An analysis of the effects of depth-dependent aggregate modulus on articular cartilage stress-relaxation behavior in compression

Christopher C-B. Wang\textsuperscript{a,b}, Clark T. Hung\textsuperscript{b}, Van C. Mow\textsuperscript{a,*}

\textsuperscript{a}Orthopaedic Research Laboratory, Department of Orthopaedic Surgery, Columbia University, 630 W 168th Street, Black Building, Room 1412, New York, NY 10032, USA
\textsuperscript{b}Cellular Engineering Laboratory, Department of Biomedical Engineering, Columbia University, New York, NY 10027, USA

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Abstract

An accurate description of the mechanical environment around chondrocytes embedded within their dense extracellular matrix (ECM) is essential for the study of mechano-signal transduction mechanism(s) in explant experiments. New methods have been developed to determine the inhomogeneous strain distribution throughout the depth of the ECM during compression (Schinagl et al., 1996, Annals of Biomedical Engineering 24, 500–512; Schinagl et al. 1997. Journal of Orthopaedics Research 15, 499–506) and the corresponding depth-dependent aggregate modulus distribution (Wang and Mow, 1998. Transactions of the Orthopaedics Research Society 23, 484; Chen and Sah, 1999. Transactions of the Orthopaedics Research Society 24, 635). These results provide the motivation for the current investigation to assess the influence of tissue inhomogeneity on the chondrocyte milieu in situ, e.g. stress, strain, fluid velocity and pressure fields within articular cartilage. To describe this inhomogeneity, we adopted the finite deformation biphasic constitutive law developed by Holmes and Mow (1990 Journal of Biomechanics 23, 1145–1156). Our calculations show that the mechanical environment inside an inhomogeneous tissue differs significantly from that inside a homogeneous tissue. Furthermore, our results indicate that the need to incorporate an inhomogeneous aggregate modulus, or an anisotropy, into the biphasic theory to describe articular cartilage depends largely on the motivation for the study. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Articular cartilage is an aneural and avascular tissue which functions to distribute the high loads of joint articulation across the underlying bony structures (Mankin et al., 1994). In conjunction with synovial fluid, articular cartilage provides the joint with an extraordinarily efficient lubrication mechanism characterized by very low wear rates and low frictional coefficients (Mow and Ateshian, 1997; Ateshian et al., 1998). These functional characteristics rely on the multiphasic compositional nature of articular cartilage that provide the tissue with many of its unique mechano-electro-chemical characteristics (Lai et al., 1991; Mow et al., 1980; Mow and Ratcliffe, 1997). The biphasic theory treats cartilage as a mixture of two intrinsically incompressible materials, one solid and one fluid, that can account for any variation of inhomogeneities and anisotropies, and finite deformation (e.g., Ateshian et al., 1997; Bachrach et al., 1998; Cohen et al., 1998; Mow et al., 1980). In the biphasic theory, the tissue is treated as a hydrated soft material consisting of two mechanically interacting phases: (1) a porous-permeable, hyperelastic, composite organic solid phase composed of collagen, proteoglycans and other quantitatively minor glycoproteins; and (2) a viscous fluid phase, which is predominantly water, and a variety of mobile electrolytes that maintain the electroneutrality condition of the charged proteoglycan aggregates of the solid matrix.\textsuperscript{1} Thus, the aim of this study was to assess the influence of tissue inhomogeneity on the stress, strain, fluid velocity and pressure fields within articular cartilage, and on the deformation of the articular surface.\textsuperscript{2} We looked

\textsuperscript{1} For a complete description of the interaction between proteoglycan charges and ions in the interstitial fluid, the reader is referred to Lai et al. (1991) and Gu et al. (1998).

\textsuperscript{2} For cell-ECM biomechanical interactions, reader is referred to Guilak et al. (1997) and Guilak and Mow (1999).
specifically at the influence of an inhomogeneous matrix stiffness by incorporating depth-dependent compressive aggregate modulus (Chen and Sah, 1999; Schinagl et al., 1997; Wang and Mow, 1998) into the biphasic model (e.g., Mow et al., 1980). Prior to these studies, few analytical studies were available in the literature that included a tissue inhomogeneity in compression and the deformational behavior of chondrocytes under loading (Gore et al., 1983; Guilak, 1995; Guilak et al., 1990, 1995, 1997, Schinagl et al., 1996; Schinagl et al., 1997; Wang et al., 2000). Previous investigators have quantified inhomogenous matrix properties of cartilage using discrete-layered (i.e., layerwise-discontinuous) modeling (Schinagl et al., 1997; Askew and Mow, 1978; Eberhardt et al., 1991). In view of the available data on the displacement field within cartilage (Schinagl et al., 1996; Schinagl et al., 1997), we adopt a continuously distributed approach to the inhomogeneity of the matrix.

