

Poroviscoelastic Behavior of Gelatin Hydrogels Under Compression—Implications for Bioelasticity Imaging

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Ultrasonic elasticity imaging enables visualization of soft tissue deformation for medical diagnosis. Our aim is to understand the role of flow-dependent and flow-independent viscoelastic mechanisms in the response of biphasic polymeric media, including biological tissues and hydrogels, to low-frequency forces. Combining the results of confined and unconfined compression experiments on gelatin hydrogels with finite element analysis (FEA) simulations of the experiments, we explore the role of polymer structure, loading, and boundary conditions in generating contrast for viscoelastic features. Feature estimation is based on comparisons between the biphasic poro-elastic and biphasic poroviscoelastic (BPVE) material models, where the latter adds the viscoelastic response of the solid polymer matrix. The approach is to develop a consistent FEA material model (BPVE) from confined compression-stress relaxation measurements to extract the strain dependent hydraulic permeability variation and cone-plate rheometer measurements to obtain the flow-independent viscoelastic constants for the solid-matrix phase. The model is then applied to simulate the unconfined compression experiment to explore the mechanics of hydrogels under conditions of quasi-static elasticity imaging. The spatiotemporal distributions of fluid and solid-matrix behavior within the hydrogel are studied to propose explanations for strain patterns that arise during the elasticity imaging of heterogeneous media. [DOI: 10.1115/1.3127250]

Keywords: biphasic, elasticity imaging, finite element, hydrogel, poroviscoelastic

1 Introduction

Elasticity imaging has emerged in recent years as a powerful diagnostic technique for classifying tumors [1]. Applying quasi-static compressive loads while imaging tissues ultrasonically, we obtain strain maps of viscoelastic features that reveal disease patterns. In addition to material properties, the appearance of strain images is influenced by artifacts caused by internal tissue boundaries and the unknown details (e.g., shape) of the applied stress field. Recent clinical trials show that elastic strain imaging is diagnostic for benign-malignant discrimination of large palpable breast tumors [2] despite strain artifacts because of the naturally large shear modulus contrast observed for many malignant tumors [3]. In addition, images of time-varying (viscoelastic) strain can provide new information that enable discrimination of clinically nonpalpable breast lesions [4]. The diagnostic performance of elasticity imaging depends on our ability to recognize and exploit disease specific contrast mechanisms.

Connective-tissue stroma is the component of breast tissue primarily responsible for its mechanical properties. Stroma is a collection of mesenchymal cells attached to a collagenous extracellular matrix (ECM) that is embedded in an interstitial fluid. Viscoelastic properties of the stroma, as summarized by the time-varying shear modulus/compliance, depend on the density of weak chemical bonds within the ECM polymer, the concentration of associated proteoglycan macromolecules [5], and by the movement of fluids through the ECM, which is driven by the interstitial pore pressure developed under the applied load. Stromal tissues are remodeled by tumor cells through molecular signaling path-

ways to create an environment for tumor growth. Cell signaling mediates increases in ECM and cell densities (fibrosis and hyperplasia) that lead to tissue edema, acidosis, and a cascade of inflammatory processes that together modulate local stiffness. The in situ tumor results in a complex and heterogeneous mechanical structure with unknown internal boundaries. While the overall tendency is for tumors to be stiffer than their surroundings, the appearance of breast tumors in strain images varies widely among patients. Inter-patient variability in the appearance of tumors with similar histology must be understood and controlled to improve diagnostic imaging performance.

Our long-term goal is to understand how disease mechanisms alter the dynamics of perfused mammary-tissue deformation. From that knowledge, we hope to design elasticity imaging techniques that maximize contrast for disease-specific features. In this study, we begin the investigation by examining macroscopically homogeneous gelatin hydrogels with a biphasic polymeric structure analogous to breast stroma [6]. An immediate aim is to understand the role of fluid flow and matrix viscoelastic relaxation that occurs under a uni-axial load and with varying degrees of confinement.

The extensive literature on cartilage and tendon tissues from the past three decades provides important experimental/computational approaches for understanding the deformation behavior in other biphasic connective tissues such as breast [7–12]. “Poroelasticity” theory, which emerged more than 50 years ago to describe consolidation of wet soil under a load [13,14] and later expanded in a series of papers by Biot to include dissipative and thermodynamic effects for engineering applications where mechanical waves propagate in a porous media [15], have been adapted to the study of biological materials. The biphasic poroelastic (BPE) model developed by Mow and co-workers [7–9] to model rheological behavior of cartilage is equivalent to the Biot

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theory when modeling saturated poro-elastic materials where the behavior can be attributed to frictional drag from motion between the two phases. A recent article on poro-elastic imaging sheds light on the evolution of biphasic models in the context of mechanics of biomaterials [16].

The biphasic modeling approach has shown that the rheological behavior of cartilage depends on the hydraulic permeability and the elastic modulus of the solid matrix [8]. Hydraulic permeability of the solid-matrix phase has been found to play a key role in the flow-dependent deformation of cartilage from experiments [17,18] and has been incorporated in the modeling approach through permeability functions to capture the effects of strain and void ratio (ratio of fluid to solid volume) on the deformation behavior [19–27]. BPE model predictions are found to match experimentally observed behavior of cartilage under confined compression [7,20,28–30]. More recently, biphasic models have been applied to advance poro-elastic imaging methods [31,32]. Although the BPE model is capable of predicting the response of cartilage in confined compression, findings from several researchers [33–36] indicate that frictional interactions between the phases are insufficient to completely account for the viscoelastic behavior exhibited under loading conditions other than confined compression. Also, the flow-independent viscoelastic behavior in cartilage [37] and the viscoelastic nature of collagen fibers [38] and proteoglycan gel [39,40] have been demonstrated. These observations lead us to believe that a biphasic poro-viscoelastic (BPVE) model [10,11], which takes into account the viscoelastic behavior generated from the flow-dependent frictional interactions, as well as the flow-independent viscoelastic nature of the porous solid matrix, is essential to model the behavior of soft tissues and hydrogels. Recent research has shown that a single set of material parameters can be applied to model the response observed in the unconfined compression, indentation, and confined compression tests for cartilage using a BPVE model [12].

While much is known about the mechanical properties and deformation behavior of predominately connective-tissue structures such as cartilage and tendon, relatively little is known about the mechanical behavior of parenchymal organ tissues with mixed stromal-epithelial components. Breast tissues are highly vascular and heterogenous at all spatial scales and can be broadly classified as glandular and adipose. The glandular component is of greatest interest; it consists of epithelial cells lining alveoli and ducts (where most breast cancers begin). Malignant breast tumors grow chaotically, often beginning with regions of high cell density surrounded by a stiff, fibrotic, desmoplastic reaction in the surrounding stroma. As they outgrow the supporting blood supply, soft hypoxic regions develop and can eventually form a fluidic core of necrosis. Some of these regions are separated by facia that confine the motion of tissue compressed during elasticity imaging.

We simplify the aforementioned complex tumor geometry in our study by adopting gelatin hydrogels as an experimental model. The collagen in gelatin is denatured and devoid of the proteoglycan component found in native stroma. Yet it retains a biphasic dynamic response to deformation with some features that mimic breast stroma [6]. Despite the lack of proteoglycan molecules, the water in gelatin hydrogels is structured because of the negatively charged side chain sites that are exposed on the denatured peptide molecules. Structured water molecules are more tightly bound and thus respond only to larger mechanical forces than does free water. The water in gelatin hydrogels has been classified into four types with decreasing binding forces: (i) inaccessible water bound by high-energy sorption centers, (ii) monomolecular-layer structured water, (iii) polymolecular-layer structured water, and (iv) free unbound water [41]. The simplicity of gelatin hydrogels and the large body of literature describing its structure and mechanical behavior led us to begin modeling biological media with a study of gelatin hydrogels, which are classified as *lightly cross-linked amorphous polymers* [42]. This class of polymer exhibits a bimodal loss compliance spectrum (imaginary part of the temporal

Fourier transform of the creep-strain curve). The bimodal spectrum suggests that the rheological response of the two constituent phases may be separable.

The current study combines the experimental and numerical models developed for dense connective tissues to explore the role of loading, boundary conditions, fluid movement, matrix viscoelasticity, and porous surfaces in determining elasticity image contrast. We find that the BPVE model provides distinct advantages over the BPE model when predicting the mechanical behavior.

2 Mathematical Models for Biphasic Polymeric Media

2.1 BPE model. The porous material model available in the commercial FEA software ABAQUS [43] (Dassault Systemes, Providence, RI) has been adapted to perform FEA simulations in this study for both BPE and BPVE materials. Details regarding the continuity condition, relationship between momentum, diffusion drag, and hydraulic permeability are presented in the ABAQUS manual [43] and in several cartilage modeling investigations [7,26,44].

In the ensuing discussion, we adopt the notations used in the ABAQUS manual [43] and by Suh and DiSilvestro [44]. The superscripts s and f refer to the solid and fluid phases, respectively. The physical quantities that characterize the biphasic material state and the field quantities such as stress, strain, pore pressure, and void ratio vary with vector position \mathbf{x} and time t . The porosity $n(\mathbf{x}, t)$ of the medium is the ratio of the volume of voids (or pores) $dV_v(\mathbf{x}, t)$ to the total volume $dV(\mathbf{x}, t)$ and is given by

$$n(\mathbf{x}, t) = \frac{dV_v(\mathbf{x}, t)}{dV(\mathbf{x}, t)} = \frac{\phi^f(\mathbf{x}, t)}{\phi^f(\mathbf{x}, t) + \phi^s(\mathbf{x}, t)} = \phi^f(\mathbf{x}, t) \quad (1)$$

where $\phi^\alpha(\mathbf{x}, t)$ is the volume fraction of the α phase and $\phi^f(\mathbf{x}, t) + \phi^s(\mathbf{x}, t) = 1$, since we are considering a biphasic material where the voids are completely filled with the fluid phase.

