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A New Constitutive Model for Hydration-Dependent Mechanical Properties in Biological Soft Tissues and Hydrogels

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Abstract

It is challenging to noninvasively determine the mechanical properties of biological soft tissues in vivo. In this study, based on the biphasic theory and the transport models, a new constitutive model for hydration-dependent mechanical properties in hydrated soft materials was derived: $H_A = A(1-\phi^f)^n(\phi^f)^{2-n}/(2-\phi^f)^2$, where $H_A = \lambda + 2\mu$ is the aggregate modulus, ϕ^f is the volume fraction of fluid (i.e., hydration), A and n (>2) are two parameters related to the transport properties of the biphasic materials. A linear model for hydration-dependent shear modulus in the literature was verified for hydrogels. The effects of tissue hydration on mechanical properties (aggregate modulus and Poisson's ratio) were investigated. It was found that the value of Poisson's ratio was very sensitive to the tissue hydration in soft materials with high water content. The predictions of the aggregate modulus and shear modulus for hydrogels by the model compared well with those from experimental results. This study is important for developing new techniques for noninvasively assessing the mechanical properties of biological soft tissues using quantitative MRI methods as well as for designing scaffolds with proper mechanical properties for tissue engineering applications.

Keywords

Soft materials; Cartilage; Agarose gel; Water content; Water diffusivity; Aggregate modulus; Shear modulus; Poisson's ratio

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Introduction

The mechanical and transport properties of biological soft tissues and hydrogels play an important role in governing the extracellular environment (e.g., stress, strain, and nutrition distributions) in such materials, and the knowledge of these properties are important for understanding tissue growth and degeneration, or designing scaffolds with hydrogels for tissue engineering applications.

Numerous experiments have been conducted on studying the mechanical properties of soft tissues and hydrogels. It has been reported that the effective mechanical properties of the porous materials are dependent on the composition of the solid matrix and the deformation (Armstrong and Mow, 1982; Best et al., 1994; Hu et al., 2012; Li et al., 2003; Watase and Nishinari, 1983). Armstrong and Mow found a strong correlation between the equilibrium modulus and water content in cartilage tissues. Their results showed that the equilibrium modulus increases with the decrease in water content (Armstrong and Mow, 1982). In other soft tissues, such as annulus fibrosus and cornea, this correlation has also been found (Hatami-Marbini and Etebu, 2013; Klisch and Lotz, 2000). The dependence of mechanical properties on water content has been reported in agarose gels as well (Gu et al., 2003; Normand et al., 2000). The mechanical properties of both soft tissues and hydrogels also show to be dependent on the deformation (Chahine et al., 2004; Chen et al., 2001; Stammen et al., 2001). This may be partially due to the change of water content caused by deformation (Lai et al., 1991; Mow et al., 1980). It may be also due to the intrinsic nonlinear mechanical behaviors of these materials (Iatridis et al., 1998).

It has been found experimentally that the mechanical properties of these materials are correlated with the transport properties (Aoki et al., 2012; Evans and Quinn, 2005), since both the mechanical and transport properties of porous materials are dependent on material composition and structure (Armstrong and Mow, 1982; Best et al., 1994; Hu et al., 2012; Julkunen et al., 2008; Mow et al., 1984; Roberts et al., 1996; Williamson et al., 2001). Evans and Quinn showed that an increase in Young’s modulus is correlated with the decrease of solute diffusivities in articular cartilage and cartilage-like materials (Evans and Quinn, 2005). The emerging quantitative magnetic resonance imaging (MRI) techniques have been used to probe the transport properties and water content of biological tissues (Chiu et al., 2001; Edelman et al., 1994; Kerttula et al., 2001; Kerttula et al., 2000; Liess et al., 2002; Xia et al., 1994). However, the noninvasive determination of the mechanical properties in biological tissues is very challenging.

