: Bibliography ('Bibliography') consisting of 10 pages and two corresponding summaries, one of which is in English 'Summary' (1 page) and the other in Polish 'Summary in Polish' (2 pages). It should be noted that the Bibliography list is not included in the table of contents at the beginning of the thesis – pages 5 and 6. In addition, on pages 112 and 114, where the summaries (Summary) are located, chapter markers entitled 'Bibliography' are placed at the top of the pages instead of 'Summary'.

In terms of technical and editorial aspects, the structure of the thesis is complete, it has all the elements typical of doctoral theses, and the chapters are divided in a logical and clear manner. Apart from the errors described above, the text of the thesis has been edited correctly and carefully. The drawings and tables are well-designed and clearly presented, and the entire thesis makes a positive impression as a coherent whole. At the same time, the vocabulary used by the doctoral Candidate allows for an understanding of the presented content.

5. Critical comments on the dissertation

Nevertheless, the presented dissertation on the analysis of medical data presents results based on a very limited number of patients (3 people), which, in the reviewer's opinion, severely limits the possibilities of defining conclusions in terms of the quality and reproducibility of the results obtained with the proposed methodology based on real medical data, as well as in identifying problems that may arise when analyzing data obtained from patients with significant disease changes.

In his dissertation, the Author used the open-source FEBio FEA software for his analyses, which specialises in performing analyses in the field of biomedical engineering. However, the results obtained have not been verified against other recognised FEA software (e.g. ANSYS, ABAQUS, COMSOL, etc.), which is often practised in medical cases. This is particularly evident for analyses based on a small number of experimental samples (actual materials of the patients being examined) or the desire to verify the influence of a given solver on the results obtained.

6. Final conclusion

Mateusz Mesek, M.Sc. Eng., submitted an interesting doctoral dissertation for evaluation, the subject of which was appropriately chosen and is in line with modern trends in research conducted in the field of biomedical engineering.

The non-invasive procedure for estimating the Young's modulus of the left common carotid artery (LCCA) based on ultrasound measurement of the displacement of the artery wall and measurement of the pressure inside the artery using applanation tonometry, proposed by the doctoral Candidate, and in detail the application of the inverse problem solution method based on the double extended Kalman filter, including a description of the respective components of the developed method and verification of the results based on the experiment.

Therefore, the topic of the dissertation is not only of theoretical importance, but also has utilitarian significance, as it may be applied in the future to develop a diagnostic method used in medical clinics to assess the stiffness of arterial walls in individual patients, which translates into an evaluation of the advancement of vascular system diseases (e.g. such as heart attack, heart failure, stroke, ventricular fibrillation, etc.) and help in choosing a more effective personalized treatment process.

Mr Mateusz Mesek, M.Sc. Eng., demonstrated very good theoretical knowledge and skills in the implementation of simulation and experimental research. The content of the thesis is appropriate and intelligently structured, and the comments and suggestions presented in chapters 3 and 4 of this review do not affect the content value of the thesis or its overall positive perception.

To summarize this review, I conclude that the doctoral dissertation by Mateusz Mesek, M.Sc., entitled 'The noninvasive technique of determining local stiffness of human arteries' meets the requirements for doctoral theses as defined by the Higher Education and Science Act of 20 July 2018 (Journal of Laws of 2014, item 1571). Therefore, I hereby apply to the Council of Biomedical Engineering at the Silesian University of Technology for the admission of Mr Mateusz Mesek, M.Sc., Eng., to the further stages of the procedure for awarding the degree of Doctor of Engineering and Technical Sciences in the discipline of Biomedical Engineering.

Podpisał prof. Michał Rychlik (podpis odręczny)