REVIEW

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Constitutive Modeling of Cartilaginous Tissues: A Review

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An important and longstanding field of research in orthopedic biomechanics is the elucidation and mathematical modeling of the mechanical response of cartilaginous tissues. Traditional approaches have treated such tissues as continua and have described their mechanical response in terms of macroscopic models borrowed from solid mechanics. The most important of such models are the biphasic and single-phase viscoelastic models, and the many variations thereof. These models have reached a high level of maturity and have been successful in describing a wide range of phenomena. An alternative approach that has received considerable recent interest, both in orthopedic biomechanics and in other fields, is the description of mechanical response based on consideration of a tissue's structure—so-called microstructural modeling. Examples of microstructurally based approaches include fibril-reinforced biphasic models and homogenization approaches. A review of both macroscopic and microstructural constitutive models is given in the present work.

Key Words: cartilage, biphasic models, viscoelastic models, microstructural models

The function of synovial joints is largely governed by the mechanical properties of their structural materials, that is, the ligaments, tendons, menisci, articular cartilage, and so on. Significant effort has therefore been devoted to the elucidation of such properties (through experimental testing) and to the analysis of observed mechanical responses with mathematical models. This review is concerned with constitutive modeling of cartilaginous tissues. The most popular mechanical testing configurations for cartilaginous tissues have been confined and unconfined compression (Armstrong, Lai, & Mow, 1984; Ateshian, Warden, Kim, Grelsamer, & Mow, 1997; Chen, Bae, Schinagl, & Sah, 2001a; Hunter, Noyes, Haridas, Levy, & Butler, 2003; Korhonen et al., 2002a; Leslie, Gardner, McGeough, & Moran, 2000; Mow, Kuei, Lai, & Armstrong, 1980), uniaxial tension (Charlebois, McKee, & Buschmann, 2004; Goertzen, Budney, & Cinats, 1997; Huang, Stankiewicz, Ateshian, & Mow, 2005; Kempson, Muir, Pollard, & Tuke, 1973; Lechner, Hull, & Howell, 2000; Roth & Mow, 1980; Schmidt, Mow, Chun, & Eyre, 1990; Sweigart & Athanasiou, 2005b; Tissakht & Ahmed, 1995), pure shear (torsion) (Anderson, Woo, Kwan, & Gershuni, 1991; Hayes & Bodine, 1978; Spirt, Mak, & Wassell, 1989; Zhu, Chern, & Mow, 1994; Zhu, Mow, Koob, & Eyre, 1993), and indentation (Hori & Mockros, 1976; Jurvelin, Kiviranta, Arokoski, Tammi, & Helminen, 1987; Jurvelin, Kiviranta, Saamanen, Tammi, & Helminen, 1990; Kempson, Freeman, & Swanson, 1971a; Mow, Gibbs, Lai, Zhu, & Athanasiou, 1989; Sweigart & Athanasiou, 2005a, 2005b). Such configurations are chosen as they greatly simplify the analysis of the sample deformation and allow more rigorous assessment of the validity of a given model.

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The overall response of cartilage is complex, and this fact has driven several decades of model development. However, deconstruction of this complexity becomes more tractable once a number of key features of the response are identified:

1. Stresses and strains in the tissues vary with time, giving rise to the well-documented creep and stress relaxation behavior (Mow et al., 1980). It is generally accepted that two distinct mechanisms contribute to this time dependence (DiSilvestro & Suh, 2001; DiSilvestro & Suh, 2002; DiSilvestro, Zhu, & Suh, 2001a; DiSilvestro, Zhu, Wong, Jurvelin, & Suh, 2001b; Mak, 1986a, 1986b; Setton, Zhu, & Mow, 1993): frictional drag forces from interstitial fluid flow through the porous extracellular matrix, and the inherent viscoelasticity of the extracellular matrix itself (Mow, Mak, Lai, Rosenberg, & Tang, 1984; Sanjeevi, Somanathan, & Ramaswamy, 1982).
2. The response of cartilage is strain dependent in both tension (Charlebois et al., 2004; Huang, Mow, & Ateshian, 2001; Lechner et al., 2000; Roth & Mow, 1980; Tissakht & Ahmed, 1995; Uezaki, Kobayashi, & Matsushige, 1979; Woo, Akeson, & Jemmott, 1976) and compression (Bader, Kempson, Egan, Gilbey, & Barrett, 1992; Lai, Mow, & Roth, 1981; Leslie et al., 2000; Maroudas, 1975; Zhu et al., 1993).
3. The response of cartilage is strain rate dependent—generally appearing stiffer under higher strain rates (DiSilvestro et al., 2001a; Lai et al., 1981; Langelier & Buschmann, 2003; Oloyede & Broom, 1993; Oloyede, Flachsmann, & Broom, 1992; Radin, Paul, & Lowy, 1970; Silver, Bradica, & Tria, 2004; Verteramo & Seedhom, 2004).
4. Cartilage properties are anisotropic (Chahine, Wang, Hung, & Ateshian, 2004; Huang et al., 2005; Jurvelin, Buschmann, & Hunziker, 2003; Kempson et al., 1973; Leslie et al., 2000; Mow, Ratcliffe, & Poole, 1992; Myers, Lai, & Mow, 1984; Proctor, Schmidt, Whipple, Kelly, & Mow, 1989; Roth & Mow, 1980; Verteramo & Seedhom, 2004; Whipple, Wirth, & Mow, 1985; Woo et al., 1979).
5. Cartilaginous tissues are structurally heterogeneous, and this endows them with depth- and location-dependent mechanical properties (Boschetti, Pennati, Gervaso, Peretti, & Dubini, 2004; Chen et al., 2001a; Chen, Falcovitz, Schneiderman, Maroudas, & Sah, 2001b; Erne et al., 2005; Gore, Higginson, & Minns, 1983; Jurvelin, Buschmann, & Hunziker, 1997; Laasanen et al., 2003; Schinagl, Gurskis, Chen, & Sah, 1997; Verteramo & Seedhom, 2004; Woo et al., 1976; Woo et al., 1979).
6. Cartilaginous tissues generally behave differently in tension and compression (Akizuki et al., 1986; Chahine et al., 2004; Huang et al., 2005; Laasanen et al., 2003).