Many constitutive models have been proposed for the hydraulic permeability and solute diffusivity in porous tissues and hydrogels (Clague et al., 2000; Ehlers and Markert, 2001; Gu et al., 2003; Holmes and Mow, 1990; Lai and Mow, 1980). For example, Gu et al. proposed an empirical model for hydraulic permeability in agarose gels. This model works well for cartilage and agarose gels with a wide range of water content (Gu et al., 2003). Many constitutive models have been developed for solute diffusivity in hydrated porous materials as well (Masaro and Zhu, 1999). One of them is the well-known Mackie and Meares’ model. In this model, the ratio of solute diffusivity in tissue to that in aqueous solution, i.e., the relative solute diffusivity, is a function of volume fraction of fluid (i.e.,

hydration) only (Mackie and Meares, 1955). This model was developed for small solutes only because the effect of solute size has not been taken into consideration. Gu et al. proposed a model for the spherical solutes in biological tissues and hydrogels. In this model, the diffusivity is an exponential function of the ratio of the solute size to the square root of intrinsic Darcy Permeability of tissue (Gu et al., 2004). This model is able to predict the diffusivity of the molecules in agarose gels and in the porcine annulus fibrous tissues (Gu et al., 2004).

Theoretical and empirical constitutive models have been developed for porous elastic, hyperelastic, and viscoplastic materials, such as ceramics and elastomeric foam, to study the porosity-dependent mechanical properties (Agoras and Castaneda, 2014; Danielsson et al., 2004; Poutet et al., 1996; Roberts and Garboczi, 2000). However, these models were proposed for the rigid and low porosity materials which may be not capable for predicting the hydration-dependent mechanical properties in biological soft tissues and hydrogels. For example, Danielsson *et al.* developed a constitutive model for a porous hyperelastic material based on the micromechanics framework. They assumed that the porous material was represented as a thick-walled sphere and the pores were not openly connected with each other (Danielsson et al., 2004). This theoretical model may be not suitable for biological soft tissues and hydrogels since the pores in these materials are openly connected.

Therefore, the objective of the present work was to theoretically develop a new constitutive model for hydration-dependent mechanical properties for biological soft tissues and hydrogels. This study is important for developing a new technique for noninvasively assessing the mechanical properties of biological soft tissues using quantitative imaging methods as well as for designing scaffolds with proper mechanical properties for tissue engineering applications.

Method

A hydrated porous material (such as biological soft tissues and hydrogels) may be modeled as a biphasic mixture consisting of a porous solid phase and an interstitial fluid phase (Mow et al., 1980). Both phases are assumed to be intrinsically incompressible, but the volume of the whole mixture may be changed due to the fluid inflowing in or exuding out of the mixture. Each phase α ($\alpha = s$ for the solid phase and $\alpha = f$ for the fluid phase) has a volume fraction φ^{α}, and the mixture is assumed to be saturated (i.e., $\varphi^{s} + \varphi^{f} = 1$). Therefore, the continuity equation for the mixture reduces to (Ateshian, 2007; Gu et al., 1998; Lai et al., 1991; Mow et al., 1980)

$$\nabla \cdot (\phi^{f} \mathbf{v}^{f} + \phi^{s} \mathbf{v}^{s}) = 0, \quad (1)$$

where $\mathbf{v}^{\alpha}$ is the velocity of phase α. Neglecting the body force and inertia, the conservation of momentum for the mixture at the quasi-static condition states:

$$\nabla \cdot \boldsymbol{\sigma} = \mathbf{0}, \quad (2)$$

where $\boldsymbol{\sigma}$ is the Cauchy stress for the mixture. For an isotropic mixture with linear elastic solid phase with infinitesimal deformation, the total stress of the mixture may be written as (Mow et al., 1980)

$$\boldsymbol{\sigma}=-p\mathbf{I}+\lambda(\nabla\cdot\mathbf{u})\mathbf{I}+\mu[\nabla\mathbf{u}+(\nabla\mathbf{u})^T], \quad (3)$$

where p is the fluid pressure, λ and μ are the Lamé constants, and $\mathbf{u}$ is the displacement. A fluid volume flux (relative to the solid phase) is defined as $\mathbf{J}^f = \phi^f(\mathbf{v}^f - \mathbf{v}^s)$ and is related to fluid pressure p by Darcy's law:

$$\mathbf{J}^f=-k\nabla p, \quad (4)$$

where k is the hydraulic permeability. Using Eqs. (1), (3) and (4), together with the saturation assumption, one can derive that

$$\frac{\partial e}{\partial t}=H_A k\nabla^2 e, \quad (5)$$

where $H_A = \lambda + 2\mu$ is the aggregate modulus (Mow et al., 1980), and $e = \nabla\cdot\mathbf{u}$ is the dilatation of the mixture. With the assumption of infinitesimal deformation, the volume fraction of fluid is a linear function of e with $\phi^f=\phi_r^f+(1-\phi_r^f)e$ (Gu et al., 1998; Lai et al., 1991), where ϕ_r^f is the fluid volume fraction in the reference state. Thus, Eq. (5) can be written (in terms of variable ϕ^f) as

