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A molecular theory of cartilage viscoelasticity

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Abstract

Recent work on the subject of cartilage mechanics has begun to focus on the relationship between the microscopic structure of cartilage and its macroscopic mechanical properties (Bader et al., Biochem. Biophys. Acta, 1116 (1992) 147–154; Buschmann, PhD Thesis, Massachusetts Institute of Technology, 1992; Kovach, Biophys. Chem., 53 (1995) 181–187; Lai et al., J. Biochem. Eng., 113 (1991) 245–248; Armstrong and Mow, J. Bone Jt. Surg., 64A (1982) 88; Jackson and James, Biorheology, 19 (1982) 317–330). This paper reviews recent theoretical developments and presents a comprehensive explanation of the viscoelastic properties of cartilage in terms of molecular structure. In doing this, a closed form hybrid solution to the non-linear, cylindrical Poisson–Boltzmann equation is developed to describe the charge-dependent component of the equilibrium elasticity arising from polysaccharide charge (Benham, J. Chem. Phys., 79 (4) (1983) 1969–1973; Einevoll and Hemmer, J. Phys. Chem., 89 (1) (1988) 474–484; Fixman, J. Chem. Phys., 70 (11) (1979) 4995–5001; Ramanathan and Woodburg, J. Chem. Phys., 82 (3) (1985) 1482–1491; Wennerstrom et al., J. Chem. Phys., 76 (9) (1982) 4665–4670). This solution agrees with numerical solutions found in the literature (Buschmann, PhD Thesis, Massachusetts Institute of Technology, 1992). The charge-independent, entropic contribution to the equilibrium elasticity is explained in a manner similar to that recently presented for concentrated proteoglycan solution (Kovach, Biophys. Chem., 53 (1995) 181–187). This approach exploits a lattice model of the solution, subject to a Bragg–Williams type approximation to derive the volume dependence of polysaccharide configuration entropy (Flory, Principles of Polymer Chemistry, Cornell University Press, Ithaca, NY, 1953; Huggins, Some properties of Solutions of Long-chain Compounds, 1941, pp. 151–157; Stanley, Introduction to Phase Transitions and Critical Phenomena, Oxford University Press, Oxford, 1971). Together, these two contributions accurately reproduce the experimentally determined osmotic pressure of cartilage as previously determined by Maroudas (Maroudas and Bannon, Biorheology, 18 (1981) 619–632). The time-dependent, or creep, phenomena which cartilage exhibits when subject to mechanical load is explained in terms of frictional drag on the polysaccharide chain monomers in terms of a Kirkwood–Riseman type model (Kirkwood and Riseman, J. Chem. Phys., 16 (6) (1948) 573–579). This approach is shown to accurately predict the hydraulic permeability of cartilage as previously determined by Maroudas (Madouras, Ann. Rheum. Dis., 34 (suppl. 3) (1975) 77). By use of a quasi-static approximation (neglecting inertial effects) the time-dependent response to a uniform compressive force is determined and also found to be in good agreement with experimental values from the literature.

Keywords: Articular cartilage; Viscoelasticity; Osmotic swelling pressure; Configurational entropy; Hydraulic permeability; Poisson–Boltzmann equation; Cartilage

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1. Introduction

Recent developments in cartilage research necessitate rethinking our understanding of how cartilage and other connective tissues respond to mechanical load. As the understanding of the microscopic, molecular structure of cartilage evolves the question as to how the details of this structure are manifest in its mechanical properties recurs. Pathologic degeneration of articular cartilage is ultimately at the molecular level. It is likely that successful efforts to prevent or alter diseases of cartilage will draw on a molecular understanding of their pathogenesis. In order to understand the diseases effecting cartilage and design a rational approach to their prevention or cure, it is important that we understand cartilage and its load bearing function in terms of molecular interactions. To date, the majority of theoretical work addressing cartilage mechanics has remained at a macroscopic level, without reference to the microscopic structural details.

The "biphasic" theory treats cartilage as a mixture of solid and liquid phases [1–7]. The solid phase is assumed to have prescribed equilibrium mechanical properties. The liquid phase, treated as incompressible, is described as existing in a porous network within the solid phase. Friction associated with flow through this network gives rise to the time dependence, or creep, phenomena. The triphasic theory of cartilage is an extension of the biphasic theory to explicitly include charge effects [8]. The charge effects are treated by means of a Donnan approximation in which the details of molecular structure are not included. These descriptions of cartilage have done well in reproducing experimental results. They are, however, macroscopic models which are inherently disconnected from the microscopic, molecular structure of cartilage. They are dependent on such artificial parameters as the modulus of the "solid phase". In reality, cartilage is a complex liquid, more like a hydrated gel than a porous rock. The origin of its equilibrium compressive modulus arises from intermolecular interactions and entropic effects which can often be directly computed. The pressure drop from flow of fluid through cartilage originates from frictional drag on hydrated polysaccharide chains as opposed to flow through small pores.

Several recent works have recognized and begun to quantitatively explain the molecular origin of the mechanical properties of articular cartilage. The charge-independent component of the swelling pressure of concentrated proteoglycan and the bulk modulus of cartilage has recently been explained in terms of volume dependence of the configurational entropy of GAG chains [9]. At ionic strengths of 1.5 M this charge-independent effect was responsible for about one third of the swelling pressure. The charge-dependent component of the bulk modulus has been treated in different manners, with the most recent one involving the numerical solution of the Poisson–Boltzmann equation for charged rods as model GAG chains, simulating the relevant molecular structure [10]. Other recent work has attempted to explain the hydraulic permeability of hyaluronic acid and chondroitin sulfate in terms of hydrodynamic models treating the polysaccharides as cylinders in a uniform array [11,12]. This approach has had limited success in reproducing the permeability of cartilage, generally overestimating it by roughly an order of magnitude.