In view of the complexity, a plethora of mathematical models have been developed for describing the mechanical response of cartilaginous tissues. Macroscopic (i.e., those that make no consideration of the underlying tissue structure) constitutive models of varying form and level of sophistication have been formulated over the past several decades. Microstructural formulations have also been developed to allow greater insight into the relationship between tissue structure and function.

Macroscopic Models of Cartilage Mechanical Behavior

Generalized Hooke's Law for Linear Elasticity

A number of studies have treated cartilage as a linear elastic material. While a linear elastic model by itself would probably constitute an inadequate description of cartilage response for many applications (in view of the pronounced time, strain, and strain rate dependence, as mentioned), it has nonetheless been applied in several simplified analyses and in cases where time-dependence effects are secondary (discussed below). Additionally, the linear elastic constitutive framework is integral to many of the more sophisticated models to be discussed.

For a linear elastic material, the generalized Hooke's law may be written in direct tensor notation as

$$\boldsymbol{\sigma} = \mathbf{C} : \boldsymbol{\varepsilon}, \tag{1}$$

where $\boldsymbol{\sigma}$ and $\boldsymbol{\varepsilon}$ are (Cauchy) stresses and infinitesimal strains, $\mathbf{C}$ is a stiffness tensor, and the operator ":" denotes a double inner product. Equation 1 is often expressed in matrix equation form as

$$\begin{bmatrix}\sigma_{11}\\ \sigma_{22}\\ \sigma_{33}\\ \sigma_{23}\\ \sigma_{13}\\ \sigma_{12}\end{bmatrix}=\begin{bmatrix} C_{1111} & C_{1122} & C_{1133} & C_{1123} & C_{1113} & C_{1112}\\ & C_{2222} & C_{2233} & C_{2223} & C_{2213} & C_{2212}\\ & & C_{3333} & C_{3323} & C_{3313} & C_{3312}\\ & & & C_{2323} & C_{2313} & C_{2312}\\ & Sym & & & C_{1313} & C_{1312}\\ & & & & & C_{1212}\end{bmatrix}\begin{bmatrix}\varepsilon_{11}\\ \varepsilon_{22}\\ \varepsilon_{33}\\ 2\varepsilon_{23}\\ 2\varepsilon_{13}\\ 2\varepsilon_{12}\end{bmatrix}, \tag{2}$$

in which the fully populated stiffness tensor is representative of a fully anisotropic material.

In the isotropic case, the constitutive Equation 1, may also be expressed as

$$\boldsymbol{\sigma}=\lambda e\mathbf{I}+2\mu\boldsymbol{\varepsilon}, \tag{3}$$

where λ and μ are so-called Lamé constants, $\mathbf{I}$ is the identity tensor, $e = \mathrm{Tr}(\varepsilon)$ is the infinitesimal cubic dilatation, and $\mathrm{Tr}(\cdot)$ is the trace operator.

As mentioned, a significant limitation of linear elastic models is their inability to account for the time dependence of mechanical response. In spite of this, such models have been applied to the study of cartilage, particularly in the analysis of indentation tests (Hayes, Keer, Herrmann, & Mockros, 1972; Hoch, Grodzinsky, Koob, Albert, & Eyre, 1983; Hori & Mockros, 1976; Jin & Lewis, 2004; Jurvelin et al., 1987; Jurvelin et al., 1990; Jurvelin et al., 1988; Kempson et al., 1971a; Kempson, Spivey, Swanson, & Freeman, 1971b; Newberry, Zukosky, & Haut, 1997; Sakamoto, Li, Hara, & Chao, 1996) and joint contact problems (Blankevoort, Kuiper, Huiskes, & Grootenboer, 1991; Carter & Wong, 2003; Chand, Haug, & Rim, 1976; Eberhardt, Keer, Lewis, & Vithoontien, 1990; Eberhardt, Lewis, & Keer, 1991a, 1991b; Meakin, Shrive, Frank, & Hart, 2003). In such situations, linear elastic solutions may be interpreted as representing instantaneous (time, $t \to 0$) or equilibrium responses ($t \to \infty$) (Armstrong et al., 1984).

Monophasic Viscoelastic Models

In order to account for time and strain rate dependence of mechanical response, a number of investigators have proposed single-phase (monophasic) viscoelastic (MPVE) models for cartilage. Initial models were derived from analogies with arrangements of mechanical spring and dashpot (viscous dampers) elements (Coletti, Akeson, & Woo, 1972; Hayes & Mockros, 1971; Parsons & Black, 1977)—whence the name *viscoelastic* was derived. These models were inherently one-dimensional, however, and were therefore of limited use. Of much greater utility were subsequent continuum-based formulations, for example, Fung's quasi-linear viscoelasticity (e.g., see [Fung, 1993] and the references cited therein). Such models extend elastic formulations by incorporating so-called relaxation functions $G(t)$—typically exponential functions in time—which effectively convert constant elastic moduli (e.g., λ and μ) into functions of time t. Most commonly, isotropic symmetry is assumed, so that the constitutive equation may be presented as a generalization of Equation 3 in the form of a convolution integral:

$$\boldsymbol{\sigma}(t)=\lambda\int_0^t G(t-t')\frac{\partial(e\mathbf{I})}{\partial t'}\mathrm{d}t'+2\mu\int_0^t G(t-t')\frac{\partial\mathbf{e}}{\partial t'}\mathrm{d}t', \tag{4}$$

where

$$G(t)=1+\int_0^\infty S(\tau)e^{-t/\tau}\mathrm{d}\tau \tag{5}$$

is the relaxation function,

$$S(\tau)=\begin{cases}\dfrac{\acute{c}}{\tau} & \text{for} \quad \tau_1\le\tau\le\tau_2\\ 0 & \text{for} \quad \tau<\tau_1,\tau>\tau_2\end{cases} \tag{6}$$

is a continuous relaxation spectrum, $\mathbf{e}=\boldsymbol{\varepsilon}-\frac{1}{3}e\mathbf{I}$ is the deviatoric strain component, $\tau_{1,2}$ are short- and long-term relaxation time constants, and $\acute{c}$ is the relaxation power spectrum magnitude.