$$\frac{\partial\phi^f}{\partial t}=D\nabla^2\phi^f, \quad (6)$$

where

$$D=H_A k. \quad (7)$$

Equations (5) and (6) are both in the form of diffusion equation. D is the mutual diffusivity of fluid (water) in the biphasic mixture with intrinsically incompressible constituents (see Appendix), and it is also known as the cooperative diffusivity (Tanaka and Fillmore, 1979) or water diffusivity (Hu et al., 2012) in the literature.

For the biphasic materials with intrinsically incompressible solid and fluid phases, the following constraints must be satisfied:

$$\lim_{\phi^f\to 0} k=0,\ \lim_{\phi^f\to 0} H_A=+\infty,\ \lim_{\phi^f\to 0} D=0, \quad (8)$$

$$\lim_{\phi^f\to 1} k=+\infty,\ \lim_{\phi^f\to 1} H_A=0,\ \lim_{\phi^f\to 1} D=D_0, \quad (9)$$

where D_0 is the diffusivity of fluid in the aqueous solution. For example, the value of water self-diffusion coefficient in pure water is 2.3×10^{-9} m^2/s at 25 °C (Holz et al., 2000).

The dependence of hydraulic permeability on water content for biological soft tissues and hydrogels may be expressed as (Gu et al., 2003)

$$k=a\left(\frac{\phi^f}{1-\phi^f}\right)^n, \quad (10)$$

where a and n are two material parameters of the material. It has been shown that this model works well for predicting the hydraulic permeability of biological tissues and agarose gels over a wide range of hydration from ~0.7 to ~0.98 (Gu and Yao, 2003; Gu et al., 2003).

In this study, we adopted the Mackie and Meares model (Knauss et al., 1999; Mackie and Meares, 1955) to estimate the water mutual diffusivity, which is given by the following equation:

$$\frac{D}{D_0}=\left(\frac{1-\phi^s}{1+\phi^s}\right)^2=\left(\frac{\phi^f}{2-\phi^f}\right)^2. \quad (11)$$

Knauss et al. showed that this model could satisfactorily predict the results of water self-diffusion coefficient in cartilage and cartilage components over a wide range of hydration from ~0.4 to ~0.95 (Knauss et al., 1999). From Eqs. (7), (10), and (11), the constitutive model for the hydration-dependent aggregate modulus can be obtained:

$$H_A=A\frac{(1-\phi^f)^n}{(2-\phi^f)^2}(\phi^f)^{2-n}, (\mathrm{n}>2) \quad (12)$$

where $A = D_0/a$. Note that Eq. (12) satisfies the constraints descripted in Eqs. (8) and (9) when the value of n is greater than 2.

The aggregate modulus is a linear combination of two Lame constants. In order to explicitly separate the Lamé constants from the aggregate modulus, we adopted the following model for the second Lame constant (i.e., shear modulus) in the literature (Danielsson et al., 2004):

$$\mu=\mu_0(1-\phi^f), \quad (13)$$

where μ_0 is a parameter which represents the shear modulus of the solid without pores.

Using the constitutive models for the aggregate modulus and shear modulus, i.e., Eqs. (12) and (13), one can determine the dependence of Poisson's ratio (υ) of the mixture on water content, by

$$\upsilon=\frac{H_A-2\mu}{2(H_A-\mu)}. \quad (14)$$

Results

In these constitutive relations for k, H_A, and μ, there are three unknown parameters a, n, and μ_0. The values of these parameters can be determined by experiments.

For agarose gels with concentration in the range of 2–14.8% (w/w), and the corresponding water content is in the range of ~0.98–0.88, the values of material parameters a and n are: $a = 3.39\times10^{-18}$ m^4/(Ns) and n =3.236 (Gu et al., 2003). For this type of materials, the variation of aggregate modulus H_A with water content is presented in Fig. 1. It was shown that our theoretically calculated aggregate modulus decreases nonlinearly with increasing hydration of the tissue. The experimental data of H_A for agarose gels, obtained from our previous study (Gu et al., 2003), are also plotted in Fig. 1 for comparison.

