Gliwice, 15 lipca 2017

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Recenzja rozprawy doktorskiej

Tytuł rozprawy: **Mathematical modeling of blood volume control and body fluid shifts during hemodialysis**

Autor rozprawy: **Mauro Pietribiasi**

Promotor: Prof. dr hab. Jacek Waniewski

1. Scientific problems analyzed in the dissertation.
   The PhD thesis is focused on mathematical modeling of fluxes of fluids, proteins and electrolytes during hemodialysis. The main objective, clearly stated, was to develop a novel, physiologically-based model (as opposed to a black-box one) that would represent the changes in blood volume and concentrations of important molecules with adequate accuracy, corresponding to clinical measurements. Though various models have already been proposed in the literature, they have been usually concerned with transport of only a single molecular specie. The Author aimed to combine description of several processes in one model, hoping to improve modeling quality and stepping towards using such models in control of hemodialysis process. The latter aim is not explicitly worded in the thesis but is visible in the title "[...] *blood volume control* [...]".
   Problems discussed in the dissertation are very important from clinical point of view, as more and more people require dialysis and control of this process is still far from perfect.
   The work is theoretical, based on clinical data.

2. Literature review and discussion
   The bibliography list contains 201 items. A lot of them date back to the 80s and 90s but this is caused by the relatively small number of new works in the field (when compared to other biomedical modeling topics). The range of papers and books cited by the Author proves that he has a good overview of the state-of-the art in the field. The conclusions drawn from the literature review are valid and constitute a good starting point for the dissertation. However, it would be interesting to see how the Author referred to the following recent papers: Casagrande et al., *Int J Artif Organs*, 2016; 39(5):220-227, Eloot et al., *PLoS One*, 2016; 11(1):e0147159, Kim et al, *Hemodial Int*. 2016; 20(2):226-234. Moreover, it seems that, at least partially, another two papers are relevant (though they deal with either other aspects of hemodialysis or with a different clinical technique): Maduell et al., *Blood Purif*, 2015; 39(4):288-296 and Debowska et al., *Artif Organs*, 2015; 39(12):1005-1014.

3. Adequacy of the assumptions, methods and proposed solutions
   Assumptions for all models investigated in this work are appropriate. Changes introduced into the models are based on careful analysis of drawbacks of existing models and on physiological processes that should be taken into account in their improvement.

4. Originality of the dissertation.
   The dissertation is based on two papers published in international journals included in the JCR list, whose first Author was the PhD candidate, and additional original models and their

analysis. These results constitute an added value to knowledge gathered so far and available in the world literature.

5. Clarity of the work
   The structure of the thesis is correct with subsequent chapters and sections introducing the way of reasoning and conclusions in a logical sequence. Numerical results and their analysis are presented clearly (in most cases; some comments are listed in section 8 of this review).

6. Weak points of the thesis The Author made a great effort to make the analysis comprehensive and put a lot of attention to the details. However, there are some shortcomings that should be pointed out:
   6.1. The title includes a phrase "blood volume control", suggesting a control aspect in the modeling. This is particularly important, as such models should be used not only to describe the processes, but they should constitute some framework for improvement of clinical procedures. I haven't found any comments regarding application of the results in the actual hemodialysis. Moreover, it is not clear throughout the work, what is the form of J_{UF} (most importantly – is it the control or the output? If it is the control, what is its time course and how should it be shaped, taking into account the conclusions of the work? If it is the output, what is the control variable?).
   6.2. When referring to the results of statistical tests, the Author states in a few sections that something was similar (e.g. pages 103, 107, 13). Such claims are not true. A higher (than some threshold) *p-value* means that we cannot reject the null hypothesis that two samples are similar but does not validate the statement that they are similar.
   6.3. Concerning the description of parameters estimation. First of all, in my opinion they should not be called "*optimal parameters*". While some performance index have been minimized to find their values, it was the process of parameter estimation. Optimization of parameters means that we search for values that provide the best possible performance of a system. More important here is the question of constrained optimization. Although the Author is right on imposing the constraints, the question about the meaning of the estimation resulting in reaching the constraints remains unanswered. Is it due to too conservative constraint setting or does it prove that the model might be inappropriate (if so, how to improve the model)? Were the constraints reached for all parameters for the same patients (the tables contain only the number of such cases) or not? What would be the result of estimation if much larger range of feasible parameters was assumed? (Besides, in constrained optimization one cannot say that an optimal value has not been found, if the procedure applied led to a boundary value. The boundary value **IS** optimal)

