The Journal of Physiology JP

Multiscale model of the physiological control of myocardial perfusion to delineate putative metabolic feedback mechanisms

Hamid Gharahi, Alberto Figueroa, Johnathan D. Tune, and Daniel A Beard
DOI: 10.1113/JP282237

Corresponding author(s): Daniel Beard (beardda@umich.edu)

The following individual(s) involved in review of this submission have agreed to reveal their identity: Nikolaos Tsoukias (Referee #1)

Review Timeline:

Submission Date:	06-Aug-2021
Editorial Decision:	28-Sep-2021
Revision Received:	02-Dec-2021
Editorial Decision:	23-Dec-2021
Revision Received:	18-Jan-2022
Accepted:	31-Jan-2022

Senior Editor: Bjorn Knollmann

Reviewing Editor: Eleonora Grandi

Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. Depending on transfer agreements, referee reports obtained elsewhere may or may not be included in this compilation. Referee reports are anonymous unless the Referee chooses to sign their reports.)

Dear Professor Beard,

Re: JP-RP-2021-282237 "Multiscale model of the physiological control of myocardial perfusion to delineate putative metabolic feedback mechanisms" by Hamid Gharahi, Alberto Figueroa, Johnathan D. Tune, and Daniel A Beard

Thank you for submitting your manuscript to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 2 expert Referees and I am pleased to tell you that it is considered to be acceptable for publication following satisfactory revision.

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Yours sincerely,

Bjorn Knollmann

Senior Editor
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-A Data Availability Statement is required for all papers reporting original data. This must be in the Additional Information section of the manuscript itself. It must have the paragraph heading "Data Availability Statement". All data supporting the results in the paper must be either: in the paper itself; uploaded as Supporting Information for Online Publication; or archived in an appropriate public repository. The statement needs to describe the availability or the absence of shared data. Authors must include in their Statement: a link to the repository they have used, or a statement that it is available as Supporting Information; reference the data in the appropriate sections(s) of their manuscript; and cite the data they have shared in the

References section. Whenever possible the scripts and other artefacts used to generate the analyses presented in the paper should also be publicly archived. If sharing data compromises ethical standards or legal requirements then authors are not expected to share it, but must note this in their Statement. For more information, see our Statistics Policy.

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EDITOR COMMENTS

Reviewing Editor:

The reviewers highlight several strengths of the manuscript, including the advances in the modelling of physiological systems and the thought-provoking new physiologic insight. The authors are invited to provided the needed clarifications in model assumptions and methods.

REFEREE COMMENTS

Referee #1:

The authors integrate mathematical models at two scales to analyze in vivo myocardial hemodynamics and probe the mechanism(s) underlying vascular metabolic regulation. More specifically, the authors utilize a myocardial three-layer lumped-parameter perfusion model by Maynard et al (ref 5) and a vessel autoregulation model by Carlson and Secomb (ref 6). They fit data on coronary flow and zero-flow coronary pressure recordings obtained after epicardial occlusions in vivo in pigs. The study has several strengths including the integration of model with experiments, the innovative approach to fit data with the lumped parameter perfusion model first and refine the simulation with the more detailed vessel model, the approach to compare alternative model formulations for the metabolic signal, and the use of independent data for model validation.

Even though the model utilizes several simplifying approximations (and thus may fail to capture aspects of the system) and that the confidence in the estimation of parameter values is somewhat reduced (given the large number of optimized parameters and the potential for unidentifiability issues that this may result) the study provides novel insights particularly with respect to the limitations of previously presented hypotheses for the metabolic signal to explain experimental data.

1)Page 4, Equations 1 & 2: Is it a concern that the Poiseuille resistance-volume relationship utilized in the published lumped parameter model holds for a single vessel but may fail to capture changes in the total resistance with pressure/volume in a vascular network even under passive (no myogenic regulation) conditions? Are there evidence that this represent a good approximation for the drop in resistance as pressure/volume increases? Does Eq 1 provide a good estimate for the resistance following a collapse of vessels with negative transmural pressures (with Vij= Vc)?

2)How does the vessel response to pressure captured by Eq 1,2 compares with the one described by Eq 13? Is there similarity between the behavior of the two models in the absence (or at a constant level) of myogenic constriction? Could a common approach to capture the passive elastic properties of the resistance vasculature in the two models allow a more focused examination of the myogenic and metabolic signaling?

3)Page 5, Table 1; and Page 14 Table 2: Details for the minimization of the cost function and the estimation of parameters are not provided (optimization algorithm, tolerance, constrains, initial values etc). What do the ranges represent (confidence regions based on some statistic or distribution following different data fittings)? Please consider rounding the reported numbers to reflect the level of anticipated accuracy in your estimates.

