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A novel chemo-mechano-biological model of arterial tissue growth and remodelling

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ABSTRACT

Arterial growth and remodelling (G&R) is mediated by vascular cells in response to their chemical and mechanical environment. To date, mechanical and biochemical stimuli tend to be modelled separately, however this ignores their complex interplay. Here, we present a novel mathematical model of arterial chemo-mechano-biology. We illustrate its application to the development of an inflammatory aneurysm in the descending human aorta.

The arterial wall is modelled as a bilayer cylindrical non-linear elastic membrane, which is internally pressurised and axially stretched. The medial degradation that accompanies aneurysm development is driven by an inflammatory response. Collagen remodelling is simulated by adaption of the natural reference configuration of constituents; growth is simulated by changes in normalised mass-densities. We account for the distribution of attachment stretches that collagen fibres are configured to the matrix and, innovatively, allow this distribution to remodel. This enables the changing functional role of the adventitia to be simulated. Fibroblast-mediated collagen growth is represented using a biochemical pathway model: a system of coupled non-linear ODEs governs the evolution of fibroblast properties and levels of key biomolecules under the regulation of Transforming Growth Factor (TGF)-β, a key promoter of matrix deposition.

Given physiologically realistic targets, different modes of aneurysm development can be captured, while the predicted evolution of biochemical variables is qualitatively consistent with trends observed experimentally. Interestingly, we observe that increasing the levels of collagen-promoting TGF-β results in arrest of aneurysm growth, which seems to be consistent with experimental evidence. We conclude that this novel Chemo-Mechano-Biological (CMB) mathematical model has the potential to provide new mechanobiological insight into vascular disease progression and therapy.

1. Introduction

The arterial wall is a highly dynamic tissue. In response to changing environmental conditions, its properties can change in an attempt to restore a healthy/*homeostatic* state (Humphrey, 2008). Understanding the responses of vascular cells to such perturbations is essential to understand the growth and remodelling (G&R) of tissue and thus predict the evolution of vascular diseases such as genetic hereditary conditions (Lindsay and Dietz, 2011), atherosclerosis (Montecucco and Mach, 2009) or aneurysms (Sakalihasan et al., 2005). For instance, fibroblasts in the adventitia, and smooth muscle cells in the media, are highly sensitive to the properties of their surrounding environment: the fibrous, load-bearing matrix is a channel for transmission of mechanical stimuli (Chiquet et al., 2003); in the interstitial fluid, biochemical signals are relayed via diffusible signalling molecules (Leask, 2010).

Several computational models of arterial adaption during disease evolution have been developed (Baek et al., 2006; Volokh and Vorp, 2008; Watton et al., 2009). To date, such models have focussed on predicting the geometrical evolution of the arterial wall by coupling altered vascular mechanics to microstructural changes (Wilson et al., 2012; Balakhovsky et al., 2014). However, the chemo-biological mechanisms behind homeostasis maintenance or impairment in disease are not explicitly modelled. Conversely, in the cell biology and biochemistry communities,

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numerous models of the signalling pathways governing cell-to-cell communication and production of active species exist, e.g. McDougall et al. (2006) and Warsinske et al. (2015). However, these models do not consider mechanical stimuli.

We propose a novel Chemo-Mechano-Biological (CMB) mathematical model to describe the interdependent chemical, mechanical and biological states of the arterial wall. Our model builds on the mechanobiological model of Watton et al. (2009) by coupling it with a representation of the biochemical signalling networks of collagenous tissue G&R based on the model of Dale et al. (1996). Moreover, we explicitly model the changing functional role of the adventitia from a protective sheath to playing a load bearing role in aneurysms. This is achieved by modelling a distribution of collagen attachment stretches and proposing that the (homeostatic) distribution can adapt, Section 2. The model is parameterised to the descending human aorta (Appendix A.3). We illustrate the application of the model (Section 3) to simulate the evolution of an inflammatory aneurysm (Study 1), and its response to pharmacological intervention, i.e. the effects of applying a collagen-promoting drug to an enlarging aneurysm (Study 2). Our coupled CMB model is a first step towards investigating the evolution of diseased arteries on both mechanical and biochemical levels, as well as their response to pharmacological therapy.

