Mechanics Research Communications 42 (2012) 126–133

Contents lists available at SciVerse ScienceDirect

Mechanics Research Communications

journal homepage: www.elsevier.com/locate/mechrescom

Constrained mixture models as tools for testing competing hypotheses in arterial biomechanics: A brief survey

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ARTICLE INFO

Article history:
Received 21 October 2011
Received in revised form 1 February 2012
Available online 23 February 2012

Keywords:
Model verification
Vasoactivity
Deposition stretch
Stress
Vascular growth
Remodeling

ABSTRACT

Hypothesis testing via numerical models has emerged as a powerful tool which permits the verification of theoretical frameworks against canonical experimental and clinical observations. Cleverly designed computational experiments also inspire new methodologies by elucidating important biological processes and restricting parametric spaces. Constrained mixture models of arterial growth and remodeling (G&R) can facilitate the design of computational experiments which can bypass technical limitations in the laboratory, by considering illustrative special cases. The resulting data may then inform the design of focused experimental techniques and the development of improved theories. This work is a survey of computational hypothesis-testing studies, which exploit the unique abilities offered by the constrained mixture theory of arterial G&R. Specifically, we explore the core hypotheses integrated in these models, review their basic mathematical conceptualizations, and recapitulate their most salient and illuminating findings. We then assess how a decade's worth of constrained mixture models have contributed to a lucid, emerging picture of G&R mechanisms.

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1. Introduction

Arteries possess a set of mechanisms by which they accomplish several crucial tasks. They must deliver an unfaltering supply of oxygenated blood to the distal vasculature, not only under conditions of acute changes in metabolic demand, but also during diseased states and under varying degrees of irreversible, aging-related damage to key constituents. This organ system must also ensure that blood, being pumped cyclically by the heart, perfuses the distal beds at a nearly constant flowrate. These requirements must be met with as little energy expenditure as possible. Also, the arterial system must endure on the order of a billion cardiac cycles. Perhaps the most extraordinary aspect of the arterial system is that it meets all of its diverse demands through what appears to be a set of common (though complex and still mostly unelucidated) chemomechanobiological mechanisms, which work complementarily (Humphrey, 2008). It follows that an enhanced understanding of these mechanisms would yield improved insights into a wide variety of arterial behaviors in health and disease. The associated complexities, however, pose several formidable conceptual and methodological challenges.

Hypothesis testing is a widely appreciated feature of the scientific method, and since the work by Popper (1959), more attention has been given to the importance of formulating hypotheses which may potentially be falsified. Of course, by rejecting the null hypothesis, one may gain additional confidence in the validity of a hypothesis. Numerical experiments, as with experiments in the laboratory, should be designed so as to facilitate the rejection of a hypothesis or null hypothesis. Thus, hypothesis testing is also useful for verifying increasingly complex computational models of biological systems (Anderson et al., 2007). We therefore seek frameworks which permit the transformation of questions and conjectures into testable hypotheses.

Clearly, there exists great motivation to develop theories of arterial growth and remodeling (G&R). Several frameworks have been proposed for modeling G&R of soft tissues, with applications in cardiovascular mechanics (Kuhl and Holzapfel, 2007; Rachev et al., 1998; Rodriguez et al., 1994; Skalak, 1981; Taber, 1998), but they focus more on the consequences of G&R, rather than the fundamental mechanisms which drive G&R. Humphrey and Rajagopal (2002) introduced a framework based on mixture theory and motivated it, in large part, by the ability to investigate G&R's governing principles via the testing of competing hypotheses. Humphrey and Rajagopal also posited that such theoretical

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doi:10.1016/j.mechrescom.2012.02.003

and computational studies would catalyze the clarification of complex mechanisms and the narrowing of parametric spaces, while simultaneously motivating increasingly sophisticated experimental techniques, thus yielding more detailed and complete empirical observations. Over the course of a decade, this framework has proven useful for elucidating the processes and trends associated with arterial G&R. The resulting numerical experiments predict trends and behaviors which may then be compared to experimental observations.

Other theories of arterial G&R exist and may be used to test various postulated mechanisms which yield expected or observed behaviors. Driessen et al. (2004) demonstrate a computational model and its predictions based on the hypothesis that synthesizing cells align and turnover fibrillar collagen in response to evolving principal stretches. Similarly, Hariton et al. (2007) test the hypothesis that principal stresses govern fiber alignment and compared their predicted results to observed and expected behaviors. These models make different assumptions about tissue homeostasis, and they compute homeostatic fiber alignment distributions accordingly. Watton et al. (2004) also note that their model can be used to test hypotheses concerning fiber alignment. Subsequent works investigate the effects of altering the model's various assumptions and thereby compare competing hypotheses; for a comprehensive review see Watton et al. (2011). As can be seen, arterial G&R hypothesis testing is by no means limited to any particular theoretical framework. However, we restrict our attention to constrained mixture models to emphasize their particular strengths.