4)"Therefore, ... our analysis argues against the hypothesis that ATP derived from red blood cells represents the primary metabolic signal for coronary blood flow regulation." Does the data analysis suggest that ATP is not the primary metabolic signal or that it is not the only metabolic signal? Could it be that multiple mediators/mechanisms work in parallel and that under hemodilution conditions the effect observed is attributed to additional, non RBC-derived mechanisms?

Page 2 par 3: "In addition, prior observations that coronary venous PO2 does not directly correlate with changes coronary blood ...". Please correct the typo.

Page 2 par 5: "This mechanism can be interrupted as representing an .." Please correct the typo.

Page 4, Eq 2: Shouldn't it be the max of the two terms?

Page 8 par 5: "The layer-wise average flow $\bar{F}_j$, transmural pressure Ptm,j, and resistance $\bar{R}_j$ are computed from the cycle averaged simulated of the lumped Model 1 under each experimental condition for each experimental animal." Not clear, please consider rephrasing.

Page 8, Eq 28: You account for the dependence of blood viscosity on Hct. I assume that this is to simulate the hemodilution data. Is the Hct provided under control and hemodilution?

Page 10 Eq 36: What does 10 represent ?

Page 14 par 5: "Predicted resistance vessel diameters are plotted as functions of transmural pressure at different CPP values for the midwall layer in one experimental animal in Error! Reference source not found." Please correct the reference

Referee #2:

Overall this paper offers an interesting analysis of developed models that are designed to predict metabolic control of the coronary circulation. I will admit to the authors and the editors, that my sophistication in mathematics does not compare to the authors; accordingly, I viewed this paper through the lens of one who is interested in how blood flow is controlled in the heart, and what insights are offered by the models.

I would like to see is some mention of the assumptions used in the analysis. Perhaps this is naive, but I thought models were based on assumptions and having an explicit listing of those involved in your analysis would be helpful.

You stated: "Analysis identifies a maximally likely metabolic mechanism among the seven tested models, in which production of a metabolic signaling factor is proportional to MVO2 and delivery proportional to flow." Because oxygen extraction is nearly maximal in the heart (maybe it can increase by 10%), coronary blood flow is directly proportional to MVO2. Is not some of the conclusion expected?

I was intrigued by the lack of fit of the non-linear model. I say this because some aspects of the coronary microcirculation appear to be non-linear (Trzeciakowski J and Chilian WM. Chaotic behavior of the coronary circulation. Med Biol Eng Comput. 2008;46:433-42). I am not sure of your rationale for using the square of the myocardial oxygen consumption rate as the metabolic signal. This is why I ask you to list assumptions. What if the square of MVO2 is not the non-linearity for metabolic control--how would the analysis handle this?

I am curious as to why the model using the signal of coronary venous PO2 was better in prediction than the model using ATP release from RBC's since they are related? Any thoughts?

I found the paragraph on sympathetic control/exercise response to be a bit selective. There is evidence that alpha-adrenergic contraction does not redistribute flow to the subendocardium--in a model involving a regional sympathectomy in exercising dogs. The fact that such an effect may occur during a stenosis is really not pertinent as that would be more in line with auto regulation during hypoperfusion and tissue ischemia--which may be very different than metabolic dilation to maintain aerobic metabolism.

Overall, an interesting paper that will provoke a lot of thought.

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END OF COMMENTS

Confidential Review **06-Aug-2021**

Dear Editors,

We are grateful for the referee's and reviewing editor's comments and suggestions, which have helped us to improve the clarity of our paper. A point-by-point response to referee concerns follows.

Sincerely,
Dan Beard, on behalf of all authors

Response to Referee #1

1) Page 4, Equations 1 & 2: Is it a concern that the Poiseuille resistance-volume relationship utilized in the published lumped parameter model holds for a single vessel but may fail to capture changes in the total resistance with pressure/volume in a vascular network even under passive (no myogenic regulation) conditions? Are there evidence that this represent a good approximation for the drop in resistance as pressure/volume increases?

The reviewer is correct that the model's resistance-volume relationship represents a simplifying assumption. We have added the following text following Eq. (1) to better describe this assumption: "This resistance-volume relationship represents a major simplifying assumption of the model, where it is assumed that two representative lumped resistances govern conductivity to a given layer. Equivalently, this assumption implies that: (1.) perturbations in total microvascular blood volume are allocated throughout the elements of the microvascular network in proportion to the volume in those elements; (2.) the radii of all resistance vessels in the microcirculation are proportional to the square roots of the volume of blood in those vessels; and (3.) the pressure drops across these vessels is inversely proportional to the radius of vessel diameter."

