VASCULAR GROWTH AND REMODELING WITH STOCHASTIC OPTIMAL STRESS-DRIVEN FIBER DEPOSITION

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INTRODUCTION
The progression of cardiovascular disease is closely related to the functional adaptations of arteries to mechanical stimuli. To better understand this adaptive behavior, a mathematical framework of vascular growth and remodeling (G&R) was proposed by Humphrey et al. based on a constrained mixture theory [1] in which a vessel is assumed to be able to adapt to mechanical stress to recover a homeostatic stress state. This framework was first applied to idealized geometries to simulate aneurysm expansion and later extended to 3D geometries, and has been coupled with computational fluid dynamics to incorporate the influence of the evolving hemodynamics.

In the vascular G&R, the vessel wall is modeled as fiber-reinforced material with collagen (and potentially smooth muscle) treated as fiber and elastin is modeled as ground matrix. The angle defining the collagen fiber direction is very important to the overall mechanical property of the vascular mixture. In prior works, newly produced collagen fiber is only allowed to be deposited in predefined directions, while in reality the fibers are not so rigidly constrained. Indeed, it is known that fibers within one collagen fiber family are not precisely aligned, but rather fiber dispersion is observed, and this dispersion can be important for accurately characterizing vessel wall mechanics [2]. In the work herein, we implement a vascular G&R computational framework in which newly produced collagen fibers can be deposited more freely based on the solution of an optimization problem inspired by [3]. The directions depend on the ratio of the two largest principal stresses, and thus allow fiber deposition to adapt to the stress state. In addition, fiber dispersion is also controlled by a stress-dependent stochasticity to account for sources of dispersion not explicitly modeled.

METHODS
Constrained mixture theory of growth and remodeling
The vessel wall is modeled as a constrained mixture made of two constituents: elastin and collagen, in a 3D continuum geometry. Smooth muscle fibers are ignored to focus on the passive mechanical stress generated by vessel wall. The kinetics of G&R is characterized by the mass density evolution equations for elastin and collagen fibers:

\[ M_e(t) = M_e(0)Q_e(t) \quad \text{(elastin)} , \]

\[ M_i(t) = M_i(0)Q_i(t) + \int_0^t m_i(\tau)q_i(t-\tau)d\tau \quad i=1,2 \quad \text{(collagen)} , \]

where \( i \) is the index for two collagen fiber families oriented in two helical directions, \( m_i(\tau) \) is the mass production rate for collagen fiber family \( i \) at time \( \tau \). Functional elastin is thought to be only produced in early development, therefore there is no second term to take account production new elastin. \( Q_e(t) \), \( Q_i(t) \) and \( q_i(t) \) are functions characterizing the natural decay of elastin and collagen.

The constitutive relation for collagen is assumed to follow Fung-type exponential form, and the strain-energy density function is given by

\[ W(C_{i_{n(\tau)}}(t)) = \frac{c_2}{4c_3} \left\{ \exp \left[ c_3 \left(I_{n(\tau)}(t) - 1 \right)^2 \right] - 1 \right\} \]  

where \( I_{n(\tau)}(t) \) is the fiber invariant in the direction of collagen family \( i \). On the other hand, elastin is modeled using Neo-Hookean material,

\[ W_e(C(t)) = \frac{c_1}{2} (I_1(t) - 1) , \]

where \( I_1 \) is the first invariant of the right Cauchy-Green deformation tensor. The overall strain-energy function of the vessel wall mixture is modeled based on the Holzapfel model [6] for nearly incompressible material

\[ \Psi(C) = U(J) + M_e(t) W_e(C) + \sum_{i=1,2} M_i(0)Q_i(t) W(C_{i_{n(\tau)}}(t)) + \int_0^t m_i(\tau)q_i(t-\tau)W(C_{i_{n(\tau)}}(t))d\tau , \]

where \( U(J) \) is a penalty term ensures nearly incompressibility. At each G&R step, the solid mechanics problem is solved using finite element method to obtain local stress.