The total stress $\sigma_{ij}(\mathbf{x}, t)$ is given by Eq. (2) and is expressed as a sum of the solid-matrix stress $\sigma_{ij}^s(\mathbf{x}, t)$ and fluid stress $\sigma_{ij}^f(\mathbf{x}, t)$. Based on the mechanics of deformation in porous media [45], the total stress comprises of the effective solid stress $\bar{\sigma}_{ij}^s(\mathbf{x}, t)$, resulting from deformation of the solid matrix and the fluid pressure $p(\mathbf{x}, t)$. The effective solid stress represents the portion of the total solid stress that is in excess of the fluid pressure, as shown in Eq. (3). The stress in the fluid phase $\sigma_{ij}^f(\mathbf{x}, t)$ can be expressed in terms of the volume fraction of the fluid phase $\phi^f(\mathbf{x}, t)$ and the fluid pressure $p(\mathbf{x}, t)$, as shown in Eq. (4).

$$\sigma_{ij}(\mathbf{x}, t) = \sigma_{ij}^s(\mathbf{x}, t) + \sigma_{ij}^f(\mathbf{x}, t) = \bar{\sigma}_{ij}^s(\mathbf{x}, t) - p(\mathbf{x}, t)\delta_{ij} \quad (2)$$

$$\sigma_{ij}^s(\mathbf{x}, t) = \bar{\sigma}_{ij}^s(\mathbf{x}, t) - \phi^s(\mathbf{x}, t)p(\mathbf{x}, t)\delta_{ij} \quad (3)$$

$$\sigma_{ij}^f(\mathbf{x}, t) = -\phi^f(\mathbf{x}, t)p(\mathbf{x}, t)\delta_{ij} \quad (4)$$

where δ_{ij} is the Kronecker delta. Applying Lamé's constants, λ^s and μ^s , of the solid matrix, the effective solid stress $\bar{\sigma}_{ij}^s(\mathbf{x}, t)$ in the case of a BPE model can be written as

$$\bar{\sigma}_{ij}^s(\mathbf{x}, t) = \lambda^s \text{tr}(\epsilon_{ij}^s(\mathbf{x}, t))\delta_{ij} + 2\mu^s \epsilon_{ij}^s(\mathbf{x}, t) \quad (5)$$

where $\epsilon_{ij}^s(\mathbf{x}, t)$ is the strain tensor of the solid matrix and $\text{tr}(\epsilon_{ij}^s(\mathbf{x}, t))$ is its trace.

2.2 BPVE model. The BPE model (Eq. (5)) assumes an elastic behavior for the solid-matrix phase. The intrinsic flow-independent viscoelastic nature of the solid matrix was included in a BPVE model [10,11] using an integral representation shown in Eq. (6):

$$\begin{aligned}\bar{\sigma}_{ij}^s(\mathbf{x}, t) = & K^s \int_{-\infty}^t dt' k_R(t-t') \frac{\partial \text{tr}(\epsilon_{ij}^s)}{\partial t'}(\mathbf{x}, t') \\ & + 2G^s \int_{-\infty}^t dt' g_R(t-t') \frac{\partial \epsilon_{ij}^s}{\partial t'}(\mathbf{x}, t')\end{aligned}\quad (6)$$

where $K^s = (3\lambda^s + 2\mu^s)/3$ and $G^s = \mu^s$ represent the intrinsic bulk and shear modulus, respectively, of the solid matrix. $\epsilon_{ij}^s(\mathbf{x}, t)$ is the deviatoric strain tensor of the solid matrix and can be expressed as $\epsilon_{ij}^s(\mathbf{x}, t) = \epsilon_{ij}^s(\mathbf{x}, t) - \frac{1}{3}\text{tr}(\epsilon_{ij}^s(\mathbf{x}, t))$. $k_R(t)$ and $g_R(t)$ represent the normalized relaxation amplitudes for the bulk and shear moduli, respectively.

To reduce the computational burden imposed during the evaluation of the convolution integrals for the continuous relaxation spectrum of Eq. (6), a discrete relaxation spectrum of the type indicated in Eq. (7) was introduced by Suh and Bai [46].

$$g_R(t) = 1 + \bar{g} \sum_{i=1}^N e^{-t/\tau_i} \quad (7)$$

where τ_i are the relaxation time constants, N is the number of discrete terms of the series, and \bar{g} is the spectrum magnitude. For cartilage the value of $N=3$ in the discrete representation has been shown to be sufficient to model the change in the relaxation modulus predicted by the continuous spectrum model, which uses an integral representation [46]. A similar result has been found from investigations on gelatin hydrogels [47].

In this study, a cone-plate rheometer is used to measure the creep response of the hydrogel under a constant applied shear stress. Creep compliance $J(t)$ obtained from the shear-creep strain experiment is used in ABAQUS to obtain the relaxation function for the shear modulus $g_R(t)$. Under generalized loading and boundary conditions, the relaxation functions for the hydrostatic and deviatoric components of the solid-matrix stress $\bar{\sigma}_{ij}^s(\mathbf{x}, t)$ can be different leading to $k_R(t) \neq g_R(t)$. Although it is possible to obtain the flow-independent relaxation of the deviatoric component of stress, the measurement of the flow-independent relaxation of the hydrostatic component (bulk modulus $k_R(t)$) is difficult, since any hydrostatic deformation of the solid matrix causes exudation of interstitial fluid leading to a flow-dependent relaxation of stress. Hence, studies on cartilage were conducted by Suh and DiSilvestro using two biphasic poro-viscoelastic models BPVE-1 and BPVE-2 [44]. A constant bulk modulus $k_R(t)=1$ (hydrostatic component governed by an elastic law) and a relaxing shear modulus $g_R(t)$ (deviatoric component governed by a viscoelastic law) was assumed in the BPVE-1 model. In the BPVE-2 model, the relaxation of the bulk and shear modulus was assumed to be governed by the same relaxation function, $k_R(t)=g_R(t)$. Their FEA studies on cartilage under unconfined compression using these two models illustrated that the strain energy from deviatoric deformation was considerably larger than from its counterpart, the volumetric deformation. Also the relaxation of deviatoric strain energy was significantly larger than the relaxation observed in the volumetric strain energy. FEA of the confined compression-force relaxation experiment using the BPVE-2 model was conducted for a Type-B gelatin hydrogel, and the predicted force relaxation response was marginally smaller than the corresponding prediction using the BPVE-1 model. Our observations from the FEA studies using BPVE-1 and BPVE-2 models for hydrogels and conclusions from studies on modeling cartilage [44] have led us to assume in this study a BPVE model that considers the relaxation in shear modulus (i.e., the BPVE-1 model used for modeling cartilage [44]).

3 Materials and Methods

The gelatin hydrogel construction is described in Sec. 3.1, followed by Secs. 3.2–3.4 describing the three experiments. The rheometer experiment provides estimates of the viscoelastic proper-

ties of the hydrogel's solid matrix. The confined compression experiment allows us to determine poro-elastic properties of the hydrogel. Finally, these measurements are validated through FEA of an independent experiment, namely, the unconfined compression-creep strain experiment on the hydrogel.

3.1 Gelatin Hydrogels. Hydrogels are made from 250 bloom-strength, Type-B gelatin (refers to the use of a base agent to process the animal hide to make gelatin) provided by Rousselot Inc. (Dubuque, IA), which has an iso-electric pH between 4.8 and 5.2. The same gelatin composition and manufacturing procedure is used in all the experiments conducted. The gelatin phantom consists of 6% w/w gelatin powder, 93.6% de-ionized water, and 0.4% formaldehyde. Under these conditions, the pH of the hydrogel is found to be in the range between 5.6 and 5.7. The combination of gelatin and water is heated in a water bath at temperatures maintained between 55°C and 65°C for 1 h and periodically stirred. The molten gelatin is removed from the heat and allowed to cool to 50°C before formaldehyde (chemical cross linker) is added. Once the media cools to 45°C, it is poured into molds where it quiescently congeals. Depending on the experiment conducted, the mold containers vary in their configurations and are discussed in Secs. 3.2–3.4. The polymerization time (t_p) is considered to be the time from when the gelatin begins to cool to laboratory air temperature until the time the specimen is tested mechanically. t_p is nominally 24 h in all the experiments conducted. The experimental measurements are made at a laboratory air temperature of 23°C. The experimental techniques and the mathematical framework adopted to obtain the various material properties are discussed in Secs. 3.2–3.4, 4.1, and 4.2.

3.2 Shear-Creep Strain. The shear compliance $J(t)$ was measured by performing a shear test using a Haake cone-plate rheometer (Thermo Electron Corp., Model RS150, Waltham, MA). Molten gelatin is poured into the rheometer plate covering the edges of the cone. The sample is sealed to prevent air movement and desiccation, and cured for 24 h (t_p) before testing. Specimens are tested under an applied torque that generates a shear stress σ_a . A short duration ramp torque corresponding to a shear stress of $\sigma_a = 40$ Pa is applied and held constant while shear strain $\gamma_{12}(t)$ is recorded at the rate of 3 samples/s for a duration of 30 min. Figure 1 shows the measurements of $\gamma_{12}(t)$ and creep compliance $J(t) = \gamma_{12}(t)/\sigma_a$ for an experiment. $\gamma_{12}(t)$ may be related to the corresponding tensorial strain $\epsilon_{12}(t)$ via $\gamma_{12}(t) = 2\epsilon_{12}(t)$. The geometrical considerations of the cone-plate rheometer in obtaining the shear strain $\gamma_{12}(t)$ and the constitutive behavior of a hydrogel using discrete viscoelastic models are discussed in an earlier study [47].