Nomenclature

- $h$: initial cartilage thickness
- $H_{A0}$: modulus under zero strain (material parameter for finite deformation theory)
- $H_{A_{app}}$: apparent aggregate modulus under infinitesimal strain
- $I$: identity tensor
- $k$: cartilage permeability function
- $k_0$: cartilage permeability under zero strain (material parameter for finite deformation theory)
- $K$: cartilage diffusive drag constant
- $M$: non-linear permeability coefficient (material parameter for finite deformation theory)
- $p$: cartilage interstitial fluid pressure
- $t, t_0$: time variable and constant
- $U_e$: distribution function of equilibrium displacement
- $u$: axial solid matrix deformation in the material reference frame
- $v_s, v_f$: solid and fluid phase velocities
- $v_0$: ramp speed for a stress-relaxation test
- $Z$: axial coordinate
- $\beta$: compressive-stiffening coefficient (non-dimensional material parameter for finite deformation theory)
- $\phi_0$: solid content under zero strain (initial porosity)
- $\phi_s, \phi_f$: solid and fluid contents, $\phi_s + \phi_f = 1$
- $\lambda$: solid matrix stretch
- $\lambda_e$: solid matrix stretch at equilibrium
- $\pi$: momentum exchange force
- $\sigma_{app}$: applied stress
- $\sigma_e$: elastic stress
- $\sigma_{equilibrium}$: equilibrium total stress in a stress-relaxation test
- $\sigma^s, \sigma^f$: solid and fluid stresses
- $\sigma^t$: total stress ($\sigma^t = \sigma^s + \sigma^f$)

3 For the effects of proteoglycan charges and dissolved electrolytes on mechanoelectrochemical effects, the reader is referred to Lai et al. (1991), Gu et al. (1998) and Mow et al. (1998).
compressive aggregate modulus (Wang and Mow, 1998) in our description of cartilage inhomogeneity using biphasic theory.

2. An inhomogeneous finite deformation biphasic model

For a tissue with continuous distribution of inhomogeneous compressive aggregate modulus, a region of local low aggregate modulus may result in finite deformation in the corresponding region during loading. Thus, in the present study, a finite deformation formulation will be employed, using the constitutive laws developed by Holmes and Mow (1990). Under one-dimensional (1D) confined compression conditions, the axial stress-stretch law can be derived as

$$\sigma_{zz} = \frac{1}{2} H_{A0} \frac{\lambda^2}{\beta - 1} \exp(\beta (\lambda^2 - 1)), \quad (1)$$

where $H_{A0}$ represents the aggregate modulus, $\beta$ is the kinematic compressive-stiffening coefficient which measures the sensitivity of $\sigma^e$ to large strains (Ateshian et al., 1997), and the stretch $\lambda = 1 + \frac{\partial u}{\partial Z}$, where $u(Z,t)$ is the axial deformation expressed in a material (Lagrangian) reference frame, and $Z$ is the axial material coordinate. Thus, the governing equations for finite deformation of the tissue can be simplified to the following 1D non-linear partial differential equation:

$$\frac{\partial u}{\partial t} = \frac{k}{\lambda^2 Z} \exp(\beta (\lambda^2 - 1)) \lambda^2, \quad (2)$$

In finite deformation, large strains can significantly alter the tissue porosity. In this 1D confined compression case, the solid and fluid fractions and the permeability are related to the stretch ($\lambda$) such that

$$\phi^s = \frac{\phi_0}{\lambda^\beta}, \quad (3a)$$

$$\phi^f = 1 - \frac{\phi_0}{\lambda^\beta}, \quad (3b)$$

$$k = k_0 \left( \frac{\phi_0^s \phi_0^f}{(1 - \phi_0^s)} \right)^2 \exp(1/2M (\lambda^2 - 1)), \quad (3c)$$

where $\phi_0^s$ and $k_0$ are the porosity and permeability of the tissue in the initial uncompressed state, and $M$ is the non-dimensional permeability coefficient weighting the exponential functional dependence on strain (Ateshian et al., 1997; Lai and Mow, 1980).

