STATE VARIABLES FOR MODELLING PHYSICAL ASPECTS OF ARTICULAR CARTILAGE

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Abstract—Deformation in soft biological connective tissue is intimately coupled to interstitial fluid movement, tissue solute concentration, and electrical fields. The role of deformation and of the associated electrical and chemical gradients in connective tissue physiology is currently unknown, and is of major interest in the study of growth, healing, and remodelling in the tissue. A quantitative study aimed at assessing relevant physiologic effects in connective tissue awaits accurate physical analysis. This paper reviews the available poroelasticity formulations with specific emphasis on establishing physically relevant continuum variables and on methods for including coupling between electrical or chemical gradients and deformations, then proposes a new set of state variables useful for engineering analysis of the tissue. Since solid and fluid components intermingle on a molecular scale, phase boundaries do not exist and thus a porosity cannot be defined. Further, in a material which includes fixed charge groups, which must be balanced by mobile species to maintain electroneutrality, the physics inside the tissue are not amenable to standard analysis. Relevant continuum state variables can be defined relative to a reference medium, however. The chemical, electrical, and mass transfer potentials of a differential element are defined by the potentials of a medium into which an excised differential element can be immersed at constant strain without transferring energy. Given this new definition of state variables, an energy differential is written, and a new incremental equation of state is derived based on a definition of coenergy.

INTRODUCTION

Biological connective tissue, particularly the "soft" tissues of animals, is ubiquitous. It both contributes to vertebrate survival through the natural selection process and is the site of many disorders in them. The rheology of connective tissues (such as cartilage, tendon, and ligaments) has been explored by many biomedical scientists in the continuing effort to understand physiological function through quantitative study. While these studies have produced many theories on the role of various mechanical factors affecting tissue physiology, the extant literature shows that even the most mundane physical explorations of a biologic function strain the limits of current mechanical analysis techniques. Viscera often deforms in highly complex patterns, undergoes large strains, and is physically coupled to concentrations of water and solutes. Such behavior often renders even the most sophisticated numerical analysis techniques inadequate.

In the face of this dilemma, the fundamental question to be addressed is not how to make models of arbitrary complexity, but what level of complexity is necessary and sufficient to answer the research question at hand. Clearly, the inaugural model should most simply represent (qualitatively) the physics judged most important. Recourse to more complex models is warranted only when extant tissue models clearly ignore important physical considerations or fail to predict relevant behavior.

This paper will review the relevant literature describing models for connective tissue, review pertinent elements of the theory of fluid infiltrated media, and propose a set of state variables for biological connective tissue considered appropriate for the understanding of physiologic function. Adult mammalian articular cartilage is emphasized here, but the results of this analysis should apply to connective tissues in general and to other osmotically active materials.

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ARTICULAR CARTILAGE

Articular cartilage lines all mammalian joints. When healthy, dense, and whitish, it endows joints with the ability to move with very low friction and often lasts many years without perceptible wear. This unique tribology has motivated study of synovial joints and cartilage as a lubrication system. In almost 10% of older adults, however, the tissue has deteriorated to the point where pain occurs. Since adult cartilage is without nerves or blood circulation, this indicates that the process of wear in the joint has affected the supporting bone. The resulting condition is referred to as osteoarthritis, distinct from rheumatoid arthritis, which is primarily an autoimmune condition. Joint lubrication and the possible role of mechanical factors in osteoarthritis have made articular cartilage the most extensively studied vertebrate soft tissue, producing perhaps a better understanding of the relevant physics in cartilage deformation than in deformation of any other biological tissue.

In reviewing the existing literature on the mechanics of cartilage, one must keep in mind the variety of approaches used. The geometric scope of these studies, the research questions posed, and the approximations made differ widely from study to study. Much of the controversy between investigators in this sub-field stems from differences in scope and interpretation rather than differences in data. For instance, the approximations used for cartilage behavior in a global analysis of a joint are clearly not appropriate for one-dimensional confined compression tests on cartilage samples. Also, solutions of two-dimensional boundary value problems where cartilage layers are loaded by a free-draining indenter provide only scant insight into the operating characteristics of a joint consisting of two opposing cartilage layers in contact and under relative motion.

Elastic and viscoelastic studies have been done by Hayes *et al.* (1972) and Woo *et al.* (1980) in order to understand the studies of Kempson (1979) who correlated *in situ* short-term indentation stiffness with biologic assays of the tissue. McCutchen (1982) has shown, however, that for the analysis of lubrication, poroelasticity must be used.

POROELASTICITY

For some time now, cartilage has been recognized as a porous elastic material, and the flow of fluid through it has been studied in some detail. For the most part, analyses have employed established poroelasticity formulations arising in the engineering mechanics literature, with some additions to account for osmotic and electrical effects in the tissue.

Much of the early work on cartilage relative to lubrication is due to McCutchen (1962, 1975, 1978, 1980, 1982) who proposed the "weeping lubrication" theory, and who showed through several simple but definitive experiments that articular cartilage is self-lubricating during deformation due to movement of fluid out of the tissue and into the space between cartilage and whatever surface it rubs against. Experiments in which cartilage was opposed to glass surfaces under static loading explored the effects of resoaking and altered salt concentrations over time; some boundary lubrication effects of synovial mucin were also studied. Although these experiments were based on a very simple model for articular cartilage, many of the results have yet to be surpassed. McCutchen's experiments are excellent examples of the axiom that the model necessary for an analysis depends heavily on the physics one wishes to study. McCutchen's cartilage layer model was essentially a two-dimensional distributed series of springs and dashpots (McCutchen, 1975), and included a representation of the flow of fluid between the cartilage layers. More sophisticated experiments and computerized calculations on the global human hip joint using similar models by Tepic' (1982) which incorporate precise three-dimensional cartilage layer geometry and measured constitutive data have produced results consonant with McCutchen's predictions.

