Investigating the relationship between AAA Wall Stress and symptoms exhibited by patients.

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Abstract:

Abdominal aortic aneurysm (AAA) is a permanent and irreversible dilation of the lower region of the aorta. It is an asymptomatic condition that if left untreated can expand to the point of rupture. Mechanically-speaking, rupture of an artery occurs when the local wall stress exceeds the local wall strength. It is therefore understandable that numerous studies have attempted to estimate the AAA wall stress. Recently our Intelligent Systems for Medicine Laboratory (ISML) presented a very efficient method to compute AAA wall stress using geometry from CT, and median arterial pressure as the applied load. The ISML's method is embedded in the software platform *BioPARR - Biomechanics based Prediction of Aneurysm Rupture Risk*, freely available from http://bioparr.mech.uwa.edu.au/. The uniqueness of our stress computation approach is three-fold: i) the results are insensitive to unknown patient-specific mechanical properties of arterial wall tissue; ii) the residual stress is accounted for, according to Y.C. Fung's Uniform Stress Hypothesis; and iii) the analysis is automated and quick, making our approach compatible with clinical workflows. In this study we evaluated 22 cases of AAA. A proportion of these was classified as symptomatic. The results of the analysis demonstrate, contrary to the common view, that neither the wall stress magnitude nor the stress distribution correlate with clinical symptoms.

Keywords: Abdominal Aortic Aneurysm, Patient-Specific Modelling, Finite Element Method, Stress, Symptoms

1 Introduction

Abdominal aortic aneurysm (AAA) is a permanent and irreversible dilation of the lower region of the aorta, is typically asymptomatic, and if untreated can result in rupture of the aorta. AAA is found in approximately 7% of elderly men (>65 yrs) in Australia (Norman, Jamrozik et al. 2004) with similar prevalence throughout the Western world (Singh, Bønaa et al. 2001). The disease also affects women, but at a lower rate.

Because AAA is usually asymptomatic, most people are unaware of their condition. However, AAA rupture is a catastrophic clinical event with mortality rates of approximately 80-90% (Bengtsson and Bergqvist 1993; Kantonen, Lepäntalo et al. 1999; Evans, Adam et al. 2000). Currently, the most widely-used evidence-based indicator of rupture threat (based on several large clinical trials) is the maximum anterior-posterior diameter: diameters of greater than 5.5cm or expansion rates of greater than 0.5cm over the preceding six months are deemed high risk. These cut-off values must be weighed against associated co-morbidities and intra-operative mortality risk, with repair only being considered if the risk of rupture exceeds the risk of surgery. However 20% of smaller AAAs rupture, while larger cases often remain quiescent (Darling, Messina et al. 1977; Greenhalgh). The ability to predict, non-invasively, which cases are at risk of rupture will have a major clinical impact by saving lives and reducing medical costs worldwide.

When patients present with symptoms, more urgent action is required; in the case of a ruptured AAA (rAAA) showing clearly visible signs on computed tomography angiography (CTa) immediate intervention will be required. Patients presenting with symptoms but no rupture apparent on CTa create more of a challenge. These patients present with abdominal pain, back pain or symptoms from local compression caused by the aneurysm (i.e. hydronephrosis, deep vein thrombosis and early satiety) and a clinical judgment must be made about whether emergency surgery is required. Data from the IMPROVE-trial show higher mortality-rates in patients treated outside routine working hours. (investigators 2014)

Because of the limitations of the current clinical definition of ‘high-risk’, many researchers believe that patient-specific modelling (PSM) could have major clinical potential (Vande Geest, Di Martino et al. 2006; Gasser, Auer et al. 2010; McGloughlin and Doyle 2010; Gasser, Nchimi et al. 2014; Zelaya, Goenezen et al. 2014; Joldes, Miller et al. 2016). In simple mechanical terms, rupture of an artery will occur when the local wall stress exceeds the local wall strength. With advances in medical imaging technology and medical image analysis software, it has become possible to create patient-specific reconstructions of the AAA, which can then be used for computer simulations aimed at computing the wall stress. These models have steadily increased in complexity (Raghavan, Vorp et al. 2000; Doyle, Callanan et al. 2007; Gasser, Auer et al. 2010; Li, Sadat et al. 2010). Major research efforts have been preoccupied with material models and simulations so comprehensive that they require computing resources and specialist expertise that are not likely to be available in a typical clinical setting.