In Equation 4, viscoelasticity is incorporated into both volumetric and deviatoric components of deformation. Both modes are here modeled with the same relaxation function $G(t)$, but this need not be so. Another common approach is to assign relaxation behavior to the deviatoric component only, so that Equation 4 reduces to

$$\boldsymbol{\sigma}(t) = \lambda e\mathbf{I} + 2\mu\int_0^t G(t-t')\frac{\partial \mathbf{e}}{\partial t'}\mathrm{d}t' . \qquad (7)$$

Finally, in place of the continuous spectrum relaxation function described above, $G(t)$ is often presented as a series of discrete exponentials (or Prony series):

$$G(t) = 1 + \sum_{K=1}^{N} G_K e^{-t/\tau_K} , \qquad (8)$$

where G_K are relaxation moduli, and τ_K are time constants.

Monophasic viscoelastic models have been applied in the analysis of cartilage in confined and unconfined compression (Bader et al., 1992; DiSilvestro et al., 2001a; DiSilvestro et al., 2001b; Hayes & Mockros, 1971), pure shear (Anderson et al., 1991; Hayes & Bodine, 1978; Hayes & Mockros, 1971; Spirt et al., 1989; Zhu et al., 1993), uniaxial tension (Simon, Coats, & Woo, 1984; Woo, Simon, Kuei, & Akeson, 1980), and indentation (Parsons & Black, 1977, 1979). They have also been widely applied in the analysis of other soft tissues, including brain (Miller, 1999; Miller, 2002; Miller & Chinzei, 1997, 2002; Miller, Taylor, & Nowinski, 2005), passive myocardium (Huyghe, van Campen, Arts, & Heethaar, 1991), and tendon (Pioletti & Rakotomanana, 2000).

Linear Biphasic Models

A second constitutive framework that accounts for time dependence of mechanical response is the linear biphasic (LBP) model introduced by Mow and coworkers (Mow et al., 1980); it describes the tissue as a binary mixture of immiscible solid and fluid phases. The tissue is envisaged as a porous linearly elastic intrinsically incompressible solid matrix permeated by an inviscid incompressible fluid. Neither phase is intrinsically dissipative. As a significant portion of the fluid is free to move under an imposed pressure gradient, loading and subsequent deformation of the tissue causes pressurization and flow of interstitial fluid. The time dependence of the tissue mechanical responses (e.g., creep and stress relaxation) is seen as a manifestation of the dissipative effects of this fluid flow. Although conceptually different, the LBP model is mathematically equivalent to the poroelastic model of Biot (Biot, 1941), assuming the fluid phase is inviscid (Simon, 1992). Since its introduction in 1980 (Mow et al., 1980), the LBP model has become the most widely employed formulation for modeling of cartilage mechanical behavior. It has also been used in modeling of such other biological tissues as brain (Miller et al., 2005; Taylor & Miller, 2004), skin (Oomens, van Campen, & Grootenboer, 1987), bone (Cowin, 1999), and tendon (Yin & Elliott, 2004).

The constitutive equations for the solid and fluid phases, and for the tissue as a whole are given by

$$\boldsymbol{\sigma}_s = \boldsymbol{\sigma}_E - V_s p\mathbf{I} , \qquad (9)$$

$$\boldsymbol{\sigma}_f = -V_f p\mathbf{I} , \qquad (10)$$

$$\boldsymbol{\sigma}_t = \boldsymbol{\sigma}_s + \boldsymbol{\sigma}_f = \boldsymbol{\sigma}_E - p\mathbf{I} , \qquad (11)$$

where $\sigma_{s,f,t}$ are solid, fluid, and total stresses, respectively; σ_E is the effective stress (interpreted as the stress component borne by the solid phase); p is the fluid pressure; and $V_{s,f} \in [0,1]$ are solid and fluid volume fractions, respectively. The solid phase is assumed to be linear elastic, so that in the most general case the effective solid stress may be given by Equation 1, that is,

$$\boldsymbol{\sigma}_E = \mathbf{C} : \boldsymbol{\varepsilon} \qquad (12)$$

where ε is the total elastic strain tensor. Important special cases of Equation 12 relating to different levels of material symmetry are described in sections below.

The continuity of both phases requires

$$\nabla \cdot \left(V_s \mathbf{v}_s + V_f \mathbf{v}_f\right) = 0 , \qquad (13)$$

where $\mathbf{v}_{s,f}$ are solid and fluid phase velocities, respectively. Under quasi-static conditions (so that inertial body forces may be ignored), the governing equations of motion are

$$\begin{aligned} \nabla \cdot \boldsymbol{\sigma}_s + \boldsymbol{\pi} &= 0 \\ \nabla \cdot \boldsymbol{\sigma}_f - \boldsymbol{\pi} &= 0 \end{aligned} , \qquad (14)$$

where

$$\boldsymbol{\pi} = \kappa\left(\mathbf{v}_f - \mathbf{v}_s\right) \qquad (15)$$

is the momentum exchange between the phases (associated with frictional drag forces arising from the relative velocity between phases), and κ is the diffusive drag coefficient. Coefficient κ is related to the hydraulic permeability k through

$$\kappa = \frac{V_f^2}{k} . \qquad (16)$$

While in the linear case k is treated as constant, it has been shown in reality to be strain dependent. To quantify the dependence, Lai and coworkers (Lai & Mow, 1980; Lai et al., 1981) proposed an exponential form that has often been employed (Boschetti et al., 2004; Holmes, Lai, & Mow, 1985):

$$k = k_0 e^{Me_s}, \tag{17}$$

where k_0 is the intrinsic (strain-free) permeability, M is a constant, and e_s is the solid dilatation. Models that employ this relation are, of course, no longer linear.

Isotropic Models

By far the most popular LBP models have been those that assume isotropic material symmetry for the solid phase. The effective solid stress in such models is then given by Equation 3:

$$\boldsymbol{\sigma}_E = \lambda_s e\mathbf{I} + 2\mu_s\boldsymbol{\varepsilon}, \tag{18}$$

where λ_s and μ_s are solid-phase Lamé constants. The isotropic LBP model is therefore defined by three parameters: λ_s, μ_s, and k.