Mow and co-workers (1979, 1980, 1984, 1986) have published extensively on poroelasticity in cartilage, and has focused on the detailed mathematical analysis of McCutchen's weeping lubrication hypothesis using mixture theory. To this end, Torzilli and Mow (1976a, b) formulated and solved a boundary value problem in which a layer of cartilage is loaded by a stress field with a free-draining surface. McCutchen (1977), however, noted substantial errors in both the formulation and solution of that boundary value problem.

Subsequent reformulation of the analysis, closely following the developments of Craine *et al.* (1970) has been made (Mow and Lai, 1979, 1980). A specialization to mutually incompressible constituents was made using the method of Mills (1966), as suggested by Craine *et al.* (1970) and used by Kenyon (1976a, b). A term which accounts for osmotic swelling was later added to the constitutive equations, but no physical motivation for the form of this addition was given. Subsequently, large deformation effects have also been added into the theory (Mow *et al.*, 1986).

In connection with the rheological study, one-dimensional analysis of confined cartilage specimens has also been conducted for the theories above. Curve fits between the predictions of the above analyses and experimental data have been used to determine material coefficients which best represent experimental data. As material and geometric nonlinearities were incorporated into the analyses, the experimental data was fit with increasing accuracy (Mow *et al.*, 1986). Whether this reflected better knowledge of the physical processes or better fits due to more undetermined parameters is unclear, however, since independent determination of material properties was not undertaken.

Several two-dimensional boundary value problems in cartilage have been solved using a linear mixture theory formulation (Kwan *et al.*, 1984). Brown and Singerman (1986) have recently tried without success to fit the results of one such solution to experimental data. It appears that improper boundary conditions in the theoretical analysis made the curve fitting unsuccessful.

Two general poroelastic formulations are available. A total stress formulation, where pore pressure is an extra potential which couples fluid flow into the stress field, and mixture theory, where the total stress is broken up into stresses acting on each constituent. When modelling a chemically inert solid containing a chemically inert fluid, the two treatments are identical theoretically, but given the physical characteristics of cartilage, and the physical processes to be represented by models for the joint (particularly electric and osmotic effects), theory based on extensions of Biot theory offers the clearest and most concise analytical method.

Biot (total stress) theory et sequalae

The now-classical work of Biot (1941, 1973) forms the basis of most of the current analyses of fluid-infiltrated solids. Rice and Cleary (1976) and Cleary (1978) have recently provided some important and very useful extensions of Biot's work, providing a basis for enhanced resource extraction techniques for the energy industry. In this formulation, the porous material is modelled as a linearly elastic solid skeleton which entraps a compressible inert fluid. The total stress on a solid element and the pore pressure are taken as state variables, and under a condition of reciprocity, the isotropic case requires only four material constants: G and v, the shear modulus of the solid skeleton and the "drained Poisson ratio" (i.e. the Poisson ratio for loading under constant pore pressure); and B and v^*, the back-stress coefficient and the undrained Poisson ratio (i.e. the Poisson ratio for loading under constant fluid mass density).

To apply this theory to soft tissues, we first note that cells make up less than 5% of the volume of articular cartilage, so they are usually ignored in the study of mechanical factors. The extracellular space in articular cartilage is composed of four major components: an interconnected array of collagen fibrils, which forms the primary structural component; very high molecular weight proteoglycan aggregates entrapped within the collagen matrix; water; and small ionic solutes. The proteoglycan aggregates are made up of a hyaluronate central chain, linked (via an intermediate protein) to many protein chains, each of which is covalently linked to many long sugar chains. The sugar chains are approximately 40 nm long; the protein chains are 300–400 nm long and the central hyaluronate length is approximately 1.2 μm in length. The huge number of negatively charged sugar groups in these aggregates requires moderately high concentrations of mobile cations to maintain electroneutrality, and these concentrations, relative to those in the joint fluid, cause an osmotic pressure within the tissue estimated to be 1–2 atm (Maroudas, 1979; Maroudas *et al.*, 1985). This osmotic pressure is resisted by the collagen matrix, resulting in tension within the fibrils at zero strain (Tepic' *et al.*, 1983). The collagen fibrils have water

partially bound to them and molecular entanglement between proteoglycans and collagen is postulated (Freeman, 1979). Mobile ions are attracted to both proteoglycans and collagen. Thus all components of the extracellular matrix in cartilage are intermingled on a molecular scale.

In a molecularly disperse material such as cartilage, care must be taken to choose variables which describe the material state in a physically meaningful manner. Since the pore fluid and the solid are intermingled on a molecular scale, phase boundaries do not exist, thus a "porosity" of the material cannot be defined in a meaningful sense. More precisely, if one wishes to define a porosity in a macroscopic continuum sense, one must be able to identify constituents in a microscopic continuum sense. That is, each "phase" must consist of many contiguous smaller units (molecules here) so that a definite identification of the phase can be made.