Recently an entirely new, very simple approach to compute AAA wall stress was proposed and validated (Joldes, Miller et al. 2016) (but see also (Fung 1991; Zelaya, Goenezen et al. 2014; Biehler, Gee et al. 2015)). The inputs to the model are the (loaded) geometry of an aneurysm (obtained from a CT reconstruction), wall thickness and blood pressure. Our approach also efficiently incorporates residual stresses according to Fung’s Uniform Stress Hypothesis (Joldes

2017). The method is embedded in the software platform *BioPARR - Biomechanics based Prediction of Aneurysm Rupture Risk* (Joldes, Miller et al. 2017), freely available from http://bioparr.mech.uwa.edu.au/. This simple approach does not require any information on arterial tissue material parameters; this supports the development and use of PSM, where uncertainty in material data, until recently (Miller and Lu 2013), has been recognized as a key limitation. Furthermore, the computation itself is so simple that incorporating it into existing clinical workflows does not represent a significant challenge. In this study, we aimed to investigate the use of BioPARR in predicting AAA rupture risk in symptomatic and asymptomatic patients. (Joldes, Miller et al. 2017) We have applied our methodology to investigate whether the wall stress fields (both the patterns and magnitude) correlate with clinical definition of symptomatic and asymptomatic AAAs.

Population

Anonymized data from twenty-five patients with radiographically clear un-ruptured AAA were included in the study. All patients were treated in the University Hospitals Leuven, Belgium. Five patients presented with a symptomatic aneurysm, 20 patients were asymptomatic. In both groups, patients were selected independent of age, sex or comorbidities. Data from patients were selected retrospectively and were provided to the University of Western Australia Intelligent Systems of Medicine Laboratory. The study was approved by the local ethics committee of the University Hospitals Leuven. Patient demographics are listed in table 1.

Table 1: Patient demographics

Patient demographic		Value	%
Gender (Male/Female)		24/1	96%/4%
Age (Mean + range)		72y (58-83)	
BMI (kg/cm²) (Mean + range)		27 (16-33)	
Maximum diameter AAA (Mean + range)		61mm (37-86)	
Pulse (Mean + range)		74 bps (51-116)	
Blood pressure (mmHg)			
Mean diastolic BP (range)		79 (44-120)	
Mean systolic BP (range)		145 (110-204)	
Mean arterial pressure (range)		100 (69-148)	
Smoking: (N)	**Non-smoker**	5	20%
	Active smoker	8	32%
	Stop > 10 y	6	24%
	Stop < 10 y	6	24%
Diabetes mellitus (N)			
	None	21	84%
	Type 1	0	0%
	Type 2	4	16%
PAD (N)	**Yes**	2	8%
	No	23	92%
Arterial hypertension (N)		15	60%
Hypercholesterolemia (N)		20	80%
Open/endovascular approach (N)		10/15	40%/60%

Note: Bps: beats per second; PAD: peripheral arterial disease

2 Methods

Complete stress analyses of each AAA were conducted using our freely available software BioPARR (Joldes, Miller et al. 2017). Excluding the 3D reconstruction time, the entire analysis of a single load case scenario, including the incorporation of residual stress, took approx. 6 minutes on an Intel(R) Core(TM) i7-5930K CPU @ 3.50GHz with 64GB of RAM running Windows 8 OS. The analysis steps are briefly described below.

2.1 Problem Geometry

We used 25 real-world, patient-specific 3D geometries of patients, with all the irregularities that can be expected in clinical simulations, Figure 1.

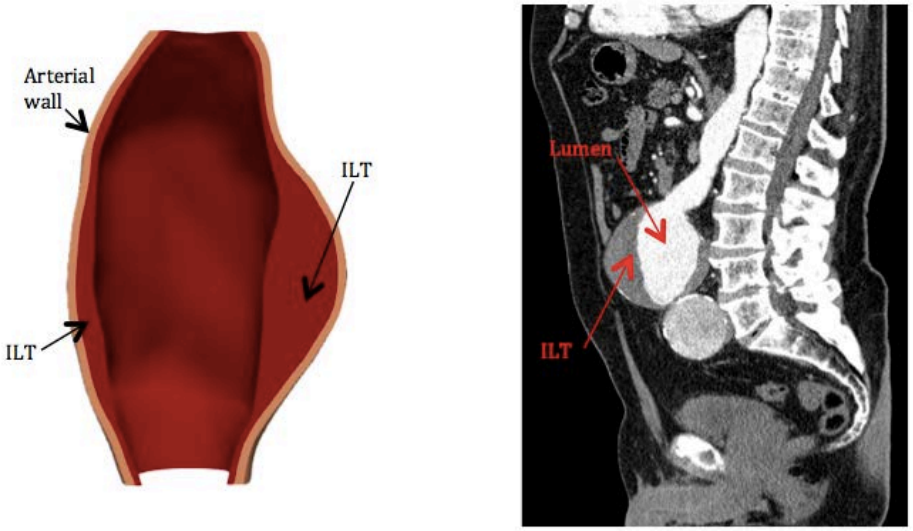


Figure 1. An example AAA case considered in this study. a) Region of interest, showing the lumen and portions of the AAA wall and intraluminal thrombus (ILT); b) CT image;