Isotropic LBP models have been employed in the analysis of cartilage in confined (Hunter et al., 2003; Hunter, Noyes, Haridas, Levy, & Butler, 2005; Joshi, Suh, Marui, & Woo, 1995; Mow et al., 1980; Soltz & Ateshian, 1998; Spilker & Suh, 1990; Suh, Li, & Woo, 1995) and unconfined compression (Armstrong et al., 1984; Brown & Singerman, 1986; DiSilvestro et al., 2001a; DiSilvestro et al., 2001b; Joshi et al., 1995; Spilker & Suh, 1990), indentation (Athanasiou et al., 1995; Athanasiou, Liu, Lavery, Lanctot, & Schenck, 1998; Hale, Rudert, & Brown, 1993; Herzog et al., 1998; Mak, Lai, & Mow, 1987; Mow et al., 1989; Spilker, Suh, & Mow, 1992; Sweigart & Athanasiou, 2005b), joint contact (Ateshian, Lai, Zhu, & Mow, 1994; Ateshian & Wang, 1995; Donzelli & Spilker, 1998; Herzog et al., 1998; Hou, Holmes, Lai, & Mow, 1989; Wu, Herzog, & Epstein, 1997; Wu, Herzog, & Epstein, 1998, 2000; Wu, Herzog, & Ronsky, 1996), and impact studies (Atkinson & Haut, 1995; Atkinson, Haut, & Altiero, 1998).

Anisotropic and Inhomogeneous Models

There is some microstructural evidence that some cartilaginous tissues exhibit at least transversely isotropic symmetry. In view of this, a number of transversely isotropic LBP models have been proposed for the analysis of confined and unconfined compression (Bursac, Obitz, Eisenberg, & Stamenovic, 1999; Cohen, Lai, & Mow, 1998; DiSilvestro et al., 2001b; Lanir, 1987), indentation (Korhonen et al., 2002b), uniaxial tension (LeRoux & Setton, 2002), contact (Donzelli, Spilker, Ateshian, & Mow, 1999; Spilker, Donzelli, & Mow, 1992; Wilson, van Rietbergen, van Donkelaar, & Huiskes, 2003), and impact loading (Garcia, Altiero, & Haut, 1998). In such cases, the effective solid stress is given by Equation 1, with the stiffness tensor $\mathbf{C}$ of the form

$$\mathbf{C} = \begin{bmatrix} C_{1111} & C_{1122} & C_{1122} & 0 & 0 & 0 \\ & C_{2222} & C_{2233} & 0 & 0 & 0 \\ & & C_{2222} & 0 & 0 & 0 \\ & & & \frac{C_{2222}-C_{2233}}{2} & 0 & 0 \\ & Sym & & & C_{1313} & 0 \\ & & & & & C_{1313} \end{bmatrix}. \tag{19}$$

A small number of papers have reported the use of orthotropic LBP models. Bachrach, Mow, and Guilak (1998) used such a model in their examination of the commonly used incompressibility assumption for solid-phase elements of biphasic models, but no assessment of the performance of the model against more common test regimes as above was reported. More recently, Wang, Chahine, Hung, and Ateshian (2003) and Chahine et al. (2004) demonstrated experimentally the orthotropic symmetry (within the context of tension-compression nonlinearity) of articular cartilage. The solid phase stiffness tensor $\mathbf{C}$ in such cases is given by

$$\mathbf{C} = \begin{bmatrix} C_{1111} & C_{1122} & C_{1133} & 0 & 0 & 0 \\ & C_{2222} & C_{2233} & 0 & 0 & 0 \\ & & C_{3333} & 0 & 0 & 0 \\ & & & C_{2323} & 0 & 0 \\ & Sym & & & C_{1313} & 0 \\ & & & & & C_{1212} \end{bmatrix}. \tag{20}$$

A similarly small number of papers have reported the inclusion of cartilage heterogeneity into the

solid phase description—that is, depth-dependent stiffness. Wang, Hung, and Mow (2001) studied the effects of nonuniform moduli (using a finite deformation biphasic formulation, which will be discussed in the following section) on the chondrocyte mechanical environment, whereas Korhonen et al. (2002b) studied the implications for indentation response. In view of the abundance of experimental evidence for heterogeneity in cartilage, and the relative ease of including such effects in, for example, finite element analyses, the dearth of theoretical investigations is surprising.

Finite Deformation Biphasic Models

Linear biphasic models employ linear elastic constitutive formulations for the tissue solid phase, and are therefore strictly valid only for small deformation problems. Since cartilage deformations in vivo are conceivably large, a number of finite deformation biphasic (FDBP) models employing hyperelastic solid-phase formulations have been developed (Holmes & Mow, 1990; Kwan, Lai, & Mow, 1990). In such models, effective solid stresses are defined in terms of a Helmholtz free energy function:

$$\boldsymbol{\sigma}_E = \frac{\partial W}{\partial \mathbf{E}}, \tag{21}$$

where W is the Helmholtz fee energy per unit volume and $\mathbf{E}$ is an appropriate strain tensor (chosen so as to be energetically conjugate with $\boldsymbol{\sigma}_E$). Many forms for W are possible. Use of such a kinematic formulation leads to slight modifications of the expressions for momentum exchange π, and the strain-dependent permeability k (Ateshian et al., 1997; Holmes & Mow, 1990; Kwan et al., 1990). Finite deformation biphasic models have been applied in the analysis of confined compression (Ateshian et al., 1997; Kwan et al., 1990; Wang et al., 2001; Wayne, Woo, & Kwan, 1991), indentation (Suh & Spilker, 1994), and ultrafiltration (Holmes & Mow, 1990) of cartilaginous tissues. As many studies have found cartilage equilibrium moduli to be approximately linear over a reasonable strain range (Jurvelin et al., 2003; Khalsa & Eisenberg, 1997; Mow et al., 1980), it is unclear whether incorporation of a hyperelastic solid-phase model is of great importance—at least compared to the inclusion of finite deformation stress and strain measures, intrinsic viscoelasticity (see next section), or anisotropy.

Poroviscoelastic Models

Poroviscoelastic (PVE) models are generalizations of the LBP models that include flow-independent viscoelasticity in the solid-phase description. Only isotropic formulations have thus far been proposed (excepting the conewise poroviscoelastic formulation of Huang et al. [2001]; see next section), so the model is constructed by replacing the linear elastic effective solid stress equation (Equation 12) with either of the integral forms in Equations 4 and 7. Additionally, either continuous or discrete relaxation functions may be employed. Suh and Bai (1998) compared the two relaxation function formulations and found that results from the discrete formulation were little different from the continuous formulation, but the use of the former was significantly more computationally efficient.