Given this caveat, the pore fluid pressure can be interpreted as follows. Imagine cutting a differential volume element from the material, keeping the mass, fluid content and shape constant, and immersing the element in a reference fluid phase: the pore pressure is then defined by Rice and Cleary as the pressure in the reference fluid necessary to prevent mass exchange.

With this definition of pore pressure, recourse to the energy differential in the porous material (see e.g. Rice and Cleary (1976) or Biot (1973))

$$dU = \sigma_{ij}\, d\varepsilon_{ij} + P\, dV \tag{1}$$

with σ_{ij} the total stress, $d\varepsilon_{ij}$ the increment in solid strain, P the fluid pressure, and dV the volume of fluid exchanged per unit sample volume, yields the following natural interpretations of apparent fluid volume and fluid density: the apparent incremental fluid volume exchanged in an energy transfer is the volume change of fluid in a reference reservoir, at the given pore pressure, which would result in an equivalent energy transfer. The fluid density would then be the density of reference fluid at the given pore pressure.

Consideration of fluid mass transport is the only aspect of the Rice and Cleary formulation which requires consideration of an apparent volume fraction of fluid, here defined unambiguously by using a reference fluid medium.

Using this formulation, the equilibrium equations are the same as in classical elasticity. The constitutive relations are

$$2G\varepsilon_{ij} = \sigma_{ij} + \frac{v}{1+v}\sigma_{kk}\delta_{ij} + \frac{3(v_u - v)}{B(1+v)(1+v_u)}P\delta_{ij} \tag{2}$$

$$m - m_0 = 3\rho_0 \frac{v_u - v}{B(1+v)(1+v_u)}\left(\sigma_{kk} + \frac{3}{B}P\right) \tag{3}$$

where B can be identified by an increase in the hydrostatic stress with constant fluid mass content as

$$\Delta P = B\frac{\sigma_{kk}}{3} \tag{4}$$

and the compatibility equations are

$$\nabla^2((1+v)G_{ij} - v\sigma_{kk}\delta_{ij}) + \frac{\partial^2\sigma_{kk}}{\partial x_i \partial x_j} + \frac{3(v_u - v)}{B(1+v_u)}\left[\nabla^2 P\delta_{ij} + \frac{\partial^2 P}{\partial x_i \partial x_j}\right] = 0. \tag{5}$$

To close the system of equations, Darcy's law and fluid continuity can be stated as

$$q_i^f = -\rho_0 K\left(\frac{\partial P}{\partial x_i} + f_i\right)$$

(6)

$$\frac{\partial q_i^f}{Fx_i} + \frac{\partial m}{\partial t} = 0$$

(7)

where q_i^f is mass flux, ρ_0 the (reference) fluid density, and m mass content. There are many advantages to this approach over the mixture formalism (summarized below) and they are substantial. In a total stress formulation, the simpler mathematics maintains the clarity of the physics involved. By contrast, the equations and manipulations necessary in partial stress methods often complicate interpretations to the point where the physics become obscured. Volume fractions in this total stress formulation are defined only for the purposes of fluid transport, and thus molecularly disperse media can be approached directly, with one extra parameter needed to define the fluid mass increase due to hydrostatic pressure at constant strain.

A very useful reduction to a field equation is also given in Rice and Cleary, which is

$$c\nabla^2\left(\sigma_{kk} + \frac{3}{B}P\right) = \frac{\partial}{\partial t}\left(\sigma_{kk} + \frac{3}{B}P\right)$$

(8)

with

$$c = K\left(2G\frac{(1+v)}{(1-2v)}\right)\left(B^2\frac{(1+v_u)^2(1-2v)}{q(1-v_u)(v_u-v)}\right).$$

(9)

This specialization shows that pore pressure satisfies a diffusion equation if the hydrostatic total stress does. In one-dimensional confined compression, this leads naturally to a diffusion equation in pore pressure, a result that dates from Terzaghi (see Biot (1941)).

Mixture theory

Vodak (1981) has said "The theory of mixture, built on the principle of superposition of components tends toward one very old dream of the alchymists: it is attempting to express the property of the whole as a function of the property of its parts. ... The validity of the principle of superposition of the components is limited by the extent to which the components can be separated."

Drumheller (1978) has said, regarding the treatment of a porous solid using mixture theory, "In essence the need for the inclusion of density gradients can be removed by introducing the concept of volume fraction. On a physical level this implies microscopic separation between the constituents of the mixture. More directly said, the porous solid will be modelled by a theory for an immiscible mixture, whereas Muller's conclusions [1968] apply only to miscible mixtures in which microscopic separation does not exist and where volume fraction has no meaning."

Currently, the most widely published analysis of cartilage as a poroelastic material uses mixture theory as specialized to incompressible mixtures. This requires the use of volume fractions throughout the formulation to balance mass and to provide boundary conditions. Given the above quotes and the knowledge that cartilage is a miscible mixture, in which the solid and fluid intermingle on a molecular scale, the authors are surprised by the persistence and acceptance of the mixture theory approach. A discussion of the theory of mixtures and its shortcomings vis-à-vis cartilage is warranted to identify the specific weaknesses of this approach.