Note that Eq. (2) has been derived with no assumptions made on tissue homogeneity. Thus, Eq. (2) can be used, in a 1D confined compression problem, to study the effects of one or any combination of inhomogeneously distributed material properties ($H_{A0}$, $K_0$, $M$ and/or $\beta$). Limited by the existing information on inhomogeneities of other cartilage properties, we have included only the effects of inhomogeneous $H_{A0}$ in this study, considering all other material properties constant (i.e., homogeneous) (Fig. 1). For a brief description of effects of other inhomogeneities, the reader is referred to Mow and Wang (1999). In the confined compression test, both stress-relaxation and creep studies can be performed depending on the nature of load applied to the explant (Fig. 2). For brevity, in this paper, only the stress-relaxation test configuration was analyzed. Since the tissue is sitting against an impermeable platen ($Z = h$) while being compressed through a porous platen (Fig. 2), the boundary conditions are:

$$u(h,t) = 0, \quad (4a)$$

$$u(0,t) = U_0(t), \quad (4b)$$

where $h$ is the initial thickness of cartilage, $U_0(t)$ is a prescribed surface displacement as a function of time; in
Fig. 2. Diagram of 1D confined compression experiment used for the stress-relaxation and creep experiments; the material coordinate \( Z = 0 \) defines the loading surface, and \( Z = h \) defines the interface between the confining chamber and the specimen. The figures at right define the loading configuration of a ramp-displacement stress-relaxation test, and a Heaviside load creep test.

Finally, to have a complete formulation of this initial-boundary value problem, the initial condition for Eq. (2) is \( u(Z,0) = 0 \).

This system of partial differential equations is solved numerically by a finite difference method. Central difference discretization in space and backward discretization in time were used to yield an implicit scheme for the displacement variable \( u \). The resulting non-linear tridiagonal system of equations was solved at each time step using the Newton–Raphson method.

3. Inhomogeneous aggregate modulus

Schinagl et al. (1996) described an optical fluorescence method to quantify the displacement field within an articular cartilage specimen, using chondrocytes as fiducial markers for displacements, at an equilibrium state under confined compression. In this study, they reported displacement results from specimens that included only the upper part of the cartilage (500 \( \mu \)m), and did not measure the compressive load. In a follow up study, Schinagl and co-workers (1997) presented a layerwise discontinuous-distribution of compressive moduli for their full thickness cartilage samples using compressive loads specified for some “peer” specimens. In our present study, rather than approximating the material properties with a layerwise discontinuous distribution of values for the aggregate modulus, we found that by using Eq. (1) and the results of the displacement field from Schinagl et al. (1997), a continuous-distribution of aggregate modulus throughout the entire depth of the specimen could be determined for a prescribed applied load (Wang and Mow, 1998).

For more details of the method used for these calculations, the reader is referred to the references by Ateshian et al. (1997), and Sun et al. (1999).

\[
U_0(t) = \begin{cases} 
  v_0 t, & 0 \leq t \leq t_0, \\
  v_0 t_0, & t > t_0. 
\end{cases} \quad (5)
\]
To accomplish this, the displacement fields were first curve-fitted to a third-order polynomial of $Z$ ($U_s(Z)$, or any appropriate function) with an origin placed on the articular surface. The result for a third-order polynomial representation of a single displacement data set (32% compression of a cartilage explant) of Schinagl et al. (1997) is given in Fig. 3a. From the axial stress-stretch law given by Eq. (1), the inhomogeneous aggregate modulus $H_{A0}$ can be calculated as follows:

$$H_{A0}(Z) = 2\sigma_{app} \frac{\lambda_2 \beta + 1}{\lambda_2 - 1} e^{-c(\lambda_2 - 1)} \frac{dU_s(Z)}{dZ},$$

(6)

where $\sigma_{app}$ is the applied stress, and $\lambda_s = 1 + dU_s(Z)/dZ$, is the equilibrium axial stretch within the tissue. The profile of aggregate modulus calculated from the displacement field of Fig. 3a is shown in Fig. 3b.