Poroviscoelastic models have been used in the analysis of cartilage in confined and unconfined compression (DiSilvestro & Suh, 2001, 2002; DiSilvestro et al., 2001a; DiSilvestro et al., 2001b; Huang et al., 2001; Mak, 1986a, 1986b; Setton et al., 1993; Suh & Bai, 1998; Suh & DiSilvestro, 1999), volumetric (hydrostatic) compression (Ehlers & Markert, 2001), indentation (DiSilvestro & Suh, 2001; Ehlers & Markert, 2001), pure shear (Ehlers & Markert, 2001), and uniaxial tension (Huang et al., 2001).

Conewise Linear Biphasic Models

As discussed in the introductory paragraphs, cartilaginous tissues exhibit different tensile and compressive responses. That is, they are bimodular. In an effort to incorporate such a feature, Soltz and Ateshian (2000) used a conewise linear elastic constitutive formulation to describe the solid-phase response in the biphasic model. In its implemented form, the resulting conewise linear biphasic (CLBP) model has cubic mechanical symmetry. The effective solid stress equation (12) is replaced with Equation 22:

$$\boldsymbol{\sigma}_E(\boldsymbol{\varepsilon}) = \sum_{a=1}^{3}\left[\lambda_1(\mathbf{A}_a:\boldsymbol{\varepsilon})\,\mathrm{Tr}(\mathbf{A}_a\cdot\boldsymbol{\varepsilon}) + \sum_{b=1,b\neq a}^{3}\lambda_2\,\mathrm{Tr}(\mathbf{A}_a\cdot\boldsymbol{\varepsilon})\mathbf{A}_b\right] + 2\mu\boldsymbol{\varepsilon}, \tag{22}$$

where $\mathbf{A}_a = \mathbf{a}_a \otimes \mathbf{a}_a$ is a texture tensor corresponding to material directions $\mathbf{a}_a$, Tr(·) is the trace operator, ⊗ represents a dyadic product, and λ_2 is the "off-diagonal" modulus. The bimodularity of the formulation arises from the dependence of the Lamé constant λ_1 on the normal strain in the a^{th} direction:

$$\lambda_1(\mathbf{A}_a : \boldsymbol{\varepsilon}) = \begin{cases} \lambda_{-1} & \text{for} \quad \mathbf{A}_a : \boldsymbol{\varepsilon} < 0 \\ \lambda_{+1} & \text{for} \quad \mathbf{A}_a : \boldsymbol{\varepsilon} > 0 \end{cases}. \quad (23)$$

Conewise linear biphasic models have been used in the analysis of cartilage in confined and unconfined compression, pure shear, and uniaxial tension (Huang et al., 2001; Huang, Soltz, Kopacz, Mow, & Ateshian, 2003; Soltz & Ateshian, 2000). Wang et al. (2003) also used an orthotropic symmetry single-phase conewise linear elastic model to investigate the anisotropic equilibrium response of articular cartilage. The CLBP model has been further generalized to include a viscoelastic solid phase (Huang et al., 2001).

Analysis of the Macroscopic Models

By far the most popular model for describing cartilage behavior has been the LBP model of Mow and coworkers (Mow et al., 1980) (or equivalently, the poroelastic model), and its derivative formulations (e.g., the FDBP, PVE, and CLBP models). There are several reasons for the predominance of this framework over, for example, the MPVE formulations. Firstly, the biphasic formulations allow discrimination of stresses borne by the solid and fluid phases in the tissue. Such a feature may be of importance in, for example, analysis of damage or degenerative processes (Ateshian et al., 1994), where knowledge of the load proportion borne by solid components is required. Secondly, they allow computation of fluid flow fields within the tissue as a result of deformation. Such features have been used in the analysis of synovial joint lubrication mechanisms (Ateshian, Wang, & Lai, 1998; Kwan, Lai, & Mow, 1984), and investigations concerning fluid transport within cartilage (see [Mow, Holmes, & Lai, 1984]). And thirdly (and probably most importantly), the phenomenon of time dependence of mechanical response is explained on the basis of an experimentally established (Lai & Mow, 1980; Lai et al., 1981) physiological mechanism (i.e., dissipative fluid flow). In contrast, MPVE models are phenomenological in nature—they make no reference to underlying physiological mechanisms that give rise to the observed phenomena (i.e., time dependence, rate dependence, etc.), but simply provide equations with which certain of these phenomena may be predicted.

Although these are important points, there are also areas in which biphasic models have been shown to be inadequate. It may be seen from Equation 15 that LBP models predict dissipative effects only in cases in which there is appreciable relative velocity between the two phases. Clearly, such conditions (i.e., fluid flow) may occur only when the tissue undergoes volumetric deformation. This has important implications for the performance of the models in the analysis of cartilage response to different loading configurations. Many reports have described confined compression testing of cylindrical cartilage specimens (Mow et al., 1980; Soltz & Ateshian, 1998; Suh et al., 1995), and generally good agreement has been found with the response predicted with the LBP model. During such experiments, fluid is forced to flow from the tissue through the top surface of the specimen. Since the motion of the solid phase has no lateral components, and since both phases are considered incompressible, the relative phase velocity is then equal to the solid phase velocity; by careful specification of permeability and stiffness values, the observed time dependence can be satisfactorily explained. In the case of unconfined compression, however, impermeable load platens are generally used so that fluid flow must occur laterally. Since the solid components also expand laterally, the relative phase velocity must be small, meaning that dissipative effects will be much reduced. Brown and Singerman (1986) analyzed unconfined compression tests of fetal chondroepiphysis using an isotropic LBP model and found that it was inadequate for fitting experimental data, especially during the transient load phase. Armstrong et al. (1984) had earlier encountered similar difficulties but had attributed them to interfacial adhesion (or equivalently, friction) effects. Spilker, Suh, and Mow (1990) conducted numerical studies of the effects of friction and found that these could not wholly explain the discrepancies. Brown and Singerman instead suggested that since flow-related dissipation is necessarily small in unconfined compression, but significant dissipation is still observed, the solid phase itself must be recognized as inherently dissipative. A similar problem appears in the case of

tissue subjected to pure shear. Significant dissipation is observed experimentally (Hayes & Bodine, 1978; Zhu et al., 1993), yet the lack of any volumetric deformation precludes fluid flow, and so the LBP model predicts no dissipation. Again the inherent viscoelasticity of the solid phase is concluded.