Hu et al. characterized the shear modulus of pH-sensitive hydrogels at different swelling conditions using an unconfined stress relaxation test (Hu et al., 2012). Based on the reported swelling ratio [$\theta = (1 - \phi^f)^{-1/3}$], the hydration ($\phi^f$) of their hydrogels was converted, and found to be in the range from ~0.94 to ~0.88. Least-squared curve-fitting of the shear modulus of hydrogels to the model [i.e., Eq. (14)] yielded μ_0 =120.65 kPa (R^2=0.97) and μ_0 =117.53kPa (R^2=0.88) for two different compositions of poly (DMAEMA-co-AAm) hydrogels (Fig. 2). The linear shear model, i.e., Eq. (13), is verified for highly hydrated soft materials.

The constitutive relationship between the Poisson's ratio and water content (Eq. 14) is shown in Fig. 3. Various values of material parameter μ_0 are used to show this hydration-dependent Poisson's ratio. It is shown that the Poisson's ratio approaches to 0.5 as hydration is lower than 0.7. The Poisson's ratio decreases with increasing hydration slightly in the range of ~0.7–0.85, and dramatically in the range of ~0.85–0.95.

Discussion

Equation (7) can be written as

$$D=\frac{k'}{\eta}H_A \quad (15)$$

where k' is the Darcy permeability and η is the viscosity of fluid (e.g., water). The value of Darcy permeability k' represents the characteristic area of the pores in solid matrix (Gu et al., 2004). Equation (15) indicates that the value of water diffusivity is proportional to the area available for water diffusion, and proportional to the stiffness of the solid matrix, but inversely proportional to the interactions among water molecules (viscosity). This is because, at the microscopic level, the larger the pore size, the lower the probability for the water molecules to collide on the solid matrix, thus the longer the mean distance that water molecules could travel. When it collides with the solid matrix, the water molecule will lose its momentum or kinetic energy. The loss of momentum or kinetic energy of water molecules during the collision would be less if the stiffness of the solid matrix is higher.

Therefore, at the macroscopic level, the water diffusivity is related to the permeability and aggregate modulus of a biphasic material.

The mechanical properties and transport properties are related in hydrated materials (Eq. 7). That is, the diffusivity of water in these materials is related to the hydraulic permeability and the aggregate modulus if the material consists of intrinsically incompressible solid and fluid phases. Equation (7) indicates that it is unrealistic to have an isotropic hydrated material with both high stiffness and hydraulic permeability since the product of aggregate modulus and hydraulic permeability has an upper limit, which is equal to the value of water diffusivity (Fig. 4). Understanding this limit is important for choosing a scaffold for in-vitro engineering avascular tissues such as cartilage. For example, if an isotropic scaffold with high porosity is desired for the transport of nutrients, the material must be soft, not suitable for load support.

Compared with hydrogels, biological tissues usually have more complicated composition and microstructure. For example, articular cartilage has been shown as an anisotropic material with reinforced collagen fibers embedded in the isotropic matrix (Mow and Guo, 2002). The experimental results of aggregate modulus (H_A) and hydraulic permeability (k) for human and animal cartilage tissues (at the macroscopic level) have been reported (Athanasiou et al., 1994; Athanasiou et al., 1991; Froimson et al., 1997; Mow et al., 1989). We found that the values of H_Ak are smaller than the value of D_0 for most cases, where D_0 is the water self-diffusivity in pure water, i.e., the upper limit for H_Ak (Fig. 4). We also found that the values of H_Ak are close to the values of water diffusivity predicted by Eq. (11) with ϕ^f in the range from ~0.7 to 0.8 (Figs. 4 and 5). This range of hydration is consistent with the experimental results for cartilage (Mow and Guo, 2002; Mow et al., 1984). These results indicate that Eqs. (7) and (11) can be used for the material properties of cartilage determined at the macroscopic level. Note that the values of cartilage material properties at the macroscopic level are different from those determined by nanoindentation tests (Oyen et al., 2012).

With quantitative MRI techniques or nuclear magnetic resonance (NMR) method, one could measure the water content and diffusion coefficient in hydrated soft tissues such as articular cartilage and intervertebral disc (Chiu et al., 2001; Kerttula et al., 2001; Kerttula et al., 2000; Liess et al., 2002; Xia et al., 1994). Equations (12) and (13) can be used to noninvasively determine the mechanical properties of biological soft tissues in vivo if the values of material parameters in Eqs. (12) and (13) are known. Conversely, if the relationship between aggregate modulus and water content is known, one could noninvasively determine the hydraulic permeability of soft tissues using Eq. (7) by measuring water diffusivity using quantitative MRI techniques.