BioPARR allows the analyst to extract and combine data from images of different modality (such as CT and MRI), by implementing a segmentation-based inter-modality image registration algorithm in 3D Slicer (Fedorov, Beichel et al. 2012). The analyst has control over many parameters influencing the analysis results: the thickness of the AAA wall; inclusion of thrombus; geometry meshing; finite element type selection; and finite element simulation scenarios. The software can be used in the case when both CT and MRI data are available for a patient or, the more typical situation, when only CT is available. CT images are acquired as part of routine care and are available for most clinically relevant AAAs.

The program automatically generates 3D colour-contoured visualizations of the key patient-specific components of the analysis, namely, ILT thickness and the normalized ratio of the maximum AAA diameter and the diameter in the proximal neck of the aneurysm (NORD).

2.2 Image Segmentation

The high variability in AAA geometry, as well as low discrimination between the AAA and the surrounding tissue in parts of the image, make automatic AAA segmentation practically impossible. Therefore, our software uses segmentation tools available in the free open-source image analysis software 3D Slicer (Fedorov, Beichel et al. 2012). We have found that using the 3D Slicer extension *FastGrowCut* for segmentation (Zhu, Kolesov et al. 2014) can help reduce the segmentation time. Manual intervention is still required to define the region of interest in the image, to crop the image, and to define the seeds for the *FastGrowCut* algorithm. Manual corrections and smoothing of the resulting label maps is also necessary. Using this method, we can extract the AAA geometry from CT (or MRI if available).

2.3 Geometry creation

The label maps segmented from images combined with the assumed wall thickness of 1.5 mm (measurement of wall thickness from CT images is not possible) are used to create the AAA geometry. The external AAA wall surface, the internal AAA wall surface and the internal intraluminal thrombus (ILT) surface are automatically created.

2.4 Finite Element Meshing, Model Creation and Analysis

Meshing of the AAA wall and ILT, based on external and internal AAA wall surfaces and the internal ILT surface, is performed using open source meshing software Gmsh (Geuzaine and Remacle 2009; Geuzaine and Remacle 2016) called from within BioPARR. A tetrahedral volumetric mesh is created using the element size specified by the user. This process ensures a conforming mesh between the ILT and AAA wall. The meshing approach implemented in BioPARR uses very small elements on the surfaces to maintain their geometric accuracy. At the same time, by increasing the element size inside the ILT volume and in the thicker areas of the AAA wall, the overall mesh size is reduced along with the consequent computational cost of the finite element analysis.

The element types can be configured as linear or quadratic, displacement only or hybrid displacement-pressure formulation. Finally, Abaqus (ABAQUS 2010) input (.inp) files are generated and sent for finite element analysis. Figure 2 shows a typical AAA mesh.

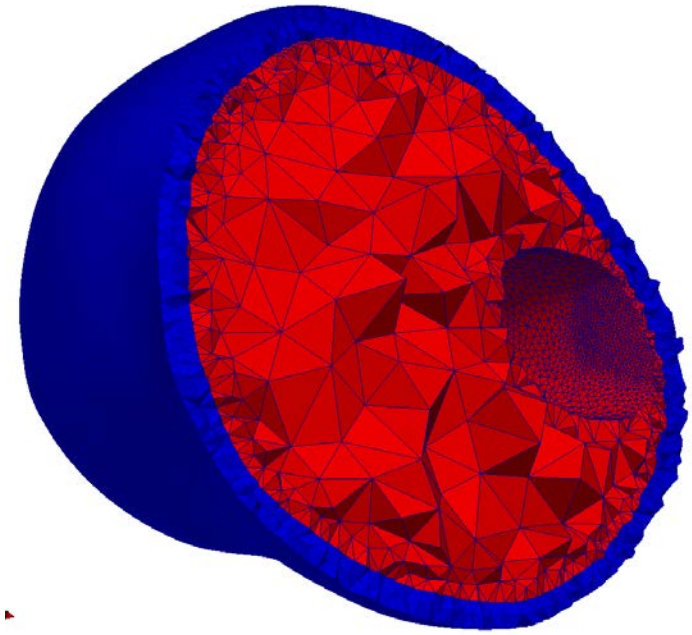


Figure 2. **Example of meshing.** The AAA wall is meshed using 2 layers of elements (configurable). The ILT is meshed using a minimum of 2 layers of elements (configurable); the element size is increased in the middle of the ILT layer to reduce the number of elements in the mesh. To alleviate volumetric locking we used 8-noded parabolic tetraheadra. A typical mesh contained 500k elements.

