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Mechanics of a two-fiber model with one nested fiber network, as applied to the collagen-fibrin system

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ABSTRACT

The mechanical behavior of collagen-fibrin (col-fib) co-gels is both scientifically interesting and clinically relevant. Collagen-fibrin networks are a staple of tissue engineering research, but the mechanical consequences of changes in co-gel composition have remained difficult to predict or even explain. We previously observed fundamental differences in failure behavior between collagen-rich and fibrin-rich co-gels, suggesting an essential change in how the two components interact as the co-gel's composition changes.

In this work, we explored the hypothesis that the co-gel behavior is due to a lack of percolation by the dilute component. We generated a series of computational models based on interpenetrating fiber networks. In these models, the major network component percolated the model space but the minor component did not, instead occupying a small island embedded within the larger network. Each component was assigned properties based on a fit of single-component gel data. Island size was varied to match the relative concentrations of the two components. The model predicted that networks rich in collagen, the stiffer component, would roughly match pure-collagen gel behavior with little additional stress due to the fibrin, as seen experimentally. For fibrin-rich gels, however, the model predicted a smooth increase in the overall network strength with added collagen, as seen experimentally but not consistent with an additive parallel model. We thus conclude that incomplete percolation by the low-concentration component of a co-gel is a major determinant of its macroscopic properties, especially if the low-concentration component is the stiffer component.

Statement of significance

Models for the behavior of fibrous networks have useful applications in many different fields, including polymer science, textiles, and tissue engineering. In addition to being important structural components in soft tissues and blood clots, these protein networks can serve as scaffolds for bioartificial tissues. Thus, their mechanical behavior, especially in co-gels, is both interesting from a materials science standpoint and significant with regard to tissue engineering.

1. Introduction

Models for the behavior of fibrous networks have useful applications in many different fields, including polymer science, textiles, and tissue engineering [1–9]. Such networks are key structural components of soft tissues, clots, and wounds. In addition, fibrillar protein networks made up of collagen and fibrin can serve as scaffolds for bioartificial tissues [10–15]. Thus, their mechanical behavior, especially in co-gels, is both interesting from a materials science standpoint and significant regarding tissue engineering.

Single-component fiber networks can be modeled by various methods [16], but, as is the case for many composite materials [8,17–22], predicting the emergent properties of a co-gel from those of its individual components remains a considerable challenge. In a previous study [8], we compared uniaxial tensile tests performed on collagen-fibrin co-gels at various compositions with computational model predictions. The model used either parallel (two distinct interpenetrating networks) or series (one network made of fibers randomly assigned as one protein or the other) interactions between the two networks. The results of that study

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suggested a transition from series to parallel behavior as collagen content increased even though there is no evidence that the two proteins form a single interconnected (series) network.

Another important observation made in our previous study [8] was that the failure Green strain of the co-gels decreased smoothly and rapidly from ~500% for pure fibrin to ~100% for the 40%-collagen gel, but decreased gradually to ~70% strain as the collagen concentration was increased from 40% to 100% (pure collagen). In the same series of experiments, the First Piola-Kirchhoff stress (PK1) at failure for the co-gels was roughly constant at about 5 kPa regardless of composition [8]. The nonlinear dependence of failure strain on collagen concentration constitutes a transition from series-like to parallel-like behavior with increasing collagen concentration and is obviously inconsistent with a parallel or constrained mixture model.

Taken together, these observations, in addition to second harmonic generation microscopy (Fig. 1), suggested the hypothesis that the more dilute fiber network does not percolate the entire space. Rather, it appears that two distinct structures exist: a continuous network of the concentrated component, decorated in some areas by a second, interpenetrating but not percolating network of the more dilute component. To test that hypothesis, we constructed a detailed catalogue of double-network models made up of a wide range of collagen/fibrin concentrations and subjected them to simulated uniaxial testing.