The Mackie and Meares' model was originally developed for ion diffusion in gels by assuming that the polymer network acts as a rigid sieve which is not permeable to the solute or solvent. The motionless polymer chains increase the movement path length of the solute and solvent (Mackie and Meares, 1955; Masaro and Zhu, 1999). Therefore, this model may be more suitable to predict the self-diffusion coefficient (diffusivity under zero chemical potential gradient) of water rather than the mutual diffusion coefficient.

To our knowledge, there is no theoretical model for the mutual diffusivity of water in biological tissues and hydrogels. In this study, we adopted the Mackie and Meares' model to estimate the mutual diffusivity of water in biological soft tissues and hydrogels. The water diffusivity in the agarose gel and cartilage measured by the NMR method is believed to be the self-diffusion coefficient of water, which can be predicted by the Mackie and Meares' model (Fig. 5). The values of $H_A k$ for agarose gels determined by confined compression creep test are about 50% of the predicted values (Fig. 5). But, interestingly, the values of $H_A k$ in cartilage determined with indentation tests (Froimson et al., 1997) are close to the predicted values, see Fig. 5. These may be explained by the different methods used to determine the water diffusivity and the values of H_A and k. For example, it has been reported that the elastic modulus for cartilage obtained from the indentation test is about 30–79% higher than the value determined by confined and unconfined compression creep tests (Korhonen et al., 2002).

In this study, we derived a hydration-dependent equilibrium Poisson's ratio model for agarose gels. The Poisson's ratio for the gels approaches 0.5 as the hydration becomes lower than 0.7. This means that the gel is almost incompressible at low hydrated condition, which is consistent with the incompressible assumption of the solid phase. For gels with higher water content, the Poisson's ratio decreases nonlinearly with the increase of water content. This result is consistent with the experimental data found experimentally for other hydrogels (Hu et al., 2012). Since the Poisson's ratio is very sensitive to tissue hydration in gels with high water content, much attention should be paid to in analyzing the mechanical behavior for highly hydrated materials (e.g., nucleus pulposus).

In summary, a new constitutive model for hydration-dependent mechanical properties of hydrated materials has been developed. This new model has been checked with experimental data for hydrogels and cartilage tissues in the literature. With this model, one can noninvasively measure the mechanical properties of the soft materials by determining the water content using NMR and MRI techniques. The model is also useful for designing the scaffold with proper mechanical properties for tissue engineering applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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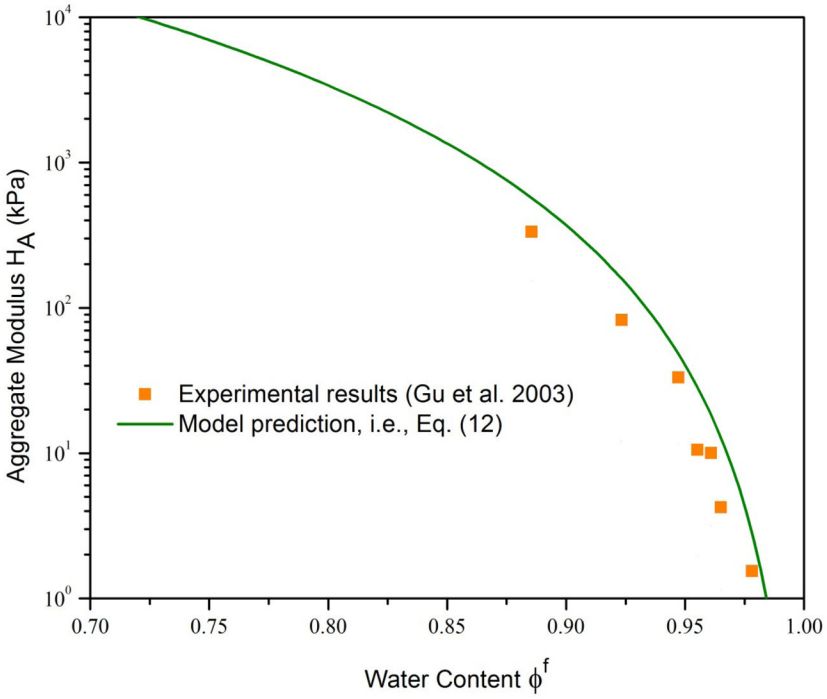

Fig. 1.
Variation of aggregate modulus with water content for agarose gels.