4. Results

The following material properties associated with the third-order polynomial aggregate modulus were used in our numerical analysis of the stress-relaxation phenomenon: $k_0 = 7.6 \times 10^{-15} \text{m}^2/\text{N}s$, $M = 2.2$, $\beta = 0.35$, $\phi_0 = 0.25$; $h = 1.5 \text{mm}$ (Ateshian et al., 1997; Mow et al., 1980). For the stress-relaxation test the ramp speed has been specified to be $t_0 = 0.375 \mu\text{m}/\text{s}$, and the duration of ramp to be $t_0 = 400 \text{s}$. All the results for an inhomogeneous tissue are presented in comparison with the results for an “equivalent” homogeneous tissue with an apparent aggregate modulus. The “equivalence” between homogeneous and inhomogeneous tissues is defined such that both tissues, which have the same values for all the material properties except aggregate modulus, should achieve the same equilibrium stress in the stress-relaxation test.

To examine how an intrinsically inhomogeneous compressive modulus might have influenced the compressive strain and interstitial fluid flow occurring within the tissue, the inhomogeneous continuous distribution of compressive modulus used in this study, Fig. 3b, shows a nearly 20-fold difference between the surface zone and the deep zone. The difference in the transient load-history response in the stress-relaxation problem between the homogeneous case and that of the inhomogeneous case is shown in Fig. 4. There is a noticeable difference between the two cases in the stress response during the ramp phase of the stress-relaxation problem. Minor differences are seen in the relaxation phase, and no differences are noted at equilibrium (by definition). Clearly, from Fig. 4, one is not able to delineate between the effect of inhomogeneity of the aggregate modulus and that of other factors (e.g., strain-dependent permeability). In other words, from a single surface-to-surface measurement, it is not possible to determine the variation of inhomogeneity of the tissue. However, it must be emphasized that within the tissue, where chondrocytes reside, the stress, strain, flow and pressure fields are significantly affected by the inhomogeneous aggregate modulus.

The strain distributions within the tissues for both the homogeneous and inhomogeneous cases, at three different time points (200 s = half way through the ramp period, 400 s = beginning of the stress relaxation phase, 1000 s = equilibrium) are shown in Fig. 5. Clearly, the inhomogeneous tissue can no longer achieve a uniform equilibrium strain state through the depth as it does in a homogeneous tissue ($t = 1000 \text{s}$). This should be quite obvious and is dictated by the theoretical formulation of the problem. The surface zone of the inhomogeneous tissue, with its very low compressive modulus, has the highest level of strain that can reach nearly 50%. Thus, under the porous-permeable loading platen, for such inhomogeneous tissues in a typically loaded explant experiment, the volume change per unit volume can be as high as 50% during the ramp loading phase. The deep zone, however, experiences only low strains ($< 10\%$). Thus these calculations show that a finite deformation.

![Fig. 4. The total stress ($\sigma^t = \sigma^t + \sigma^e$) responses of the inhomogeneous and homogeneous tissues defined in Fig 3b. Note that the equilibrium values of both cases are identical because of the definition of the equivalency.](image)

![Fig. 5. Calculated strain distributions inside the sample at three different times (200, 400, 1000 s). Note that the ramp time $t_0 = 400 \text{s}$, $Z = 0$ corresponds to the loading surface.](image)
theory such as those employed by Ateshian et al. (1997) must be used to accurately determine the deformational fields in these explant experiments. Note that the variability of the mechanical environments of chondrocytes within the ECM is greatly accentuated for inhomogeneous tissues, Figs. 5–6.

