NONEQUILIBRIUM ELECTROMECHANICAL INTERACTIONS IN CARTILAGE:
SWELLING AND ELECTROKINETICS

by

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Submitted in Partial Fulfillment of the
Requirements for the
Degree of

DOCTOR OF SCIENCE

at the

MASSACHUSETTES INSTITUTE OF TECHNOLOGY

February, 1983

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January 17, 1983

Certified by

Thesis Supervisor

Accepted by

Chairman, Department Committee

Archives

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

MAY 27 1983
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ABSTRACT

An electromechanochemical swelling model is developed to describe equilibrium and nonequilibrium swelling behavior of polyelectrolyte materials. A constitutive relation for the swelling pressure as a function of tissue deformation and external bath electrolyte concentration is developed, introducing the concept of the chemical stress. This constitutive relation is then used to describe the mechanical response of a tissue sample in uniaxial confined compression to a change in the salt concentration of the external bath. A coupled set of differential equations results. Expressions are derived that clearly show that when the surface displacement is held constant, the system response is at least as fast as the shortest of the mechanical and chemical diffusion time constants. When the stress is held constant, the creep deformation proceeds with the longer of the two time constants.

The material properties of bovine articular cartilage and corneal stroma are measured as a function of concentration and empirical constitutive relations describing the observed behavior are developed. These relations are then used in the model to numerically solve the coupled set of differential equations for chemically induced stress relaxation. The results of the numerical model compare favorably with experimental results obtained for cartilage and corneal stroma samples for reasonable values of the material parameters.

The phenomenological equations of nonequilibrium thermodynamics are introduced to describe electrokinetic interactions in charged porous materials. A first order electrokinetic micromodel is developed to describe the coupling coefficients in terms of microscopic structural and compositional parameters. A unit cell technique is used where the solid matrix of the tissue is modeled as an ordered array of electrically insulating cylinders supporting a fixed surface charge density. The double layer is modeled as a Helmholtz capacitor, with all of the mobile double layer charge located one Debye length from the surface of the charged cylinder. The coupling coefficients are derived for flow perpendicular and parallel to the axes of the charged cylinders. The coupling coefficients appropriate for a random assemblage of cylinders are obtained from a weighted average of the coefficients
for parallel and perpendicular flow. Using appropriate parameter values, the electrokinetic micromodel predicts values for the coupling coefficients that are the same order of magnitude as coupling coefficients previously measured for cartilage. The micromodel also predicts an initial rise in the effective conductivity of cartilage which has been observed experimentally, and cannot be explained with traditional ion exchange macromodels.

Thesis Supervisor: Alan J. Grodzinsky
Title: Associate Professor of Electrical and Bioengineering
ACKNOWLEDGEMENTS

First and foremost, I want to thank Professor Alan J. Grodzinsky for all the time and effort he has spent in helping me complete this thesis. He has been a constant source of inspiration throughout my years of association with him. Working with Al on this and other projects has been one of the most rewarding experiences I have had in my years at MIT. I have also benefited from many discussions with Dr. Van Mow and Dr. David Eyre. My understanding of cartilage has been enhanced through these interactions. I would like to thank Professor T.F. Weiss for his careful review of this thesis and his helpful suggestions, and Professor M.P. Cleary for teaching me so much about the mechanics of porous media.

Several people in our research group have been involved in this project. Paul Grimshaw was particularly helpful as a sounding board for new ideas, and for rehashing old ones. Susan Phillips and Jackie Brenner performed some of the preliminary experiments that helped shape the final protocols used in this study. My officemates Jeremy Nussbaum, Aryeh Weiss and Eliot Frank were always ready to listen, discuss, and argue about ideas and formulations related to this project. Many good suggestions and comments resulted from these discussions. Eliot also took upon himself the development of the text processing software that made the production of this document possible. Martha Gray spent an inordinate amount of time reading drafts of this thesis. Her comments, suggestions and encouragement are deeply appreciated. I thank Dr. Raphael Lee for the use of his computer, and for helping to peak my interest in cartilage electromechanics. I also thank Dr. Tom Koob for
his help with the uronic acid analysis, and for helpful discussions about cartilage biochemistry.