Patient-specific median arterial pressure applied to the ILT surface was used as the loading condition, with ILT assumed to be 20 times more compliant than the wall. The finite element simulations are carried out using the procedure described in (Joldes, Miller et al. 2016), which allows the computation of stress in the AAA wall without exact knowledge of the material properties. This is of great practical significance, as patient-specific material properties for the AAA wall and ILT are currently impossible to obtain *in vivo*. For a detailed discussion of the problem of obtaining solutions without knowing mechanical properties of tissues please see also (Wittek, Hawkins et al. 2009; Miller and Lu 2013).

The results of finite element simulations (maximum principal stresses in the AAA wall) are extracted by BioPARR for visualization and analysis.

2.5 Incorporation of residual stress

Blood vessels in humans exhibit characteristics of a pre-stressed vessel i.e. one that is stressed, even when unloaded by external forces (Fung 1991). This phenomena is thought to be caused by biological remodelling of protein fibres and smoothing of muscle tone to reach a uniform stress state across the arterial wall thickness. This natural tendency of arteries to remodel towards a state which reduces stress concentrations is referred to in the literature as the *Uniform Stress Hypothesis*.(Fung 1991; Polzer, Bursa et al. 2013)

Typical analyses have omitted these residual stresses, however they have been shown to have a significant impact on the distribution of the wall stress (Raghavan and Vorp 2000; Joldes, Noble et al. 2017). In this study we account for residual stresses present in the aortic wall *in vivo*.

Recently, Joldes, Noble et al. (2017) presented a new method for adding these residual stresses as a post-processing step. The method uses the Uniform Stress Hypothesis and seeks to average the wall stress over the wall thickness. This method gives consistent results that are comparable to existing iterative methods (Polzer, Bursa et al. 2013). Crucially, the simplicity of this method is faster and less computationally expensive than existing alternatives (Joldes, Noble et al. 2017).

The entire analysis workflow is presented in Figure 3.

