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MODELLING THE INFLUENCE OF ENDOTHELIAL CELL HETEROGENEITY ON ABDOMINAL AORTIC ANEURYSM EVOLUTION: A PATIENT-SPECIFIC SIMULATION USING A NOVEL FLUID-SOLID-GROWTH (FSG) FRAMEWORK

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SUMMARY

We sophisticate a fluid-solid-growth (FSG) model of aneurysm evolution and apply it to simulate abdominal aortic aneurysm (AAA) evolution. A realistic constitutive model of the arterial wall is integrated into a patient-specific geometry of the descending aorta. This enables realistic distributions of wall shear stress (WSS) to be input to growth and remodelling (G&R) algorithms. The theoretical framework is updated to link both the growth and the remodelling of the collagenous constituents to the cyclic deformation of vascular cells. The degradation of elastin is explicitly linked to reductions in WSS below a homeostatic threshold. Given that the endothelium exhibits heterogeneity within the vasculature tree, we define the homeostatic WSS threshold distribution as spatially and temporally heterogeneous. We observe that the definition of vascular homeostasis significantly influences AAA evolution.

INTRODUCTION

AAA is the excessive, permanent and localised dilation of the abdominal aorta. Prevalence of AAA is relatively high (1-9% of the population) and the mortality rates associated with rupture are between 80-90%. Treatment (open surgery, endovascular intervention) is available, albeit with non-negligible 5% mortality rates. The criterion for predicting rupture is statistically based on the diameter of the aneurysm exceeding 5.5cm. Evidently, there is a need for more sophisticated and reliable diagnostic criteria.

Watton et al. [1] proposed the first mathematical model of AAA evolution, which incorporates variables related to the concentration of the elastinous and collagenous constituents and the reference configurations in which the collagenous constituents are recruited to load bearing. It has been implemented into a novel FSG framework [2] to couple the G&R of aneurysmal tissue to local haemodynamic stimuli.

In this study, we apply a novel FSG framework to simulate AAA evolution on patient-specific geometries. In previous studies, the loss of elastinous components was prescribed. However, local aortic hemodynamic conditions may influence the risk for, and the progression of, AAA. Therefore, a key hypothesis here is that elastin degradation is driven by deviations of the WSS from homeostatic values.

The endothelium is heterogeneous and adapts in time [3, 4], and thus endothelial cells (EC) may act as mechanotransducers of the local haemodynamics.

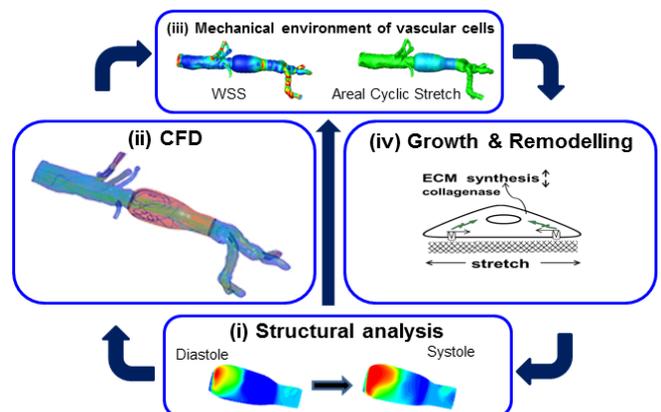


Figure 1: FSG framework for modelling aneurysm evolution.

METHODS

A novel update to the FSG computational framework from [2] is introduced to link the growth and the remodelling of the collagen fabric to the cyclic deformation of the arterial wall. The modelling cycle starts with a quasi-static structural analysis to solve the equilibrium deformation fields in the systolic and diastolic configurations (Figure 1(i)). The geometry of the aneurysm undergoes computational fluid dynamics (CFD) analysis by integration into a physiological domain and meshing (Figure 1(ii)); physiological flow rate and pressure boundary conditions are applied; the flow is solved with ANSYS CFX (Figure 1(iii)). G&R algorithms then simulate cells responding to the mechanical stimuli and adapting the tissue (Figure 1(iv)). The constitutive model of the aneurysmal tissue is then updated. The cycle continues and as the tissue adapts, an aneurysm evolves.

In this study, a patient-specific geometry of an advanced stage AAA is utilised to generate the pre-aneurysmal geometry of the abdominal aorta. The aneurysm is removed and a hypothetical geometrical representation of the original healthy abdominal aorta is constructed. This is used in the FSG framework so that the haemodynamic stimuli that are used in G&R algorithms have realistic magnitudes and

spatial distributions. The degradation of elastin is firstly prescribed to create a small AAA. The aneurysm is allowed to stabilise. Subsequently, it is assumed that low WSS drives elastin degradation and that values of WSS lower than a homeostatic WSS threshold, denoted τ_h , give rise to degradation of elastin, i.e.

$$\frac{\partial m^E}{\partial t} = -\zeta m^E f(\tau, \tau_H)$$

where ζ is a proportionality constant, τ is the local WSS and m^E is the normalized mass (concentration) of elastin.