The validity of the approach is reflected in its ability to fairly well match the observed data, both in the context of the current paper and of previous publications on which our model was developed (Spaan et al. 2000; Mynard and Smolich 2016).

Does Eq 1 provide a good estimate for the resistance following a collapse of vessels with negative transmural pressures (with Vij= Vc)?

To justify our approach for modeling collapse, the following sentence was added to the text (page 4, line 151): "Following Guiot et al. (PMID: 2337190), we assume that the laminar flow assumptions for the un-collapsed vessel (Eq. 1) are effectively valid for collapsed vessels."

2)How does the vessel response to pressure captured by Eq 1,2 compares with the one described by Eq 13? Is there similarity between the behavior of the two models in the absence (or at a constant level) of myogenic constriction? Could a common approach to capture the passive elastic properties of the resistance vasculature in the two models allow a more focused examination of the myogenic and metabolic signaling?

This is a point that needs clarification: the vessel responses captured by the two models are equivalent and equal. Specifically, first the zero-flow pressure data are analyzed with the model (Model 1) where Eqns. (1) and (2) represent the relationship between pressure and volume in the coronary microvessels. Next, models (Model 2) that use Eqn. (13) are analyzed to determine if/how they can predict the same pressure/flow relationships as the simpler model.

This point is summarized in modeling overview (line 112). Furthermore, the point is re-emphasized in the revised results section, lines 348-350.

3)Page 5, Table 1; and Page 14 Table 2: Details for the minimization of the cost function and the

estimation of parameters are not provided (optimization algorithm, tolerance, constrains, initial values etc). What do the ranges represent (confidence regions based on some statistic or distribution following different data fittings)? Please consider rounding the reported numbers to reflect the level of anticipated accuracy in your estimates.

The details of the parameter estimation were added to the paper. The ranges in Table 1 show the minimum and the maximum value of each parameter estimated in Model 1.

A genetic algorithm was used for the parameter estimation in both models, as detailed in the revised ms. on lines 285-290. For Model 1 parameters, a population size of 600 and number of generations 1200 was used although the procedure converged before reaching the 1200 generations in all cases. For Model 2 parameters, we set the population size and number of generations to 1000 and 10000, respectively. For both models, the cross-over and mutation probabilities were fixed to 0.8 and 0.01, respectively, and the convergence tolerance was 10^{-8}. The last generation was evaluated in each case to ensure unique results.

4)"Therefore, ... our analysis argues against the hypothesis that ATP derived from red blood cells represents the primary metabolic signal for coronary blood flow regulation." Does the data analysis suggest that ATP is not the primary metabolic signal or that it is not the only metabolic signal? Could it be that multiple mediators/mechanisms work in parallel and that under hemodilution conditions the effect observed is attributed to additional, non RBC-derived mechanisms?

Our analysis challenges the role of ATP as the primary **or** sole metabolic mediator in the coronary flow regulation. More specifically, we show that the ATP mechanism, on its own and as formulated here, cannot effectively explain the data. We added a paragraph (last paragraph of the discussion) to add clarification along these lines:

“Finally, although our analysis points to a single candidate mechanism as representing the metabolic signaling pathway for control of myocardial perfusion, it is possible and even likely that multiple different specific mediators operate under the aegis of this general framework. Moreover, the analysis conducted here is limited to considering each putative metabolic mechanism on its own and does not rule out the likely possibility of multiple mechanisms acting in parallel. Most concretely, this analysis reveals which of the tested mechanisms are unable to effectively explain the observed in vivo autoregulatory behavior, and does not unambiguously identify the correct mechanism that is operative in vivo. How coronary perfusion is regulated to be directly proportional to oxygen demand is a fundamental question in coronary physiology. The general framework that survives testing against these data explicitly invokes a direct proportionality between a vasodilatory signal and oxygen consumption rate. Thus this framework may ultimately prove to be a convenient temporary placeholder against which to judge more detailed specific hypotheses. Alternatively, it may prove to be the mechanistically correct foundation on which to build more detailed specific hypotheses.”

Page 2 par 3: "In addition, prior observations that coronary venous PO2 does not directly correlate with changes coronary blood ...". Please correct the typo.

Thanks for pointing this out. The typo is corrected now.

Page 2 par 5: "This mechanism can be interrupted as representing an .." Please correct the typo.