Similar to the discrete relaxation spectrum assumption [46], ABAQUS [43] assumes the viscoelastic material to be defined by a Prony series expansion of the dimensionless relaxation modulus:

$$g(t) = g_R(t) - \sum_{i=1}^N g_i = G(t)/G_0 = 1 - \sum_{i=1}^N g_i(1 - e^{-t/\tau_i}) \quad (8)$$

where $G_0 = G(t=0)$ is the instantaneous shear modulus, N is the number of terms chosen in the Prony series, and g_i and τ_i are the associated amplitudes and time constants. The dimensionless relaxation modulus has the limiting values $g(0)=1$ and $g(\infty) = G_\infty/G_0$. The time-dependent behavior of the viscoelastic solid matrix can be specified by the creep test data obtained from the shear experiment and are used by ABAQUS to calculate the terms of the Prony series in Eq. (8). The normalized shear compliance $j(t)$ is defined as

$$j(t) = G_0 J(t) = J(t)/J_0 \quad (9)$$

where $J(t) = \gamma_{12}(t)/\sigma_a$ is the shear compliance obtained from the shear-creep strain experiment (Fig. 1(b)) and $J_0 = J(t=0)$. ABAQUS is used to convert the creep data $j(t)$ into relaxation

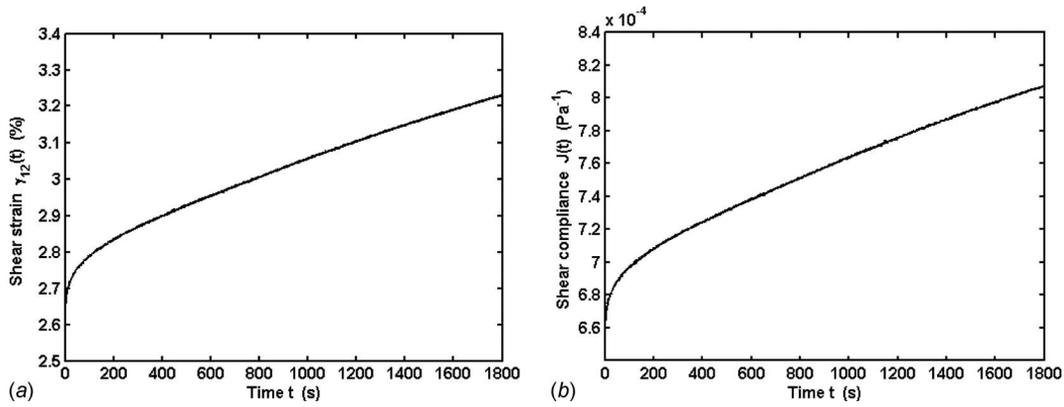


Fig. 1 Shear-creep-strain experiment performed using a cone-plate rheometer. (a) Shear-creep strain $\gamma_{12}(t)$ is measured with an applied step stress of $\sigma_a=40$ Pa. (b) Shear compliance $J(t)$ estimates versus time are obtained from creep-strain data.

data through the convolution integral shown in Eq. (10).

$$\int_0^t dt' g(t') j(t-t') = t \quad (10)$$

ABAQUS uses the normalized shear modulus $g(t)$ in a nonlinear least-squares fit to determine the Prony series parameters. The ERRTOL parameter specifies the allowable average root-mean-square error of data points in the least-squares fit, and a value of ERRTOL=0.0003 was chosen in our analysis. The parameter NMAX specifies the number of terms of the Prony series. The ABAQUS theory manual provides a guideline for the choice of the number of terms of the Prony series based on the logarithmic “decades” spanned by the test data, $N \leq \log_{10}(t_{\max}/t_{\min})$. The total duration of the test is denoted by t_{\max} and the sampling time interval between consecutive data points by t_{\min} . A value of $N=3$ is chosen to fit the Prony series in our FEA and is smaller than $\log_{10}(1800/0.33)=3.73$, estimated from the $t_{\max}=1800$ s and $t_{\min}=0.33$ s of the shear-creep strain experiment. The relaxation function $g(t)$ obtained from ABAQUS represents the fluid flow-independent viscoelastic behavior of the solid-matrix. The constants of the Prony series determined for the 6% Type-B gelatin hydrogel (pH=5.6) using ABAQUS are amplitudes $g_1=2.09 \times 10^{-2}$, $g_2=2.87 \times 10^{-2}$, and $g_3=0.29$, and time constants $\tau_1=7.73$, $\tau_2=76.04$, and $\tau_3=4210$ s (the standard deviations are found to be within $\pm 10\%$ of the average time constant values).

3.3 Confined Compression-Force Relaxation. Gelatin solution is poured into the aluminum chamber base and care is exercised to remove any air bubbles. Parafilm (Structure Probe Inc., West Chester, PA) is placed on top of the gelatin hydrogel to create a flat surface and prevent desiccation and is wrapped around the aluminum chamber. The aluminum chamber and the parafilm together create an airtight mold during polymerization. Before experimentation, the parafilm is carefully removed and the top surface of the hydrogel is exposed for testing. Figure 2(a) depicts the cylindrical specimen (height $H=18.4$ mm and diameter $D=13.9$ mm), which is bound laterally and on the bottom by the aluminum chamber. The elastic modulus of the aluminum chamber (70 GPa) is much greater than that of the specimen (≈ 3.65 kPa). Porous rods of diameter 13.5 mm made from polytetrafluoroethylene (PTFE) material with controlled porosity were procured from Small Parts Inc. (Miramar, FL) and were machined to obtain 25 mm long pistons for use in these experiments. Porous pistons with two different pore sizes are used to compress the specimens. Pore size is varied to test whether it influences the exudation impedance of the fluid during the experiment for a given applied strain ϵ_a and hydrogel composition. The piston pore

sizes tested are $35 \mu\text{m}$ and $120 \mu\text{m}$. A constant displacement compressive deformation is ramped on over 1.3 s and held constant for 60 min by the porous PTFE piston. The piston provides a 0.2 mm clearance with the side walls of the aluminum chamber. The hydrogel specimens are strained 2% (0.37 mm), while the decaying force is measured as a function of time using a 5 kg load cell (± 0.1 g uncertainty) in the TA.XTplus Texture Analyzer (Stable Micro Systems Ltd., Surrey, UK).

Uni-axial confined compression tests performed to observe the force relaxation behavior of hydrogels are also simulated using FEA. Gelatin is a biphasic material consisting of a denatured collagen network with bound water component that forms the solid matrix (viscoelastic porous matrix) and fluid (free water) that fills the interstitial space. The hydrogel parameters used in the FEA using the BPE model are the elastic modulus E_m , Poisson’s ratio ν_m of the matrix, hydraulic permeability $\kappa(\mathbf{x}, t)$, and the initial void ratio $e_0(\mathbf{x})=e(\mathbf{x}, t=0)$ (ratio of fluid to solid content before deformation). The spatiotemporally varying void ratio $e(\mathbf{x}, t)$ is related to the porosity of the hydrogel via $n(\mathbf{x}, t)=1/1+e(\mathbf{x}, t)$ [43]. The change in Poisson’s ratio with time was estimated by applying a uni-axial step strain on a gelatin hydrogel cube by measuring the change in lateral strain with time using time-of-flight ultrasound [47]. It was observed that the specimen responds incompressibly initially with $\nu(t=0) \approx 0.5$ falling rapidly to settle at $\nu(t > 100 \text{ s})=0.47$. The equilibrium value $\nu_m=0.47$ is chosen in

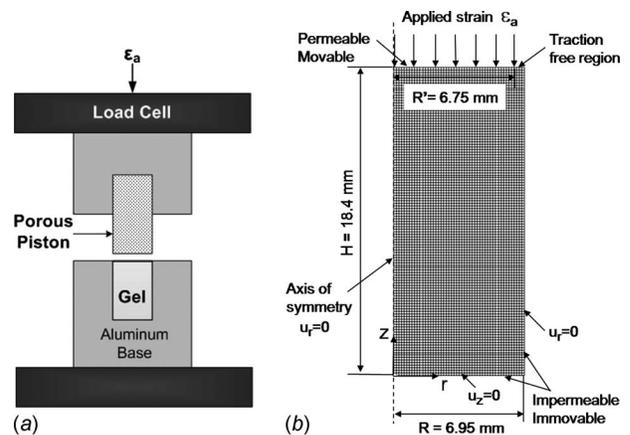


Fig. 2 (a) Schematic of the confined compression-force relaxation experiment. (b) Finite element model of the hydrogel specimen under confined compression.

our FEA as Poisson's ratio of the solid matrix. An initial estimate of the elastic modulus $E_m=2G_m(1+\nu_m)=2939$ Pa is obtained from the shear modulus $G_\infty=G_m=1000$ Pa estimated from the shear-creep strain experiments using Poisson's ratio $\nu_m=0.47$. Preliminary FEA studies revealed that the strain ϵ_z in the direction (z -axis) of the uni-axial applied stress and at the end of the loading ramp in an unconfined compression experiment is strongly influenced by the choice of the solid-matrix modulus E_m . Hence, a parametric study using FEA is conducted with different values of E_m in the range from 3000 Pa to 4000 Pa to capture the unconfined compression loading ramp (i.e., $\sigma_a=0-638$ Pa applied in 1.8 s). The value of $E_m=3650$ Pa is found to predict the strain ϵ_z at $t=1.8$ s most accurately and hence is chosen as the solid-matrix modulus for the 6% gelatin hydrogel. The porous material model in ABAQUS is used and the hydrogel is assumed to be fully saturated at the beginning (all the voids are filled with the fluid). For example, a 6% gelatin specimen has a fluid content of 94% by net weight during preparation. Studies have shown that less than 10% of the water remains bound to the collagen structure and is immobile even under large applied mechanical forces [41]. Hence, an initial void ratio of $e_0=e(\mathbf{x},t=0)=9$ is chosen in our FEA, which corresponds to 90% of the material being water that is free to exude under mechanical forces.

The confined compression experiment is also simulated using the BPVE model. In addition to the material properties used in the BPE model mentioned above, the solid-matrix is assumed to exhibit viscoelastic behavior with the material constants estimated using a rheometer as described in Sec. 3.2.

FEA is performed using CAX8P, eight-node axisymmetric finite elements, which includes pore pressure. The displacement field within the finite element is obtained by quadratic interpolation of all eight nodal values. However, the pore pressure field is obtained by bilinear interpolation of the four corner nodal values. The finite element model shown in Fig. 2(b) is well represented by one-half of the specimen (radius $R=6.95$ mm and height $H=18.4$ mm) due to axisymmetry. Although a small frictional force arises between the aluminum chamber side surface and the hydrogel specimen when the hydrogel slips during deformation in the axial (z -axis) direction, calculations reveal that the frictional force is negligible ($5.6 \times 10^{-5}\%$ of F_{peak}) in comparison to the compressive force F_{peak} generated by the applied strain and is hence neglected in our FEA. Symmetry dictates that there is no fluid flow along the z -axis and the radial displacement $u_r=0$. The bottom of the specimen, at $z=0$, has no vertical displacement, i.e., $u_z=0$ and has an impermeable boundary condition. The top of the specimen is the only permeable surface and is the only movable boundary. Studies have shown that the clearance between the piston and the confined compression chamber should be included in the FEA to obtain the peak force observed in the confined compression experiments performed on cartilage specimens [12]. Along similar lines, displacements in our FEA are applied along the top surface from $r=0$ to 6.75 mm by the porous rod. The 0.2 mm clearance between the aluminum chamber and the porous rod is modeled as a traction free surface. Figure 2(b) indicates the loading and boundary conditions used in the FEA.