The compressive stress acting on the ECM throughout the homogeneous and inhomogeneous tissues vary with depth and time, Fig. 6. The fluid pressure throughout the homogeneous and inhomogeneous tissues also varies with depth and time, Fig. 7. For both the solid matrix stress and fluid pressure, the inhomogeneous aggregate modulus accentuates the depth and time dependence of these two important field variables. Note that at equilibrium (assumed to be $t = 1000\text{s}$), Fig. 7 shows that the fluid pressure vanishes, and Fig. 6 shows that the solid matrix stress is a constant for both the homogeneous and inhomogeneous cases; moreover, that equilibrium stress ($t = 1000\text{s}$) must equal the applied stress ($\sigma_{\text{Equilibrium}}$, a constant). Indeed, Eqs. (4a), (4b) and (5) state that, after equilibrium, the total stress ($\sigma' = \sigma + \sigma_f$) at any level of the tissue ($Z = \text{constant}$) must be a constant that equals $\sigma_{\text{Equilibrium}}$. However, before equilibrium is reached, i.e., during the transient phase, the total load support provided by the solid matrix and the fluid pressure must be partitioned between the solid matrix and the fluid phase. From Figs. 6 and 7, it can be seen that prior to equilibrium, the net effect of the tissue inhomogeneity is to relieve the solid matrix stress and increase the fluid pressure. This effect, which can be observed to progress from the articular surface to the deeper zones as the compression increases during the ramp period, can have major ramifications for chondrocytes residing within the tissue, and therefore on the interpretation of the mechano-signal transduction mechanisms occurring within an explant during loading (Mow et al., 1999). Due to the non-linear strain-dependent permeability effect, Eq. (3c), the severe matrix compaction near the surface (Fig. 5) would dramatically decrease the permeability in this zone (Lai and Mow, 1980). This would make it even more difficult for the interstitial fluid to flow through the surface region of the ECM. By the law of conservation of mass, and the imposed displacement ramp at the surface, Eq. (5), there will always be a surface exudation during the ramp phase ($t < 400\text{s}$), Fig. 8. This forced interstitial fluid flow and efflux is a requisite of interstitial fluid pressure. By virtue of the inhomogeneous aggregate modulus, Fig. 3b, there is not only a greater compaction in the surface zone, Fig. 5, but also greater fluid pressure and fluid flow in the sub-surface region. The greater efflux during the ramp period at the surface ($Z/h \approx 0$) for the inhomogeneous case, Fig. 8, results from the greater compaction and thus greater changes in $\phi'$ and $\phi_f$. Also, as a result of the inhomogeneity, fluid flow in the deeper zone of the tissue (lower 50%) is more uniform, and hence this zone experiences a slightly more uniform stress and pressure state than that of a homogeneous tissue (Figs. 6–8).

Finally, the total stress response of the same tissue disk loaded axially from two different directions (e.g., I and II; Fig 9, left-hand side) can be quite different (Fig. 9, right-hand side). This difference can be directly attributed to
the asymmetric, inhomogeneous aggregate modulus distribution through the depth that has been obtained optically (Schinagl et al., 1997). In other words, the matrix inhomogeneity would be expected to give rise to disparate transient stress-relaxation responses for the disk when loaded in directions I and II, Fig. 9. Thus, this bi-directional loading protocol can presumably provide a new and independent method to test the hypothesis that tissue inhomogeneity exists within articular cartilage.

5. Discussion

Over the past 25 years, the stress-relaxation experiment has been performed on articular cartilage thousands of times to test the biphasic hypothesis for articular cartilage using a constant aggregate modulus, i.e., homogeneous. In all such experiments, the only measurable data are those obtained from the specimen surface, e.g., the applied load and the surface displacement. It is impractical, if not impossible, to extract an inhomogeneous material property (determined as its distribution through the depth) from this approach. Thus, only apparent (i.e., homogeneous) material properties can be extracted. While one can cut a cartilage specimen into thin strips to be used in biomechanical tests (Akizuki et al., 1986; Chang et al., 1999; Kempson, 1979; Roth and Mow, 1980; Woo et al., 1976), this method of measuring material properties still relies on data gathered from the surface of the specimen. Historically, such tests have been usually performed in tension and the tissue is represented by a discontinuous layer model. Models based on such discretized data (e.g., Chen and Sah, 1999; Schinagl et al., 1997) still constitute another approximation of the true variation of the material properties throughout the depth as would have been suggested by the tissue’s morphology (e.g. Clarke, 1971).