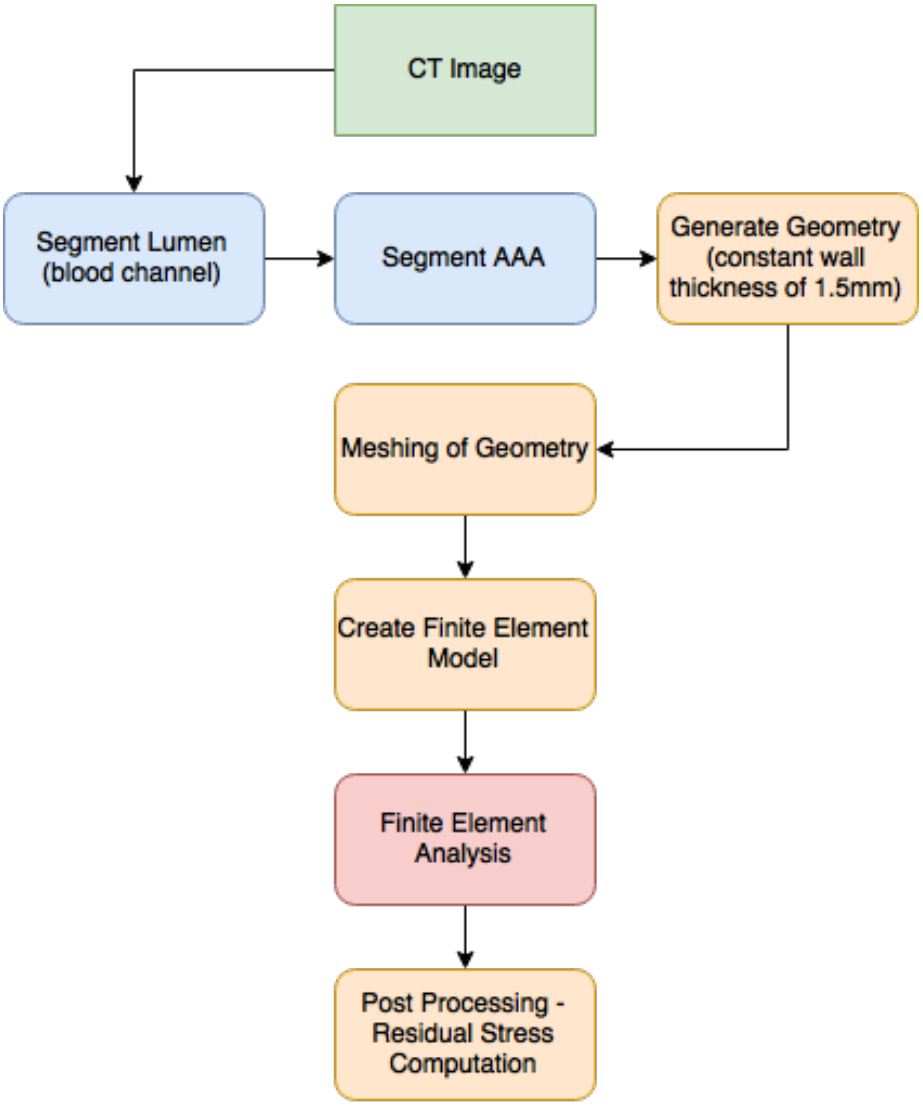


Figure 3 – AAA analysis workflow using BioParr. Steps in blue are performed in 3D Slicer. Step in red is performed in Abaqus (other linear FEM solvers could be used). BioPARR performs the remaining orange steps semi-automatically

3 Results

We chose to use a 99 percentile maximum principal stress as a scalar indicator of the internal forces being withstood by the wall tissue.

3.1 Effect of Different User Segmentations

A potential source of variability when analysing AAA's could occur during the image segmentation stage. Segmentation is challenging, and the output is heavily user-dependant. One case was selected (case 13), and four equally experienced users were asked to segment the scans. The results were analysed and the stress contour plots compared. Only one case was studied with the purpose of confirming the results presented by (Joldes, Miller et al. 2017).

The procedure for preparing and analysing the case is detailed below:

1. A single AAA case (case 13) was selected and distributed to four users; all having similar levels of experience segmenting CT scans in 3D slicer. Figure 4 shows a 3D Slicer GUI used for segmentation.
2. Each user worked individually to segment the scan, with no contact allowed between users to ensure the results were unbiased.
3. Once the segmented geometry had been created, each user followed the steps outlined above in Section 2 to produce stress contour maps. After the segmentation is completed, no additional judgement from the user is required; hence there is no further scope for user variability to affect the outcome.

The resulting contour plots are shown in Figure 5, and the maximum stress values are summarised in Table 2.