3.4 Unconfined Compression-Creep Strain. The mold for the hydrogel specimen is an acrylic cylinder with flat acrylic end plates that are clamped together to provide an air-tight seal. Mold release (Pol-Ease 2300 by Polytek Development Corp., Easton, PA) is coated to the inside of the mold to prevent adhesion of the gel with the acrylic surface. Molten hydrogel is poured into the cylinder, sealed through a syringe attached to its side, and left to congeal at room temperature for the next 20 h. The acrylic mold with the specimen is placed in a 2°C refrigerator for 30 min, a few hours prior to the experiment to help ease the release of hydrogel from its mold. The extracted specimen is transferred to

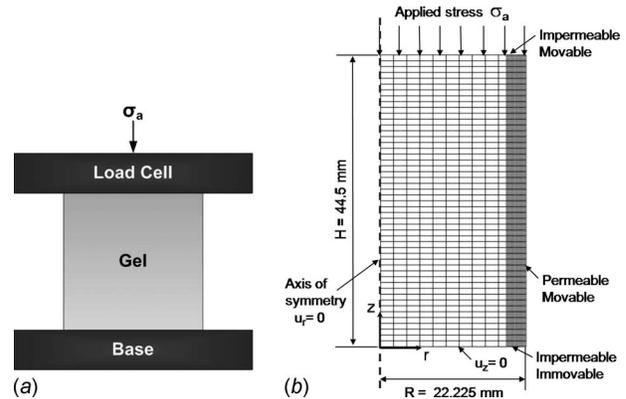


Fig. 3 (a) Schematic of the unconfined compression-creep strain experiment. (b) Finite element model used for simulating the unconfined compression experiment.

an air-tight container at room temperature for 3 h before it is tested.

The experimental protocol used in this study is the same as that used in our earlier studies on gelatin hydrogels [48]. The experiments are conducted in the Texture Analyzer, used for the confined compression-force relaxation experiments. The hydrogel specimen is placed between aluminum plates (diameter of 60 mm) and a fixed compressive stress σ_a is applied as illustrated in Fig. 3(a). The cylindrical hydrogel specimen (height H and diameter D are 44.45 mm) is free to move laterally and has a free slip boundary condition with the aluminum plates placed in the bottom and top of the specimen. The elastic modulus of the aluminum plates (70 GPa) is much greater than that of the hydrogel specimen (3.65 kPa). A 1 kg load cell (± 0.01 g uncertainty) is attached to the Texture Analyzer since the loads developed in this experiment are much smaller than those observed in the confined compression-force relaxation experiment. The load cell attached to the compression plate senses the applied stress and provides feedback to the system to adjust the height of the probe and maintain a constant load. The compression plate displacement versus time corresponds to the time varying strain $\epsilon_z(t)$ (creep) response of the hydrogel.

The study began by finding the linear region in the stress-strain response. Stress-strain curves are obtained by applying 30 g preload ($\approx 3\%$ strain) followed immediately with a cyclic strain. The variation in stress versus time (Fig. 4(a)) suggests that the hydrogel stabilizes after about 35 cycles, a phenomenon referred to as preconditioning [49,50]. Figure 4(b) shows that the stress-strain variation (extracted from the loading part of the cycle) is nearly linear over the range from 0% to 10% engineering strain. Based on this observation, the testing protocol adopted is as follows: (i) precondition the specimen by applying 30 g of preload and cycle from 0% to 10% engineering strain at 0.04 Hz for 40 cycles and (ii) initiate the unconfined compression under a constant applied stress σ_a for creep-strain measurements immediately following the preconditioning. $\sigma_a=638$ Pa is within the linear response of the hydrogel and also falls within the range of applied stress used in the unconfined imaging experiments [48]. The stress is applied within 1.8 s and held constant for 30 min while the variation of the strain is sampled at the rate of 10 Hz.

The experiment was simulated using the CAX8P, eight-node axisymmetric finite elements including pore pressure (same finite element used in the FEA of confined compression-force relaxation experiment). The FEA model shown in Fig. 3(b) represents one-half of the axisymmetric specimen (radius $R=22.225$ mm, height $H=44.45$ mm) with a finer mesh near the lateral ($r=R$) permeable surface since a large gradient in stress and pore pressure is expected in this region due to more fluid movement. A frictionless boundary condition is assumed on the top and bottom surfaces of

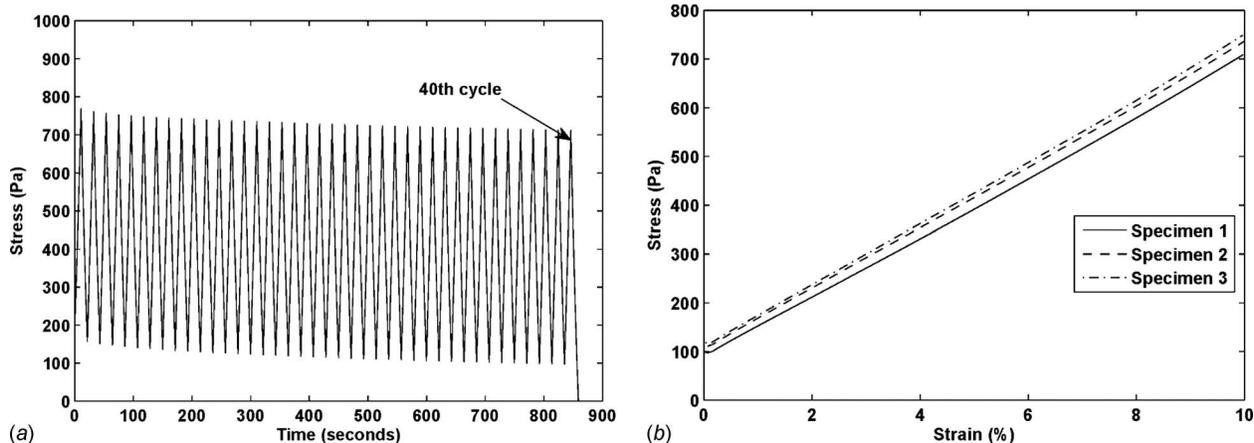


Fig. 4 Preconditioning of the hydrogel under unconfined compression (a) Stress versus time (cyclic engineering strain of 0–10%). (b) Stress-strain curves from the loading part of the 40th cycle.

the unconfined FEA model, such that the hydrogel surface slips freely along the radial direction during compressive deformation. The bottom surface of the specimen ($z=0$) has no vertical displacement ($u_z=0$) and both the bottom and top surfaces have an impermeable boundary condition. The lateral surface of the specimen is the only permeable surface in this FEA. Although a constant stress is applied to the unconfined hydrogel in the FEA, the force computed from the FEA matches the applied force measured in the experiments within 1% throughout the creep process. The material constants used in the FEA to predict the force relaxation response observed in the confined compression experiments are used to model the creep strain behavior exhibited by the unconfined hydrogel specimen under σ_a .

4 Results

The experimental measurements discussed above provide the material constants for the biphasic models used to predict the confined compression-force relaxation behavior of hydrogels. Further, spatiotemporal heterogeneity in hydraulic permeability $k(\mathbf{x}, t)$ with void ratio $e(\mathbf{x}, t)$ changes that occur during deformation are considered to accurately model the poro-viscoelastic behavior of the hydrogel.

4.1 Confined Compression. The confined compression experiment performed using a porous piston provides us with a viscoelastic response that is controlled primarily by the exudation

of water from the hydrogel. Hence we apply it to estimate the hydraulic permeability $k(\mathbf{x}, t)$. Figure 5(a) shows the force relaxation behavior of the hydrogel observed during confined compression experiments. It also clearly illustrates that both pore sizes give very similar results, and hence the 35 μm pore size is sufficient for the applied 2% compressive strain. Figure 5(b) displays the loss spectra corresponding to the force-relaxation curves in Fig. 5(a).

The BPVE model is applied to the data in Fig. 5 along with parameters obtained independently to understand the role of fluid flow in confined compression-force relaxation. The parameter $E_m=3650$ Pa is estimated and $\nu_m=0.47$ was measured as discussed in Sec. 3.3. The viscoelastic parameters of the discrete shear relaxation spectrum, $g_1=2.09 \times 10^{-2}$, $g_2=2.87 \times 10^{-2}$, and $g_3=0.29$ and the corresponding time constants, $\tau_1=7.73$, $\tau_2=76.04$, and $\tau_3=4210$ s. Figure 6(a) shows the results obtained from FEA by applying the BPVE model while using the constant values of hydraulic permeability $k(\mathbf{x}, t)=k_0$ ranging from 1.0×10^{-11} m/s to 3.0×10^{-10} m/s. The value $k_0=1.0 \times 10^{-11}$ m/s predicts the measured relaxation behavior at short times, $k_0=3.0 \times 10^{-10}$ m/s predicts the behavior at long times, and the best overall fit for a constant hydraulic permeability is predicted using $k_0=3.0 \times 10^{-11}$ m/s. Hence, $k_0=3.0 \times 10^{-11}$ m/s is chosen in the parametric studies conducted to observe the effects of different

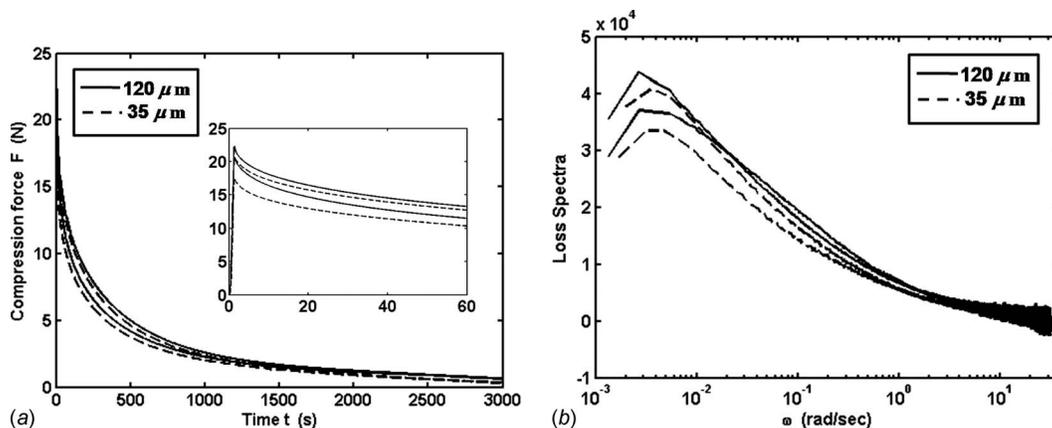


Fig. 5 Confined compression-force relaxation experiment. (a) Force measured with applied uni-axial step strain of $\epsilon_a=2\%$. (b) Loss spectra obtained from force versus time experimental data for the hydrogel. Two measurements for each pore sizes 35 μm and 120 μm are shown.