Further difficulties arise when strain rate effects are considered. DiSilvestro et al. (2001a) tested articular cartilage in unconfined compression at various strain rates and found that the LBP model was unable to account for the observed strain rate dependence. Brown and Singerman reported similar findings in their study of chondroepiphysis (Brown & Singerman, 1986). Miller has also previously noted the inadequacy of LBP models in accounting for such effects (Miller, 1998). In each case, there is a clear implication that the flow-associated dissipation mechanism alone is inadequate. The MPVE model used by DiSilvestro et al. (2001a) was shown to account for the strain rate dependence of reaction force.

Such considerations led to the development of PVE models (Mak, 1986a), the most popular formulations of which included viscoelastic moduli in the deviatoric terms only (as in Equation 7). The justification for this is that since the biphasic mechanism acts during volumetric deformation, the inclusion of relaxation functions in volumetric terms would cause ambiguity regarding the contributions of each mechanism. DiSilvestro et al. (2001a; 2001b) compared the performance of the LBP, MPVE, and PVE models in the analysis of unconfined compression results. The MPVE model was of the form given in Equations 7 and 8, and the PVE solid phase used an identical formulation. It was found that the MPVE model could account for the reaction force very well, but not for the lateral displacement, whereas the LBP model could account for the lateral displacement but not for the reaction force. The PVE model was able to account for both data, leading the authors to conclude that inclusion of both the biphasic mechanism and the viscoelastic shear mechanism were necessary for a complete description.

An alternative interpretation may be given, however: models that include only shear (MPVE model) *or* volumetric (LBP model) dissipation mechanisms are inadequate, and dissipation mechanisms must be included for *both* deformation modes—as in the PVE model. If this more general statement is accepted, then it is possible that, for example, an MPVE model of the form of Equation 4 (i.e., with both deviatoric and volumetric relaxation terms) would perform just as well as the PVE model. Such a model was not investigated by those authors, and to our knowledge has not been investigated elsewhere.

It has also been suggested that the anisotropic nature of cartilage is an important confounding factor in the analysis of unconfined compression data with isotropic LBP models (Cohen et al., 1998). As a result, several authors proposed transversely isotropic LBP models. Cohen et al. (1998) reported good agreement between measured and predicted reaction force for confined and unconfined compression using such a model. However, DiSilvestro et al. (2001b) measured both reaction force and lateral expansion during unconfined compression and reported that the transversely isotropic LBP model was able to independently fit either data, but importantly was not able to fit both data with one set of parameters. Additionally, the fits of Cohen et al. were achieved using a value of 0 for the out-of-plane Poisson ratio, based on their observation that equilibrium axial stresses for confined and unconfined compression were almost equal (Cohen et al., 1998). However, as pointed out by Bursac et al. (1999), this implies that the radial confining stress in the confined compression experiment is also 0—a notion experimentally refuted by Khalsa and Eisenberg (1997), and by Bursac et al. (1999) themselves. When the relevant Poisson ratio is left unconstrained and the radial stress is included as a measured quantity, the model is unable to account for all data (Bursac et al., 1999). It would appear then that inclusion of both deviatoric and volumetric relaxation terms is more important than inclusion of anisotropy.

A further modification of the LBP model is the CLBP model of Soltz and Ateshian (2000). The motivation for such a model was the apparent tension-compression nonlinearity of cartilage response (see introductory paragraphs herein). The model also included anisotropic (cubic symmetry) properties. It was shown that reaction forces from both confined and unconfined compression experiments could be accounted for using this model (Soltz & Ateshian, 2000) but that reaction force and lateral expansion during unconfined compression could not be predicted simultaneously. This is similar to the problem encountered with the transversely isotropic LBP model and suggests that there may be

confusion regarding the precise nature of anisotropy and tension-compression nonlinearity in cartilage response. Features of the response attributed to anisotropy effects may in fact be manifestations of inherent tension-compression nonlinearity, or vice versa. Issues of this sort were studied recently by Wang et al. (2003), who claimed that both features were required for a full description of cartilage response. Reaction forces and lateral expansions were measured during compression of cube-shaped cartilage samples along three mutually perpendicular directions (linked to the split line directions). No direct measurements of tensile responses were conducted, however, so the issue appears to be still open.

To further extend the capabilities of the CLBP model, Huang et al. (2001) incorporated a viscoelastic solid-phase description. The resulting model could then account simultaneously for reaction forces from uniaxial tension and unconfined compression under stress relaxation and dynamic loading.

Microstructural Models of Mechanical Behavior

All of the models described thus far may be designated as macroscopic models since they make no consideration of the underlying structure of the tissue, but characterize the tissue only on the basis of its bulk mechanical response. They are therefore of limited use in, for example, assessing the effects of microstructural variation (e.g., concentration and morphology) of tissue components, which may arise among individuals or as a result of pathology. In response to this issue, various models based on microstructural features of the tissue have been proposed. A review of such models is presented in this section.

Fibril-Reinforced Biphasic Models

Fibril-reinforced biphasic (FRBP) models are here classified as microstructural models since they differentiate the contributions of fibrillar and nonfibrillar tissue components, and can incorporate specific fibril arrangements. Such models consider the tissue to consist of a linear biphasic continuum (representing a fluid-saturated proteoglycan matrix) reinforced with fibrils. The fibrils are considered to support load in tension only, so that compressive loads are carried by the biphasic continuum and tensile loads are supported by both biphasic and fibril components. One of the primary strengths of these models is that fibrillar and nonfibrillar solid components are modeled separately. This is in contrast to other biphasic models described above, which *lump* all solid components together, and in doing so mask the potentially different manner in which each component may support load.