This paper attempts to integrate and extend recent developments in the understanding of the molecular basis of cartilage mechanics to form a comprehensive, molecular-based theory of the viscoelastic properties of cartilage. The results of this theory are presented in the form of an osmotic equation of state and a differential equation relating strain rate to strain and extrinsic, applied force. This approach does away with a number of artificial fit parameters in the biphasic and triphasic theories, i.e. porosity and bulk modulus of the solid phase. The theory developed here manifestly reflects the molecular structure of cartilage and can be used to determine how changes in this structure are manifest in changes in macroscopic, mechanical properties.

The significance of this work lies in the fact that the detailed molecular structure of cartilage is incorporated into the theory. Such a model is important in our attempts to understand the normal function of cartilage and its derangement in disease. The pathogenesis of diseases affecting articular cartilage ultimately occurs at the molecular level. In order for us to better understand these disorders and to formulate thoughtful strategies in prevention and treatment, a molecular understanding of these tissues and their mechanical function is needed.

2. Charge-independent equilibrium contribution

The charge-independent contribution to the swelling pressure of concentrated proteoglycan has recently been derived in terms of the configurational entropy of GAG chains [9]. In that description the configurational entropy of the GAG chains, and its volume dependence, are derived using a lattice model like that of Flory and Huggins [13,14]. The description here parallels those calculations.

The contribution to the swelling pressure, which arises from the mixing entropy of the aggrecans, has been shown to be vastly over-shadowed by the pressure arising from the internal, configurational entropy of the GAG chains within the aggrecans [9]. In order to determine the swelling pressure and modulus associated with the GAG configurations it is first necessary to calculate the configurational entropy of the GAG chains.

The problem of determining the configurational entropy of the terminal GAG chains differs somewhat from the problem in more traditional polymer systems. In the aggrecan, the structural unit of proteoglycan aggregate in cartilage, the proximal end of the GAG chain, is attached to the core protein, which in turn is fastened to the HA backbone. One terminus of the terminal GAG chain is thus attached to an object of immense size on molecular scale (MW $\approx 10^8$ D). As a result of this configuration, the proximal end of the GAG chain can be treated as fixed in space. The extracellular matrix will be treated as an ensemble of such GAG chains fixed at one end. A lattice model type approach, like that of Flory, is still applicable.

The number of possible configurations a polymeric GAG chain fixed at one end can adopt, Ω_i, is readily determined using a lattice model.

$$\Omega_i = z(z-1)^{n-1} \tag{1}$$

where z is the coordination number of the lattice and n is the number of subunits within the chain. Eq. 1 must be modified to include volume exclusion effects which result from adjacent GAG chains and collagen with its bound water. The effects of volume exclusion due to collagen and bound, "fibrillar" water will be included as a correction to the effective proteoglycan concentration, as proposed by Maroudas and Bannon [15]. The problem at hand then becomes that of swelling pressure due to proteoglycan. Consistent with a mean field theory, the corrected version of Eq. 1 can be written approximately as

$$\Omega_i \approx z^n(1-\phi)^n \tag{2}$$

where ϕ is the excluded volume fraction [13,16,17]. The corresponding entropy of an ensemble of such chains is obtained from the statistical definition of entropy in terms of the number of allowed states, $S = R\ln\Omega$, and the fact that entropy is an extensive thermodynamic variable.

$$S_a = N_c nR[\ln z + \ln(1-\phi)] \tag{3}$$

where R is the gas constant, N_c is the number of chains in moles in the aggrecan, and other symbols are as previously defined.

Volume dependence of the entropy is introduced through the volume exclusion term, ϕ, which can be written as

$$\phi = \frac{V_0}{V}\phi_0 \tag{4}$$

where subscripts denote the initial state. By using Eq. 4, the entropy in a given volume of solution can be written with manifest volume dependence as

$$S = N_a N_c nR\ln z + \ln[1 - \phi_0(V_0/V)] \tag{5}$$

where N_a is the number of aggrecans within the volume.

The pressure exerted by such an ensemble of GAG chains can be readily determined from the resulting contribution to the Helmholtz free energy, TS. The pressure contribution is determined by taking the volume derivative of the entropic portion of the free energy [18].

$$\Pi = T\frac{\partial S}{\partial V} \tag{6}$$

The charge-dependent component of the free energy will give rise to the charge-dependent component of the swelling pressure, to be discussed below. The charge-independent component of the free energy and swelling pressure is due primarily to the configurational entropy of the GAG chains – the aggrecan mixing entropy can be neglected [9]. The pressure arising from the ensemble of GAG chains by virtue of changes in configurational entropy associated with volume changes is given by

$$\Pi_{\text{config}} = -\frac{\partial E_{\text{config}}}{\partial V} = \frac{N_a N_c nRT}{V_0}\left(\frac{\phi_0 (V_0/V)^2}{1-\phi_0 (V_0/V)}\right) \tag{7}$$

This can be reexpressed and simplified by noting that $\phi_0 V_0 = (N_a M_w / \rho_0)$ and $(N_a/V) = (c/M_w)$, where ρ_0 is the specific density of proteoglycan, c is the concentration of proteoglycan in mg/ml, and other symbols are as previously defined. In addition, because the majority of the molecular weight of the proteoglycan molecule comes from the terminal GAG chains one has $M_w = N_c n M_0$, where M_0 is the average molecular weight of a monomeric subunit. These results allow us to write the internal configurational entropic contribution to the osmotic swelling pressure as

$$\Pi = \frac{c^2 RT}{M_0(\rho_0 - c)} \tag{8}$$

This will be used to describe the charge-independent component of the swelling pressure of cartilage with a knowledge of the proteoglycan and collagen concentrations. The effect of collagen and its bound water will be included as a correction to the effective concentration of proteoglycan, as previously suggested by Maroudas and Bannon [15]. The volume exclusion effects of collagen and fibrillar water can be explicitly included in the configurational entropic swelling pressure, and for a detailed discussion of this with the resultant equations the reader is referred to the recent work by this author [9].