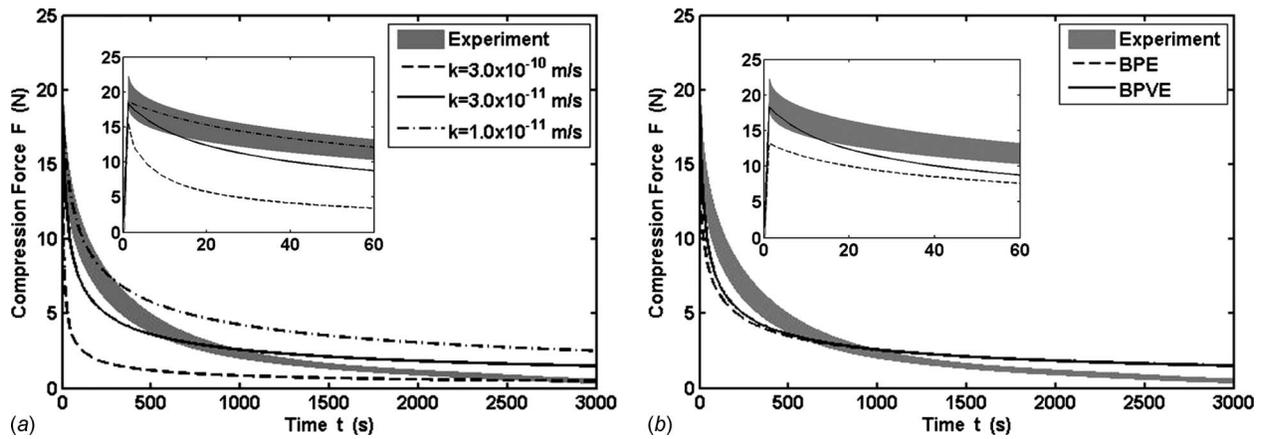


Fig. 6 Comparison of predicted and observed confined compression-force relaxation behavior. Compressive force $F(t)$ is predicted from FEA (a) using constant values of hydraulic permeability, $k(x, t) = k_0$, and (b) using different biphasic models for $k(x, t) = k_0 = 3 \times 10^{-11}$ m/s. The shaded region indicates the range of measured values; see Fig. 5(a).

biphasic models, varying elastic modulus E_m and varying Poisson's ratio ν_m .

Figure 6(b) shows the prediction from the FEA using the BPE and BPVE models. The predicted force relaxation from both models are very similar but neither matches the measured data. The BPVE model predicts a much higher peak compressive force (seen in Fig. 6(b) at $t = 1.3$ s) in comparison to the prediction from the BPE model. Based on these observations, the BPVE model is chosen for further FEA conducted in this study.

To understand the effect that changes in E_m can have on the predicted relaxation responses, three different values, $E_m = 3250$, 3650, and 4050 Pa ($\pm 11\%$ about 3650 Pa), are chosen in a parametric FEA study. All other material properties are fixed. The results, shown in Fig. 7(a), reveal that increasing the E_m yields a proportional increase in the peak compressive force.

The scatter observed in the experimental measurement of Poisson's ratio [47] is used as a guideline to determine the range of variation of the Poisson's ratio in the parametric study. The Poisson's ratio of the solid-matrix is varied over the range $\nu_m = 0.46$, 0.47, and 0.48 ($\pm 2.1\%$ about the average value of 0.47) while maintaining all the other material properties constant. Figure 7(b) illustrates that there is some effect of varying Poisson's ratio on the force relaxation behavior and also on the equilibrium force

response of the hydrogel (the changes are more pronounced than the effect observed from changing E_m). The experimental results exhibit more gradual relaxation behavior at short times ($t < 600$ s) and also more overall relaxation in comparison to the FEA results. Variation in these parameters cannot explain the differences observed between the experimental relaxation behavior and the FEA predictions. Similar observations were made in the modeling studies on the compressive behavior of cartilage [27].

During the confined compression-force relaxation experiment, the exudation of fluid from the hydrogel varies with time, causing a significant spatiotemporal change in the ratio of fluid to solid volume $\phi^f(x, t) / \phi^s(x, t)$ in regions near the porous piston. The considerable change in the local dilatational strain $\epsilon_{ii}(x, t)$ near the piston surface produces concomitantly large change in the void ratio $e(x, t)$ (ratio of pore to solid volume). Changes in dilatational strain have been known to alter the hydraulic permeability $k(x, t)$ of cartilage [18]. Using the experimental observations on cartilage, constitutive models for the nonlinear variation of $k(x, t)$ with the changing strain $\epsilon_{ii}(x, t)$ and solidity $\phi^s(x, t)$ was proposed by Holmes and Mow [23] to explain finite deformation of soft gels and hydrated connective tissues. Based on their work, the following expression for hydraulic permeability has been widely

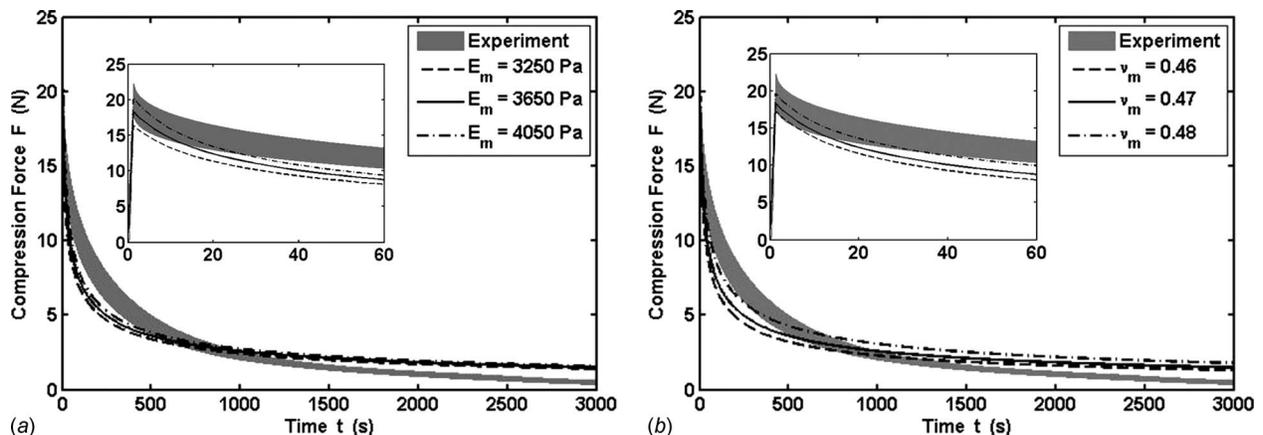


Fig. 7 Comparison of experimentally observed and predicted (FEA) confined compression-force relaxation behavior. Compressive force $F(t)$ is predicted from FEA using BPVE material model and constant hydraulic permeability $k(x, t) = k_0 = 3.0 \times 10^{-11}$ m/s by varying solid-matrix properties (a) elastic modulus E_m and (b) Poisson's ratio ν_m . The shaded region indicates the range of measured values; see Fig. 5(a).

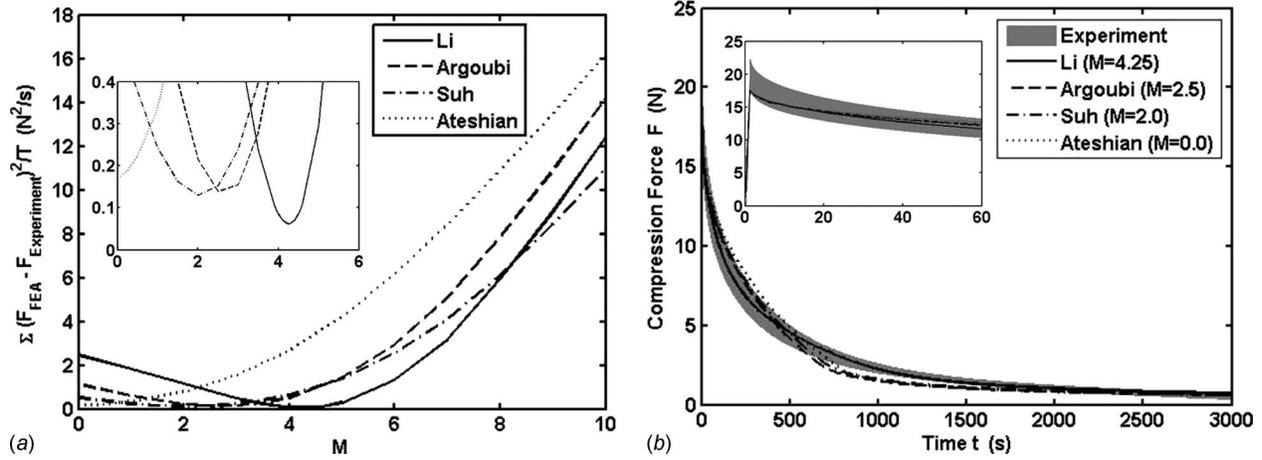


Fig. 8 Confined compression-force relaxation experiment. (a) Time-averaged error ($T=3000$ s) is estimated by comparing experimentally measured and predicted compressive forces while varying M values for each of the models Eqs. (12)–(15) depicting hydraulic permeability. (b) $F(t)$ versus time predicted from FEA performed using various models using the minimum M value obtained for each model from Fig. 8(a). The shaded region indicates the range of measured values; see Fig. 5(a).

adapted and used by researchers to study the effects of nonlinear variation in hydraulic permeability on deformation behavior of cartilage, gels, and other connective tissues.

$$k(\mathbf{x}, t) = k_0 \Phi^\kappa(\mathbf{x}, t) e^{M(\Delta(\mathbf{x}, t) - 1)/2} \quad (11)$$

where $\Phi(\mathbf{x}, t) = [\phi_0 \phi^f(\mathbf{x}, t)] / [(1 - \phi_0) \phi^s(\mathbf{x}, t)]$, κ is a measure of the rate at which the permeability approaches zero as fluid leaves the hydrogel, and M is a constant. $\Delta(\mathbf{x}, t)$ is the determinant of the left Cauchy–Green strain tensor $B_{ij}(\mathbf{x}, t)$ [51] of the solid matrix, and ϕ_0 is the volume fraction of the solid matrix in the hydrogel before a load is applied. For small strains, $\kappa < 0.1$ and $\Phi^\kappa(\mathbf{x}, t) \approx 1$. It was shown that in the small strain scenario, the expression for hydraulic permeability given in Eq. (11) reduces to the constitutive law $k(\mathbf{x}, t) = k_0 e^{M \epsilon_{ii}(\mathbf{x}, t)}$ [23], which was obtained from flow permeation experiments performed on cartilage [18].

