Review of: "Physiologically Based Multiphysics Pharmacokinetic Model for Determining the Temporal Biodistribution of Targeted Nanoparticles"

Richard Upton[1]

1 University of South Australia

Potential competing interests: The author(s) declared that no potential competing interests exist.

General comments.

This paper addresses a novel topic, and it is important that we better understand the fate of nanoparticles in the body. The authors cover a lot of territory in this paper, including methods for solving stiff differential equations. Maybe the paper would better split in two? Models A and B in one paper, and the branched model in another?

The authors comment that PBPK models for small molecules are empirical, and propose that more complex models are required for nanoparticles. They proposed larger multi-scale models, but eventually these are simplified via steady-state assumptions and model reduction techniques. The final models have 9 equations, which I would contend is back in empirical territory? Nevertheless, models are judged by their fitness for purpose, and I suspect the branched model will become more useful as more nanoparticle deposition data are available for different levels of the vascular system.

Specific comments:

Line 39. References 11 and 12 seem obscure and indirect references in support of a description of “what is traditional pharmacokinetics”.

Line 40. “Existing PBPK models for small molecules or biologics use an empirically derived framework”. In what sense are existing PBPK models of small molecules empirical (i.e. by practical experience and not theory)? They are based on a knowledge of the circulation and a theory that small molecules rapidly cross biological membranes. They fact that they would not be extendable to describing nanoparticles that adhere to endothelium is not surprising nor does it detract from them being fit for purpose for small molecules.

Figure 1. I’m not sure what Model configuration A wasn’t rejected on first principles. We know the circulation of the spleen is in series with the liver, not in parallel as depicted.

Figure 1. For Model configuration B, it’s not clear if the heart compartment is represented here as a pump supplying the lungs (right side) or body (left side) or whether the heart compartment represents the myocardial tissues (supplied by the coronary arteries, drained by the coronary sinus). I imagine the latter is of more interest for nanoparticle deposition (as implied by Eqn 9)? If so, the circulatory layout in the figure is confusing?

Equations 8 & 9. My confusion over the vascular layout in Model configuration B is compounded by Equations 8 and 9.

There are blood flow terms for Qvein and Qart and Qlung, but these should all the same value – the cardiac output. Eqn 9 in particular sums Qlung with the other organs of the body. This shouldn't be the case as the lungs are in series with the other organs of the body. Similarly, Qhep is given as the sum of liver, spleen and gut. This shouldn't be the case as the liver is in series with the spleen and gut. I would also like to see a table of the blood flow values used in the models. Do they all add up to cardiac output? The last term of Eqn 8 should be checked. The units don't resolve to mass/time unlike the others terms in the equation, and the equivalent term in Eqn 9.

Line 235. The branched vascular model is very interesting and an impressive bit of coding.

Line 363. Could the sensitivity analysis be expanded upon here? How was the comparison of the model predictions with the data done? By eyeball, or was some kind of formal optimization process used to achieve the best values of the normalized root mean squared deviation (NRMSD)? The latter is much preferred.

Line 375. Most textbooks would have 1/3 of the blood volume in the arterial system, 2/3 in the venous system. Not equal volumes.

Line 403. Please check whether a log term is necessary in the equation for Koff? I followed through to the quoted paper, and I wasn't able to confirm. Seems strange as a dissociation rate constant is typically Kon/Koff?

Line 409. As per Line 363. How was this comparison done? Estimating parameters from data really needs to be an optimization process of some sort. More information is needed.

Figure 4. What are the x-axis units and what are the symbols? Please describe in the legend or plot.

Figure 5. What is the y-axis units and what are the units? Please describe in the legend or plot.

Figure 6. Is the y-axis normalized (legend) or relative (plot) concentration? Please define what is meant by this.

Figure 9. The simulated and observed should be shown on the same plot, whereby the large discrepancies between the two are apparent. This is a very concerning difference between model and data. Why is it dismissed so lightly?

Figure 12, Top left panel. Four curves can't be distinguished in this plot. If the are super-imposed, please state as much in the legend.

Line 719. The statement that traditional PBPK models are empirical is contestable, and no model describes the full behaviour of a system. Only the bits that are important for a particular task.

Thank you for making the model code available on github.