This research was partially supported by NIH Grant AM26440 and NSF Grant ENG79-18781. I also gratefully acknowledge the support I received from the Whitaker Health Sciences Fund in the form of a Whitaker Health Sciences Fund Doctoral Fellowship.

Finally, I would like to thank Terri for all her support and understanding over the years, as well as all the time she spent drawing (and redrawing) the figures in this thesis. Without her help, completing this thesis would have been substantially more difficult.
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CHAPTER I
INTRODUCTION

1.1 Articular Cartilage: Swelling and Electrokinetic Transduction

Articular cartilage is the dense connective tissue that covers the articulating surfaces of bone and functions as a bearing material in synovial joints. It is composed of ~80% aqueous electrolyte and a solid organic matrix of collagen, proteoglycans, glycoproteins, lipids and cells. In normal tissues, the solid matrix is ~65% collagen, ~25% proteoglycan and ~10% other noncollagenous proteins [1]. The tissue is aneural and avascular, and has a low density of cells (chondrocytes). The chondrocytes are responsible for synthesizing and maintaining the organic matrix. Healthy articular cartilage is essential to normal joint function. It is believed that cartilage significantly reduces contact stresses in joints and protects the underlying bone from rapidly applied impact loads [2].

The collagen fibrils in articular cartilage form a coarse, crosslinked network that stabilizes the tissue and is responsible for the tensile strength of the composite matrix [3,4]. The gross organization of the network can be seen in the SEM shown in Fig. 1.1. It is the relative inextensibility of the collagen network that limits the water content of the tissue, and maintains tissue integrity [5,6] in the face of the repulsive interactions between the charged proteoglycans that are embedded within this network [5,6]. The distribution of proteoglycans in the tissue is seen in the TEM of canine articular cartilage in Fig. 1.2, where the tissue has been stained for

Section 1.1
Figure 1.1 Scanning electron micrograph of the surface of articular cartilage depicting the coarse collagen network.
Figure 1.2 Transmission electron micrograph of canine articular cartilage. The cartilage has been stained to highlight the proteoglycans (dark specks). The proteoglycans can be seen to be enmeshed in the collagen framework. (courtesy of Dr. D.R. Eyre).
proteoglycans.

Proteoglycans (PGs) are composed of a protein core to which a large number of glycosaminoglycan (GAG) macromolecules are covalently bound. Each GAG macromolecule is itself a linear polymer of repeating disaccharide units which are negatively charged at physiological pH. There are predominately four types of GAGs found in cartilage: hyaluronic acid, chondroitin 4-sulfate, chondroitin 6-sulfate, and keratan sulfate. The repeating disaccharide unit for each of these is shown in Fig. 1.3. Note that the charge sites are shown for physiological pH. The chondroitin sulfate and keratan sulfate covalently bind to the protein core to form what is called the PG subunit or PG monomer. In normal cartilage the PG subunits form large multimolecular aggregates through a highly specific interaction with hyaluronic acid [7]. The entire PG aggregate has the appearance of a bottle brush, as seen in the electron micrograph shown in Fig. 1.4. The current working model of the structure of the PG aggregate is shown schematically in Fig. 1.5. These aggregates are thought to be entrapped in the collagen matrix by physical entanglement and specific interactions between the collagen and the PG aggregates [1]. This arrangement is shown schematically in Fig. 1.6. It is interesting to note that PG aggregation is restricted to the PGs of cartilage [1]. While the biological function of PG aggregation is not yet known, it presumably has a role that is specialized to the function of cartilage.