Eq. 8 is presented together with charge-dependent theoretical results from below and experimental data from the literature for comparison. It should be noted that the correction of the charge-dependent swelling pressure resulting from configurational effects as described in this section is about ten percent. This is in contrast to the results at higher ionic strength where these effects are responsible for thirty percent of the osmotic pressure of chondroitin sulfate [9].

3. Charge-dependent contribution to the equilibrium elasticity

The Donnan equilibrium method can be used to calculate the charge-dependent contribution to the swelling pressure of polyelectrolyte solutions [19–21]. This method has already been applied to concentrated proteoglycan, and for further details regarding this method the reader is referred to Urban et al. [22]. The premise of this method is that in the bulk macromolecular and bath phases there must be charge neutrality, and that equilibrium is established across the boundary between these phases. The results of this theory will not be presented here as it is essentially a macroscopic description of charge effects. In addition, it is described in detail in the above-mentioned sources.

The Donnan model of the osmotic effects of charge interaction can be improved upon by taking the molecular structure of cartilage into account. The problem of charge interactions in polyelectrolytic linear chain molecules has been the subject of numerous studies [23–28]. The approach which has obtained the most success involves using the Poisson–Boltzmann (PB) equation to characterize the ionic solvent while treating the polyelectrolyte as a uniformly charged cylinder. This method has been applied to the problem of proteoglycan by Buschmann with accurate predictions regarding the charge-dependent contribution to the swelling pressure and elastic modulus [10]. The results Buschmann obtained were, however, obtained from a numerical solution of the PB equation. In the work below we will present a closed-form solution to this problem in the form of a hybrid potential as suggested by Katchalsky et al. [26].

The PB description of cartilage starts by subdividing the portion of cartilage occupied by hydrated proteoglycan, i.e. that portion not occupied by collagen or its bound water, into cells assigned to individual GAG chains. In order that the problem be tractable, these cells are approximated as being around parallel aligned GAG chains. In these cells, the GAG chain is treated as a uniformly charged cylinder with radius a. The intervening solution between the GAG chains is treated as an ideal PB electrolyte. The PB equation for model GAG chains in a 1:1 symmetric electrolyte of ionic strength m

can be written in terms of normalized cylindrical coordinates as

$$\frac{\mathrm{d}^2\psi}{\mathrm{d}\xi^2} + \frac{1}{\xi}\frac{\mathrm{d}\psi}{\mathrm{d}\xi} = \frac{n_0^+}{m}\mathrm{e}^{\psi} - \frac{n_0^-}{m}\mathrm{e}^{-\psi} \qquad (9)$$

where $\psi = q\phi/kT$, $\xi = r\kappa$, κ is the inverse Debye screening length [25,26]. The constants n_0^+ and n_0^- are determined by normalization conditions, being $n_0^+ = m + Z$ and $n_0^- = m$. Z is the fixed charge density. The cell radius, R, is easily determined by subdividing the volume into cells as

$$R^{-2} = \frac{\pi bNc}{M_0} \qquad (10)$$

where b is the GAG charge separation distance, N is Avogadro's number, c is the proteoglycan concentration and M_0 is the average molecular weight per GAG monomer.

The next step is to obtain a solution to Eq. 9 for an isolated GAG chain. A completely general solution in closed form does not exist [2,3]. A method to overcome this problem by constructing a hybrid solution from the closed-form solutions for small and large radius limit approximations to the PB equation has been proposed [26]. Region I $(r < d)$ is that region in which the charge distribution is dominated by counterions. In this region the potential is such as to virtually exclude co-ions, and the PB equation is well approximated by

$$\frac{\mathrm{d}^2\psi_\mathrm{I}}{\mathrm{d}\xi^2} + \frac{1}{\xi}\frac{\mathrm{d}\psi_\mathrm{I}}{\mathrm{d}\xi} = \frac{n_0^+}{m}\mathrm{e}^{\psi_\mathrm{I}} \qquad (11)$$

Eq. 11 does have a closed-form solution [26].

$$\psi_\mathrm{I} = \ln\left(\frac{\xi^2 \sinh^2[B\ln(A\xi)]}{2B^2}\right) \qquad (12)$$

where A and B are integration constants to be determined by the boundary conditions.

The second region $(r > d)$ is the one where the ion–potential interaction is overshadowed by thermal effects, i.e. $\psi \ll 1$. In this region the PB equation can be linearized. Furthermore, in this region the excess of counterion needed to balance the fixed charge can be neglected as it is concentrated in region I. These simplifications transform Eq. 9 into

$$\frac{\mathrm{d}^2\psi_\mathrm{II}}{\mathrm{d}\xi^2} + \frac{1}{\xi}\frac{\mathrm{d}\psi_\mathrm{II}}{\mathrm{d}\xi} = \psi_\mathrm{II} \qquad (13)$$

where the approximation $n_0^+ \approx n_0^- \approx m$ has been made. Eq. 13 is readily recognized to be the modified Bessel equation of order zero [29]. The general solution to this is a linear combination of the two zeroth order modified Bessel functions, $DI_0(\xi) + CK_0(\xi)$, where

$$I_0(\xi) \approx \frac{\mathrm{e}^{\xi}}{(2\pi\xi)^{1/2}}\left(1 + \frac{1}{8\xi} + \frac{9}{128\xi^2} + \cdots\right) \qquad (14)$$

$$K_0(\xi) \approx \frac{\mathrm{e}^{-\xi}(\pi)^{1/2}}{(2\xi)^{1/2}}\left(1 - \frac{1}{8\xi} + \frac{9}{128\xi^2} - \cdots\right) \qquad (15)$$