In the current study, four different models for hydraulic permeability variation in hydrogels are investigated using FEA of the confined compression-force relaxation experiment. The models used by Suh et al. [24] (Eq. (12)), Argoubi and Shirazi-Adl [25] (Eq. (13)), and Ateshian et al. [26] (Eq. (14)) are considered and include the effects of dilatational strain and solidity on the hydraulic permeability of connective tissues. The fourth model considered is the expression for hydraulic permeability (Eq. (15)) used by Li et al. [27] to study the load relaxation behavior of cartilage under uni-axial unconfined compression.

$$k(\mathbf{x}, t) = k_0 \left[\frac{\phi_0 \phi^f(\mathbf{x}, t)}{(1 - \phi_0) \phi^s(\mathbf{x}, t)} \right] \exp[M(J_3 - 1)/2] \quad (12)$$

$$k(\mathbf{x}, t) = k_0 \left[\frac{e(\mathbf{x}, t)(1 + e_0)}{e_0(1 + e(\mathbf{x}, t))} \right]^2 \exp \left[M \left(\frac{e(\mathbf{x}, t) - e_0}{1 + e_0} \right) \right] \quad (13)$$

$$k(\mathbf{x}, t) = k_0 \left[\frac{\phi_0 \phi^f(\mathbf{x}, t)}{(1 - \phi_0) \phi^s(\mathbf{x}, t)} \right]^2 \exp[M(J_3 - 1)/2] \quad (14)$$

$$k(\mathbf{x}, t) = k_0 \exp \left[M \left(\frac{e(\mathbf{x}, t) - e_0}{1 + e_0} \right) \right] \quad (15)$$

Equation (15) considers the effect of strain alone on the hydraulic permeability and hence is equivalent to the original idea proposed by Lai and Mow [18]. The nonlinear effect of strain and solidity (Eq. (12)–(14)) and strain alone (Eq. (15)) on the hydraulic permeability $k(\mathbf{x}, t)$ is included in the FEA performed using ABAQUS. The variation in hydraulic permeability is specified as a function

of instantaneous void ratio $e(\mathbf{x}, t)$ in the ABAQUS FEA using the “PERMEABILITY” command of the porous material model.

The results in Fig. 6(a) demonstrate that the FEA using a constant value of hydraulic permeability $k(\mathbf{x}, t) = 3 \times 10^{-10}$ m/s predicts the peak force at the end of the loading ($t = 1.3$ s) as well as the relaxation behavior at long times ($t > 1500$ s). From this result and using the observations made by Li et al. [27] that the inclusion of nonlinear hydraulic permeability in the FEA causes the load to relax more slowly, a value of $k_0 = 3 \times 10^{-10}$ m/s is chosen in our FEA study conducted with the BPVE material model. It is also noticed that the value of hydraulic permeability is very similar to those measured for cartilage [17,18,23]. A parametric study is conducted, where M is varied between 0.0 and 10.0 to obtain the nonlinear permeability $k(\mathbf{x}, t)$ that generates FEA force predictions that best fit the measured values in the confined compression-force relaxation experiment. Figure 8(a) shows the time-averaged error between the measured and predicted force curves as a function of M and that the model of Li et al. (Eq. (15)) with a value of $M \approx 4.25$ gives the best fit. Figure 8(b) compares the predicted force variation obtained through FEA using the best M value (least error estimated from Fig. 8(a)) for each permeability model. It shows that the model of Li et al. (Eq. (15)) gives a solution very close to the experimentally measured force relaxation, suggesting the need to account for spatiotemporal variation of permeability within the hydrogel during deformation.

4.2 Unconfined Compression. The BPVE model and the material properties estimated from the confined compression-force relaxation experiment are now applied to predict the unconfined compression-creep strain experimental data to check for consistency. In unconfined compression of a hydrogel specimen, solid-matrix deformation occurs throughout the specimen causing concomitant movement in the interstitial fluid. Figure 9(a) shows a good agreement between the creep strain response observed in the experiment and the predicted axial strain $\epsilon_z(\mathbf{x}, t)$ obtained from the FEA. Due to the change in specimen geometry and boundary conditions for the same hydrogel, comparison of the unconfined compression-creep strain experimental measurements and FEA predictions provides an independent verification of the material constants found in Sec. 4.1. Figure 9(b) shows the creep strain variation obtained for the three values of hydraulic permeability assumed in the FEA. Clearly, variation in hydraulic permeability

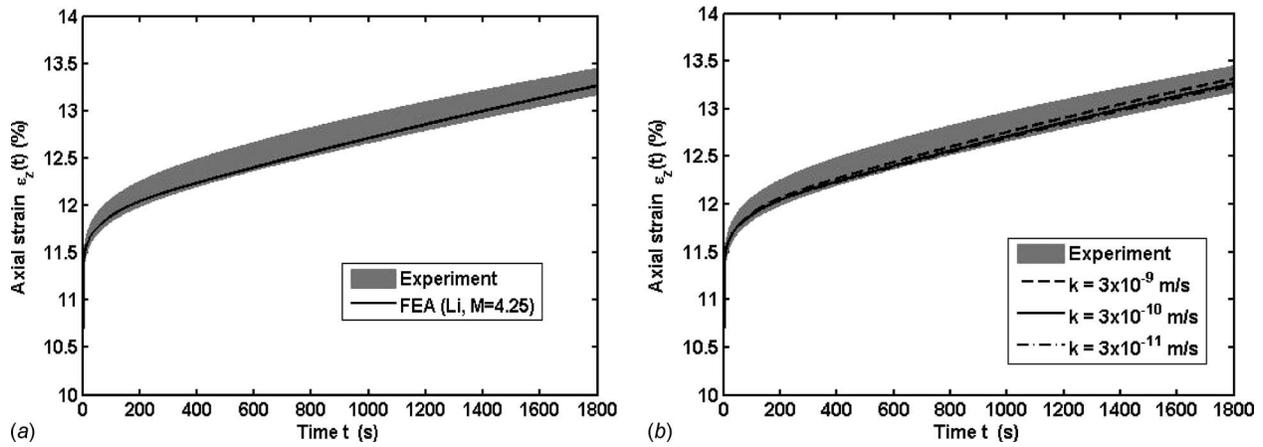


Fig. 9 Comparison of unconfined compression-creep strain $\epsilon_z(t)$, measured experimentally for 6% gelatin hydrogel ($\sigma_a = 638$ Pa) and obtained from FEA using BPVE material model with material constants $E_m = 3650$ Pa, $\nu_m = 0.47$, and $e_0 = 9.0$. (a) Hydraulic permeability of Eq. (15) is used with $k_0 = 3 \times 10^{-10}$ m/s, $M = 4.25$ that also predicts the confined compression-force relaxation data (Fig. 8(b)). (b) Variation with k_0 from Eq. (15). The shaded region indicates the range of measured values.

is a less significant factor in the prediction of creep response under unconfined compression.

A parametric study is conducted, where the solid-matrix elastic modulus is varied ($E_m = 3600, 3650, 3700$ Pa) and Poisson's ratio is varied ($\nu_m = 0.46, 0.47, 0.48$) to understand their effects on the predicted creep strain. Figures 10(a) and 10(b) show the variation in the predicted creep strain response when the elastic modulus is varied by ± 50 Pa and the Poisson's ratio is varied by ± 0.1 , respectively. The sensitivity of creep strain to changes in the solid-matrix properties indicates the strong contribution from solid-matrix deformation in the case of unconfined compression of the hydrogel. In contrast, we recall from Figs. 7(a) and 7(b) that the influence of the solid-matrix properties on the force relaxation response is much smaller in confined compression, since the load shared by the fluid phase in the form of pore pressure is much higher over most of the region of the specimen.

5 Discussion

The current study addresses two important aspects relevant to elasticity imaging contrast (i.e., regional changes in stiffness). (i) What are the appropriate rheological models for characterizing the deformation behavior of biphasic hydrogels such as hydrogels and parenchymal tissues? (ii) How is an applied load shared between the fluid and solid-matrix phases?

5.1 Mechanical Characterization of Hydrogels. Much is known about the load response of individual collagen fibers that comprise the solid matrix [52]. Small deformations are entropically elastic, becoming increasingly energetically elastic at larger deformations until the fiber fails. However, once the collagen fibers are assembled into a hydrogel, the response to a load is poro-viscoelastic as we have shown. FEA studies reveal that the variation of hydraulic permeability with strain and void ratio suggests a response that cannot be fully described using discrete linear viscoelastic models [47] or fractional derivative approaches [53].

The fluid-flow dominated viscoelastic response in a confined compression-force relaxation experiment provides valuable information for obtaining the nonlinear variation in hydraulic permeability with dilatational strain and solidity. A creep shear strain experiment using a rheometer provides information for obtaining the fluid-flow independent viscoelastic response of the solid matrix. We have determined that a third order model captures the solid-matrix behavior within experimental error, and we relied on time-tested models that reflect the effects of variation in hydraulic permeability to capture the fluid-flow behavior. Using such an approach, we have identified different experiments to obtain a unique set of material constants (E_m , ν_m , g_1^P , g_2^P , g_3^P , τ_1 , τ_2 , τ_3 , k_0 , and M) for a BPVE model that can be employed in the FEA of a hydrogel under generalized loading and boundary conditions. This

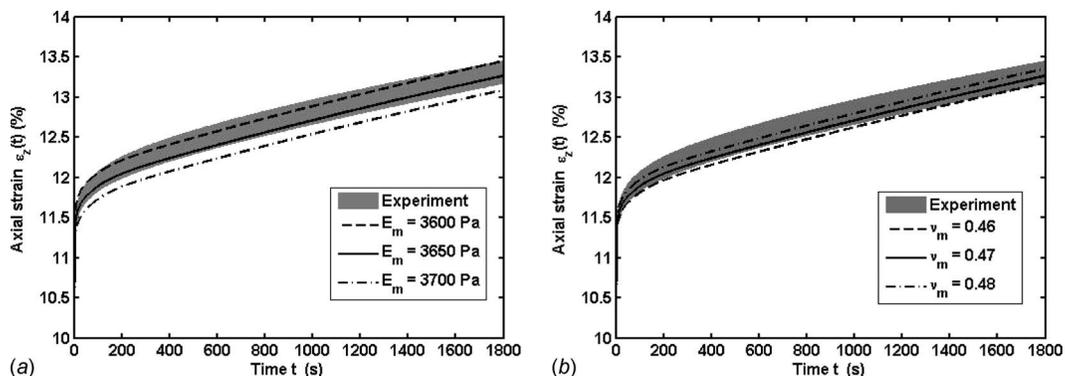


Fig. 10 Comparison of experimentally observed and predicted (FEA) creep strain, $\epsilon_z(t)$ of the hydrogel specimen under unconfined compression. Creep strain is predicted from FEA using BPVE material model by varying solid-matrix properties: (a) elastic modulus E_m and (b) Poisson's ratio ν_m . The shaded region indicates the range of experimentally measured values.

