

Reviewer Comments

Reviewer 1

Basic reporting

The text is written in extremely simple language and implies that it was written by someone not altogether experienced in the research area. The introduction contains explanations about ATP production which have no relevance to the presented model. There is no validation with experiment. This reviewer would have expected some comment concerning reference 8 or 9. How does this work vary from ref 6 ? There are no captions on the figures .

Experimental design

Why use Maple ? and why is this stated as a "novel" solution, essentially using a previous solution to aid the next one? The velocities of plasma and RBCs are kept constant when it is known that varying arteriolar diameter (which should have been a major factor in this model but was missing) induces a substantial and non-linear change in effective viscosity (see work by Pries and Secomb). The details of the solution methods are sketchy for both Maple and COMSOL.

Validity of the findings

Firstly it is not clear what new knowledge is brought to the public domain. Results of decreasing PO₂ as a function of increasing distance has been shown before (see work of Bassingthwaite and Beard). Figure 12 looks exactly like figure 3-C yet no mention is made

of this. Why are there no explanations of the oscillations in the solution for y values in $[7, 10]$? Is this numerical error or a true result (this reviewer considers it to be the former). Statements such as "concentration of ATP is very steep near the wall of tube" implies that the author does not understand the basic concept of concentration boundary layers governed essentially by the Peclet number.

RESPONSE FROM AUTHOR: Reference 8 or 9 is omitted and explanation on biological oscillations. No experiments were conducted. Results are clear now in terms of Figure 2C in reference [6]. Captions have been added. Maple and Comsol results are in agreement. Major problem for varying viscosity has been fixed. Validity of findings is shown as profiles for time dependence are now included, not done in previous models. Oscillations in the solution have now been corrected, thanks to implementation of correct model.

Reviewer 2

Basic reporting

The author presents finite element simulations for the convective and diffusive transport of oxygen and ATP in a channel or tube with a local region of reduced PO_2 on the wall. The channel configuration being considered is the same as that assumed by Sove et al. (2013). Also, an axisymmetric geometry is considered and time-dependent effects are included. It is stated that the problem is solved "in a novel way" using Maple and COMSOL software. The presentation is poorly organized and the objectives are not clearly stated. It is difficult to discern a "relevant and meaningful research problem", one of the

criteria of this journal.

Experimental design

1. Line 12, there is no reason to assume a larger plasma velocity near the wall than the RBC velocity at the centerline. 2. Line 142 - what is Slp ? The Dm value is implausible. 3. Line 168. There is no reason to assume that v_{RBC} is significantly less than v_p . Also, the parabolic profile is questionable.

Validity of the findings

1. Figure 3C. The oscillations are not expected physically and suggest numerical artifacts. 2. Figure 4. The physical or biological relevance of the time-dependent behavior over the first 0.1 s after initiation of the system is not clear. 3. Figure 5. The step-like gradients in the z-direction suggest that axial diffusion should be included in the computation. This could be readily done using COMSOL. 4. Figure 13 and 14. The oscillations at 8-10 microns are evidently numerical artifacts.

Comments for the author

1. References are made to biochemical oscillators at several points but the relevance of the results to such phenomena is unclear. 2. Lines 35-40 are redundant. 3. Line 47: What important information? 4. Figure captions are missing. 5. Throughout, "it's" is used where "its" should be used. 6. P. 15: micro-mole is not a unit of concentration.

RESPONSE FROM AUTHOR(To reviewer 2)

Biorythms and oscillatory biology section is now removed. Numerical artifacts are removed as the correct model is now used in two distinct regions, a cell-rich and cell-free region. Re-simulated the work based on the comments of reviewer and now the results are correct.

Reviewer 3 (Vinod Suresh)

Basic reporting

I have only carried out a cursory review of this aspect since I have serious concerns about the methods that make the article unsuitable for publication in its current form. The author should carefully go through the manuscript to improve readability. Some examples:1) In lines 74-77 tube and discharge hematocrits must be mentioned before stating that they both decrease.2) Notation changes from PO_2 in eqn (1a) to P in eqn (1b)3) Eqns (2) and 5 are unnecessary, eqn (12) is a repeat of eqn (8).4) R is indicated to be a function of HT in eqn 3, but actually depends on SO_2 in eqn (4).

Experimental design

The paper states that "there is a core region of blood flow with RBCs and plasma and a cell-free region with only plasma flowing". However, in equations (1) and (8) the plasma velocity and the RBC velocity are applied over the entire channel/tube cross-section. This is incorrect and makes all the results invalid. A consistent formulation will specify the thickness of the plasma and cell-free regions and

apply the relevant velocity field in each region. An alternative is to average the convection-diffusion equation over the cross section (i.e. over y) and determine axial (z) variations in oxygen tension and ATP concentration.

Validity of the findings

I have not reviewed this aspect since the concerns about the methods impact upon the results.

RESPONSE FROM AUTHOR: Major problem for varying viscosity has been fixed. Validity of findings is shown as profiles for time dependence are now included, not done in previous models.

A consistent formulation now specifies the thickness of the plasma and cell-free regions with application of relevant velocity field in each region. Simulations were made with these changes and new results and figures are now uploaded to PeerJ.

Reviewer 4

Basic reporting

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Experimental design

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Validity of the findings

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Comments for the author

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