In contrast to our previous work [7], the current study introduces an island structure, and introduces crosslinks between the two networks in a concentration dependent manner. Therefore, this model is neither series (single network of alternating fibrin and collagen fibers), nor parallel (independent noninteracting networks), but it is a concentration-dependent hybrid of the two. As such, we anticipated a smooth transition in mechanical behavior consistent with constituent concentration. The results of this study are potentially significant to the design of implantable bioartificial tissues composed of cell-remodeled fibrin gels that can adapt, repair, and grow with the patient [13,23], especially if mechanical conditioning of the gel is introduced [24].

2. Methods

2.1. Multiphoton microscopy of collagen-fibrin co-gels

Prior to performing simulations, we conducted a brief confocal imaging study to assess the feasibility of our hypothesis. Collagen-fibrin co-gels were fabricated at a 10/90, 25/75, and 50/50 (v/v) collagen/fibrin concentration in a six-well plate as described previously [8]. Briefly, reconstituted acid-solubilized rat-tail collagen type I (Invitrogen, Carlsbad, CA, 3.0 mg/mL) was prepared with bovine fibrinogen (Sigma) and thrombin/Ca^{2+} (Sigma). Second harmonic generation microscopy [25,26] was then used to image the collagen component of co-gels (Fig. 1) with a multiphoton laser scanning microscope (Prairie Technologies, now Bruker Nano) workstation. A heterogeneous co-gel microscale structure was observed with a random assortment of collagen clusters that increased in number with increasing collagen concentration.

2.2. In silico co-gel network generation

We [27] and others [28] have found that a Voronoi network percolating a cube has network characteristics similar to type I collagen gels, so Voronoi networks were used to represent the fiber

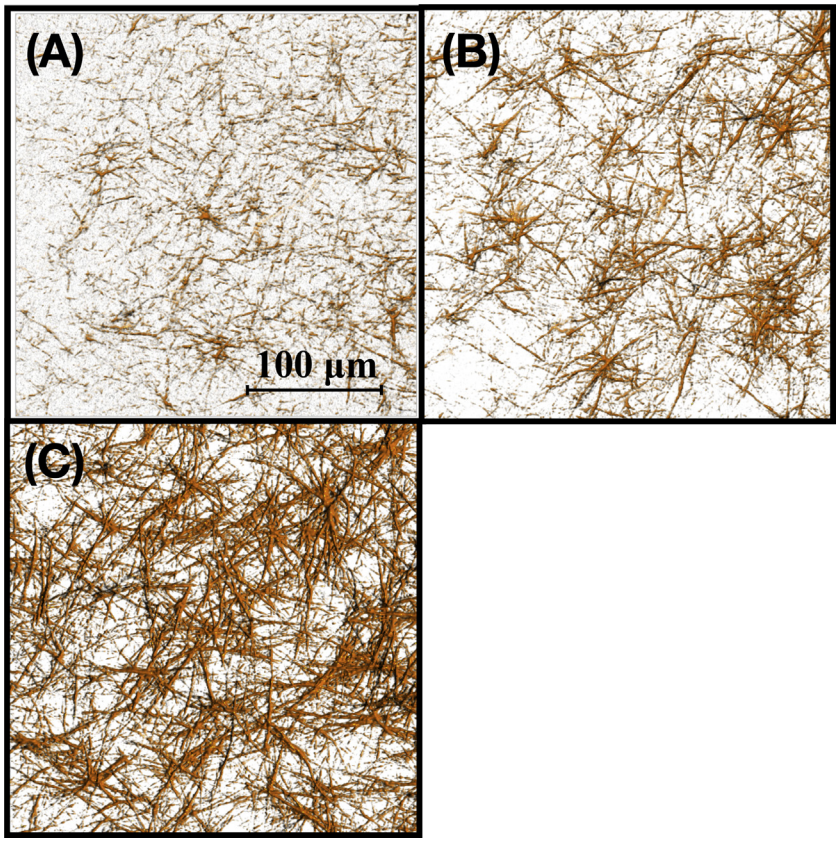

Fig. 1. Second Harmonic Generation (SHG) microscopy of Col-fib co-gels where only collagen is visible at: (A) 10%, (B) 25%, and (C) 50% (v/v) concentrations. An increase in the number of heterogeneous areas of high collagen concentration was observed with increasing collagen concentrations. Scale bar; 100 µm.

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