# Point-to-point response for manuscript TBME-00561-2016

Reviewer: 1  
  
In this manuscript, the authors have reviewed the fundamentals of widely-used theoretical models underpinning perfusion estimation, including tracer kinetics and deconvolution formulations, as well as the continuum models based on porous media flow. The definitions of perfusion have been reviewed, and a new measure that clarifies some of the shortcomings of the traditional approach had been proposed. The results were studied in synthetic and cerebrovascular CT perfusion dataset. The study targets an important unaddressed problem in the imaging and medical communities, and there is no major concern with the methodologies used. However, my main concern is that much of the proposed work is recapitulating widely-available knowledge, and I feel there is little that can be regarded as a substantial new result which merits publication in TBME.

For instance, what is practical use for the new perfusion measure Ps? It requires one to know various pieces of information (such as flux and streamlines), which are likely to be part of the unknowns we are trying to estimate along with perfusion. The radius of the ensuing pseudo-streamsurface (for a lack of a better name) has no clear physical interpretation compared to, say, the partial pressure of oxygen in the blood passing through the volume which may be the real quantity of interest. Related to this, the results presented in figure 1 is showing merely the fact that if one analytically discretises the continuous PDE consistently, the results will agree better as the discretisation is refined. The fact

that consideration of transport requires the knowledge of upstream flows is something I would regard as being self-evident, and a detailed treatment focussing on that aspect avoids confronting the real elephant in the room which is, *how do we deal with the unknown upstream flow?*

**Response**: In our work we apply known knowledge from fluid mechanics to the theory of perfusion. The concept of perfusion is problematic when the physics behind is explored since perfusion becomes discretization dependent. This is not an ideal situation for a quantitative measure, and the main novelty in our paper is to prove and highlight the problematic issues related to perfusion as a measure of flow, and that it should be used with care within traditional one-compartment models until the theory is more appropriate. We consider this to be new knowledge to the perfusion community by our observation that voxel wise perfusion studies are published without awareness of the challenges related to perfusion measurements (see inserted text below). We are not suggesting a complete solution to the perfusion problem in this paper, as this task would be comprehensive and fits into a separate publication. Certainly, in follow up studies we want to address this problem. Instead, at the moment we seek to create awareness in the medical community that currently available methods for voxel wise perfusion estimates must be used with care and that more appropriate models are needed. The essence of these considerations has now been inserted into the discussion: “Our results strongly support the usage of traditional models for entire regions which are exclusively fed by the measured arterial input. However, they also show that if traditional models are applied only to parts of the system, they tend to overestimate the actual perfusion. These limitations are only partly known within the community, and studies reporting voxel wise perfusion maps without discussing their possible limitations are continuously published [26], [27]. Thus, a major motivation for our study is to stimulate the awareness around this topic and to push the development of more appropriate models for future applications.

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This is not to say the paper is without merit – particularly the sections showing what type of errors can be accrued by using a voxel-based quantification, or local/global AIF, the inconsistency of the existing definition of perfusion, and the superior observability of CBV are useful information to be presented systematically in a single source. The discussion and conclusions are clearly expressed. I believe the authors may be able to find a more suitable outlet for their work.

**Minor Comments**

In general, boldface fonts should be used for vector quantities to make the mathematics clearer.

**Response**: This has been added.

P2L29 I think impulse is spelled with an ‘e’ (also found in other places)

**Response**: This has now been corrected.

P3L2 k is intrinsic permeability?

**Response**: That is correct yes. The manuscript has been updated accordingly.

P3L40 “…can hence ***be*** phrased as”

**Response**: This has now been corrected.

P3L45 “… the assumption of stationary ***for*** phi\_i was used” ?

**Response**: This has now been corrected.

P3L9 In the second column, the variables in the PDE are generalised to be a function of space and time after certain simplifications have been made up to that stage in the derivation already, which obscures the true assumptions. For example, porosity, concentrations (and implicitly the permeability) were assumed to be uniform within the control volume, leading to there being no spatial derivatives of these variables in the PDE.

**Response**: Thank you for notifying us about this inconsistency. We have now changed to continuous variables.

P4L6 What was the actual setup for the recursive convolution (i.e. level of discretisation) ?

**Response**: Figure 1 shows the recursive and the deconvolved impulse response function at location (1,20), meaning that convolution was performed with 19 exponential functions. This information was added to the paper.

P5L34 The equation (24) is for porosity, rather than the volume

**Response**: The porosity and CBV have equal definition. We have now clarified the proof.

P7L23 Was motion artefact an issue, with almost 2 minutes of scan time?  
**Response**: Prior to the perfusion analysis, intra patient registration was performed. Based on bone-structures (>600HU), the alignment was carried out with respect to the first timepoint using rigid transformations (rotation, translation). After the registration, motion was visually determined to be negligible. We have added this information and reference [25], were more details on the real data can be found.

Reviewer: 2  
  
Comments to the Author  
This manuscript examines the limitations of kinetic models of tissue perfusion that are often applied with intravascular tracers to create voxelwise maps of tissue perfusion.  Specifically, the manuscript focuses on the issue that conventional definitions of perfusion based on blood entering and leaving a control volume are not scale invariant. A percolation network model is proposed that enables solving for blood flux in a manner that is self consistent when discretized into voxels.  The manuscript then examines how to relate this flux to conventional notions of perfusion using control volumes derived from streamline. Simulation and experimental data are presented.    
  
Overall, I found this to be a thought provoking paper and can recommend it for publication.  Some specific issues that should be addressed are as follows:  
  
1. In the introduction it would be useful to make clear that the issues discussed pertain to intravascular tracers and not perfusion measurements in general.  Microsphere experiments and, to a lesser extent, diffusible tracer techniques such as arterial spin labelling MRI where the tracer is trapped by the tissue do not suffer from the limitations described.