In the case of a cylindrical polyelectrolyte potential, the potential must decay with increasing distance, necessitating $D = 0$. By using the large distance approximation to Eq. 15, we can further simplify the result to give [23]

$$\psi_\mathrm{II} \approx \frac{C\mathrm{e}^{-\xi}}{\xi^{1/2}} \qquad (16)$$

Eq. 16 is the leading term in the powers of the inverse normalized distance from the cylinder. The general solution, Eq. 15, rapidly converges to Eq. 16. At typical GAG separations, at least several Debye lengths, the next term in Eq. 15 is only a few percent correction to Eq. 16.

By dividing the unit cell into two distinct regions we are thus able to obtain general closed-form solutions for the PB equation. To obtain a useful hybrid solution it remains only to impose boundary conditions and select an appropriate radius for the transition from region I to region II. That a hybrid solution is viable and relatively insensitive to the transition radius, d, has been recognized to result from the similarity of Eqs. 12 and 16 over a relatively large region [26]. The value of d used here corresponds to two Debye screening lengths, or $\approx 14 \times 10^{-10}$ m.

There are three "boundaries" at which there are constraints on the isolated GAG chain solution, at the GAG surface, at the transition radius d, and at large r or infinity. The solutions and their derivatives must match at the transition radius d. In considering similar problems previously, a boundary condition at the cell radius has often been imposed, however, this condition is a natural consequence of the symmetry of having adjacent cells with their corresponding potentials, and is incorrect if imposed on the single-cell solution. These conditions are expressed quantitatively as $\psi_{I}'(a) = -\sigma$, $\psi_{I}(d) = \psi_{II}(d)$, $\psi_{I}'(d) = \psi_{II}'(d)$, $\psi_{II}(\infty) = 0$. In the preceding sentence, σ, is the effective surface charge density if the GAG charge were assumed to be spread out over the corresponding model cylinder.

Ultimately, the only integration constant of significance in determining the swelling pressure is C in Eq. 16. This is the case because the unit cell radius in the physiologic and experimental range of proteoglycan concentration corresponds to the regime where Eq. 16 accurately describes the potential. An alternative method of determining the constant in Eq. 16 is to vary C to optimize the fit of Eq. 16 to numerical solutions of Eq. 9 such as those obtained by Buschmann [10]. The results of either of these approaches yield a value for C of, $C \approx 9.1$, for realistic GAG chain parameters ($a = 0.55$ nm, $b = 0.64$ nm; a = GAG chain radius, b = intercharge separation).

We have at this point obtained a closed-form solution to the cylindrical Poisson–Boltzmann equation for the electrostatic potential of GAG chains in cartilage. It remains to determine the resulting swelling pressure. It has been shown that this pressure is equivalent to the ideal osmotic pressure resulting from ions in solution at the cell boundary minus the osmotic pressure of the ionic bath [26,30].

$$\Pi_e = RT[n^+(R) + n^-(R) - 2m] \tag{17}$$

This can be simplified by noting that the ions in solution are expected to distribute themselves in a manner consistent with a Boltzmann distribution, i.e., $n^+(R) = m\ \exp[\psi(R)]$, and $n^-(R) = m\ \exp[-\psi(R)]$. Noting that $e^x + e^{-x} = 2\cosh(x)$, we can rearrange Eqs. 17 in terms of the hyperbolic cosine as

$$\Pi_e = 2RTm\{\cosh[\Psi(R)] - 1\} \tag{18}$$

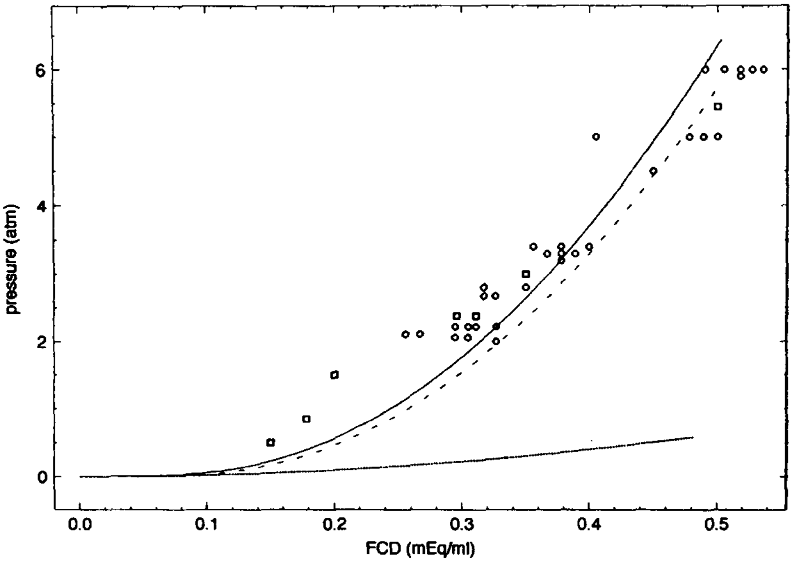

Fig. 1. The dashed line is the charge-dependent component of the swelling pressure of cartilage as determined from the closed-form solution of the non-linear, cylindrical PB . The dotted line is the swelling pressure arising from configurational entropic effects amongst the GAG chains. The solid line is the sum of these two contributions. The data presented are taken from prior work of Maroudas [15]. The circles are for various samples of cartilage with the fixed charge density having been corrected for volume exclusion effects of collagen and its bound water, and the squares are concentrated chondroitin sulfate solution.