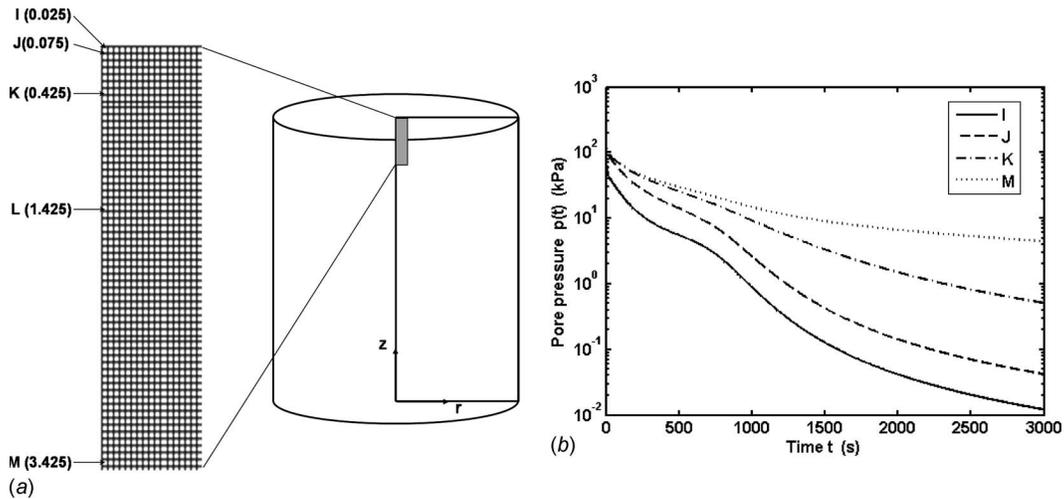


Fig. 11 FEA predictions of pore pressure variations during confined compression-force relaxation experiments. (a) Locations are identified along the central z -axis of the cylindrical specimen. (b) Pore pressure variation with time and position (I – M).

has been demonstrated by the use of material constants obtained from different testing geometry (rheometer and confined compression) to accurately predict the hydrogel response in other testing configurations (unconfined compression), thus validating the modeling methodology.

5.2 Fluid and Solid-Matrix Phase Behavior. Ultrasonic elasticity imaging techniques can detect changes occurring in breast stroma using strain images and viscoelastic parameter based images. A discussion of the breast stroma ultrastructure and the fluidic and structural changes that accompany the formation of tumors provides sufficient evidence that understanding the behavior of the various phases under compressive loads is of paramount importance in interpreting the contrast observed in elasticity images.

Stromal breast tissues share many structural similarities to hydrogels. However, they contain naturally porous boundaries—skin layers, blood vessels, cyst walls, interstitial, and basement membranes—that resist local deformation for an applied load. Internal boundaries confine the tissues enclosed by them; consequently, in vivo breast tissues are expected to behave mechanically somewhere between a confined and unconfined hydrogel, depending on the local conditions. Normal glandular breast tissue responds to uni-axial compressions very much like a linear viscoelastic polymer at strains up to 4% [6], which is simulated by our unconfined hydrogel experiments. If a tumor is growing within the glandular tissue, the regional stiffness becomes heterogenous with locally increased cell density (hyperplasia), reduced interstitial lymphatic flow (edema) and increased collagen density (fibrosis and desmoplasia). All these changes tend to stiffen breast tumors, making them clinically palpable, but tumor stiffness can be spatially and temporally modulated by several factors including hyper- or hypovascularity and extracellular acidosis [54]. Hence malignant breast disease includes changes in stroma that alters the local biphasic mechanical structure. Depending on the nature of the boundaries between these heterogenous tumor regions, the movement of interstitial fluids can be reduced, increasing the pore pressures and further increasing the apparent regional stiffness. Boundary effects can be significant in highly confined regions because of the exponential dependence of fluid permeability $k(\mathbf{x}, t)$ on the void ratio $e(\mathbf{x}, t)$, as observed for hydrogels in Fig. 8.

We begin our investigations with a study on the behavior exhibited by the two phases (fluid and solid matrix) of the hydrogel under compressive loads, to elicit details that are relevant to various imaging modalities applied to soft biological tissues. The two phases share the stress generated from the applied load with the

relative contribution from each varying in space and time. The confined and unconfined compression experiments are the extreme cases bounding the response of soft tissues to deformation. Hence, the role played by the loading, boundary conditions, permeability of surfaces, and the material heterogeneity developed during deformation on the spatiotemporal variations of physical quantities (pore pressure, solid-matrix stress, strain and void ratio) is explored. The following discussion also provides insights into the mechanisms of creep strain that could provide clues to the apparent stiffness observed in ultrasonic elasticity imaging of tissues.

5.2.1 Confined Compression. Figure 11(a) shows five different locations, $I(z=0.025$ mm) (from the top surface of the hydrogel specimen), $J(z=0.075$ mm), $K(z=0.425$ mm), $L(z=1.425$ mm), and $M(z=3.425$ mm), chosen along the cylindrical z -axis of the confined compression FEA model. We observe the predicted pore pressure and solid-matrix stress at these locations to understand the spatiotemporal responses. For deeper locations within the specimen (3.5–18.4 mm from the top surface), pore pressures decline gradually from an initially high ($p > 150$ kPa) to a much lower ($p < 2$ kPa) value when the hydrogel relaxes. The response is similar to the relaxation predicted for location M in Fig. 11(b). For locations near the top surface (I , J , and K) the pore pressures are reduced to values close to zero. However, at locations far from the top surface, the pore pressures are nonzero even at large times ($t > 3000$ s), implying that the relaxation time varies markedly depending on the location along the z -axis. For locations I and J , a small undulation in the pore pressure relaxation curve during the time interval $300 < t < 1000$ s is observed, which is caused by the movement of fluid from the lower part of the specimen into regions closer to the piston surface during the re-equilibration of pressures.

Figure 12(a) depicts the pore pressure p and the solid-matrix stress σ_z variation with time for four locations (I , J , K , and L). The exudation of fluid causes a drop in pore pressure that increases the solid-matrix stress proportionately to support the load. σ_z and p are found to be equal at 4.5 s, 426 s, 1219 s, and 3000 s at locations I , J , K , and L , respectively, and beyond these times the stress in the solid matrix is larger than the pressure in the fluid. At interior locations (3.5–18.4 mm from the top surface), it is found that the pore pressures reduce gradually from the force relaxation and stress redistribution occurring between the solid matrix and fluid phases in the top regions (0–3.5 mm from the top surface) of

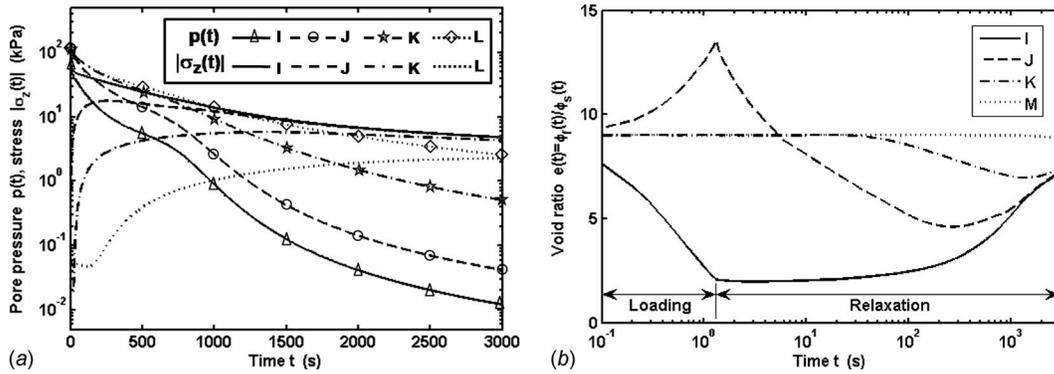


Fig. 12 FEA predictions for confined compression-force relaxation using the BPVE material model. (a) Pore pressure $p(t)$ and magnitude of the solid-matrix stress $|\sigma_z(t)|$ variation with time. (b) Void ratio $e(t)$ variation with time. Locations $I-M$ are illustrated in Fig. 11(a).

the specimen. In these interior regions, the fluid carries the entire load while the solid matrix bears negligible load all through the relaxation process of the confined hydrogel.

Figure 12(b) shows void ratio $e(\mathbf{x}, t)$ changes over time at the various spatial locations. The void ratio drops rapidly as the fluid exudes from the hydrogel near the porous piston (I and J). Interior locations (3.5–18.4 mm from the top surface) exhibit negligible change in void ratio ($e(t) \approx 9.0$) implying that negligible fluid leaves the region. The short-term increase in void ratio observed at location J during the time interval $0 < t < 5$ s is due to the accumulation of fluid flowing from the lower regions into this location before it can exude into the porous piston. As the hydrogel relaxes, there is a substantial redistribution of fluid within the regions ($17 < z < 18.4$ mm) that are close to the piston surface, causing the void ratio to increase and saturate at a value close to $e(\mathbf{x}, t) = 8.0$. A strong time dependence and spatial variation in the load bearing of the solid matrix and fluid phases is clearly evident from the FEA of the hydrogel in confined compression.