Mixture theory, as given by Truesdell (1969), considers a composite material as several overlapping continua, where the position of a material point of a given phase is studied as a function of initial position and time. Thus at each point, there are material particles of each phase. The density of each phase is taken as the mass per unit bulk volume, and the

stress on each phase is taken as an areal (or volume) average. Using these concepts, mass, momentum, and energy balances are written, with extra variables emerging to describe momentum, diffusion, and energy exchanges between phases.

Up to this point, the mixture formulation is perfectly valid without restriction, but the next two steps are quite controversial in the general case, and can introduce serious errors in the particular case of cartilage. They are (a) the restriction of the constitutive equations using the second law of thermodynamics, and (b) specialization to incompressibility.

Until Muller (1968) published a paper showing that diffusive fluxes between phases must be considered as primitive constitutive variables, no satisfactory statement of the second law of thermodynamics was available using mixture theory. Drumheller (1978) discusses the second law and its application to mixture theory applied to compaction of fluid-filled porous aluminum. The form of the second law used in a particular case depends heavily on the constitutive assumptions used. The interplay between constitutive assumptions and the second law is shown in Craine *et al.* (1970) and Green and Naghdi (1970). In these papers and two by Kenyon (1976a, b) an entropy inequality is generated and specialized using constitutive assumptions which relate terms in the inequality.

In the above studies the logic used to motivate constitutive assumptions is as follows: a set of deformation and temperature derivatives (with respect to time and space) is taken as primitive variables. These are solid strain e_{ij}, solid strain rate D_{ij}^s, fluid strain rate D_{ij}^f, relative velocity v_i^r, vorticity difference Λ_{ij}, and temperature T. The Helmholtz free energy, solid and fluid stresses σ_{ij}^s and σ_{ij}^f, respectively, entropy, heat flux q_i, diffusive forces π_i, and "extra heat fluxes" for each component are taken as dependent variables. Equipresence is assumed, but dependencies are pared down so that the entropy inequality can be satisfied for arbitrary temperature and deformation distributions and histories. Next the dependent variables are separated into equilibrium values and "extra" or "dynamic" components, and the independent variables are grouped into those which can be nonzero at equilibrium (i.e. a single constant temperature and constant component strains), and those which must be zero at equilibrium (e.g. differences in component velocities, velocity gradients, and temperature gradients).

In order to generate interrelations between equilibrium values the rate of entropy generation is taken to be minimum and equal to zero at equilibrium. Thus the derivative of entropy production with respect to each of the "non-equilibrium" variables is taken as zero at equilibrium. The "extra" or "dynamic" components are taken as polynomials in the "non-equilibrium" variables. Specializing to immiscible components, small deformations and rotations, and isotropy yields constitutive relations which are

$$\sigma_{ij}^s = \lambda_1 e_{kk}\delta_{ij} + 2\mu_1 e_{ij} + \gamma_4 \frac{\rho_f}{\rho_{f0}}\delta_{ij} - \dot{\alpha}T\delta_{ij} - \left[\frac{\rho_s}{\rho_{s0}}P\delta_{ij}\right]$$

$$+ \lambda_3 D_{kk}^s\delta_{ij} + 2\mu_3 D_{ij}^s + \lambda_4 D_{kk}^f\delta_{ij} + 2\mu_4 D_{ij}^f + c_1\Lambda_{ij}$$

$$\sigma_{ij}^f = \left(-K^f\frac{\rho_f}{\rho_{f0}} + \gamma_3 e_{kk} - \beta T\right)\delta_{ij} - \left[\frac{\rho_f}{\rho_{f0}}P\delta_{ij}\right] + \lambda_5 D_{kk}^s\delta_{ij} + 2\mu_5 D_{ij}^s$$

$$+ \lambda_2 D_{kk}^f\delta_{ij} + 2\mu_2 D_{ij}^f - c_1\Lambda_{ij} \hspace{3cm} (10)$$

$$\pi_i = c_3 v_i^r + \underline{\gamma_1 \frac{\partial}{\partial x_i}\left(\frac{\rho_f}{\rho_{f0}}\right) + \gamma_2 \frac{\partial e_{kk}}{\partial x_i}}$$

$$q_i = -k^h\frac{\partial T}{\partial x_i} + c_5 v_i^r.$$

Here, λ_i, μ_i, K^f, and γ_i are moduli, $\dot{\alpha}$ and β are thermal expansion terms, and k^h and c_i are transport coefficients. Reference solid and fluid densities are ρ_{s0} and ρ_{f0}, respectively, and actual densities are ρ_s and ρ_f. All but four terms of this relation are as derived by Crochet and Naghdi (1966). The underlined terms are as added by Green and Naghdi (1970), and

the terms in brackets are added using the method of Mills (1966) for incompressibility (discussed below).

INCOMPRESSIBILITY

Since partial stresses are used in the constitutive relations above, incompressibility must be added in as an extra constraint. Mills (1966), using a method suggested by Truesdell, approached mixtures of incompressible, immiscible, Newtonian fluids as follows. An expression for net dilation was written as

$$\frac{\rho_s}{\rho_{s0}} D_{kk}^s + \frac{\rho_f}{\rho_{f0}} D_{kk}^f + \frac{v_k^f}{\rho_{s0}} \frac{\partial \rho_s}{\partial x_k} = 0.$$

This expression, multiplied by a Lagrange multiplier p, was added to the entropy inequality and the above minimizing approach was used to generate constitutive equations which include the bracketed terms in eqns (10). Mow and Lai (1979) used the same approach, but used an equation for dilation which is the above equation divided by fluid volume fraction. Kenyon (1976b) started with a slightly different set of assumptions, and concentrated on a physically sound definition of pore pressure, with resulting equations equivalent to the above constitutive equations, without deformation rate effects.