2. Methods

Our CMB model integrates two published mathematical models, i.e. Watton et al. (2009) and Dale et al. (1996); see Fig. 1. The biochemical model of Dale et al. (1996) focusses on the temporal variation of cellular and molecular species relevant to collagen synthesis and degradation in the context of wound healing, however without considering the influence of system biomechanics on cell response. The signalling pathways biochemical model component formulated in Section 2.2 is an adaptation and extension of this model, cf. Fig. 1 (left).

2.1. Model formulation I: Biomechanical model

We model the artery as a two layered cylindrical non-linear elastic membrane. The derivation of the force-balance equation (FBE) governing the system's mechanics follows Watton et al. (2009). Let subscripts $L=M,A$ denote medial and adventitial layers, resp., and let superscripts $p=E,C$ denote elastin and collagen constituents, resp. Considering that the only load-bearing constituents are elastin and collagen in the media, and collagen in the adventitia, it follows

$$p=\frac{1}{R\lambda\lambda_z}\left[H_M\cdot\left(P_M^E(\lambda)+P_M^C(\lambda_M^C)\right)+H_A\cdot P_A^C(\lambda_A^C)\right], \tag{1}$$

where R is the unloaded inner radius; H_M,H_A the unloaded layer thicknesses; λ_z, λ the axial and circumferential stretches, resp.; p the internal pressure; and P_L^p, λ_L^p the 1st Piola–Kirchhoff stress term and stretch, resp., ofconstituent p in layer L. The medial elastinous constituent is modelled as a neo-Hookean material, and thus

$$P_M^E(\lambda)=m_M^E\cdot K_M^E\cdot\lambda\cdot\left(1-\frac{1}{\lambda_z^2\cdot\lambda^4}\right) \tag{2}$$

where $K_M{}^E$ is a stiffness-like material constant and $m_M^E(t)$ is the (dimensionless) normalised mass density of elastin.

We assume that collagen fibres have a distribution of recruitment stretches (see Watton et al., 2004, 2009 for details), with each fibre displaying a linear mechanical response, i.e.

$$\tilde{\Psi}_L^C(\lambda_L^C)=\begin{cases}0 & \lambda_L^C<1\\ \frac{K_L^C}{2}\cdot\left(\lambda_L^C-1\right)^2 & \lambda_L^C\geq 1\end{cases}, \tag{3}$$

where $K_L{}^C$ are stiffness-like material constants. In this study, for simplicity, we consider all collagen fibres to be circumferentially aligned. The strain energy density function (SEDF) for the entire collagenous tissue is obtained by integrating the fibre SEDF over the distribution of fibre recruitment stretches (Hill et al., 2012),

$$\Psi_L^C(\lambda)=\int_1^{\lambda}\tilde{\Psi}_L^C(\lambda_L^C)\cdot\rho\left(\lambda_L^R\right)\,d\lambda_L^R, \tag{4}$$

where circumferential (λ), collagen fibre ($\lambda_L{}^C$) and collagen recruitment ($\lambda_L{}^R$) stretches are related by $\lambda=\lambda_L^C\cdot\lambda_L^R$, and $\rho\left(\lambda_L^R\right)$ is the probability density function (pdf) characterising the distribution of collagen recruitment stretches in the population of fibres. We use a triangular distribution function (Chen, 2014), see Fig. 2,

$$\rho\left(\lambda_L^R\right)=\begin{cases}0 & \lambda_L^R<\lambda_L^{R,\min}\\ \frac{2\left(\lambda_L^R-\lambda_L^{R,\min}\right)}{\left(\lambda_L^{R,\max}-\lambda_L^{R,\min}\right)\left(\lambda_L^{R,mode}-\lambda_L^{R,\min}\right)} & \lambda_L^{R,\min}<\lambda_L^R<\lambda_L^{R,mode}\\ \frac{2\left(\lambda_L^{R,\max}-\lambda_L^R\right)}{\left(\lambda_L^{R,\max}-\lambda_L^{R,\min}\right)\left(\lambda_L^{R,\max}-\lambda_L^{R,mode}\right)} & \lambda_L^{R,mode}<\lambda_L^R<\lambda_L^{R,\max}\\ 0 & \lambda_L^R>\lambda_L^{R,\max}\end{cases}. \tag{5}$$