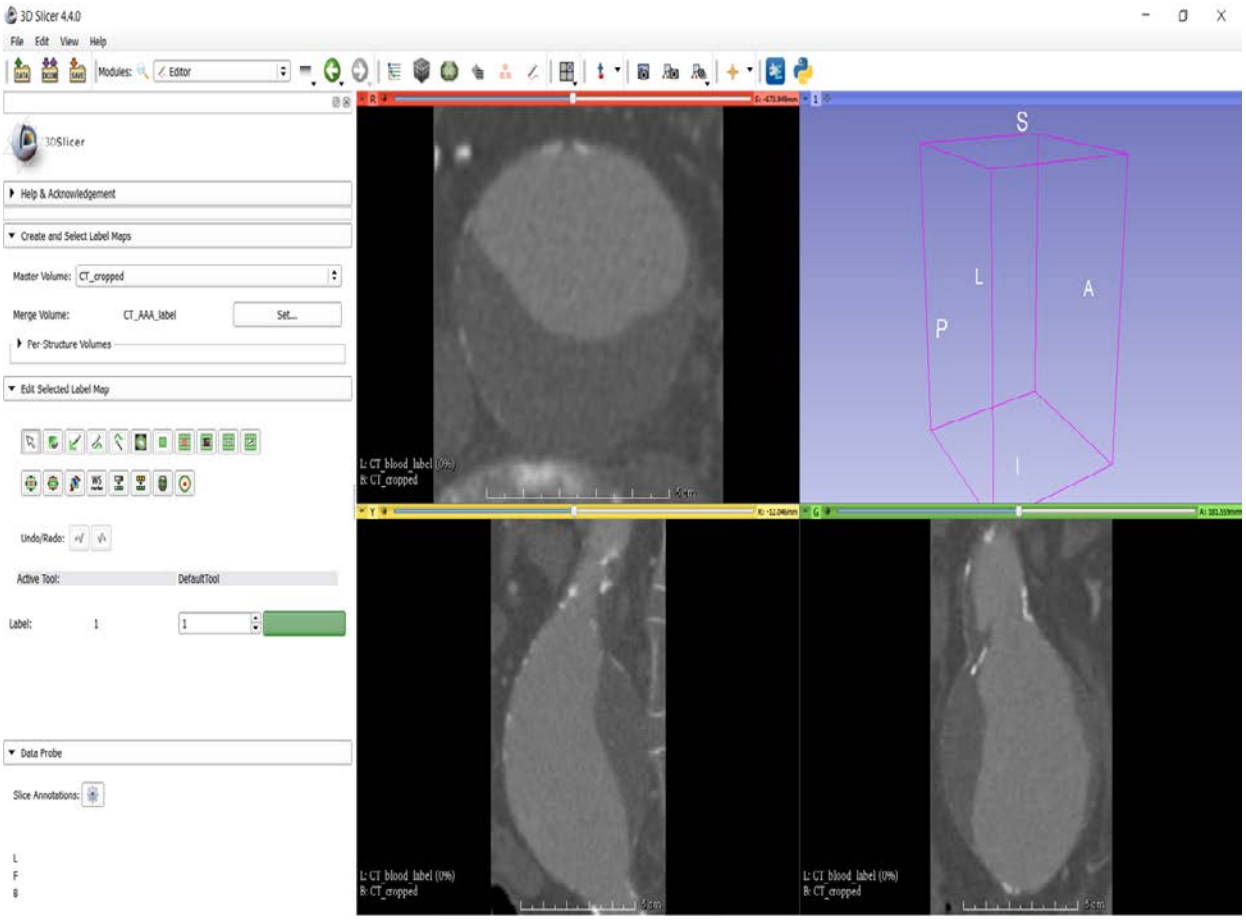
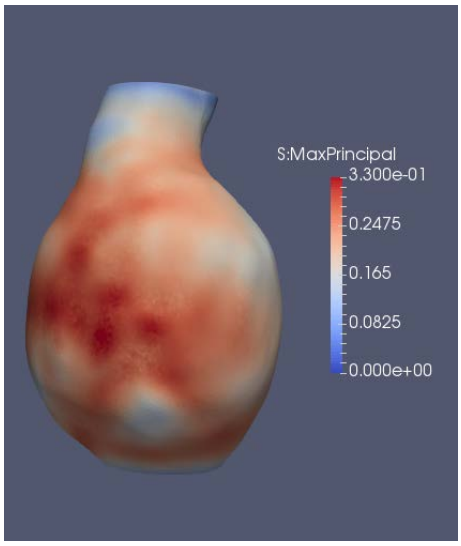
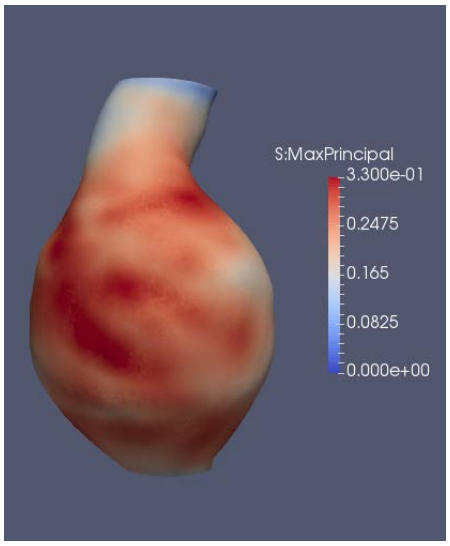


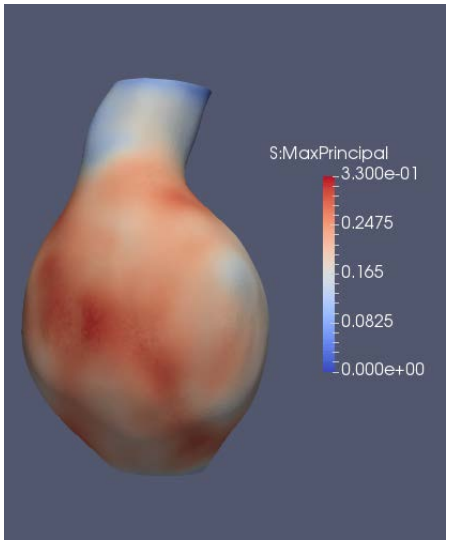
Figure. 4. 3D Slicer label map editing interface (case 13).