**Response**: It is correct that the issues discussed apply to intravascular tracers. We have now changed the following in the introduction: *“In the present work, we focus on mathematical models to estimate blood perfusion (cerebral blood flow, CBF), blood volume (cerebral blood volume, CBV), and mean transit time (MTT) of the brain from dynamic image data using* ***intravascular*** *tracers.”*

2. In discussing the difficulties of defining diffusion, it would be useful to start from the idea that perfusion is the proportion of blood flow that delivers oxygen and nutrients to a given volume of tissue as opposed to passing through en route to somewhere else.  This definition is usually operationalized by assuming the blood that passes through a capillary bed is ‘delivered’ at that location.  The proposed methodology addresses this difficulty in part by defining a control volume based on streamlines.  However, this approximation becomes less plausible as the control volume becomes larger.  Some discussion of these issues would be a useful addition to the discussion section.

**Response**: This is an important perspective, and we have now added more considerations on this topic to the second paragraph of the Discussion section, starting with *“Our results strongly support...”*.

Minor comments:  
  
1. In the abstract, it is not clear what is meant by ‘capillary tissue’.

**Response**: We have now reviewed our notion of ‘capillary tissue’ in the introduction: *“****Capillary tissue is here understood as tissue perfused by capillaries****”*

2. In the abstract, the first sentence of the results section sounds contrived. Consider deleting the phrase “We found that …”.

**Response**: The abstract has now been rephrased accordingly.

3. Page 2 line 7. The use of the word perfusion here is confusing.  Consider ‘flow’ as an alternative.

**Response**: ‘Perfusion’ has now been replaced by ‘flow’ at this location.

4. Page 2: Spelling of impuls response -> impulse response

**Response**: This has now been corrected.

5. Page 6 line 16, brain -> human brain.  
**Response**: This has now been corrected.

Reviewer: 3  
  
Comments to the Author  
Summary:  
This paper draws attention to the issues of the often used traditional mathematical one-compartment models which calculate the perfusion for larger volumes. The traditional estimation of blood perfusion is in conflict with modern imaging technology developing better resolutions and ranging to smaller scales. One conclusion of the paper is that continuous and coupled PDE models are a better choice for the calculation of the microperfusion. The paper presents a synthetic continuous PDE model for the propagation of tracer included in capillary blood flow. The model is based on porous media flow and includes the dilution of a contrast agent. In comparison to the continuous model the paper presents the theoretical outline of two traditional models: the convolution model and the maximum slope model.

One difference between the two approaches is that the continuous calculation refers to blood flow whereas the traditional models are focused on blood perfusion. An ansatz is given to handle the conversion from flow to perfusion using the normalization referring to streamlines. This approach is challenging as the flow pattern has to be known to track the streamlines and to include the accurate volume. The inclusion of wrong volumes during the normalization of the flow to the perfusion leads to overestimations of the perfusion values.    
Although no evidence for this problem is presented the designed approach could show that the continuous model can be understood as a combined traditional model composed of sections which are coupled by the arterial input from the adjacent section.  Furthermore a comparison between the continuous model and the traditional models could outline that the traditional models deliver inaccurate results in sections with smaller volumes.   
  
Critique:  
The main focus of the paper is the comparison between different models including traditional models, a continuous PDE model and the combination of both approaches. An overview of the models and the assumptions would help to get a better overview (consistent/clear denomination of the models in the text and figures).  
Equation 11 describes the change in contrast agent at time point t from ﬂuid entering the control volume. However, the equation is not equalized to the CA concentration in the tissue volume.

**Response**: This equation is consistent with the rate of change of tracer entering a control volume. To estimate the total pointwise tracer concentration as a function of time the PDE system (Eq. 9 in the current version) must be solved as a function of time with proper intial conditions. We are not entirely sure that the review refers to by “tissue”, but in our model we assume that the tracer is entirely intravascular, which is accounted for by the porosity parameter .

Later, the overall tissue tracer concentration within the control volume is computed as C = c (see the paragraph just above Eq. 6 in the current version of the manuscript).

For table 1 it is explained, that in larger volumes the BSVD model describes the perfusion more accurate than the MS model. But the results show relative errors for the bSVD with 4 % and MC with 1%.

**Response**: This inconsistency has been removed in the current version.

One open question remaining is why the continuous model is related to the traditional convolution model.

**Response**: Both models are set up with mass conservation as the underlying principle and we demonstrate that these models are consistent with each other. However, using the traditional models, a normalisation with respect to the correct distribution volume is not applied when establishing the perfusion value. We have elaborated more on these issues in the Discussion, last paragraph: *“The coupling between the continuous model and the convolution model in Section III-B demonstrates that the two approaches physically provide the same results, and there is no contradiction between them. The problematic issue of the traditional models is related to physical interpretation and normalization with respect to correct distribution volume. ”*

It would be interesting to explain the reasons why no evaluation for the maximum slope model was designed.   
**Response:** The maximum slope model underwent the same evaluation as the bSVD model. We apologize if this was not clear from the previous manuscript. We have now inserted into Section III-G: *“We tested the convolution based traditional model (bSVD) (3) as well as maximum-slope (MS) model (5) for their capability to recover perfusion,* ***and both models were compared to ground truth perfusion values****.*”

Recommendation:  
This paper presents an interesting insight into models delivering the estimation of blood flow. The conflict between the traditional models and developing hardware techniques delivering better high resolution images has been depicted. The paper is recommended for publication.