Much controversy still surrounds the use of interacting continua to model porous solids, based primarily on the superposition of component stresses to arrive at macroscopic total stresses. In gases, such superposition corresponds to Dalton's law and is well accepted with a firm basis in statistical mechanics. A similarly satisfactory physical characterization of these partial stresses in solid–fluid mixtures such as connective tissues, is not evident.

The serious errors mentioned above in the application of mixture theory to connective tissue concerns the use of volume fractions. Since, as mentioned above, phase boundaries do not exist in connective tissue, the use of volume fractions to apportion stress and to balance mass cannot be defended physically. Since both the total stress formulations as given by Biot and the partial stress formulations use porosity, a reformulation of both theories is needed. In the mixture theory formulation, the specialization to mutually incompressible components directly incorporates porosity into the constitutive equations. Thus, since porosity cannot be defined in cartilage, the connection to microstructure implied by its use does not exist, and the already complicated connection between theory and experiment becomes still more abstruse.

The successful curve fits of Mow et al. (1986) deserve some comment in this context. Since porosity has no physical meaning in cartilage, one can interpret the results of Mow et al. as follows: given a poroelastic response, one can almost always find an imaginary poroelastic material with a definable porosity which has the required response. The curve fitting done by Mow et al. corresponds to the selection of such materials. The fitted moduli and permeabilities are within reasonable limits, but these studies must be judged carefully, since there was no independent confirmation of inferred properties.

In the total stress formulations, porosity only appears in mass balance equations, and thus an effective porosity can be clearly defined. The theory to follow will be based on total stresses. The approach taken is similar to the use of superposed reference states as suggested by Vodak (1981).

OSMOTIC AND ELECTRICAL EFFECTS

Osmotic effects in cartilage have been known almost as long as poroelastic effects. The importance of osmosis in cartilage is made clear by noting that in a joint, the bone-to-bone force is necessarily compressive. If joint tissues did not tend to imbibe fluid during low-stressed conditions, the fluid in the cartilage would be completely wrung out.

Studies of the biochemistry of cartilage (see e.g. Muir in Freeman (1979)) have shown high concentrations of proteoglycans in the extracellular space of articular cartilage, and,

as poroelastic effects in the tissue became known, the importance of osmotic effects within the poroelastic framework became apparent. Also, since proteoglycans are charged at physiological pH, electrical effects and the diffusion of charged solutes have been recognized as important.

Most of the early work characterizing solute and water distributions and investigating osmotic effects in cartilage is due to Maroudas (1979). Maroudas defined the fixed charge density in cartilage and used Donnan equilibrium to relate ionic concentrations in cartilage to those of the solution bath. Maroudas and others in her group also pioneered studies of the diffusivities of charged and uncharged solutes in cartilage.

Recently, Grodzinski (1983) applied many of the tools of electromechanics and electrochemistry to articular cartilage, yielding a substantial insight into the physical processes governing fluid and solute flow in articular cartilage and the streaming potentials due to that flow. The work of Grodzinski and co-workers regarding electromechanical transduction in collagen membranes has also led to an improved understanding of the processes which govern deformation in electro-osmotically active materials. The doctoral theses of Lee (1979) and Eisenberg (1983) have been very helpful in formulating the ideas to follow on cartilage electromechanics.

As mentioned above, the osmotic swelling pressure due to proteoglycan entrapment pre-tenses the collagen network in cartilage. Proteoglycans contain many negatively charged sugar groups which have positive ions associated with them to preserve electroneutrality. The net concentration of solvent (water) in the exchangeable space in the tissue is thus lower than in the synovial fluid. As a result, water tends to diffuse into the tissue and the net osmotic pressure results from a balance between diffusive flux and pressure-driven flux. The chemical potential of a solute is defined based on this argument.

The chemical potential is defined as the energetically conjugate variable for mass transfer of a solute. In ideal liquids, it has been defined as

$$\mu_i^c = RT \ln c_i \tag{11}$$

where c_i is the species concentration, R the gas constant, and T the absolute temperature, through statistical arguments. This definition is strictly accurate only in the limit of infinite dilution, but it is physically useful in low solute concentrations.

Although Grodzinski, Maroudas, and others have modelled solute and solvent flow in the tissue in detail, the tissue has usually been modelled as a mixture of incompressible constituents, and energy storage in the tissue has not been addressed. Although for pressures and deformations experienced by joints, cartilage can be considered incompressible in "undrained deformation", compressibility in the tissue can be used via the ultrasonic impedance as a powerful tool to study deformation and fluid flow in cartilage (see Tepic' et al. (1983) and Macirowski (1983)). Also, the study of energy storage in cartilage leads to a very useful view of reciprocity between energy transfer relations in the tissue, and to an equation of state.

AN EQUATION OF STATE FOR ARTICULAR CARTILAGE

To clarify the coupling between deformation and fluid, solute and charge density in cartilage, an equation of state seems essential. Since the physical and chemical processes which occur within cartilage are extremely complex, the state variables necessary for such an equation are not available if defined within the tissue. However, an effective equation of state for increments in energy can be arrived at by careful scrutiny of the reciprocity conditions as used by Rice and Cleary (1976) and by the use of a reference medium.