2. Hypotheses in arterial G&R

Constrained mixture models of arterial growth and remodeling have, in common, three fundamental hypotheses (Valentín and Humphrey, 2009). These hypotheses are important not only individually; their combined, complementary effects are pivotal determinants of the expected behavior of arteries which must adapt in response to events such as injury, disease or evolving metabolic demands. Constrained mixture models put forward these hypothesized mechanisms as means by which arteries preserve or approach optimal behavior under changing conditions.

2.1. Hypothesis I: constitutive turnover

The first fundamental hypothesis (*hypothesis I*) relates to the degree and manner of constitutive turnover: that synthesizing cells respond to their evolving chemomechanical environment, in part, by incorporating new material and removing old material from the extracellular matrix and via cell proliferation and apoptosis. From this hypothesis follow two associated sub-hypotheses. The first (*hypothesis I-a*) is that synthesizing cells produce new structurally significant (i.e., load-bearing) proteins at individually varying rates in response to local chemomechanics. Similarly, existing constituents may be degraded as functions of their loading histories over the course of their lifespans. Turnover rates of arterial constituents have been observed to vary in response to changing mechanical and chemical cues (Dooley et al., 2007; Leung et al., 1976; Li et al., 1998; Rizvi and Myers, 1997). In the context of a theoretical hypothesis, Fung (1991) proposed a simple conceptual mathematical relation: that the rate of volumetric growth is a function of a scalar measure of stress, [1] though this concept dates back at least to Thoma (1893). Volumetric changes (i.e., growth or atrophy) are clear consequences of these hypothesized behaviors. However, relative changes in mass fractions of multiple constituents, which alter the artery's composition and mechanical responses, may more appropriately be categorized as remodeling (Humphrey and Rajagopal, 2002).

A second sub-hypothesis (*hypothesis I-b*) is that fibrillar proteins, such as collagen and smooth muscle, are deposited in preferred directions and that synthesizing cells have the ability to remodel the extracellular matrix by altering these directions in response to evolving local environmental conditions. Typically, directions of principal stresses or stretches are used to define the directions of fiber alignment. For example, Driessen et al. (2004) and Hariton et al. (2007) posit that synthesizing cells endow favorable biological functions or behaviors by affecting local anisotropy. The same concept can motivate similar hypotheses in arterial G&R models, which may then be tested by comparing predicted responses in evolved arteries.

2.2. Hypothesis II: depositional prestretches

The second cardinal hypothesis is that newly produced constituents are deposited under a state of prestretch. Mounting evidence suggests that synthesizing cells are not only capable of depositing material in varying quantities and, in the case of fibrillar collagen, different directions, but that they can also endow newly secreted material with a mechanical prestretch (Kozel et al., 2006; Wagenseil and Mecham, 2007). Also implied in this hypothesis are other related phenomena, such as spatial variations in prestretches, for which there are at least two main motivations: a gradient of prestretches for elastin, which is proposed to result from differential deposition and cross-linking over specific temporal intervals during development (Langille, 1996; Stenmark and Mecham, 1997), and the related results of effective prestretches as a result of varying constituent mass fractions (e.g., retraction lengths, opening angles), with each constituent possessing a potentially unique prestretch (Dobrin et al., 1975, 1990; Fung, 1991). This concept is thus closely interwoven with the hypothesis of evolving mass fractions and fiber directions, with interesting complementary effects.

2.3. Hypothesis III: vasoactivity

The third, and perhaps the most well-studied and appreciated fundamental hypothesis, is that of the central role of smooth muscle contractility. In an application of deductive physiology, Murray (1926) proposed that the body minimizes metabolic costs by maintaining an optimal volume of blood. It was later recognized that his conclusions implied a constancy of luminal shear stress, which arteries actively adjust their caliber to maintain (Rodbard, 1975; Zamir, 1977). Price et al. (1981) identified two distinct mechanisms governing smooth muscle activity. The first mechanism is a consequence of actin–myosin fiber overlap (Guyton and Hall, 1997), which permits smooth muscle to develop peak forces at an optimal length. The second mechanism is a chemical dosage-response; biochemical constrictors and dilators (e.g., endothelin-1, acetylcholine, and others) modulate the active force developed for a given active muscle fiber length. A well-known instance of this phenomenon is the increase in caliber in response to upregulation of the vasodilator nitric oxide by endothelial cells, when subjected to increased flow-induced shear stresses.

Through these mechanisms, active smooth muscle permits arteries to quickly accommodate changes in blood flow – to dilate in response to increased blood flow and to constrict for decreased

[1] Modeling assumptions vary as to how cells respond to mechanical stimuli. Despite ongoing progress in the field of mechanobiolgy, the current lack of detailed information requires modelers to make appropriate simplifications. Thus, the choice of metric (e.g., a measure of stress or strain) is largely a matter of convenience or utility, to be determined by the strengths and limitations of the particular framework in use (Humphrey, 2001).

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