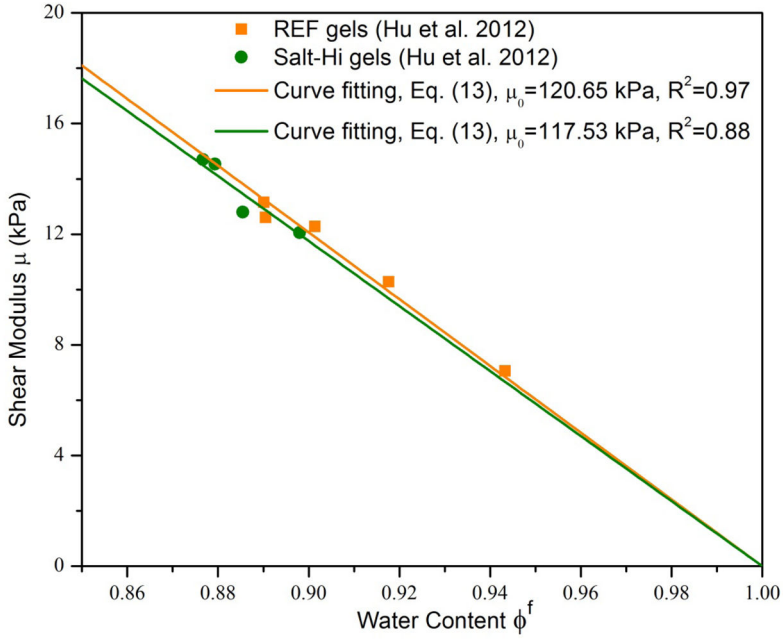

Fig. 2.

Variation of shear modulus with water content. REF gels and Salt-Hi gels are the names defined in (Hu et al., 2012) for two different compositions of poly (DMAEMA-co-AAm) hydrogels.

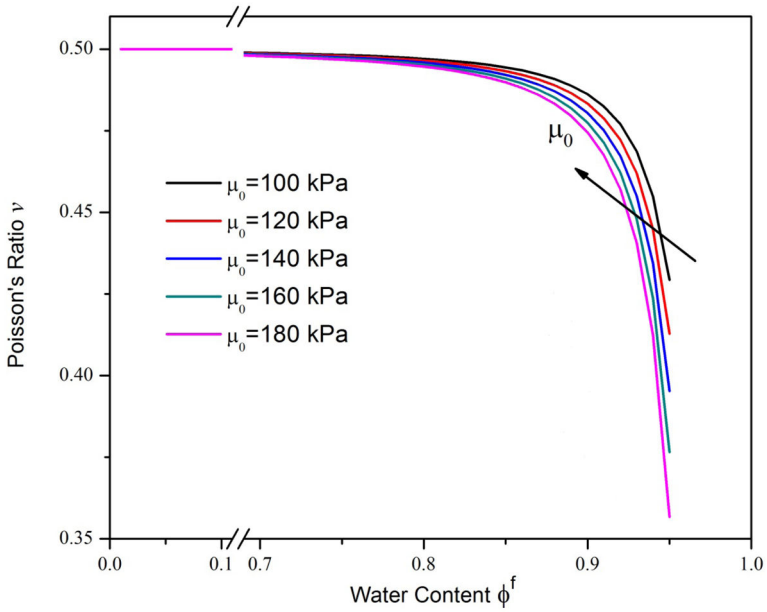

Fig. 3.

Variation of Poisson's ratio with water content for hydrogels. Poisson's ratio was calculated using Eq. (14) with the aggregate modulus of agarose gels and different values of μ_0 (as the exact value for agarose gels is not available).