We consider three illustrative definitions of τ_h :

- (i) $\tau_h(\mathbf{X}, t) = 0.5\text{Pa}$
- (ii) $\tau_h(\mathbf{X}, t) = \tau(\mathbf{X}, t = 0)$
- (iii) $\tau_h(\mathbf{X}, t) = \frac{1}{T_L} \int_{t-T_L}^t \tau(\mathbf{X}, t) dt$

In case (i), τ_h is constant whilst in case (ii), it is spatially heterogeneous with magnitudes defined by the initial WSS distribution at $t=0$. To simulate the temporal heterogeneity of ECs, we propose case (iii) in which τ_h is assumed to be both spatially heterogeneous and temporally adaptive ($T_L=5$ years). Further details can be found in [5].

RESULTS AND DISCUSSION

To enable comparison, we consider the evolution of the spatial distributions of WSS, elastin concentration m^E and the cyclic areal stretch A^{CS} ; see Figure 2 which illustrates cases (i) and (ii) and Figure 3 which illustrates case (iii).

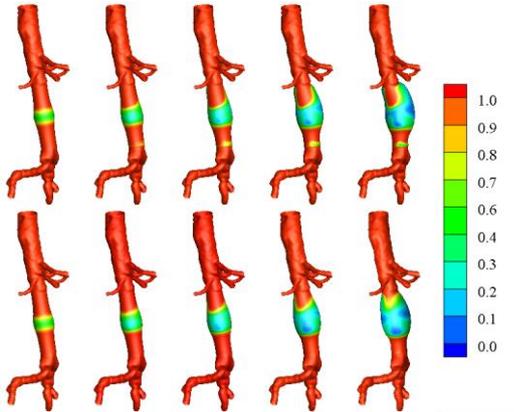


Figure 2: Evolution of elastin concentration m^E at $t=0,1,2,3,4$ years for: (upper) case (i), constant homeostatic τ_h ; (lower) case (ii), spatially heterogeneous, temporally constant homeostatic τ_h .

For all cases, the initial prescribed elastin degradation leads to a small symmetric aneurysm within which there is a band of low WSS (1st frame for all cases). Once the elastin degradation is coupled to low WSS, the low WSS leads to a band of elevated degradation which results in further elastin degradation (reduction in m^E , second to fifth frames for both rows in Figure 2), leading in turn to increased enlargement of the arterial wall diameter. This positive feedback process leads to the continuously expanding AAA.

Interestingly, the cases differ significantly in terms of the evolving AAA geometry and the spatial distribution of the quantities being studied (cf. each case's final time frame). For constant τ_h (case (i), top row of Figure 2), the AAA evolves with a more pronounced anterior bulging and preferential elastin degradation in the upstream section. The

spatially heterogeneous τ_h (case (ii), bottom row of Figure 2), though, leads to a AAA geometry that has greater axial symmetry. In case (iii) (Figure 3), i.e. adaptive spatially heterogeneous τ_h , the aneurysm evolves more slowly and becomes asymmetric; the large bulge seen in the upstream section towards the end of the simulation is due to the simulated constraint posed by the renal arteries.

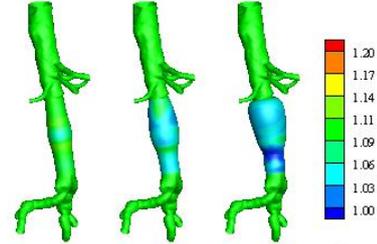


Figure 3: Evolution of Cyclic areal stretch A^{CS} at $t=0,6,14$ years for Case (iii): Spatially heterogeneous and temporally adaptive homeostatic τ_h .

Quantifying the cyclic deformation enables us to simulate its influence on the mechanobiology of vascular cells. At the beginning of the aneurysm formation, slightly elevated cyclic areal stretches are observed in the proximal and distal necks of the aneurysm. However, as collagen becomes the primary load bearer and the aneurysm develops, the magnitude of the cyclic areal stretches decreases (Figure 3).

Lastly, it is of interest to compare the simulated evolution of the aneurysms for the different cases to the actual clinical case (Figure 4). For example, the observed aneurysm enlargement in the upstream direction for the simulated cases (Figure 4(b-d)) is a result of the hypothesis that low WSS drives elastin degradation. The fact that a similar enlargement is identified in the clinical case (Figure 4(a)) provides some support for this modelling hypothesis.

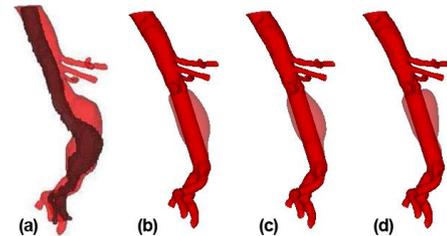


Figure 4: Computational models vs. clinical case. (a) Clinical case of AAA depicted at successive time points. Computational model of evolving aneurysm: (b) constant τ_{crit} ; (c) spatially heterogeneous τ_{crit} ; (d) spatially heterogeneous, temporally adaptive τ_{crit} .

CONCLUSIONS

A novel approach to phenomenologically simulate the spatial and temporal heterogeneity of the vascular endothelium is proposed. We observe that introducing spatial and temporal heterogeneity into the definition of vascular homeostasis significantly influences G&R and the predicted AAA evolution. We conclude that improved understanding and modelling of the heterogeneity of the vascular endothelium is needed to guide predictive models of vascular disease.

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