Although introduced as recently as 1999 (Soulhat, Buschmann, & Shirazi-Adl, 1999), significant development of the theme has occurred. The first formulation (Fortin, Soulhat, Shirazi-Adl, Hunziker, & Buschmann, 2000; Soulhat et al., 1999) modeled the fibrils as bimodular elastic with a tensile Young's modulus $E^{+}_{fib} > 0$ and a compressive modulus $E^{-}_{fib} = 0$. A cylindrical specimen was modeled with a homogeneous distribution of fibrils in cylindrical (r, θ, z) coordinates. Li and coworkers (Li, Buschmann, & Shirazi-Adl, 2001, 2002a; Li, Soulhat, Buschmann, & Shirazi-Adl, 1999) produced a finite element version that modeled fibrils as springs with strain-dependent stiffness given by

$$E_{fib} = \begin{cases} E^{\varepsilon}_{fib}\varepsilon_{fib} + E^{0}_{fib} & \text{for} \quad \varepsilon_{fib} > 0 \\ 0 & \text{for} \quad \varepsilon_{fib} < 0 \end{cases}, \quad (24)$$

where ε_{fib} is the fibril strain, and E^{ε}_{fib} and E^{0}_{fib} and are constants. Korhonen et al. (2003) also used this model to simulate the effects of extracellular matrix degradation. The model was further expanded to include depth-dependent biphasic and fibril parameters (Li, Buschmann, & Shirazi-Adl, 2000, 2003; Li, Shirazi-Adl, & Buschmann, 2002b). Li and Herzog (2004) developed a continuum finite element formulation for the fibrillar network response (as opposed to implementation with discrete spring elements as in earlier models), and used it to assess the resulting strain rate sensitivity of the model. Wilson, van Donkelaar, van Reitbergen, Ito, and Huiskes (2004) also developed a continuum formulation, but they included a strain-dependent viscoelastic constitutive model for the fibrils and a more microstructurally realistic arcade-like fibril arrangement. Depth-dependent properties were also included in this model. The viscoelastic fibril formulation was based on a mechanically analogous arrangement of parallel springs and dashpots. A quasi-linear viscoelastic fibril formulation using a relaxation

function similar to Equation 8 was incorporated by Li, Herzog, Korhonen, and Jurvelin (2005). Finally, Wilson, van Donkelaar, van Reitbergen, and Huiskes (2005) extended their model to include proteoglycan-related swelling effects.

As noted, the key contribution of these models is the distinction of roles played by fibrillar and nonfibrillar solid components. Additionally, such models may naturally incorporate both mechanical anisotropy and bimodularity as a result of the specific arrangement of fibrils and the bimodularity of the fibrils themselves. On this point it must be noted that most of the FRBP models presented do not in fact incorporate realistic fibril arrangements but instead use some regular axisymmetric assembly (Li et al., 2000, 2002a, 2003; Li & Herzog, 2004; Li et al., 2005; Li et al., 2002b; Li et al., 1999). Recent formulations by Wilson and coworkers (Wilson et al., 2004, 2005) rectify this by employing fibril arrangements based on the arcade description of Benninghoff (Benninghoff, 1925). Nonetheless, all such models achieve the aim of differentiating fibrillar and nonfibrillar contributions.

A second prominent feature is their use of strain-dependent fibril stiffness (Li et al., 1999). As such, they provide a mechanism for the well-documented strain dependence of cartilaginous tissues (see introductory paragraphs)—a feature lacking in the macroscopic models discussed. Such a feature contributes significantly to the model's response (Li et al., 1999). Some recently developed viscoelastic FRBP models (Li & Herzog, 2004; Li et al., 2005) also suggest the importance of collagen fibril viscoelasticity in cartilage mechanical response, especially with respect to its strain rate dependence.

Homogenization Models

A number of authors have developed models based on theories of the mechanics of composite materials. Homogenization theories allow computation of the effective properties of a heterogeneous material from its constituent material properties and geometric configuration. This is achieved through requiring that "under a given state of deformation a sample of the composite material and a like sample of an equivalent homogeneous material possess the same amount of stored energy" (Christensen & Waals, 1972). Various methods have been developed for deriving effective material properties based on such ideas.

Wu et al. (1999) and Federico, Herzog, Wu, and Rosa (2004) treated cartilage as a particulate composite with chondrocytes modeled as spheroidal inclusions embedded in an amorphous solid matrix. This allowed estimation of the effects of variations in chondrocyte concentration, morphology, and arrangement on overall tissue mechanical response. In both models, collagen fibers and ground substance were treated as an amorphous matrix phase. In the case of Wu et al. (1999), both matrix and cells were biphasic so that time-dependent effects could be included (within the limits of regular LBP models discussed previously). The particulate composites approach was also used by Wu and Herzog (2002) but with the explicit inclusion of fibrous structures in the form of spheroids of zero (horizontal) and infinite (vertical) aspect ratio. This expanded model therefore addressed the influence of cellular inclusions, as well as vertical and horizontal collagen fibers. The model did not allow arbitrary orientation of collagen fibers and treated only the elastic response of the tissue. Finally, Federico, Grillo, La Rosa, Giaquinta, and Herzog (2005) presented a further generalized model that included statistical distributions of fibrils (again in the form of elongated spheroids) and cells embedded in an elastic matrix, which then formed the solid phase of a biphasic model. Fibril orientation distributions were assumed from qualitative observations in the literature.

An important determinant of mechanical anisotropy and heterogeneity of cartilage is probably the microstructural arrangement of fibrous tissue components. Several fiber composite–based models have therefore been developed so that the effects of such arrangements may be incorporated directly. Ault and Hoffman (1992a) and Schwartz, Leo, and Lewis (1994) used the composite cylinders model of Hashin and Rosen (1964) and Hill (1964) as a basis for incorporating constituent material properties in the overall tissue response. An averaging procedure expounded by Christensen and Waals (1972) was used in such cases to incorporate fiber orientation information so that the resulting estimate of tissue response was a function of constituent material mechanical properties, concentration, and microstructural arrangement. Ault and Hoffman incorporated experimentally derived two-dimensional fiber orientation distributions (Ault & Hoffman,