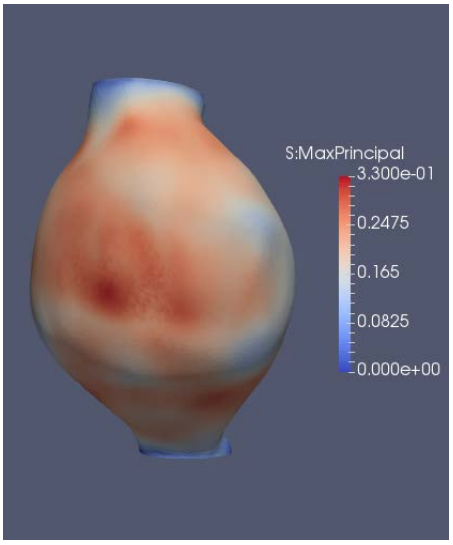
Case 13 – User 1



Case 13 – User 2



Case 13 – User 3



Case 13 – User 4

Figure 5 – Comparison of stress contour plots (99 percentile principle stress) obtained with different user segmentations.

Table 2 – Principal stress values (99th percentile) for one AAA case segmented by four different users

User	Stress (99th percentile, MPa)
1	0.3086
2	0.3305
3	0.2895
4	0.2746

These values show the largest difference between users 2 and 4 of approximately 20%. Such a variation is, for practical purposes, insignificant. Nevertheless this rudimentary sensitivity analysis

confirms previous results presented by (Mayeur, Witz et al. 2016) which suggest that changes in geometry due to segmentation variation or errors may have a significant impact on the resulting stress values.

3.2 *Stress distributions*

Results for the 19 cases we analysed are given in Figures 6 and 7.