5.2.2 Unconfined Compression. Figure 13(a) identifies the radial specimen locations, A ($r=0.3$ mm) (from the lateral surface, $r=R$), B ($r=1.3$ mm), C ($r=2.3$ mm), and D ($r=3.6$ mm) (centroids of the finite elements), selected to observe $p(\mathbf{x}, t)$, $\sigma_z(\mathbf{x}, t)$, and $e(\mathbf{x}, t)$. The analysis reveals that the pore pressures are much smaller than the solid-matrix stresses. Figure 13(b) shows $p(t)$ and $\sigma_z(t)$ in non-dimensional form (normalized using the applied stress value $\sigma_a = 638$ Pa). Figure 13(b) indicates that the pore pressure decreases as the fluid leaves from the outer regions ($r > 0.8R$) of the specimen. The decrease in pore pressure results in a corresponding increase in the solid-matrix stress for the speci-

men to be able to bear the applied stress, σ_a . Similar to our observations made from the confined compression-force relaxation FEA, for inner regions ($0 < r < 0.8R$), the changes in pore pressure and solid stress are negligible. Also evident is that the fluid carries roughly 1/3 of the total applied stress (i.e., $p(\mathbf{x}, t)/|\sigma_z(\mathbf{x}, t)| + p(\mathbf{x}, t) \approx 1/3$) (Fig. 13(b)) in the inner regions of the specimen.

Figure 14(a) shows the predicted void ratio changes in the unconfined specimen, which are much smaller than those seen in the case of confined compression, Fig. 12(b). The void ratio changes are much smaller under unconfined compression-creep strain loading although the applied strain is approximately five times the strain applied in the confined compression-force relaxation experiment. This is due to the fact that the deformation occurs over the entire volume of the specimen. Both the solid-matrix and fluid phases bear the applied load from the beginning, since there is no radial constraint for the solid-matrix deformation throughout the volume and larger surface area is available for the fluid to exude. Figure 14(a) shows that the fluid exudation causes corresponding changes in the void ratio in the outer regions ($r > 0.8R$). However, in the inner regions ($0 < r < 0.8R$), the void ratio remains nearly constant, $e(\mathbf{x}, t) \approx 9.0 = e_0(\mathbf{x})$. With the exudation of fluid from the hydrogel, the top compressing platen moves to maintain a constant stress on the specimen leading to an increase in the axial strain $\epsilon_z(\mathbf{x}, t)$ (creep response). Figure 14(b) shows that the temporal changes in radial strain $\epsilon_r(\mathbf{x}, t)$ varies depending on the radial location. However, the temporal change in the axial strain $\epsilon_z(\mathbf{x}, t)$ is the same at all locations of the specimen. When negligible fluid leaves, such as in the inner regions, it is nearly incompressible, $\epsilon_r \approx 0.5\epsilon_z$. However, as fluid exudes from the outer re-

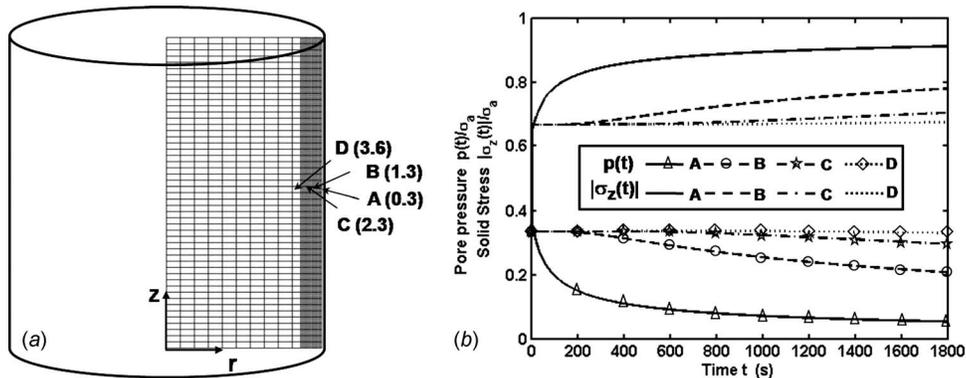


Fig. 13 Unconfined compression-creep strain. (a) Locations along the radial r -direction chosen for showing variations in field quantities. (b) Predicted pore pressure $p(\mathbf{x}, t)$ and magnitude of the solid stress $\sigma_z(\mathbf{x}, t)$ variations with time from FEA using BPVE material model.

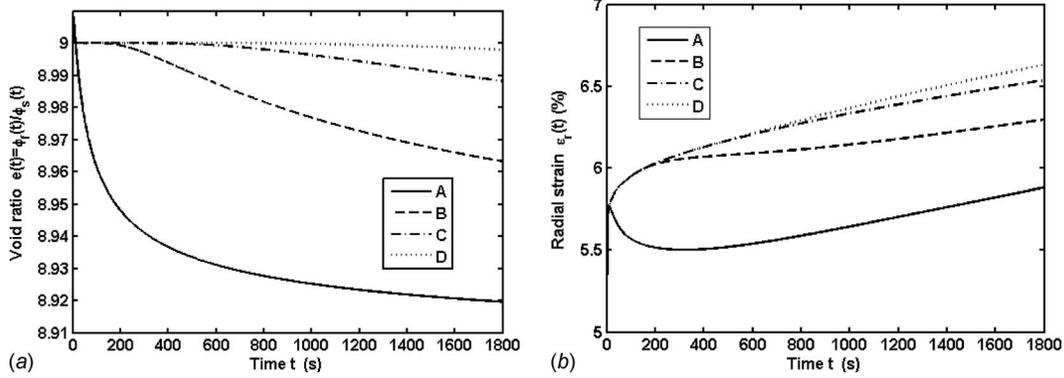


Fig. 14 Unconfined compression-creep strain. Predicted (a) void ratio $e(x, t)$ and (b) radial strain $\epsilon_r(x, t)$ variations with time from FEA using BPVE model. Locations A–D are illustrated in Fig. 13(a).

gions, the load is progressively transferred to the solid matrix with a corresponding decrease in Poisson's ratio leading to smaller radial strains ($\epsilon_r < 0.5\epsilon_z$).

Figures 15(a) and 15(b) show the temporal changes in pore pressure and solid-matrix stress, respectively, for locations along the radial direction and at half the height of the specimen. The region with a lower pore pressure ($p(x, t) < 0.34\sigma_a$) and higher solid-matrix stress ($\sigma_z(x, t) > 0.66\sigma_a$) increases gradually from the outer surface to the inside as time progresses. Figure 15 shows that near the outer surface, the pore pressure $p(x, t)$ is reduced by $0.3\sigma_a$ (correspondingly $\sigma_z(x, t)$ is increased by $0.3\sigma_a$). However, in the inner regions ($r < 0.8R$) of the hydrogel, there is no temporal change in pore pressure. The annular region, where the stress redistribution between the fluid and solid matrix occurs, increases from $0.97R < r < R$ at 50 s to $0.8R < r < R$ at 1800 s. The annular stress redistribution region increases with time and depends on the magnitude of the applied stress σ_a .

Detailed investigations of the FEA results reveal a very heterogeneous spatiotemporal variation of physical quantities within the hydrogel leading to the overall force relaxation behavior in confined compression and creep strain behavior in unconfined compression experiments. We find that for samples with unconfined boundaries, the solid matrix carries a larger portion of the uniaxial load in comparison to the fluid phase throughout the hydrogel volume with the load fraction borne by the solid matrix increasing further near the specimen boundaries where fluid movement out of the region is largest. On the contrary, when the boundaries confine the deformation of the sample and movement of fluid, the fluid bears a significant fraction of the load. Also observed is that in both the compression experiments, the redistribution of stress between the fluid and solid-matrix phases oc-

curs in a small region of the hydrogel near porous surfaces. While the unconfined geometry is more representative of breast elasticity imaging in general, it can be inferred that regional confinement of tissues can clearly affect stiffness and therefore elasticity image contrast.

It appears that the quasistatic elasticity imaging methods (low-frequency force stimuli similar to that used in this study) generate image contrast rich in material property information but can be difficult to interpret in terms of tissue structure and content. The nature of the quasistatic stimulus is to apply it to the entire medium and hold it constant. This stimulus couples the mechanical responses of each point in the medium to other points, so that internal tissue boundaries broadly influence the appearance of these images. Conversely, dynamic elasticity imaging methods (high-frequency force stimuli) [55–57] often stimulate the medium locally with shear wave pulses or high-intensity compressional wave pulses. As the stimulus is applied in a small region, the images describe local material properties. However, the spatiotemporal complexity of the applied force complicates the interpretation of the image contrast for reasons different than in the quasistatic imaging methods. In addition, the choice of force stimulus bandwidth is known to affect the poro-viscoelastic response of the medium. Consequently, we do not yet know which force stimulus bandwidth provides the greatest diagnostic information. Hence, the relative utility of quasistatic and dynamic imaging methods is still under investigation. The study of the mechanical response of hydrogels helps to define the biphasic response of the medium more clearly. As a result of this study, we now have computational tools for predicting the poro-viscoelastic response of breast-tissue-like media to quasi-static stimuli.

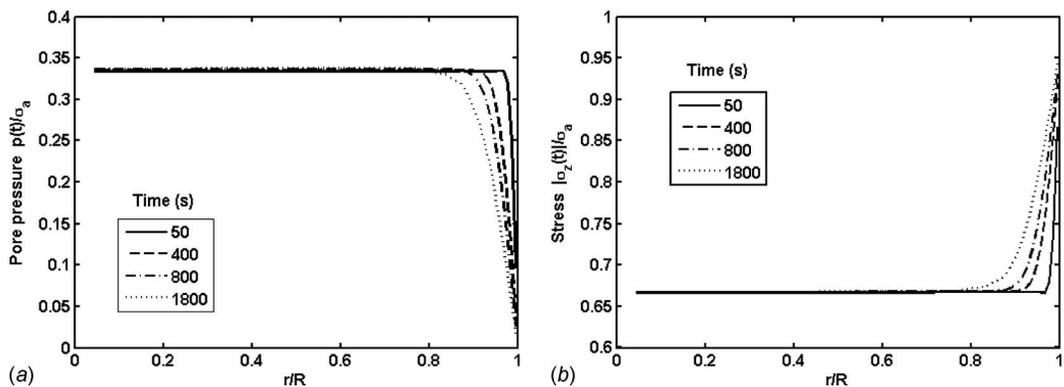


Fig. 15 Unconfined compression-creep strain. Predicted (a) pore pressure $p(x, t)$ and (b) magnitude of solid-matrix stress $\sigma_z(x, t)$ variations with time in the radial r -direction (at specimen height $h = H/2 = 22.225$ mm) from FEA using the BPVE material model.

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