or, making use of Eq. 16

$$\Pi_e = 2RTm\left\{\cosh\left(\frac{C\exp\left(-\sqrt{\dfrac{M_0\kappa^2}{\pi bNc}}\right)}{\sqrt{\sqrt{\dfrac{M_0\kappa^2}{\pi bNc}}}}\right)-1\right\} \tag{19}$$

where $C \approx 9.1$, and R is the unit cell radius related to the proteoglycan concentration (in mg/ml) by Eq. 10, κ is the inverse Debye screening length, and m is the ionic strength of the bath. The results obtained from this solution are plotted in Fig. 1, with the entropic swelling pressure from the previous section and the experimental results of Maroudas and Brannon for comparison [15].

4. Non-equilibrium properties of cartilage

The hydraulic permeability of articular cartilage has been the subject of numerous experimental and theoretical investigations [3,31–35]. The results of these efforts have left us with a sound understanding of the macroscopic fluid flow behavior in cartilage. The hydraulic permeability coefficient of cartilage has, in general, been treated as a measured, empirical parameter, or explained in terms of flow through a solid with tubular pores.

Attempts to relate the molecular architecture of cartilage to its hydraulic permeability have been limited. The permeability of concentrated polysaccharide (chondroitin sulfate and hyaluronic acid) has been described in terms of a hydrodynamic model in which they are treated as a uniform array of cylinders. In these works, the results of Happel and Brenner's calculation for drag from flow past a uniform array of cylinders, subject to the low Reynolds number limit, is utilized [36]. These theories have met with some limited success. While they reproduce the data for isolated hyaluronic acid in some experiments, they significantly underestimate the resistance to flow demonstrated by chondroitin sulfate and proteoglycan in cartilage and other tissues. This failure has been attributed to the presence of other materials such as mucoproteins [11]. While this explanation may account for the discrepancy in other tissues, it is unlikely to be the case for cartilage where water, GAG, and collagen account for the vast majority of volume.

The approach presented here is simpler than the cylinder model, yet reproduces the data more accurately. The GAG chains are modeled as polymers, with the monomeric subunits each subject to frictional drag from the passing flow of water. The flow past a monomer is obtained from the undisturbed flow field corrected by the flow disturbance from other solute. The approach taken in solving this problem is essentially that of the Kirkwood–Riseman model for frictional drag on an isolated polymer molecule in the "free draining" limit [37]. The water is treated as a classical Navier–Stokes fluid in the low Reynolds number limit. The result is in terms of a friction coefficient between monomer and fluid, which is an empirical parameter. The effective radius obtained by treating the monomers as spheres subject to Stoke's result for a sphere is calculated and found to be 11.7 Å. For the purposes of these calculations the GAG chains will be treated as stationary.

Collagen is included only in its correction to the volume fraction of solvent, and hence the corrected flow velocity. The fact that collagen contributes minimally to the hydraulic permeability of cartilage has been shown experimentally [31]. The results of this approach accurately reproduce the observed dependence of hydraulic permeability coefficient on fixed charge density [31].

Macroscopically, cartilage is well described by Darcy's law ([3,35,38]), in which the rate of volume discharge, Q, is proportional to the applied pressure gradient

$$Q = kA(\Pi_{\mathrm{frict}}/h) \tag{20}$$

where A is the area of the specimen, Π_{frict} is the pressure gradient , h is the thickness, and k is the hydraulic permeability coefficient. The speed, u, of the fluid flowing through the material is related to the rate of volume discharge and the porosity, or volume fraction occupied by fluid in the material, $u = Q/A(1-\gamma)$, where γ is the volume fraction of solute. Eq. 20 can be reexpressed as

$$\frac{\Pi_{\mathrm{frict}}}{u(1-\gamma)h} = k^{-1} \tag{21}$$

The low Reynolds number limit Navier–Stokes equation, in general steady state flow, is

$$f(\boldsymbol{r}) = -\mathrm{grad}[P(\boldsymbol{r})] + \eta\Delta \boldsymbol{v}(\boldsymbol{r}) \tag{22}$$

where P is pressure, η is viscosity, $\boldsymbol{v}$ is fluid velocity, and f is applied force density. This, taken with the continuity equation, $\mathrm{div}(\boldsymbol{v}) = 0$, forms the basis of the description. The Reynolds number is given by $R = \rho v l/\eta$, where v is the fluid flow speed, l is the distance scale of the relevant structures, η is fluid viscosity, and ρ is fluid density. When the Reynolds number is not small compared to 1, Eq. 22 must include an inertial term, $(\boldsymbol{v}\mathrm{grad})\boldsymbol{v}$, on the left-hand side.

In the case of flow in cartilage, v is typically less than 10^{-5} m/s, η is 1 cp, and ρ is 1 g/cm^3. Typical distance scales in treating GAG chains are on the order of 10 Å. Taken together these parameters provide a Reynolds number of 10^{-8}, legitimizing the use of the low Reynolds number limit version of the Navier–Stokes equation.

Imposing Darcy's law amounts to an ad hoc correction to Eq. 22 and neglecting external forces other than those arising from frictional flow through the material, Eq. 22 becomes

$$-\mathrm{grad}[P(\boldsymbol{r})]\,\eta\Delta \boldsymbol{v}(\boldsymbol{r}) + \frac{\eta}{k}\boldsymbol{v}(\boldsymbol{r}) = 0 \tag{23}$$

Eq. 23 is often referred to as the "screened" Navier–Stokes equation, with the screening length defined as, $\kappa_{\mathrm{D}} = (k/\eta)^{1/2}$, and the right most term on the left called the Darcy term.