1992b). This theory was further used by Simha, Fedewa, Leo, Lewis, and Oegema (1999) to study the response of cartilage culture tissues. In each case, fiber and matrix materials were considered linearly elastic and isotropic so that no account was made of strain rate sensitivity or time dependence of mechanical response. A viscoelastic composite cylinders model was recently used to model brain stem dynamic response (Arbogast & Margulies, 1999). Owing to the parallel arrangement of axonal fiber bundles in the brain stem, the fiber components were treated as completely aligned, and the averaging procedure of Christensen and Waals (1972) was not required. Since the fibrils in cartilage do not necessarily align with one particular direction, a weighted averaging of fibril responses is a necessary process. Similar averaging was used in the models of Farquhar, Dawson, and Torzilli (1990) and Wren and Carter (1998) (see next section) to account for the directionality of microstructural components. Unlike the particulate theories described above, these fiber composite–based models do not include the effects of cellular inclusions. Because of their significantly lower stiffness, cells act almost like voids in the tissue (Federico et al., 2005) and can therefore affect the tissue's response. Federico et al. (2005) further justify the incorporation of cellular inclusions by citing studies showing cell volume concentrations of up to 20% in small animals. In human cartilage, however, concentrations are generally much lower (Hunziker, Quinn, and Hauselmann [2002] report a value of 1.65%). Even though cellular inclusions certainly enhance the completeness and applicability of the models, it is the collagenous and matrix components, by virtue of their higher concentration and much higher stiffness, that contribute most to the tissue response.

Several authors have also developed numerical homogenization schemes for the assessment of engineered tissues (Agoram & Barocas, 2001; Breuls, Sengers, Oomens, Bouten, & Baaijens, 2002; Sengers, Donkelaar, Oomens, & Baaijens, 2004). These models employ multiscale finite element analyses in which macroscopic properties are derived from the effective response of a periodic microscale model. The microscale model incorporates microstructural details—cell and pericellular matrix distributions in the cases of Breuls et al. [2002] and Sengers et al. [2004] and fibrous components in the case of Agoram & Barocas [2001]—of a representative volume element. The response of this model is then used as the basis for assigning properties in the macroscale model. Assuming adequate computational resources, such an approach is useful as it allows the incorporation of a wide range of microstructural features.

Along with brain stem as mentioned above, homogenization techniques have also been used to model the response of tissues other than cartilage. Yin and Elliot (2005) used the method in a model of annulus fibrosus, which accounted for two populations of aligned fibers. Hollister, Fyhrie, Jepsen, and Goldstein (1991) proposed a model for trabecular bone, whereas Crolet, Aoubiza, and Meunier (1993) and Aoubiza, Crolet, and Meunier (1996) proposed models for compact bone, taking account of the material's Haversian microstructure.

Homogenization models directly relate tissue response to constituent material properties. In the case of the fiber- and particulate composite–based approaches, there are also direct relations between the geometric arrangement and concentration of structural elements. These models therefore provide a natural framework for assessment of microstructural variation.

Miscellaneous Microstructural Models

Farquhar et al. (1990) presented a model for the equilibrium elastic response of articular cartilage. The tissue was conceptualized as a composite of collagen fibrils and a charged proteoglycan ground substance. Constitutive responses for individual fibril and ground substance units were defined, and the overall tissue response was obtained from a weighted sum of fibril contributions from all directions plus an additional proteoglycan-swelling pressure. Such a summation is similar to the procedure used by Ault and Hoffman (1992a) and Schwartz et al. (1994). By explicitly summing fibril and swelling contributions, the model bears similarity to FRBP models, which instead sum fibril and biphasic continuum responses.

A later model developed by Wren and Carter (1998) adopted a "rule of mixtures" approach to compiling fiber and matrix response contributions. The rule of mixtures may be shown to be a special case (for which fiber and matrix phase Poisson ratios are equal) of the Hashin and Rosen homogenization model (Hashin & Rosen, 1964) mentioned above.

Wren and Carter incorporated nonlinear fiber and matrix responses and also an orientation distribution-weighted fiber summation scheme similar to above (Wren & Carter, 1998). Significant emphasis was placed on describing the failure behavior of fibrous tissues, and this motivated the selection of fiber and matrix constitutive models. However, combining constituent responses using the rule of mixtures has been shown to give a simplistic estimation of overall response (Christensen & Waals, 1972).

Finally, Bursac, McGrath, Eisenberg, and Stamenovic (2000) presented a model based on regular arrays of elastic interconnected cables (representing collagen fibrils) encasing a pressurized proteoglycan solution. Cables were arranged into either hexagonal or triangular networks. Comparisons were made with confined compression test data. A key achievement of the modeling approach was the separation of fiber and matrix load-bearing modes, as was done in the FRBP models. As fibers assumed a regular (and not necessarily physiological) geometric arrangement, the model is unable to predict the effects of varying fibril orientations.

Conclusions

The mechanical response of cartilaginous tissues is complex, and the importance of such tissues to the function of synovial joints has motivated several decades of investigation of this response. In particular, significant effort has been devoted to the development of comprehensive constitutive models of these tissues. Linear biphasic models have been the most popular and have been useful in describing various phenomena, but have also been shown to be inadequate for describing many aspects of tissue mechanical response. Similarly, MPVE models have been successful in describing certain features but less successful in other areas. Significant development of the biphasic theme has occurred, mainly in the form of PVE, CLBP, and FRBP formulations.

This review has highlighted a number of areas in which investigation is still required. The precise nature of the apparent tension-compression nonlinearity of cartilaginous tissues is still unclear, and in particular its relation to tissue anisotropy. Clarification of this relationship and the distinct roles played by each feature is required. Additionally, clarification of the roles and relative importance of flow-related dissipation mechanisms and intrinsic viscoelasticity (or equivalently, volumetric and deviatoric dissipation mechanisms) is required. From a constitutive modeling point of view, it would appear that recent CLBP and FRBP formulations, both of which include viscoelastic solid phase components, are the most promising candidates for such investigations. The significance of tissue heterogeneity to tissue and joint function is an area of further potential enquiry.

Various microstructural models were also discussed. Such models offer significant potential for insight into mechanisms of tissue response, and relations between tissue structure and function. Fibril-reinforced biphasic models have been successful in explaining many of the phenomena that have escaped clarification with most macroscopic models. Homogenization approaches offer a means of directly investigating the effects of variation in structural arrangement, but most models have so far used only simplified elastic formulations or biphasic mechanisms, which, as mentioned, have been shown to be inadequate in many cases.

Although a high level of maturity has been reached, there would thus appear to be many avenues for investigation in the field of cartilaginous tissue constitutive modeling.

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