The concept of a reference medium relative to which energy transfers can be judged is anticipated by Rice and Cleary (1976) and used by Eisenberg (1983) to define a reference concentration for the tissue. Specifically, a reference medium is a medium such that if a differential volume element could be removed from the material and immersed in this medium without changing strains, no mass or current exchange would occur. The thermodynamic potentials of the material element can be taken as the potentials of a medium

necessary to prevent energy transfer at constant mechanical strain. Energy transfers due to the thermodynamic potentials can then be judged relative to the reference medium.

If energy changes which do not involve strains are considered to act relative to a differential element in the reference medium, the energy increment of a differential volume, per unit volume, is

$$dU = \sigma_{ij}\, d\varepsilon_{ij} + \psi\, dm + \mu^c\, dc + \Phi\, d\rho_e \tag{12}$$

where σ_{ij} denotes total stress; ε_{ij} denotes strain; dm, dc, and $d\rho_e$ are the increments in fluid mass content, concentration, and charge density, and ψ, Φ, and μ^c are the mass potential, electric potential, and chemical potential of the reference medium. The mass potential as defined by Biot (1973) is given by

$$\psi = \int_{P_0}^{P} \frac{dP}{\rho_r} \tag{13}$$

with ρ_r the reference fluid density, taken as a function of pressure P. Defining a complementary energy as

$$U' = \sigma_{ij}\varepsilon_{ij} + \psi m + \mu c + \Phi\rho_e - U \tag{14}$$

yields a complementary energy differential which is

$$dU' = \varepsilon_{ij}\, d\sigma_{ij} + m\, d\psi + c\, d\mu + \rho_e\, d\Phi \tag{15}$$

leading to reciprocity conditions which are

$$\frac{\partial \varepsilon_{ij}}{\partial \sigma_{kl}} = \frac{\partial \varepsilon_{kl}}{\partial \sigma_{ij}}, \quad \frac{\partial m}{\partial \sigma_{ij}} = \frac{\partial \varepsilon_{ij}}{\partial \psi}, \quad \frac{\partial c}{\partial \sigma_{ij}} = \frac{\partial \varepsilon_{ij}}{\partial \mu}, \quad \frac{\partial \rho}{\partial \sigma_{ij}} = \frac{\partial \varepsilon_{ij}}{\partial \Phi}$$

$$\frac{\partial m}{\partial \mu} = \frac{\partial c}{\partial \psi}, \quad \frac{\partial \rho}{\partial \mu} = \frac{\partial c}{\partial \Phi}, \quad \frac{\partial m}{\partial \Phi} = \frac{\partial \rho}{\partial \psi} \tag{16}$$

and a linear incremental equation of state which is

$$\begin{bmatrix} \Delta\varepsilon_{ij} \\ \Delta m \\ \Delta c \\ \Delta\rho_e \end{bmatrix} = \begin{bmatrix} c_{ijkl} & a_{ij} & b_{ij} & d_{ij} \\ a_{kl} & e & f & g \\ b_{kl} & f & h & i \\ d_{kl} & g & i & j \end{bmatrix} \begin{bmatrix} \Delta\sigma_{kl} \\ \Delta\psi \\ \Delta\mu \\ \Delta\Phi \end{bmatrix}. \tag{17}$$

In small strain isotropy, only the dilational stress and strain couple with pressure, chemical, and electrical potentials. There are thus 11 coefficients necessary to characterize the tissue and a stress–strain–potential equation which can be written as

$$\varepsilon_{ij} = K'\sigma_{ij} + \delta_{ij}(a'\sigma_{kk} + b'\Delta\psi + c'\Delta\mu + d'\Delta\Phi) \tag{18}$$

where pressure, voltage, and chemical potential are taken as the state variables of the reference medium.

This matrix corresponds to an augmentation of the classical elasticity matrix. The c_{ijkl} in these equations are the elastic coefficients for cartilage if pore pressure, chemical potential, and electrical potential are constant: it is thus an extension of the "drained" response from electrochemically neutral poroelastic materials. The coefficients b_{ij} and d_{ij} are expansion

coefficients for increases in chemical and electrical potential, and a_{ij} along with c_{ijkl} characterize standard poroelastic response. The coefficients denoted e, f, g, h, i, and j account for coupling between electrical, chemical, and mass potentials.

Although this study does not attempt to measure the coefficients set out in these equations, many experiments in the literature provide data which could be used to arrive at these coefficients. Some of these are reviewed below, and they will be pursued as they become relevant to particular applications.

By choosing the potentials of the reference medium as state variables, no information is lost, since Donnan equilibrium can be used with a measurement of fixed charge density and electroneutrality to arrive at the concentrations and voltage within the tissue. Pore pressure is only defined relative to a reference medium. One real advantage of this formulation is that while the "fluid" within cartilage is hardly dilute enough to use the simple relation between concentration and chemical potential, the reference medium is. Chemical potential can thus be stated, for the case of two monovalent solutes with concentrations c_+ and c_-, as

$$\mu = RT \ln (c_+ + c_-) \tag{19}$$

and this is the only relevant chemical potential, since by quasi-electroneutrality the charge density is always much smaller than ionic concentration.

