Dear Professor Baek,  
  
Re: JP-RP-2020-280817 "A Constrained Mixture Theory Model to Study Autoregulation in the Coronary Circulation" by Hamidreza Gharahi, Daniel A Beard, Alberto Figueroa, and Seungik Baek  
  
Thank you for submitting your manuscript to The Journal of Physiology. It has been carefully assessed by a Reviewing Editor and 2 Referees and the reports are copied below for your information.  
  
I regret to say that the manuscript has not been accepted for publication.  
  
Although we are unable to offer any further consideration to your manuscript, I hope that the points raised in the reports will be helpful. Please do not feel discouraged from submitting future new work to The Journal of Physiology.  
  
Yours sincerely,  
  
Harold D Schultz  
Senior Editor  
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----------------------------------------------------------------------  
  
EDITOR COMMENTS  
  
Reviewing Editor:  
  
Both reviewers commented on a strong methodological contribution in building a sophisticated model for autoregulation of coronary blood flow - despite several weaknesses raised by reviewer 2. However, reviewer 1 found that the significance of the work is limited as it leads to no new insight on autoregulation of coronary blood flow.  
  
  
  
It should be noted that the morphometry-structure-hemodynamics tree construction relies heavily on global energy optimization with constraint of mechanical equilibrium - this work is on arxiv but not accepted anywhere yet. It puts the onus on the editors and reviewers to review multiple papers to verify this work.  
  
  
  
REFEREE COMMENTS  
  
Referee #1:  
  
  
The authors present a theoretical model for autoregulation of coronary blood flow. This topic is physiologically significant. The model is built from three main components: (i) a "constrained mixture" theory for the nonlinear elastic properties of vessel walls; (ii) synthetically generated vascular trees based on observations of coronary vasculature; (iii) a model for regulation of vascular tone based on previous work from Cornelissen et al. (2002) and Carlson et al. (2008). (Although the constrained mixture model was developed by Humphrey et al. to describe vascular remodeling, effects of remodeling are not included in this model.) The estimation of the parameters in such a model is a major challenge and the authors have made extensive efforts in parameter estimation using optimization of model fits to available data. The work is carefully done and thoroughly described. It represents a useful methodological contribution and could be used as a basis for further investigations. However, it does not lead to significant new insights or knowledge on coronary autoregulation, and the results lack broad significance outside the context of theoretical modeling in this field.  
  
  
  
Minor comments  
  
1. P. 2. "and it gradually decays for larger vessels (~150 μm) (44)." Is this the correct reference for this statement?  
  
2. P. 3, middle, should be "to estimate baseline"  
  
3. P. 5. The assumed dependence of the myogenic response on pressure rather than circumferential tension is a weakness of the model. The authors argue (p. 26) that the dependence on circumferential tension is implied, but this is not equivalent.  
  
4. P. 5. "Constrained mixture models have been widely used in the computational study of growth and remodeling of large arteries, under the general assumption that the homeostatic stress of each wall constituent is constant (2, 28, 30, 91)." See also p. 3 and 25. The claim that constrained mixture models are "widely used" in this context is not supported by the cited references, all of which include Humphrey and/or Baek as authors.  
  
5. P. 10. "is a SMC basal (homeostatic) stimuli." Should be "stimulus" (singular) not "stimuli" (plural).  
  
  
  
  
  
  
Referee #2:  
  
  
This study proposes a model for coronary autoregulation and combines three existing models in the field (including prior work by the authors). It combines simplified constraint mixture, morphometry-structure-hemodynamics models with autoregulation model, captures some of the experimental data quantitatively and some qualitatively. This manuscript is sophisticated, sizeable work from a methods standpoint and a necessary step in building a full growth and remodeling model for long term adaptation.  
  
  
  
Details of the methods, some results and lack of validation are some of the weaknesses.  
  
Major comments:  
  
- The collagen prestretch < 1 is questionable. Previous publications have put collagen prestretch between 1-1.15, including papers from the senior author. Is this a problem with the choice of your reference configuration? If not, I suggest rerunning your analysis with physiological bounds. Note that just because there is waviness it is not indicative of compression (for e.g. elastin)  
  
- Another major concern is Figure 4 - the mass fractions. Do you have any literature data to support it? Why does elastin increase from intermediate to small arteries in subendocardial vessels and why does collagen increase from LA to IA? Wouldn't you expect a monotonic trend for some of the wall constituents in the vascular tree? This figure needs solid backing from literature as rest of the model and results rely on it.  
  
- On a similar note, based on microstructure, is neoHookean in A.10 relevant for elastin in coronaries?  
  
- I appreciate the authors have done a local sensitivity analysis. I also recommend including an identifiability analysis. you could have parameters that are making no difference to the model and you should identify them. Sensitivity analysis makes more sense with identifiability analysis.  
  
- parameter estimation in section 2.2: Given passive behavior is different across coronary tree what motivated material properties and SMC parameters to be a constant across trees and prestretch to be different? Do cells lay down collagen across the tree with a different prestretch? Mass fractions being different across the coronary tress seems right, intuitively. Can you provide results for how different choices of constant/estimated parameters affects the results?  
  
- Passive fits look acceptable in Fig 5, but why is the myogenic model failing for small arterioles? - is this related to the question above on choice of keeping things constant/different across tress?  
  
- Intuitively as your inlet pressure increases you would expect the diameter in the vessels to asymptote - why don't they asymptote with pressure in Figure 11 across the tree? Its another sanity check the model should pass.  
  
  
  
- Would it be prudent to fit pressure vs. shear (in line with Pries and Secomb's work) rather than fitting Pressure vs D and pressure vs. tau? The relevance of rat/cat mesentery or any non-coronary data in Fig 7 to this work is lost on this reviewer - also, the model is not capturing the rat mesenteric data well!  
  
- Discussion talks about ischemia for a 20% reduction in diameter - what % reduction in diameter affects perfusion in various parts of the tree? If this is not known, please remove overinterpretation of equating 20% drop in diameter to ischemia.  
  
- How are b1, b2, b3 and b4 determined in eq. 12?  
  
- The morphometry data is derived for the whole coronary tree or just the left ventricle? Given RV is a low-pressure ventricle - How do some of the parameters in the model change for right ventricle? -  
  
- the manuscript has an emphasis on smooth muscle cells - what about cardiac cells, do they play any role directly/indirectly in coronary autoregulation?  
  
- The model has tried to simulate stenosis, can you simulate exercise?  
  
- What was the motivation for introducing a volume fraction for interstitial fluid in this model?  
  
  
  
Minor comments:  
  
- Constrained mixture theory is formulated as per area but homeostatic optimization is formulated per volume - any chance you can keep the formulations consistent?  
  
- Title has 'constrained mixture theory model to study...' -- the emphasis of the manuscript is more on coupling 3 models and less on the constrained mixture theory, moreover the constrained mixture theory used is a simplified version with no evolution, production and removal equations. I suggest you change the title to reflect the content.  
  
- Please pay attention to figures - color-relevant details are lost when printed in B&W  
  
- manuscript has a lot of figures and tables, you could combine them; for example, combine tables into 1 or 2 tables.  
  
- eq A.14- put the 'h' as a superscript on D to go with superscripts on other variables in the equation  
  
- Equation B.2 and B.3 are referred to in Appendix but those equations are missing - please check.  
  
- variable C in eq. D.1 is already used for cost per unit length in eq. C.1  
  
- exercise caution is relating smooth muscle mass fraction to contractility - the model doesn't have fidelity in synthetic/contractile phenotypes to draw such conclusions.