7. Main contribution
   The following should be regarded as the most important contribution of this work:
   - Critical analysis of existing models even though they provide good fit to clinical data; this aspect is often overlooked in other works dealing with mathematical modeling of biological or physiological processes, where good fit to data is sometimes the only justification for the model;
   - Showing the importance of including the lymphatic flow in modeling hemodialysis and careful analysis of the 3-pore model;
   - Development of three alternative versions of a multi-species model; though the final conclusions steer on the negative side, with the model not outperforming the previous ones, this might be an important step in further developments.

Models discussed in the thesis should provide the framework for development of hemodialysis protocols., though this aspect is not addressed in the thesis.

8. Detailed comments

The comments listed below are mostly editorial or of debatable nature. Therefore, they do not affect the final recommendation. However, **those listed in points 8.1-8.9 should be discussed during the public defense of the thesis in addition to the remarks listed in point 6 of this review**.

8.1. Sensitivity analysis. Even if the Author did not developed tools for sensitivity analysis and uses available software, the method applied should be described. This concerns both the method for creation of parameter rankings and the details of the bootstrap sample.

8.2. Optimization and regularization (pages 118-119). The value of F has been chosen to be equal to 1. However, if one looks at the reported RMSE values, it seems that the term $(Lp-5)^2$ dominates in (8.20) for F=1. A comment is needed here.

8.3. In most cases, the simulation results look like polylines, not smooth curves – why is it so? Is it due to the numerical integration step, which is too large, or is it just an artifact in results presentation, caused by the unfortunate choice to take only the values at the time points of data measurement and connect them with line segments?

8.4. When comparing simulation with data and making the claims about the models quality, only the median and quartiles are used. The question about the maximum RMSE arises naturally.

8.5. Division of a group of 9 persons in the Stockholm group into quartiles seems a bit odd.

8.6. Using the value of urea dialysance instead of diffusive dialysance (p. 102) is not sufficiently justified (the need for that is clearly explained, however replacing one parameter with another calls for a reference, at the very least).

8.7. The Lublin group is said to consist of 23 persons. However, table 7.4 shows 20, 22 and 21 patients in total for HD1, HD2 and HD3 sessions, respectively. What is the explanation?

8.8. The description of the sensitivity analysis results (p. 131) says "[...] *with α_{LP} and Lp again the most influential factors* [..]" – actually it is not in agreement with Fig. 5.7.

8.9. An interesting remark about the initialization phase is presented on page 148. How does it compare to clinical practice and could it be further investigated to improve HD protocol?

8.10. In fig. 8.31 caption of $UF(t)=\lambda(e^{0.1t}-1)$. Shouldn't it be $\lambda(1-e^{-0.1t})$ instead?

8.11. In the plots (e.g. Figs 5.2, 5.3, 5.4, 8.31, the axes should be described by the variables, not just the text).

8.12. Quartiles lines calculated for different cases in Figs. 8.3 and later are not discernible from each other.

8.13. Fig. 5.8 – it is not clear what hypothesis was statistically tested, for which the p-value is provided.

8.14. One should not compare 0.3 to 50% (p.74).

8.15. Table 4.4. caption says: "[...] *comparing to the Stockholm group*" – but it seems that data on diabetes is nowhere to be found, with the remaining pieces of information for the Stockholm group given in the plain text instead of the table – this makes it difficult to compare; there is inconsistency in parameter naming (e.g. body mass in Table 4.1 vs. body weight in Table 4.7).