Another substantial advantage of this formulation is the inclusion of compressibility. Nowhere have we made the assumption that the tissue is incompressible. Further study of these relations should yield an interpretation of ultrasonic impedance in cartilage and its relevance to the physical processes which govern cartilage deformation over longer time scales.

PERMEABILITIES AND ION FLUXES

To close this system of equations, the time evolution of the state variables due to ionic and mass fluxes is required. The two types of relations necessary for this are conservation laws and constitutive equations for flux of each solute. Before one writes these equations, it is critical to remember that the intensive variables or driving potentials (pressure, chemical potentials, and voltage) were defined relative to a reference medium, and the extensive variables per unit volume (concentrations, mass content, and charge density) were defined within the material. Thus conservation laws written within the tissue are compatible with the above equations of state. The conservation laws written for concentration and fluxes within the tissue are

$$\frac{\partial m}{\partial t} + \frac{\partial q_k^f}{\partial x_k} = 0, \qquad \frac{\partial c}{\partial t} + \frac{\partial \Gamma_k}{\partial x_k} = 0, \qquad \frac{\partial \rho_c}{\partial t} + \frac{\partial J_k}{\partial x_k} = 0 \tag{20}$$

with q_k^f the mass flux, Γ_k the solute flux, and J_k the charge flux. The flux of ions within the tissue requires some discussion, but in a phenomenological approach, the relations are fairly simple. Diffusion of solutes and electrical conduction within cartilage and other similar materials has been studied by Grodzinski (1983) and colleagues and expressions for diffusivity, conductance, and the terms which describe fluxes due to gradients of different state variables have been defined using electromechanical models, providing an excellent framework to study structure–property relationships in the tissue. For a purely phenomenological approach, the state variables in this formulation are very convenient. Since most experiments which measure diffusivities statically are conducted with the tissue immersed in solution, the driving force in experimental situations is usually the difference in potential of a reference medium. Thus, stating the transport equations as

$$\begin{bmatrix} q_i \\ \Gamma_i \\ J_i \end{bmatrix} = \begin{bmatrix} A_{ij} & B_{ij} & C_{ij} \\ D_{ij} & E_{ij} & F_{ij} \\ G_{ij} & H_{ij} & I_{ij} \end{bmatrix} \begin{bmatrix} \dfrac{\partial \psi}{\partial x_j} \\[2mm] \dfrac{\partial u}{\partial x_j} \\[2mm] \dfrac{\partial \Phi}{\partial x_j} \end{bmatrix} \qquad (21)$$

identifies a number of physical experiments which may be performed to characterize the necessary fluid, solute and charge flow in the tissue. The matrix above is often proposed to be symmetric (an "Onsager" relationship) but since the variables are not the actual physical variables, it is not clear that this holds here. However, since the Onsager argument is based on an energy argument, it may apply here.

PROPERTY MEASUREMENT

Two types of coefficients need to be measured in cartilage: transport coefficients and moduli. The theory above can be used as a framework to interpret the experimental results in the literature.

The equilibrium moduli for the tissue measured in confined compression by many investigators in normal saline and by Maroudas (1979) and Eisenberg (1983) in chemically altered baths can be easily interpreted in this formulation. The experiments by Grodzinski and Schoenfeld (1977) relating changes in isometric stresses in collagen membranes to current flow can be related to this model also, since a voltage distribution within the membrane is computed. Grodzinski et al. (1981) have also shown force changes in cartilage strips held at constant grip displacement under changes in chemical potential of the bathing solution.

Static experiments on cartilage samples to measure transport coefficients have been done by Maroudas (1979) and later by Mow and Lai (1980) but although these experiments used the same strength ionic solvent, there may have been a voltage across the tissue as well as a pressure gradient. The transport equation above shows that in general pressure, concentration, and voltage gradients can all cause current, solute, and bulk flow.

Dynamic measurements have been used by Tepic' (1982), Macirowski (1983), Eisenberg (1983) and Lee (1979) to study the interaction of fluid flow and deformation in response to mechanical and osmotic loading. Tepic' and Macirowski used oscillatory mechanical loading of cartilage plugs at constant ionic strength, and osmotic loading and reswelling of in situ joint cartilage to explore deformations in the tissue and to estimate permeability in situ for input into a computer-manipulable global mechanical model of a human hip joint. Lee and Eisenberg used oscillatory loads at constant chemical potential and chemical transients (i.e. concentration changes) to explore electrical and chemical effects during tissue deformation and fluid flow.

LARGE STRAIN AND OTHER EFFECTS

Since the formulation above is yet to be tested, a discussion of any possible short-comings may be premature. However, since the model arose from a discussion of the relevant physics, consideration of the physics which have been obviously ignored is appropriate. The state equation as given is incremental, and relies on the existence of an energy functional. This formulation could be applied in an incremental sense to analyze large deformations (e.g. using an updated Lagrangian approach). Until finite strain is shown to be important, however, the modelling approach we will take for highly collagenous tissues (e.g. cartilage, tendon, ligament, and meniscus) will be based on small strains, with possible superposed large rotations and translations. Flow-independent viscoelasticity is not addressed, but could be through the inclusion of interior state variables similar to those used in Maxwell or higher order viscoelastic models.

