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Modelling the evolution of cerebral aneurysms: Biomechanics, mechanobiology and multiscale modelling

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Abstract

Intracranial aneurysms (IAs) are abnormal dilatations of the cerebral vasculature. Computational modelling may shed light on the aetiology of the disease and lead to improved criteria to assist diagnostic decisions. We briefly review models of aneurysm evolution to date and present a novel fluid-solid-growth (FSG) framework for patient-specific modelling of IA evolution. We illustrate its application to 4 clinical cases depicting an IA. The section of arterial geometry containing the IA is removed and replaced with a cylindrical section: this represents an idealised section of healthy artery upon which IA evolution is simulated. The utilisation of patient-specific geometries enables G&R to be explicitly linked to physiologically realistic spatial distributions and magnitudes of haemodynamic stimuli. In this study, we investigate the hypothesis that elastin degradation is driven by locally low wall shear stress (WSS). In 3 out of 4 cases, the evolved model IA geometry is qualitatively similar to the corresponding in vivo IA geometry. This suggests some tentative support for the hypothesis that low WSS plays a role in the mechanobiology of IA evolution.

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1. Introduction

Intracranial aneurysms (IAs) are a focal disease of the brain vasculature. They appear as sac-like outpouchings of the arterial wall inflated by the pressure of the blood. The incidence of IAs is surprisingly high: 2%–5% of the adult population are affected. Thankfully, most remain asymptomatic and the risk of rupture is very low: 0.1% to 1% of detected IAs rupture every year [1]. However, rupture leads to fatality in 45% of cases and moderate to severe morbidity for 30% of survivors [2]. Pre-emptive treatment is possible but interventional treatments for unruptured IAs are not without risk and have associated morbidity and mortality rates of <6% and <2.5%, respectively [3]. The increased detection of

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unruptured IAs coupled with balancing the potentially fatal scenario of rupture vs. the risk of interventional treatments presents a difficult dilemma for the clinician: to administer treatment, or to monitor the patient?

The exact cause of IAs is unknown, but it is generally accepted that they are a result of a combination of multiple factors, including blood-flow dynamics, arterial wall composition, cell populations, genetics and signalling pathways [4]. Given the lack of understanding of these contributing factors and their complex interplay, modelling may assist in providing fundamental insight into the aetiology of the disease. Moreover, it offers the potential to aid clinical decisions. Current measures for predicting rupture risk are only based on aneurysm size [5]. Consequently, there is a critical need to develop improved patient-specific criteria for rupture to identify the subset of IA patients that would actually benefit from intervention. Biomechanics has an essential role to play in this respect and its application to IA research has grown extensively in the last decade (see, e.g., [6, 7] for a recent review). The focus of this paper is the computational modelling of IA evolution. Such models must quantify the mechanics, the biology and the mechanical environment of the arterial wall. Furthermore, they must account for the interactions between the biology and the mechanics i.e. the mechanobiology of the arterial wall. In this article, we briefly review the requirements of an aneurysm evolution model and present, at this point in time, a state-of-the-art model in the field.

The starting point for a realistic model of aneurysm evolution is a structurally realistic biomechanical model of the healthy artery. Cerebral arteries consist of three layers: the intima, the media, and the adventitia. The intima consists of a monolayer of endothelial cells (ECs) attached to a basement membrane [8]. Whilst ECs contribute little to the mechanical response of the artery, the EC layer has an important function in regulating the effects of haemodynamic forces on the functionality of the arterial wall and acting as a barrier to blood-flow. The media is separated from the intima by the internal elastic lamina and contains a three-dimensional network of elastin fibres and, vascular smooth muscle cells (VSMCs) and collagen fibres which form a fibrous helix with near circumferential orientation [9]. Elastin, a rubber-like, highly extensible protein, gives elasticity to arterial tissue, whilst VSMCs regulate arterial diameter via vasoconstriction and vasodilation [10]. The adventitia is composed predominantly of collagen fibres maintained by fibroblast cells. For the healthy artery, the adventitia acts as a stiff protective sheath to prevent over-distension of the artery, however, during IA evolution, as the medial layer is destroyed, it becomes the predominant load bearing layer and thus its functional role changes.

The structure of the artery is continuously maintained by vascular cells. The functionality of the cells is guided by their local mechanical environment. Cellular responses to forces exerted by the blood-flow are mediated by the extra-cellular matrix (ECM). Indeed, the ECM plays a pivotal role in signalling events that regulate cellular proliferation, migration and apoptosis [11]. The forces are transduced by cellular mechanosensors into a signalling cascade, leading to a host of intra- and inter-cellular responses. For example, ECs respond to increased flow by up-regulating the production of vasodilators. In turn, vasodilators trigger the relaxation of VSMCs to allow the expansion of the arterial wall, and thereby, a return of the wall shear stress (WSS) to baseline levels. Cyclic stretching of the ECM, arising from pulsatile flow, affects the rate of secretion and degradation of ECM material by fibroblasts, i.e., an increase in cyclic strain results in an increase in collagen production and decrease in matrix-degrading enzymes, whilst a decrease in cyclic strain produces the converse result [9]. The dynamic nature of the arterial wall enables it to rapidly respond to altered mechanical conditions, such as altered flow or increased pressure.

Collagen fibres are in a continual state of deposition and degradation with typical half-lives of two months for the healthy artery. In the in vivo configuration, fibres are configured to the ECM in a state of stretch [12]. The continual deposition and degradation of collagen fibres and the observation that they are configured in a state of stretch are essential concepts in mathematical models that simulate arterial growth