In the microscopic view of Darcy's law, the pressure drop which results from fluid flow through a material originates from frictional forces on the material constituents. In the case of concentrated proteoglycan, this is just the problem of frictional drag on the polymeric GAG chains. In calculating the drag, the GAG chains are treated as a "free draining coil", with each monomeric subunit treated separately [39]. This approach corresponds also to that of Debye and Bueche for friction on a flexible chain polymer in the zero screening limit [40]. The drag force experienced by each monomer is assumed to be proportional to the local fluid velocity.

$$\boldsymbol{F}_j = \zeta \boldsymbol{v}(\boldsymbol{r}_j) \tag{24}$$

where ζ is the friction coefficient associated with a monomer. The reason that the assumption of proportionality between the frictional force on a monomer and local fluid velocity is valid even at these microscopic distance scales arises from the low flow limit. In the low Reynolds number limit drag force is proportional to fluid velocity. In fact, drag can be expressed as an expansion in terms of powers of the Reynolds number. As shown above, even at these small scales the problem remains in the extreme low Reynolds number limit for relevant flow-rates. This assumption of linear relation between drag force and flow velocity forms one element of the Langevin equation, which is the cornerstone of the molecular theory of transport processes, and the basis of the theory of Brownian motion [41].

There are in fact different frictional coefficients corresponding to different types of subunit (two in chondroitin sulfate), however all monomers will be approximated as having the same friction coefficient. With this approximation the force density becomes

$$f(\boldsymbol{r}) = \zeta \boldsymbol{v}(\boldsymbol{r})\Sigma\delta(\boldsymbol{r} - \boldsymbol{r}_j) \tag{25}$$

The velocity in Eq. 25 represents the microscopic, local fluid velocity. This is the background flow corrected for flow disturbances resulting from other subunits, and can be written as

$$\boldsymbol{v}(\boldsymbol{r}) = \boldsymbol{v}_0(\boldsymbol{r}) + \Sigma\delta_j \boldsymbol{v}(\boldsymbol{r}) \tag{26}$$

The Oseen tensor can, in principle, be used to calculate the flow disturbance exactly, given the exact distribution of all other subunits [42]. [1]

The problem at this point is still quite general, and difficult to solve. The simplest approximation, sometimes called the "coil solution" [43] involves

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[1] The result obtained has the form

$$\boldsymbol{v}(\boldsymbol{r}) = \boldsymbol{v}_0(\boldsymbol{r}) + \int T(\boldsymbol{r} - \boldsymbol{r}')\cdot f(\boldsymbol{r}')\mathrm{d}^3 r'$$

where, T, the Oseen tensor, has components

$$T_{j,k}(\boldsymbol{r}) = \frac{1}{8\pi\eta}\left(\delta_{j,k} + \frac{r_j r_k}{|\boldsymbol{r}|^3}\right)$$

In deriving the flow disturbance a simplifying assumption is made regarding the commutativity of averaging with the spatial integral. This approximation is analogous to a mean field approximation, and was first described in this context by Felderhof and Deutch [44].

treating the monomers as independent spheres subject to a Stokes law drag, i.e.

$$\zeta = 6\pi\eta a \tag{27}$$

where a is the radius of a monomer. In this model the microscopic variations in the flow field due to other subunits is neglected. The effect of the presence of other subunits can be treated by increasing the flow-rate of the unperturbed flow field, resulting from the fact that there is less volume for the fluid to flow through by virtue of the volume occupied by the solute material. This permits us to write Eq. 26 as

$$\boldsymbol{v}(r) = \frac{\boldsymbol{v}_0}{1-\gamma} = \boldsymbol{u} \tag{28}$$

where γ is the volume fraction occupied by solute. With this approximation the force density is averaged to give

$$\Pi_{\mathrm{frict}} = \frac{\zeta v_0 hn}{1-\gamma} = \frac{6\pi\eta a v_0 hn}{1-\gamma} \tag{29}$$

where h is the sample thickness and n is the number density of subunits. Referring to Eq. 21, the permeability coefficient is readily determined

$$k = \frac{1-\gamma}{\zeta n} = \frac{1-\gamma}{6\pi a\eta n} \tag{30}$$

The results of Eq. 30 are presented in Fig. 2 where they are compared with Maroudas experimental data as a function of fixed charge density [31]. The best fit to the data is given by a friction coefficient of 2.21×10^{-11} Ns/m. This value corresponds to an effective Stoke's radius of 11.7 Å for the GAG chain subunits. The friction coefficient of the monomeric subunits is treated as an empirical fit parameter. The corresponding Stoke's radius is, however, roughly in agreement with the size of the monomeric subunits.

The manner in which collagen and its bound water is addressed becomes important to clarify at this point. Experimental work has shown that collagen contributes minimally to the fluid conducting properties of cartilage [33,45]. This is to be expected when considering that the size of collagen fibers is much larger than that of GAG chains [46]. Accordingly, one would expect the surface area of contact between collagen and solvent – and the resulting friction effects – to be small in comparison to that between proteoglycan and solvent. Collagen and its bound water are included in this model only in so far as by volume exclusion they increase the effective volume fraction of proteoglycan and the flow-rate. The collagen and its bound water serve only to reduce the volume available for the distribution of proteoglycan solution and for fluid flow. The direct