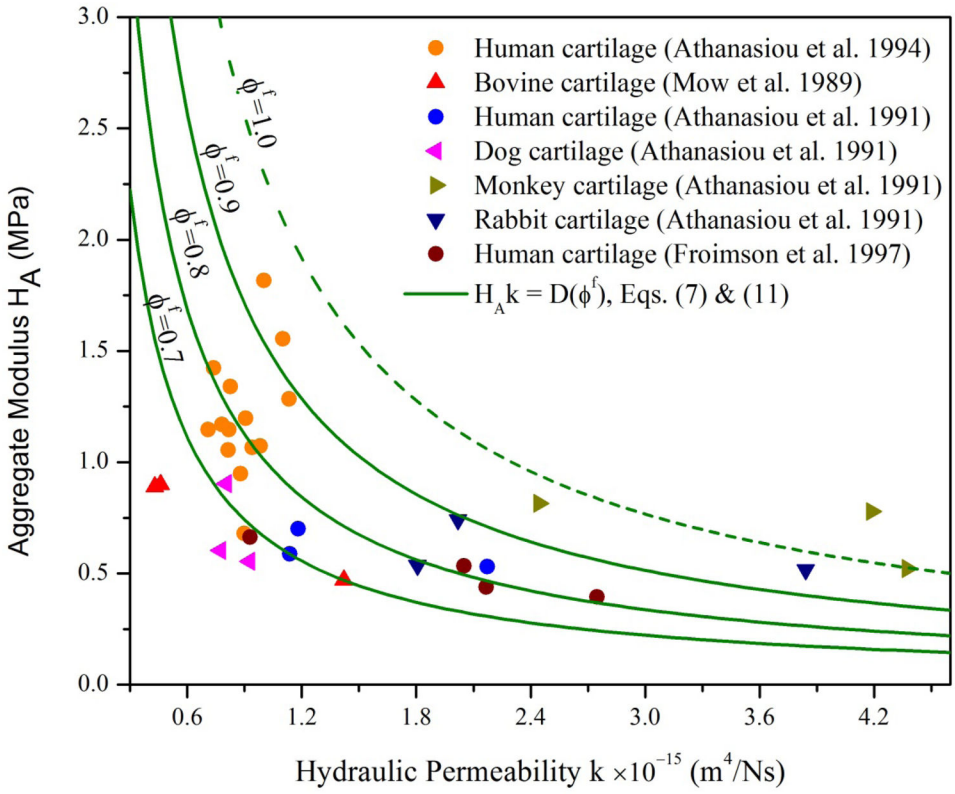

Fig. 4.

The relationship between hydraulic permeability and aggregate modulus for cartilage tissues.

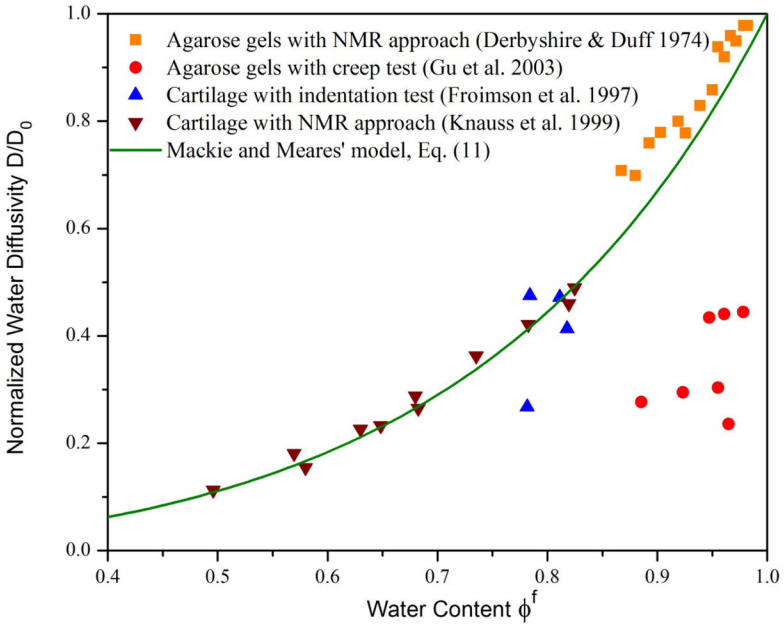

Fig. 5.

Variation of water diffusivity in cartilage tissues and agarose gels with tissue water content. The weight concentration (*c*%, w/w) of the gel reported in (Derbyshire and Duff, 1974) was converted to water content in gel by using a linear fitted relation ($\phi^f = -0.0065c + 0.9846$), which was obtained by curve fitting (R^2=0.98) our previous experimental results (Gu et al., 2003). The mass percentage of water in cartilage specimens reported in (Froimson et al., 1997) was converted to water content (i.e., volume fraction) by assuming the true mass density of solid matrix is 1.35 g/mm^3 (Gu et al., 1996).