Thanks for pointing this out. The typo is corrected now.

Page 4, Eq 2: Shouldn't it be the max of the two terms?

Yes. Thanks for pointing this out. This was corrected in the manuscript.

Page 8 par 5: "The layer-wise average flow $\bar{F}j$, transmural pressure Ptm,j, and resistance $\bar{R}j$ are computed from the cycle averaged simulated of the lumped Model 1 under each experimental condition for each experimental animal." Not clear, please consider rephrasing.

We have rephrased this as: “The layer-wise flow $\bar{F}_j$, transmural pressure $P_{tm,j}$, and resistance $\bar{R}_j$ are computed from the cycle-to-cycle averaged simulation results of Model 1, for each experimental condition and each animal.”

Page 8, Eq 28: You account for the dependence of blood viscosity on Hct. I assume that this is to simulate the hemodilution data. Is the Hct provided under control and hemodilution?

Yes. The experimental data provided Hct under all 3 conditions (Kiel et al. 2018). A sentence was added to the “Experimental Data for Model Identification and Validation” section: “In addition, arterial and venous blood samples were collected to measure blood oxygenation and hematocrit.”

Page 10 Eq 36: What does 10 represent ?

10 represent a normalization of the sensitivity index with respect to the 10% parameter change. Overall, the sensitivity index represents the fractional change in error relative to a fractional change in parameter value. For example, a value of 1 means that a 1% change in parameter leads to 1% change in the model prediction. The following sentence was added to the manuscript: “The sensitivity index $\boldsymbol{X}_i$ represents the ratio of change in error relative to a change in parameter value. For instance, a sensitivity value of 1 means 1% change in parameter corresponds to 1% change in the model prediction.”

Page 14 par 5: "Predicted resistance vessel diameters are plotted as functions of transmural pressure at different CPP values for the midwall layer in one experimental animal in Error! Reference source not found." Please correct the reference

This has been fixed.

Response to Referee #2:

I would like to see is some mention of the assumptions used in the analysis. Perhaps this is naive, but I thought models were based on assumptions and having an explicit listing of those involved in your analysis would be helpful.

Thanks for the comment. A brief description of assumptions used for each metabolic signal model has been added to each item in “Representative Vessel Model (Model 2)” section, pages 7 and 8.

You stated: "Analysis identifies a maximally likely metabolic mechanism among the seven tested models, in which production of a metabolic signaling factor is proportional to MVO2 and delivery proportional to flow." Because oxygen extraction is nearly maximal in the heart (maybe it can increase by 10%), coronary blood flow is directly proportional to MVO2. Is not some of the conclusion expected?

Yes, the reviewer raises a point that the authors have discussed. Stated a different way: is our proposed mechanism just a recapitulation of the underlying question: What is the mechanism that makes coronary flow directly proportional to flow? Ultimately, our proposed mechanism may involve circular reasoning.

We have discussed these issues in more depth in the final paragraph of the revised paper. (The point is also addressed in the response to Reviewer 1.)

I was intrigued by the lack of fit of the non-linear model. I say this because some aspects of the coronary microcirculation appear to be non-linear (Trzeciakowski J and Chilian WM. Chaotic behavior of the coronary circulation. Med Biol Eng Comput. 2008;46:433-42). I am not sure of your rationale for using the square of the myocardial oxygen consumption rate as the metabolic signal. This is why I ask you to list assumptions. What if the square of MVO2 is not the non-linearity for metabolic control--how would the analysis handle this?

The motivation for using the square of MVO_2 is described in the revised paper (lines 248-253): "Since the calculation of MVO_2 from experimental measurements of oxygen extraction depends on flow (Eq. 22), metabolic signal 6 implicitly depends on F_j^2 and oxygen extraction ($CaO_2 - CvO_2$). Therefore, as an additional candidate, we assume metabolic signal 6 to be a part of a nonlinear relationship in which the metabolic signal depends on the squares of flow and oxygen extraction."

The second part of this question—what if the square of MVO2 is not the non-linearity for metabolic control—is difficult to address specifically. The scope of candidate hypotheses to consider is long.

I am curious as to why the model using the signal of coronary venous PO2 was better in prediction than the model using ATP release from RBC's since they are related? Any thoughts?