where $\lambda_L^{R,\min}$ and $\lambda_L^{R,\max}$ define the minimum and maximum collagen recruitment stretches for the distribution resp., i.e. minimum/maximum factors' tissue much be stretch for collagen fibres of maximum/minimum undulation to begin to bear load; $\lambda_L^{R,mode}$ relates to the modal recruitment stretch of the distribution.

The stress term for the entire distribution of collagenous fibres in each layer L is obtained by multiplying the SEDF (Eq. (4)) by the respective normalised mass density term and subsequent partial differentiation with respect to λ, i.e.

$$P_L^C(\lambda_L^C)=\frac{\partial m_L^C\Psi_L^C}{\partial\lambda}=m_L^C\cdot\left(\frac{\partial}{\partial\lambda}\int_1^{\lambda}\tilde{\Psi}_L^C(\lambda)\cdot\rho\left(\lambda_L^R\right)\,d\lambda_L^R\right) \tag{6}$$

where $m_L{}^C$ denote collagen normalised mass densities in layer L. The derivation of the explicit form of Eq. (6) can be found in Appendix A.1. The normalised mass densities of the structural constituents medial elastin $m_M{}^E$, medial collagen $m_M{}^C$ and adventitial collagen $m_A{}^C$ are computed by Eqs. (8) and (12), resp., in the signalling pathways model component below.

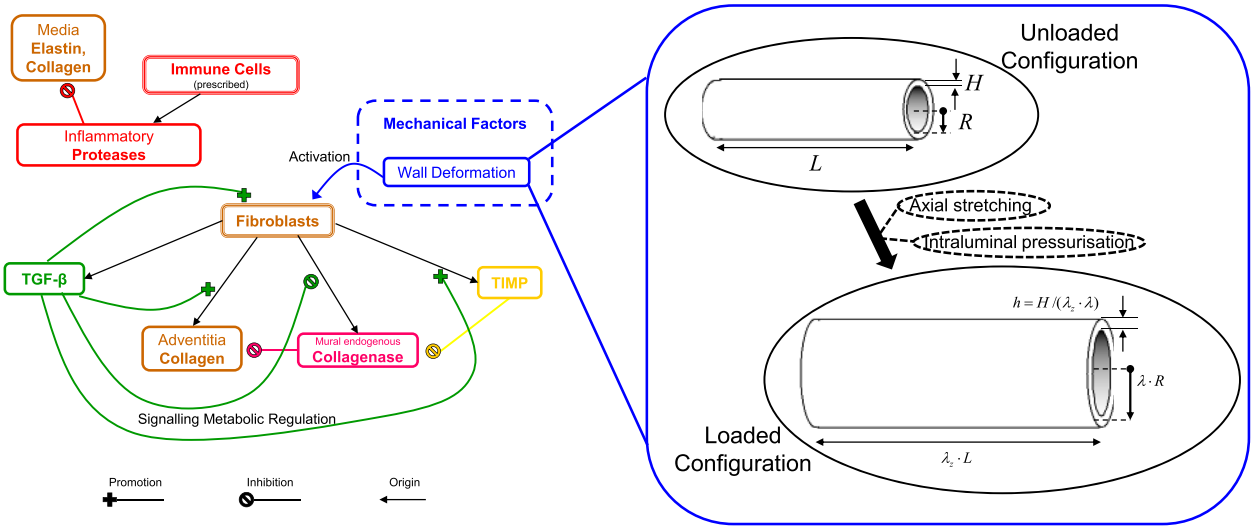

Fig. 1. Model components. Regulatory signalling pathways biochemical model component, *left*, interfacing with biomechanical model component, *right*.