Practical considerations show that an experimental implementation of the full constitutive and conservation equations shown here would be prohibitively complex, resulting in at least four coupled fields (pressure, stress, electric potential, and at least one chemical potential). Should large strains be deemed important, the incremental nature of the constitutive equations would complicate matters still further. The dictum stated at the outset of this paper should be firmly restated here: until a simple model of a problem is clearly inadequate for the application at hand, more complex models are not necessary. Experience with thermoelasticity has demonstrated the usefulness of uncoupling state variables when physically justified. Exploration of the relative influences of the processes shown here should indicate that subsets of this formulation are useful in many applications.

Chemical reactions in the tissues studied are certainly of physiologic importance, but these processes are almost certainly of second order compared to mechanically induced fluxes, and do not enter our formulation. Also, the time scale of changes in these reactions is usually much longer than those resulting from typically imposed conditions, such as locomotion.

SUMMARY

The major thrust of this paper has been the identification of a set of state variables for connective tissue which are defined relative to a reference medium in which an excised differential volume element of the material can be immersed, keeping strains constant, without exchanging energy. This definition of state variables has motivated an incremental equation of state for connective tissue which includes osmotic and electrical effects.

The second major motivation of this work was a rationalization of poroelasticity theory as applied to a molecularly disperse medium, in which osmotic and electrical effects were important. Since porosity could not be defined in a rational sense, the formulations which resort to the use of porosity must be re-thought, in order that physically meaningful formulations result and truly predictive studies can be performed.

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APPENDIX A: LIST OF SYMBOLS

a_{ij}	mass potential–strain coefficients, eqn (17)
a'	isotropic reduction of a_{ij}, eqn (18)
b_{ij}	chemical potential–strain coefficients, eqn (17)
c_i	concentration of chemical species i, eqn (11)
c_+	concentration of a single monovalent cation, eqn (19)
c_-	concentration of a single monovalent anion, eqn (19)
c_1	coefficient of antisymmetric stress due to vorticity differences, eqn (10)
c_3	coefficient for drag force due to relative velocity, eqn (10)
c_5	coefficient for heat flux due to relative velocity, eqn (10)
c'	isotropic chemical strain coefficient, eqn (18)
d_{ij}	coefficient for strains due to electrical potential, eqn (17)

d'	isotropic electrical expansion coefficient, eqn (18)
c_{ij}	solid component strain, eqn (10)
e	change in fluid mass per unit change in fluid mass potential, eqn (17)
f	change in fluid mass per unit change in chemical potential, eqn (17)
g	change in fluid mass per unit change in electrical potential, eqn (17)
h	change in concentration per unit change in chemical potential, eqn (17)
i	change in concentration per unit change in electrical potential, eqn (17)
j	change in charge density per unit change in electrical potential, eqn (17)
m	mass of fluid per unit volume, eqn (3)
m_0	reference fluid mass content, eqn (3)
p	pressure, eqn (1)
q_i	heat flux, eqn (10)
q_i^f	fluid mass flux, eqn (6)
t	time
x_i	Cartesian coordinate $(i = 1, 2, 3)$
v_i^f	relative velocity, eqn (10)
A_{ij}	fluid mass flow permeability, eqn (21)
B	back stress coefficient, eqn (2)
B_{ij}	fluid mass flow—chemical potential gradient term, eqn (21)
C_{ij}	fluid mass flow—electrical field term, eqn (21)
C_{ijkl}	isopotential stress–strain coefficients, eqn (17)
D_{ij}	solute flux—mass potential gradient term
D_{ij}^f	fluid deformation rate, eqn (10)
D_{ij}^s	solid deformation rate, eqn (10)
E_{ij}	solute flux—chemical potential gradient terms, eqn (21)
F_{ij}	solute flux—electric field terms, eqn (21)
G	solid shear modulus, eqn (2)
G_{ij}	charge flux—mass potential term, eqn (21)
H_{ij}	charge flux—chemical potential term, eqn (21)
I_{ij}	charge flux—electric field term, eqn (21)
J_i	charge flux, eqn (20)
K'	isotropic isopotential elastic modulus, eqn (18)
R	gas constant, eqn (19)
T	temperature, eqn (10)
U	internal energy
U'	coenergy, eqn (14)
$\hat{\alpha}$	solid thermal expansion term, eqn (10)
β	fluid thermal expansion term, eqn (10)
$\gamma_1-\gamma_4$	bulk coupling terms, eqn (10)
Γ_i	solute flux, eqn (20)
ε_{ij}	solid strain, eqn (1)
$\lambda_1-\lambda_5$	bulk moduli, eqn (10)
Λ_{ij}	difference in vorticity between solid and fluid, eqn (10)
$\mu_1-\mu_5$	shear moduli, eqn (10)
μ_i^c	chemical potential of the ith solute, eqn (11)
μ^c	overall chemical potential, eqn (12)
ν	drained Poisson ratio, eqn (2)
ν_n	undrained Poisson ratio, eqn (2)
ρ_0	reference fluid density, eqn (6)
ρ_s	solid density, eqn (10)
ρ_{s0}	true solid density, eqn (10)
ρ_f	fluid density, eqn (10)
ρ_{f0}	true fluid density, eqn (10)
ρ_r	reference fluid density, eqn (13)
ρ_e	electric charge density, eqn (12)
σ_{ij}	total stress, eqn (1)
σ_{ij}^s	solid stress, eqn (10)
σ_{ij}^f	fluid stress, eqn (10)
Φ	electric potential, eqn (12)
Ψ	mass potential, eqn (12).