The review of PhD thesis entitled:

Mathematical modeling of blood volume control and body fluid shifts during hemodialysis

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End-stage renal disease is an irreversible clinical condition with loss of kidney function resulting in dependence on renal replacement therapy. There are three types of renal replacement techniques, including hemodialysis, peritoneal dialysis and kidney transplantation. Each year about 440 000 individuals are introduced to renal replacement therapy worldwide. Among patients treated with hemodialysis, the most common modality of renal replacement therapy, the annual mortality rate varies from 5% to 27%, depending on the country. Even nowadays, one of the most difficult problem affecting hemodialysis patients and strongly influencing their quality of life and long-term prognosis is their body composition with a strong emphasis on hydration state, inter-dialytic fluid gain and blood pressure. Still the most commonly used methods in conducting routine practice for evaluation of excessive fluid and determining dry body weight include patient's physical examination. However, the bioimpedance analysis, a novel, thorough and practical technique of body composition measurement both in scientific and routine clinical use has become available.

In this doctoral dissertation, in order to obtain mathematical modeling of blood volume control and body fluid shifts during hemodialysis, Mauro Pietribiasi implemented a model that is simultaneously simple (cheap in term of computational power required for its solution) and still enough physiologically accurate, with physiology-grounded descriptions of fluid and solute transport. Therefore, the novelty as well as scientific level of the thesis is extremely good, considering the importance of the research subject and clinical requirements.

This PhD thesis is well structured and correctly presented. Its consists of 8 main chapters. The thesis is written on 174 pages altogether, and enriched by number of figures (93), mathematical

equations, schemes and tables (30). The theoretical principles as well as the search part were validated with 201 valuable references.

The objective of the present work is to propose a model of transport of fluid and electrolytes, describing the concurrent interactions between osmotic fluid shifts, lymphatic absorption, refilling, and water removal by hemodialysis, with the aim to improve on what is now available in the literature, especially in relation to the balance between accurate physiological basis and simplicity of implementation.

In the first chapter Mauro Pietribiasi introduces reader to the dissertation topic. Chapter 2 presents background of physiology of body compartments, describes intracellular and extracellular space, and measurement techniques for assessing body composition. Theory of microvascular membrane transport modelling is described in details in chapter 3. The whole of the theoretical part is a valid justification for the research undertaken. Author has studied carefully research subject with critical view, and used appropriate number of bibliography sources. It is an evident fact that Mauro Pietribiasi deeply understood the theoretical knowledge and the discussed problems.

Chapter 4 is dedicated to the description of the used methods and focused on clinical data (Stockholm and Lublin groups). The next part of dissertation (chapters 5-7) is focused on methods and results on the specific modelling of:

a. Protein transport in hemodialysis
b. Refilling coefficient
c. Sodium and potassium transport in hemodialysis

Each chapter is focused on a particular aspect of the general problem of modelling fluid equilibrium in HD patients and is finished with an interesting and insightful discussion. The presented mathematical formulas and statistical analyses are an attempt to interpret and explain physiological processes concerning the transport of molecules and water during hemodialysis.

The next part of the thesis, in my opinion the most important with fresh look, focused on the multi-species modelling of solute transport and refilling in hemodialysis. In chapter 8, Author described and discussed the final version of the model proposed in this dissertation. Such model was implemented taking into account the formulas and conclusions drawn from the analysis of the simpler models (chapters 5-7). The baseline version of the final model presented is able to simulate the profiles of the clinical data with good accuracy for all the interesting variables. The inclusion in this model of detailed information on different physiological mechanisms allowed a much wider interpretation of the clinical data, which is mostly practically very important. The explanation of the

interstitial pressure-volume relationship and the role of lymphatic absorption, are newly introduced parameters in the field of mathematical models for haemodialysis. These new findings in conjunction with the detailed 3-pore model of the endothelium are highlighted as the key role of the effect of the lymphatic system and the transport across the capillary wall on refilling process.

At the end of dissertation the general conclusions of the performed research were described. The conclusions confirm that the main goal of the work was successfully achieved. Proposed novel model proved to be able to reproduce the clinical data, relying on the estimation of a very small number of parameters, with computation time for parameter estimation generally less than 1 minute, employing successfully a realistic description of the structure of the capillary wall and cellular membrane interfaces.

This thesis is very well written. The figures, equations, and tables are shown properly as well. The hypothesis are very well formulated with meritorious conclusions based on properly selected and actual literature. In summary, the dissertation represents very high level scientific work. It seems to be an interesting topic for scientists and clinicians working on transport during hemodialysis. It is generally well presented and very interesting to read. The explanations are suitable and focused on the relevant topics. It is remarkable that the wide spectrum of work executed new research ideas.

However, there are minor remarks which occurred to me and need to be explained.

1. In my opinion, for better understanding of the presented results lists of abbreviations and symbols are needed at the beginning or at the end of this dissertation.
2. In the last chapter (Conclusions), there is no explanation how important performed studies and analysis are in everyday clinical practice.
3. In the final version of the PhD thesis, it would be advisable to present some of the figures in a color version to make it easier for the reader to understand.
4. Even though the thesis was written in a correct way, there are some minor errors to correct: pages 7-11, summary in polish requires editorial editing (for example page 7, first line "Strzeszczenie" should be replaced by "Streszczenie")

These shortcomings do not substantially affect the quality of the work and do not disqualify it in any way. The comments on the form of the presentations do not diminish the very high evaluation of the content of the dissertation.

In my opinion, the reviewed dissertation meets all requirements posed on thesis aimed for obtaining PhD degree. This thesis is ready to be defended orally, in front of respective committee. I would like also to propose to reward Mauro Pietribiasi doctoral thesis due to the following aspects: scientific novelty, an extensive range of research, meritorious presentation and discussion of obtained results, outstanding scientific activity confirmed by papers published in commonly known and highly ranked scientific journals.

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