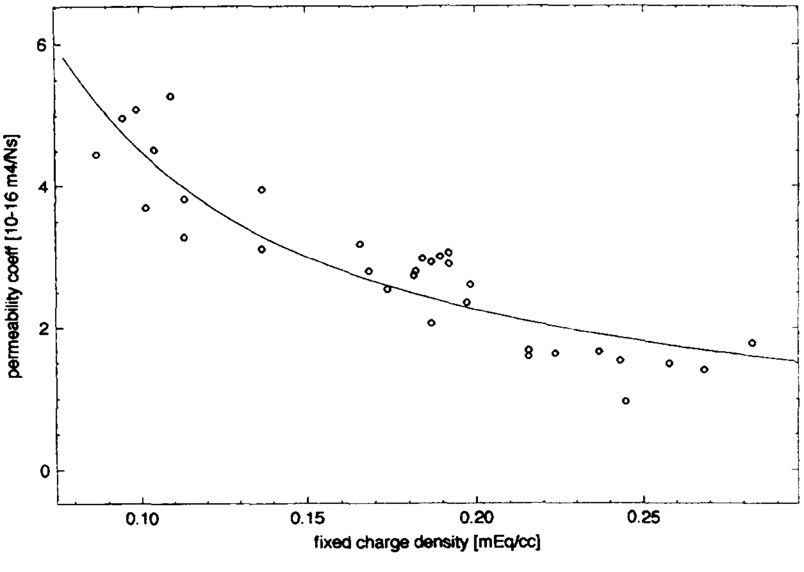

Fig. 2. This figure presents the theoretically predicted hydraulic permeability coefficient with experimental results from Maroudas [33] for comparison. The solid line is the theoretical curve, dots are Maroudas' data.

frictional force on collagen is neglected. The volume fraction of solvent can be written as

$$1-\gamma=\frac{V-V_{\mathrm{coll}}-V_{\mathrm{PG}}-V_{\mathrm{bnd}}}{V} \tag{31}$$

where V is the total volume of cartilage under consideration, V_{coll} is the volume of collagen, V_{PG} is the volume fraction of proteoglycan, and V_{bnd} is the volume of water bound to collagen ("fibrillar" water). Maroudas has experimentally determined the amount of bound, fibrillar water in terms of the dry weight of collagen [15].

The results of this description taken with the equilibrium results from previous sections can be used to derive the time-dependent or creep response of cartilage to a compressive deforming force. This will be done for the scenario of response to a constant deforming force. To derive this behavior, deformation will be treated as a quasi-static problem in which inertial effects will be neglected, i.e.

$$\Pi_{\mathrm{ext}}=\Pi_{\mathrm{eq}}(c)+\Pi_{\mathrm{frict}}(c,c') \tag{32}$$

By making use of Eqs. 8, 19, and 29 we can write this result for a confined compression experiment with constant deforming pressure in the quasi-static limit. To transform the equations in terms of strain in the small deformation limit, it is necessary only to recognize $N/[V(1-\gamma)]=(Nc)/M_0$, and $\nu/h=\partial\varepsilon/\partial t$, where N is Avogadro's number, c is the effective concentration in mg/ml, ε is strain and other symbols are as previously defined. With these observations it is possible to recast Eq. 32 in terms of strain as

$$\frac{\partial\varepsilon}{\partial t}=\frac{M_0}{\zeta N c_0 h_0^2}\left[\Pi_{\mathrm{ext}}-\Pi_{\mathrm{eq}}(\varepsilon)\right] \tag{33}$$

The results of Eq. 33 are plotted in Fig. 3 for various deforming forces. Eq. 33 can be integrated to predict the strain as a function of time for fixed deforming force. This integral has been performed numerically and the results are presented in Fig. 4. The results obtained in this manner are compared to deformation experiments performed by Maroudas [33]. The re-

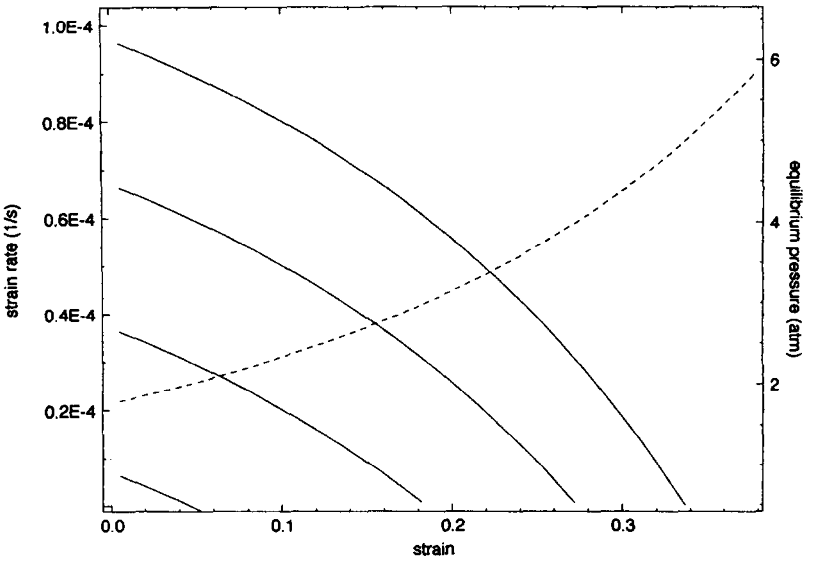

Fig. 3. Theoretical strain rate versus strain for a representative sample of cartilage – 0.15 mEq/cm^3 FCD, with volume fraction of solute equally divided between collagen and PG – subject to various constant external pressures in a confined compression type scenario. The dashed line is the equilibrium swelling pressure as a function of compressive strain. The solid lines represent different strain rate versus strain curves. The difference arises from different external pressures: 2, 3, 4, and 5 atm, respectively.