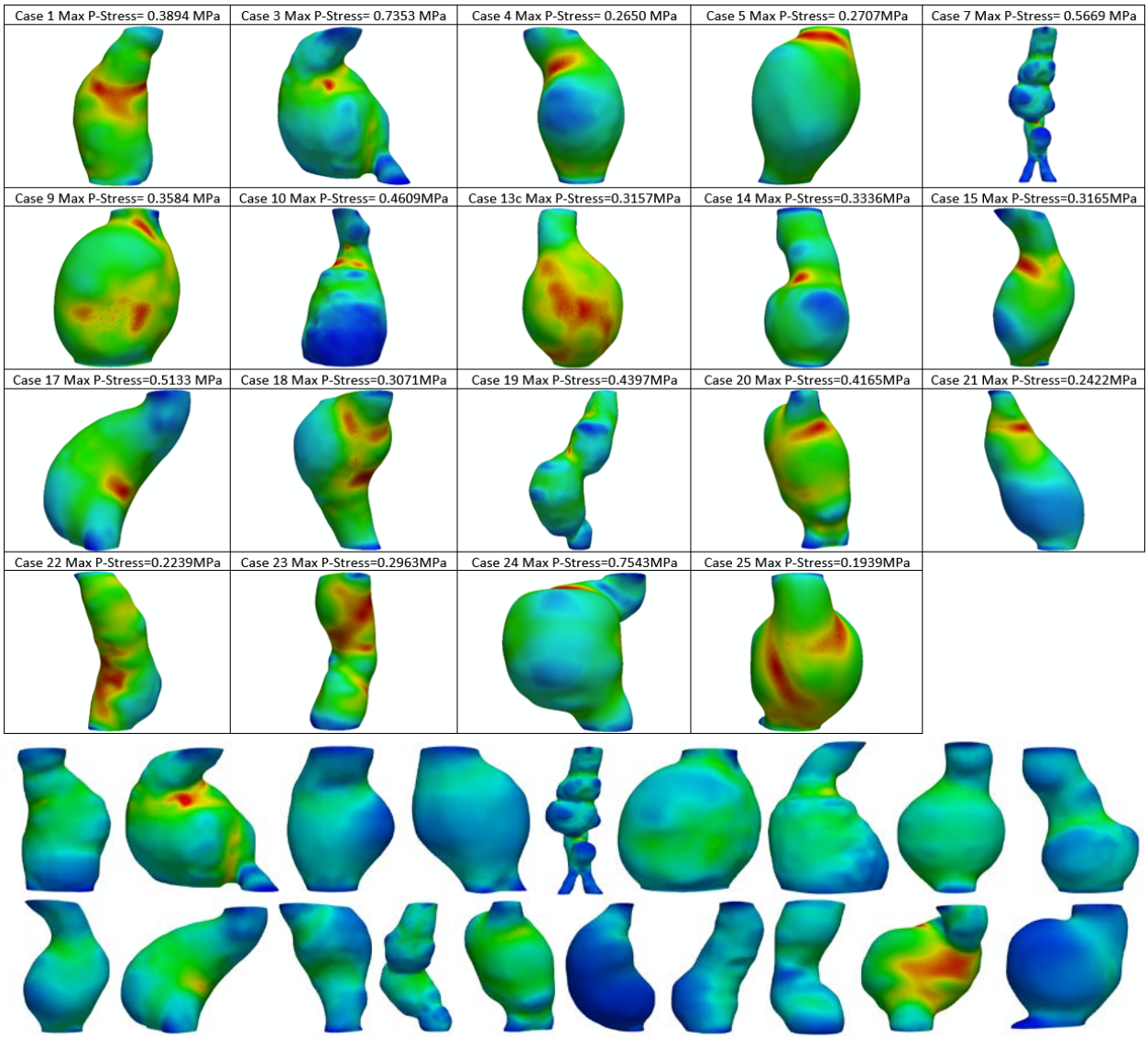


Figure 6: Contour plots of stress distributions for 19 cases. As can be seen, no pattern emerges and identifying symptomatic cases is not possible. Cases 21, 22, 23, 24 and 25 were symptomatic.

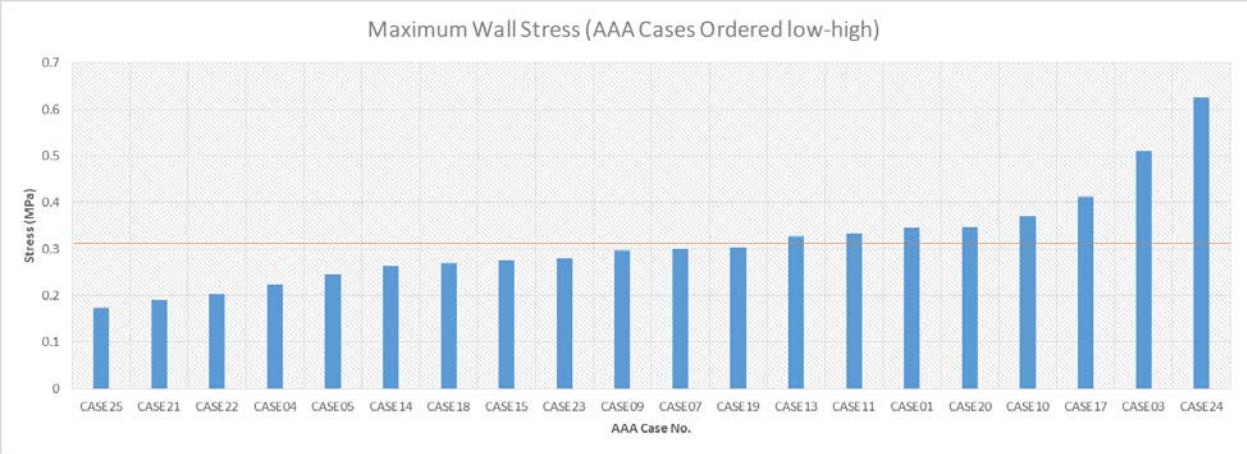


Figure 7 A range of low, medium and high max stresses – no two separate (i.e. symptomatic vs asymptomatic) groups can be distinguished. Cases 21, 22, 23, 24 and 25 were symptomatic. Case 25 has the lowest and case 24 the highest principal stress.

4 Discussion and Conclusions

We used our recently developed and freely available software BioParr (http://bioparr.mech.uwa.edu.au/) to analyse the relationship between clinically identified symptoms and wall stress distributions. The results, somewhat surprisingly, suggest that there is no correlation between the wall stress distribution and maximum principal stress values and clinical observation of symptoms.

When considering this result one needs to consider limitations of our modeling and simulation method. Firstly, due to limitations of resolution and contrast of clinical CT images used in this study we were unable to include patient-specific thickness of the AAA wall. Unfortunately most other studies suffer from the same deficiency, nevertheless our recent results suggest that maximum principal wall stress is proportional to the average wall thickness, allowing certain degree of optimism with regard to obtaining stress envelopes for a particular patient without the exact information about patient-specific wall thickness. Proportionality of maximum principal stress to average wall thickness supports our suggestion from over ten years ago that in biomechanics often apparently complex relationships conceal an approximately linear dependence (Taylor and Miller 2005).

Nevertheless, compared with other methods of analysis available in the literature, our method embedded in BioParr offers unparalleled simplicity and therefore compatibility with clinical workflows, and alleviates one of the greatest challenges in computational biomechanics for medicine – lack of knowledge of patient-specific properties of tissues (Miller and Lu 2013; Joldes, Miller et al. 2016).

Conflict of Interest Statement

The authors have no conflicts of interest in this study.

Acknowledgements

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