Our ATP release is based the Pradhan et al. model where ATP transport is modeled as a function of O_2 saturation, hematocrit, and flow. In our implementation, these variables are directly imposed from Model 1 and data, which could introduce some discrepancy between ATP release estimation and venous PO_2. In addition, the ATP release model involves one additional adjustable parameter (S_0 in Table 2). Since in our model selection analysis the models are penalized based on the number of adjustable parameters and their likelihood is quantified using an exponential function, the ATP model performs poorly compared to other models which potentially produce similar fits to data but have less parameters. Note that this is a purely statistical approach to model selection—there are not extra points for potential physiological insight. Furthermore, the ATP hypothesis may actually work better in comparison to the data analyzed here if it were adapted to the "ephemeral" signal hypothesis. That is, if the ATP signal were (reasonably) assumed to rapidly degrade in the microcirculation, it could potentially be revised to function in the general framework of the "ephemeral signal" hypothesis.

I found the paragraph on sympathetic control/exercise response to be a bit selective. There is evidence that alpha-adrenergic contraction does not redistribute flow to the subendocardium--in a model involving a regional sympathectomy in exercising dogs. The fact that such an effect may occur during a stenosis is really not pertinent as that would be more in line with auto regulation during hypoperfusion and tissue ischemia--which may be very different than metabolic dilation to maintain aerobic metabolism.

Dsicussion about the role of alpha-mediated constriction in exercise and stensosis has been revised. Please see new text on lines 501-507.

Dear Professor Beard,

Re: JP-RP-2021-282237R1 "Multiscale model of the physiological control of myocardial perfusion to delineate putative metabolic feedback mechanisms" by Hamid Gharahi, Alberto Figueroa, Johnathan D. Tune, and Daniel A Beard

Thank you for submitting your manuscript to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 2 expert Referees and I am pleased to tell you that it is considered to be acceptable for publication following satisfactory revision.

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I look forward to receiving your revised submission.

If you have any queries please reply to this email and staff will be happy to assist.

Yours sincerely,

Bjorn Knollmann

Senior Editor
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EDITOR COMMENTS

Reviewing Editor:

The reviewers deemed the revision satisfactory and commented on an interesting and solid study. One minor concern remains for the authors to consider.

Please also see the 'Required items' section above for three administrative points that must be addressed.

Senior Editor:

Please address the remaining minor concern of reviewer 2. Excellent work!

REFEREE COMMENTS

Referee #1:

The authors have addressed the points raised providing the necessary clarifications and modified the manuscript accordingly.

Referee #2:

I am satisfied with the authors revisions with one exception--your use of a quadratic as an example of a non-linear model. I cannot think of a biological system that behaves as a quadratic where a negative value, when squared, becomes a positive value. I am not going to ask yous to "redo" this analysis using a non-linear model that has been previously modeled to the coronary circulation, but will ask you to be explicit in pointing out the non-linear analysis is only applies only to a quadratic, and would not predict whether other non-linear models, e.g., chaotic attractors, would better predict coronary flow regulation.

Other than this, very nice job.

_____

END OF COMMENTS

1st Confidential Review **02-Dec-2021**

Dear Editors,

We are again grateful for the referees' and reviewing editor's comments and suggestions. A response to outstanding issue raised by reviewer 2 is below.

Sincerely,
Dan Beard, on behalf of all authors

Response to Referee #2

I am satisfied with the authors revisions with one exception--your use of a quadratic as an example of a non-linear model. I cannot think of a biological system that behaves as a quadratic where a negative value, when squared, becomes a positive value. I am not going to ask you to "redo" this analysis using a non-linear model that has been previously modeled to the coronary circulation, but will ask you to be explicit in pointing out the non-linear analysis is only applies only to a quadratic, and would not predict whether other non-linear models, e.g., chaotic attractors, would better predict coronary flow regulation.

The reviewer raises a valid point regarding our exposition of the "nonlinear" model. In fact, every iteration of the model is nonlinear in one sense or another. Even the models with linear feedback terms have nonlinearities built into the tissue mechanics model. The so-called "nonlinear" model (model #7) is not really any more non-linear than the others. We have revised the text: see line 263 for a brief motivation on the functional form of this model.

Dear Dr Beard,

Re: JP-RP-2022-282237R2 "Multiscale model of the physiological control of myocardial perfusion to delineate putative metabolic feedback mechanisms" by Hamid Gharahi, Alberto Figueroa, Johnathan D. Tune, and Daniel A Beard

I am pleased to tell you that your paper has been accepted for publication in The Journal of Physiology.

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All queries at proof stage should be sent to TJP@wiley.com

Yours sincerely,

Bjorn Knollmann
Senior Editor
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EDITOR COMMENTS

Reviewing Editor:

Remaining minor concerns have been addressed

2nd Confidential Review **18-Jan-2022**