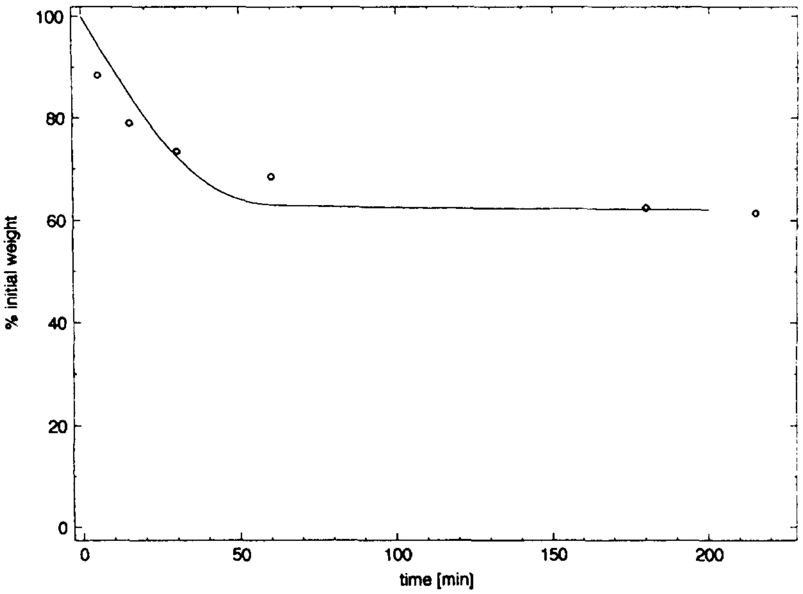

Fig. 4. Theoretical time dependence of the percent initial weight of a plug of cartilage subject to a constant 20 atm deforming force in a confined compression-type experiment. The zero strain FCD is 0.17 mEq/cm^3 with an effective FCD (corrected for collagen and fibrillar water) of 0.43 mEq/cm^3. The result is plotted with representative data from the literature for comparison [33].

sults are in good agreement with the literature data, with an accurate associated time constant.

5. Role of collagen

The role of collagen in determining the elastic and viscoelastic properties of cartilage has been investigated in considerable detail previously. In the model presented here these prior works are drawn upon heavily. As Maroudas recognized, the contribution to the equilibrium modulus which arises from collagen is essentially a volume exclusion effect. She determined that the swelling pressure of cartilage was completely explained in terms of the proteoglycan content provided one corrected the concentration of the polysaccharide to exclude the volume occupied by collagen and its bound, "fibrillar" water [15]. If the concentration of GAG is corrected for the volume exclusion effects of collagen, all of the samples of cartilage she studied exhibited the same swelling pressure curves which were identical to that of isolated chondroitin sulfate. This notion of a corrected proteoglycan concentration dictating the compressive properties of cartilage has been successfully adopted here. The collagen is, however, thought to play an important role in preventing the unchecked expansion of cartilage, thereby determining proteoglycan concentration in unstressed cartilage, and hence tissue modulus.

The role of collagen in the time-dependent or creep properties of cartilage is also primarily one of volume exclusion. The actual frictional drag associated with the collagen and its bound water has been shown to be small [45]. This could be expected on the basis of its larger size, and hence smaller surface. Since friction is essentially an effect at the macromolecule–fluid interface, one would expect the frictional drag associated with collagen to be minor in comparison with that of proteoglycan. The primary effect of collagen and its bound water in terms of time-dependent properties of cartilage is to change the velocity of flow through cartilage associated with a given strain rate by virtue of volume exclusion.

6. Discussion

The results of the preceding sections collectively give rise to a novel, microscopic explanation of the viscoelastic properties of cartilage. A closed form solution to the non-linear, cylindrical Poisson–Boltzmann equation has been used to explain charge effects. The volume dependence of the polysaccharide configuration entropy has been used to explain the charge independent portion of cartilage elasticity. The time-dependent, creep phenomena exhibited by cartilage has been described in terms of a simple ''free draining coil'' hydrodynamic model, where the frictional drag associated with fluid flux is ascribed to drag on monomeric segments of the GAG chains.

Throughout this model, the role of collagen has been treated as one of simple volume exclusion. This approach, while perhaps oversimplifying the role of collagen, is consistent with previous experimental studies, both in reference to the role of collagen in equilibrium and time-dependent behavior of cartilage. Together, these ideas accurately reproduce the experimentally determined viscoelastic properties of cartilage.

The charge-independent, entropic effects are found to be relatively less important at physiologic ionic strength. In 1.5 M salt, the conformational contribution to the swelling pressure of chondroitin sulfate was found to be about 30% [9]. In physiologic ionic strength, however, the result is closer to 10%.

The closed form of the charge-dependent contribution to the swelling pressure as calculated here is in excellent agreement with computational results in the literature [10]. This appears to be the predominant factor in determining the equilibrium swelling pressure of cartilage under physiologic conditions.

The time-dependent mechanical properties of cartilage have been explained in terms of friction on the polysaccharide chain monomers. A simple model of this process, in which the hydrodynamic effect of other proteoglycan and collagen is manifest only in a correction to the effective flow speed, reproduces the measured permeability of cartilage well. The corresponding Stokes radius from this model is larger than the actual size of a monomer by roughly a factor of two. This can in part be explained by a hydration shell associated with the charged GAG chains. In addition, at these scales, one is at the limits of applicability of a classical, macroscopic fluid theory. When the model is extended to predict creep, it predicts the experimental data and apparent time constants in a semi-quantitative manner.

Other factors such as tension within the collagen network and surface effects probably play some role in determining the mechanical properties of cartilage. These problems, and the formulation of a more detailed hydrodynamic model of flow through cartilage form the basis of ongoing work.

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