Referee Report for the Phd thesis
Flow of biological fluids in patient specific geometries
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Summary

This thesis considers the numerical computations of blood flows in two types of pathological geometries: enlarged vessels (cerebral aneurisma) and obstructed (stenotic) vessels.

I believe that *the main novelty and potential impact of the work lies in the chapter about the relative pressure estimation from full field velocity measurements (Chapter 4)*. In short time, the results have already triggered further research by other groups, including applications with real data. Mainly due to this reason I recommend the candidate for obtaining the Phd degree. Moreover, I think that some of the results in Chapter 2 may lead to further research on relevant metrics for aneurism rupture risk estimation.

In the following lines I give more detailed comments on each of the chapters. I would acknowledge that these issues are addressed in the final manuscript version, if pertinent and possible.

Chapter 2

This chapter deals with the computation of blood flows in cerebral aneurysms. I am not an expert in aneurysm modeling so I do not have an overview of the literature. But my impression is the results confirm existing literature findings.

However, the end of the chapter draw my attention where it seems that the“symmetry” of the histograms (Figure 2.18) is by far the quantity what correlates better with the “rupturing”. Since you have 20 geometries, why not to investigate for a marker that accounts the symmetry of the stresses distributions and check this value for the all unruptered and unruptured cases? The question after that could be: is this ”bad” load balance the result of the cause or the cause of the pathology? If it's previous to the end stage of the pathology, may it be used as a earlier biomarker of rupture risk, for instance?

I have also some more specific comments:

- In the patients-specific examples, how did you set up or estimate the inflow velocity for this simulations? Does the location of max WSS change when you change the inflow amplitude due to the non-linear nature of the problem? Up to what extent does this changes the symmetry of the stress histograms?
- In Figure 2.2, why is the surface mesh much coarser than the segmented mask? Why to loose geometrical details?

- You try to define TAWSS as a function of the volume, but the fitting seems very poor from Figure 2.16 and the fact that $R^2 = 0.25$.
- Equation 2.1: no backflow treatment? Does it appear in the simulations?
- Equation 2.2: why is the initial condition defined on the boundaries? Is $v_{in}(t = 0)$ on Γ_{in} not zero? Is then some spatial discontinuity in the initial condition? Does this not result in some artefacts at the beginning of the computations?

Chapter 3

This chapter presents the model and simulation setup used later. It also summarises methods for stenosis severity quantification. Itself it presents no scientific novelty, but is a needed step for the sequel.

I have some comments and questions:

- In page 47, you say "neglecting integrals containing viscosity and convective term of Navier-Stokes equations"? In the Bernoulli model, you actually neglect the "time derivative" but not the convective part, or?
- Does it make sense to plug a time varying Neumann condition? In page 65, and also in the rest of the thesis, this is used several times, even in the conclusions.
- Did you try other backflow stabilizations, like the tangential regularization method?
- How does the stability analysis for the CN scheme for the Navier-Stokes equations look like? Can you ensure it is conservative or stable? (in theory and practice?)
- Convection is treated implicitly, right? If yes, I did not see how you numerically solve the non-linear problem?
- Did you see some spurious effects (spatial oscillations due to convection) when varying the degree of stenosis? If yes, do you do something about them (e.g. mesh refinement, SUPG)?

Chapter 4

As I said above, I consider the introduction of the STE estimator as the main contribution of this thesis. However, I have few concerns about the presentation of the results:

- Figure 4.11: The error dramatically drops for the finest mesh, I guess is the L0 (the same mesh where the results where generated). But it drops for STE but not for PPE. Could you please explain why this happens? It is maybe due to some artefacts in the interpolation from P1+bubble to P1 elements in Fenics, or some regularity issue? In any case, it appears to be a numerical artefact due to the "coarse" mesh used in the reference simulation, should this may be taken out of the analysis? Or generate the reference velocity data with much finer meshes?

  Moreover, although STE seems to work always better than PPE (what is also my experience), also the results for the most relevant mesh sizes are not clearly shown due to the scale needed to catch this important error drop.

- In Section 4.2.3 it seems to me that the noise is proportional to the velocity amplitude. If I am right, this is a too favourable assumption, noise in PCMRI is indeed additive but fixed independent on the velocity amplitude. Also 10% noise is very favourable. My impression is that you run the estimates using only one realisation of the noise, or? In numerical examples of inverse problems, it is very advisable to represent the results in terms of mean and standard deviation, what requires several runs.
- In Section 5, the methods are applied to some of the aneurysm geometries of Chapter 2. However, the spatial subsampling of the data seems to be impracticable in current MRI practice: it goes from 0.295 to 0.337 mm. There are also important restrictions in the velocity-to-noise ratio that can be obtained at this scale. I recommend to include comments about this aspect.

Chapter 5

The last chapter investigates numerically the sensitivity of the computations to the modeling of the arterial wall friction. The author claims that the main conclusion of this part is that "... just provide warning that the different boundary conditions can lead to very different results ...", what is indeed well known.

I have some questions:

- Did you investigate the sensitivity of the results to the Nitsche parameter β Nitsche? In my experience if you really impose $\mathbf{u} \cdot \mathbf{n} = 0$ (e.g by a very large β) in curved geometries the results of slip are similar to no-slip.
- Did you check if you have mass loss due to the transpiration $\mathbf{u} \cdot \mathbf{n} \neq 0$ induced by the Nitsche technique?
- Do "backflow-type" instabilities appear on wall due to the transpiration?
- I am wondering why you did not include some Navier-slip type of boundary condition in the study. Fully neglecting wall friction seems to me not realistic.

I hope that my comments will be well received and that they will trigger further discussions and potentially new ideas in the research activities at your institution.

Sincerely Yours,

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