The results presented in this study show that the need to incorporate an inhomogeneous aggregate modulus, or an anisotropy, into the biphasic theory to describe articular cartilage depends largely on what one wishes to extract from these studies. For example, when taking only surface-to-surface measurements to determine the apparent aggregate modulus at equilibrium (i.e., t = 1000 s), the inhomogeneous tissue does not show any difference in its response when compared to a model with a homogeneous aggregate modulus (Fig. 4). The tissue thus can be approximated to be homogeneous, and an apparent aggregate modulus can be used for surface-to-surface measurements. Under some other situations, e.g., when precise mechanical loading of chondrocytes within the ECM is sought, the results of the present study show that material inhomogeneity should be considered to accurately determine the stress, strain, flow and pressure fields around the chondrocytes in situ. Since it is unclear to which temporal or spatially varying stimuli that chondrocytes are responding to in situ (e.g. stress, strain, fluid and pressure fields), it is therefore vital to quantify all those physical stimuli in situ wherever they (i.e., the chondrocytes) may exists. The choice of the most efficacious articular cartilage model (homogeneous or inhomogeneous) for a chondrocyte mechnotransduction study also depends on the question or the scientific goal. Edge-to-edge measurements may be sufficient when performing explant loading studies that reflect gross cell activities averaged over all the cells in the entire tissue specimen, e.g., GAG assay of the culture medium. In contrast, constitutive models of cartilage that can provide potentially better models or predictions of the cell environment (such as the current model) could be applied when using assays able to resolve spatially varying cell
metabolic responses, such as new cell-length scale quantitative autoradiography (e.g., Quinn et al., 1998) and other high-resolution techniques (Buschmann et al., 1999; Wong et al., 1997). In other words, superposition of the predicted mechanical environment with information of the spatial distribution of biosynthetic responses in the tissue can yield correlative information between stimulus and cell metabolic activity. Together, a further understanding of the local tissue structure–function relationship and chondrocyte mechanotransduction can be obtained. Moreover, the numerical predictions and biochemical findings can be used to generate specific hypotheses that can be tested in other experiments.

The degree of tissue inhomogeneity is likely to be influenced by several factors, including species, age, pathology and cellularity. The data of Schinagl et al. (1997) adopted for the inhomogeneous biphasic model used in this study was obtained from articular cartilage harvested from the patellofemoral groove of adult (2–3 year-old) bovine knee joints. Interspecies differences in cartilage biomechanical properties have been previously reported (Athanasiou et al., 1991). Interestingly, Shin et al. (1998), reported markedly less depth-dependent variability of aggregate modulus using a tissue indentation technique and mature rabbit cartilage. In contrast, Chen et al. (1999) demonstrated dramatic inhomogeneity in old human hip joint cartilage using confined compression. Predictions using our continuously distributed aggregate modulus model show no significant difference in the tissue's surface-to-surface stress response, but significant changes in the mechanical environment within some regions of the ECM when this inhomogeneous aggregate modulus is used (Figs. 5–8).

Consistent with the finding of depth-dependent aggregate modulus (Schinagl et al., 1996; Schinagl et al., 1997; Shin et al., 1998), Guilak et al. (1994), using confocal microscopy studies of loaded cartilage explants, have shown that cell deformation in the various zones are different, being greatest in the superficial zone. With respect to the interpretation of cartilage explant loading studies, the role of an inhomogeneous matrix is further complicated by the fact that the zonal subpopulation of cell within cartilage that are distinct in terms of their biosynthetic activities and morphology (Aydelotte et al., 1992). This fact is corroborated by mechanical loading studies of chondrocytes suspended in agarose (a homogeneous matrix) which have revealed differential responses in cells derived from the various zones of cartilage (e.g., Lee and Bader, 1997). In order to study the biomechanics of cell–matrix interactions, some investigations have considered cells embedded in a homogeneous, single-phase elastic or biphasic ECM (Bachrach et al., 1996; Guilak and Mow, 1999; Jain et al., 1990; Wu et al., 1999). Similarly, the method presented in this study can be expanded to include chondrocytes within an inhomogeneous ECM to determine effects of such depth-dependent material properties.

In conclusion, the new data on tissue biomechanical inhomogeneities offer new opportunities for further studies on cartilage biomechanics and biology. It also provides new avenues to further test the biphasic hypothesis for articular cartilage, and new ways to interpret the data that are now pouring forth from cartilage explant experiments, worldwide. The results from this study have presented an example on how to incorporate such inhomogeneities for the modeling of cartilage biomechanical studies. In view of the findings of this study, the question arises whether it is important to design tissue engineered cartilage substitutes that possess the apparent properties of the natural tissue or one that mimics the inhomogeneous properties, whereas the former maybe sufficient from a functional load-bearing point of view, it may not adequately reproduced the chondrocyte milieu in vivo so as to sustain their normal cartilage maintenance activities.

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