Optimal fiber deposition
In the current work, collagen fiber is deposited based on the local stress tensor, instead of being restricted to a pre-defined collagen fiber family direction. The optimal collagen fiber deposition angle is given by the solution from the following optimization problem

\[ \min_{M,\theta_f} M \quad \text{s.t.} \]

\[ \sigma_f M \pi \cos^2 \theta_f \geq T_{11} \]

\[ \sigma_f M \pi \sin^2 \theta_f \geq T_{22} \]

where \( T_{11} \) and \( T_{22} \) are the two largest principal values of the stress tensor \( T \), and usually these two directions corresponds to local circumferential
and axial directions of blood vessel. $\sigma_f$ is the stress a fiber can provide in normal condition. $M$ is the total mass density of the collagen fibers. $\theta_f$ is the direction of collagen fiber with respect to circumferential direction. 

The idea behind this optimization problem is that our body want to minimize the mass needed for the fibers while still sustaining the force in both circumferential and axial directions. The solution for (6) is

$$M^* = \frac{T_{11} + T_{22}}{\sigma_f}, \quad \theta^* = \arctan \sqrt{\frac{T_{22}}{T_{11}}}.$$

which defines the direction for newly produced collagen fiber.

The mass production rate of collagen fiber at time $t$ is

$$m_i(t) = \frac{M(t)}{M(0)} \left( K_\sigma (\sigma_i(t) - \sigma^h) + f_h \right)$$

where $K_\sigma$ is a feedback gain for stress deviation. $f_h$ is the baseline value for collagen mass production rate. $\sigma_i(t)$ is the stress in the nominal direction $e_{f_i}(t)$ of collagen fiber family $i$

$$\sigma_i(t) = e_{f_i}(t) \cdot T(t) e_{f_i}(t)$$

where the nominal direction $e_{f_i}(t)$ is defined as

$$e_{f_i}(t) = \frac{\int_0^t m_i(\tau) q(t - \tau) e_i(\tau) d\tau}{M_i(t)}$$

which is the average collagen fiber direction over the collagen family $i$ weighted by mass. While the above framework leads to some fiber dispersion, additional dispersion must be added to account for other influences that are not explicitly modeled. This is accomplished by imposing a stochastic deposition angle, which is assumed to follow a normal distribution

$$\theta \sim \mathcal{N}(\theta_f, \Sigma(\sigma_i))$$

where the mean deposition angle $\theta_f$ is set to be the optimal deposition angle defined in (7). The standard deviation $\Sigma(\sigma_i)$ is defined as a function of the fiber stress $\sigma_i$

$$\Sigma(\sigma_i) = \Sigma_0 \frac{\sigma_{scale}}{\sigma_i}$$

where $\sigma_{scale}$ is a scale parameter for vessel wall stress and $\Sigma_0$ is the nominal value for the standard deviation. $\Sigma(\sigma_i)$ a decreasing function with respect to $\sigma_i$, which is consistent with the fact that fibers are aligned more coherently (less dispersion) when the stress $\sigma_i$ is higher [4].

**RESULTS**

Numerical simulations are carried out in an idealized cylindrical geometry with radius of 10 mm and thickness of 1mm, which represents the health human abdominal aorta. The pressure imposed is set to 13332 Pa representing physiological blood pressure. For the parameters for stochastic fiber deposition, $\Sigma_0$ is set to be 0.1 and $\sigma_{scale}$ is set to be 200 kPa to represent physiological level of stress in human aorta.

The results show that collagen fiber dispersion can be reproduced by combining constrained mixture theory of G&R with stochastic optimal fiber deposition. Figure 1 shows the fiber dispersion patterns in the two helical directions and the vessel wall stress distribution generated by the proposed framework. It can be noticed that the generated fiber dispersion is smaller in the inner layer and larger in the outer layer (see Figure 2). This is because higher stress in the inner layer yields smaller standard deviation $\Sigma$ for stochastic fiber deposition, and thus the actual deposition angles are more concentrated around the mean deposition angle given by $\theta_f$. This fact matches with the experimental observations in [5] that dispersion is larger in the adventitia(outerior layer) than in the media(inner layer).

**REFERENCES**