MULTILAYER, MULTISCALE MODELING OF ENGINEERED TISSUES

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INTRODUCTION

Biopolymer-based tissue equivalents (TEs) have shown great promise is the basis for engineered tissues, particularly for structural tissues (e.g., blood vessels and cardiovascular valves). Collagen and fibrin form excellent scaffolds because they are highly biocompatible (being biomaterials) and gel under physiological conditions, making it possible to entrap cells directly during the gelation process. Cell-induced compaction of the gels then lead to significant densification and stiffening, which is augmented by cross-linking of the fiber network. An additional advantage is that manipulation of the compaction conditions (i.e., mechanically restricting compaction in certain directions or at certain locations) can be used to control the final orientation state of the TE. In spite of all of these advantages, TEs suffer from the disadvantage that it is difficult to achieve the mechanical properties of native tissues.

A particular challenge arises because biochemical and mechanical stimuli can be used to control various features of the TE compaction process (e.g., enhancing collagen synthesis or crosslinking), but the effect of these features on the final properties of the TE is not obvious. Towards addressing this problem of multi-scale behavior, we [1] and others [2] have recently introduced multi-scale simulation strategies that couple the macroscopic (functional) scale with the microscopic (network) scale. Our method, which we refer to as Representative Microstructure Finite Elements (RMFE), introduces a representative fiber network within each element of a finite element simulation. The network properties can be varied from element to element and are based on structural data from the TE of interest. Thus, features like orientation, fiber diameter, and degree of cross-linking can be introduced directly into the model rather than indirectly through a continuum-level constitutive law. A fiber constitutive equation is still required and must be determined experimentally. We use an exponential form to account for the fact that fibers are extremely stiff in tension but buckle in compression. The RMFE approach has been shown to be effective for TEs, in which the primary mechanism for load transfer is between fibers; in contrast, materials in which the primary mechanism is between a fiber and the surrounding matrix, fiber-composite type models are more appropriate.

It has recently been shown [3] that elastogenesis can be induced in TEs, leading to the production of an elastin layer in a collagenous TE. Given our goal of modeling TE behavior, the elastogenesis presents a new challenge. The elastin component is essentially a continuous elastic material, and it should be modeled using a continuum-level constitutive law. The collagen component, however, is still a network, and we would like to use our RMFE framework to analyze it. There is therefore a need for a multiphysics strategy that can handle both macro-micro and pure-macro models within the same sample.

Two possible situations merit consideration: micro-parallel and macro-parallel. By micro-parallel, we refer to structures in which the network and continuum phases are interspersed on a scale much smaller than the continuum scale. In such a case, a standard multiphase strategy [e.g., 4,5] could be employed, treating the two phases as independent and additive on the macroscopic scale. The challenge in this case would be to assess whether the fiber and continuous phases are coupled mechanically. If not, the problem is fairly straightforward. If so, some method for incorporating fiber-matrix interaction at the microscopic level must be introduced [cf. 6].

For this presentation, we focus on the macro-parallel case, in which there are multiple thick layers with different properties, such as a bilayered structure consisting of an elastin-free collagen network layer attached to a collagen-free elastic continuum layer. Although this model is a simplification of the physical system, it is a good first approximation of some TEs and a good initial test of the modeling strategy.

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METHODOLOGY

A two-layer structure was considered with one collagen layer and one elastin layer. Continuity of position was enforced strongly at the interface by using the same nodes for both sides, and continuity of stress was enforced weakly through the finite element method. The basic strategy of RMFE has been presented previously and is described briefly here. The standard Galerkin finite element method is used to discretize the Cauchy stress balance, but no constitutive equation is posed. Instead, a representative microstructural network (typically c. 200 fibers) is created on each element. When the element deforms, the network is deformed affinely on the edges of the element and allowed to equilibrate within the element. Once the equilibrium equations have been satisfied, the forces exerted on the edge of the element by the network are homogenized into a macroscopic stress. If the macroscopic stress balance is not satisfied, the nodal positions are updated, the microstructure is re-evaluated, and a new stress is calculated; the iteration continues until both macroscopic and microscopic scales are at equilibrium. For the continuum phase, standard nonlinear mechanics finite element methods are applicable. For convenience, we use the nonlinear neo-Hookean model, and we specify the elastin layer properties so that the collagen layer is stiffer in tension than the elastin layer but weaker in compression.

The structure was assumed to be in plane strain, and two cases were considered: (1) extension and (2) bending. For the extension case, displacement boundary conditions were imposed on the ends of the structure, and stress-free boundary conditions were imposed on the upper and lower surface. The bending case was based on an experimental system used at Minnesota to measure properties of thin tissues and TEs. The sample is held at one end, and a vertical force is applied to the other end by means of magnetic beads embedded through the thickness. This test was modeled by imposing zero displacement on the clamped end and no stress on the other surfaces. A vertical body force was introduced in the endmost elements of both the RMFE and continuum layers, representing the beads. The force was adjusted to account for changes in bead density due to dilatation of the TE.

RESULTS AND DISCUSSION

In extension, the fiber network rearranges, recruiting more fibers into the direction of stretch as the sample extends. Most of the load was borne by the fiber phase, not the elastic phase. Nonlinearity was seen in the apparent stress-strain behavior, which we attribute both to the geometric nonlinearity of the network structure and to the constitutive nonlinearity of the fibers in the network.

In the bending experiment, the collagen layer's nonlinear stiffening in tension caused a pronounced asymmetry in the mechanical response. The amount of tip displacement observed for a given force was much larger when the sample was bent towards the collagen side (tending to compress the collagen layer) than when the sample was bent towards the elastin side (tending to stretch the collagen layer).

The coupled macro-micro and continuum approach allows complex TE architectures to modelled with a relatively simple parameter set. Only four mechanical parameters are needed once microstructural information has been specified. Of course, many open issues remain, including interstitial flow, the micro-parallel structures mention in the introduction, viscoelasticity, and three-dimensionality. These are all the subject of our ongoing work.

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