8.16. Editorial and language remarks (the thesis would benefit from careful editing; only a sample of errors is listed below):

8.16.1. When writing formulae like (4.1) or (5.13) general parameters should be used, instead of their values, because these parameters are of particular dimensions – otherwise there is summation of terms with different dimensions.

8.16.2. The choice of *(t)* to denote some quantity is very unfortunate (p. 93).

8.16.3. Wrong use of the articles "a" and "the" is quite widespread in the thesis.

8.16.4. The structure of quite a few sentences is wrong, e.g. "*it is estimated the volume*" (p.34, should be "the volume is estimated"), "*is calculated like saw in eq.3.25*" (p. 63), "*it will be described an index*" (p. 79 – should be "an index is described/introduced").

8.16.5. Wrong phrasing is also quite common, e.g.: A few = several (not "*Few*" – Summary, page 6); reasonable compromise (not "*reasonable equilibrium*" – page 14); "*haemodialysis is the most diffused form of* [...]" (page 16 -??); cytoplasm is not the interior fluid of the cells (p. 21) – it comprises also various organelles; at any time (not "*at each time*" – p. 41); " *the mechanic characteristics of the cellular membrane are rather low*" (p. 47 -??); "appositely" (p. 57); "*estimation*" instead of "validation" (p. 59, last paragraph, l.2); "*Let us identify*"(p.94, should be "let us denote"); "it results difficult to model [...]" (p. 109), " it was described the kinetics" (p. 115).

8.16.6. Some sentences are incomprehensible, e.g. "*Mathematical modeling offers the possibility [...] to set optimal adequacy targets [...]*" (page 19 – what does the phrase "*optimal adequacy targets*" mean?).

8.16.7. It seems that the words "*water*" and "*fluid*" are treated as synonyms (at least in Fig. 2.1. and the text preceding it), it does not seem to be justifiable.

8.16.8. What is the reason for strange value and unit combination: $15mL/min/1.73cm^2$ (page 15)?

8.16.9. The notation is inconsistent, e.g. in the text one can find lp (p.38), and Lp (p. 79) denoting exactly the same parameter; it also seems that kd_s in (7.2) and w_s in (7.5) is the same parameter.

8.16.10. Some figures and tables description are slightly misleading, e.g. in Fig. 1.4 there is no subscript S denoting the solute. Instead, there is a two-letter subscript IS denoting interstitial space (or so it seems). In Table 4.7 TP is supposed to denote serum total protein concentration and there is no TP in the table.

8.16.11. There are errors in cross-references, e.g. Fig. 2 (page 21 – should be 2.1), Section 6.1.1. (there is no such section – sections are numbered only at the second level), Eq. 42 (p. 102 -??), Table 7.5 (p. 109, top line – it seems that the reference should point at Table 7.1; but then, Table 7.5 would not be referred to anywhere in the text).

8.16.12. Bibliography – the Author should at least avoid mistyping the Advisor's name ([12], [90]); in [63] the publisher is missing, in many places spaces are missing.

9. Final recommendation.

Taking into account that the scientific goals of the thesis have been achieved with appropriate methods, and acknowledging their importance in the field, I state that Mauro Pietribiasi proved that his knowledge and skills are adequate to the PhD degree level in the discipline Biocybernetics and Biomedical Engineering. With that in mind, and taking into account that the final models proposed unfortunately appeared not to be better than existing ones, I deem the thesis to fulfill sufficiently the requirements of the relevant regulations (*Ustawa o stopniach tytule naukowym oraz stopniach i tytule w zakresie sztuki* z dnia 14 marca 2003 roku (z późn. zmianami)).

I recommend admission to the public defense of the PhD thesis.