Osteoarthritis is a disease of articular cartilage in which cartilage degenerates. Damage progresses from focal fibrillation of the tissue to the erosion of the tissue layer covering the bone, and can

Section 1.1
Figure 1.3 Schematic of the repeating disaccharide unit of the glycosaminoglycans in articular cartilage, shown with ionized carboxyl and sulfate groups appropriate for neutral pH.
Figure 1.4 Dark field electron micrograph of large proteoglycan aggregate from bovine nasal cartilage (x40,000). (courtesy of Dr. J.A. Buckwalter).
Figure 1.5 Model of the proteoglycan aggregate: PG - proteoglycan; HA - hyaluronic acid; CS - chondroitin sulfate; KS - keratan sulfate (from Muir [1]).
Figure 1.6 Schematic representation of a proteoglycan aggregate enmeshed in collagen network.
eventually lead to total joint dysfunction. The gross deterioration of the tissue is accompanied by a deterioration in its mechanical properties and has been shown to be closely associated with changes in the biochemical composition of the tissue [8].

One of the first events associated with osteoarthritis in man and in animal disease models is increased water content and swelling of articular cartilage [9, 10]. To understand cause and effect relationships of this swelling requires a better understanding of the intermolecular forces that give rise to swelling and the mechanical entanglement and chemical crosslinkages that resist these swelling forces and hold the tissue together. Towards this goal, an electromechanochemical swelling model is developed in this thesis for cartilage and other charged polymeric materials. The model is based on a macroscopic continuum approach that does not specifically incorporate molecular level structure. However, the model clearly demonstrates the role of the charged PGs in determining the mechanical behavior of the tissue. The model focuses on changes in the tissue swelling pressure caused by changes in the imposed mechanical deformation and ionic composition of the tissue's bathing solution. Chemically induced changes in the stress for a tissue sample held at constant volume clearly highlight the importance of the PG charge interactions in determining the mechanical stiffness of the tissue.

When cartilage is compressed, the interstitial fluid is forced to flow relative to the solid PG-collagen matrix. The resistance to this flow and the equilibrium elastic modulus of the solid matrix contribute to the stiffness cartilage presents to a time varying load [11]. Thus,
both the modulus and the permeability play an important role in determining the deformation introduced in the tissue during normal tissue function in vivo. A further consequence of fluid flow past the charged proteoglycans is the development of a streaming potential. Lee [12] has shown that this electrokinetic coupling represents a significant portion of the resistance to fluid flow in cartilage. Hence, electromechanical interactions play a vital role in determining the macroscopic properties of cartilage in both equilibrium and nonequilibrium situations. This is not surprising. At physiological ionic strength, the Debye length is $\sim 10$ Å, which is approximately the same as the intermolecular spacing between GAG chains on the PG subunit [13]. This close proximity guarantees significant electrical interaction between the charged constituents of the tissue. Furthermore, because these electrical forces operate over distances that are on the order of the macromolecular constituents, they form a vital and essential link between the microscale of the macromolecular constituents of the tissue and the macroscopically measurable material properties in both normal and diseased states. These interactions form the basis for the phenomena investigated in this thesis.

To further characterize electromechanical phenomena in cartilage particularly associated with fluid flow, a first order electrokinetic micromodel is developed here. While the electromechanochemical swelling model focuses at the macroscopic level, the electrokinetic model focuses at the microscopic level. Microscopic models attempt to incorporate molecular level structural and compositional features to describe macroscopically measurable phenomena. In so doing, they attempt to get inside phenomenological constitutive relations to provide a more
fundamental view of the governing physical interactions between material components that ultimately determine macroscopic behavior. Such models will be an essential aid in determining the specific roles played by individual tissue components, and in attempting to understand the physical basis of various disease states. They may also help to delineate cause and effect relationships involved in the process of tissue degeneration.

1.2 Previous Studies of Normal and Osteoarthritic Cartilage Relating to Swelling and Electrokinetics

During the past few decades many investigators have focused on the relation between the biomechanical, electromechanical and biochemical events associated with osteoarthritis. In particular, the role of the proteoglycan, glycoprotein and collagen components, and the interaction between these components in normal and osteoarthritic cartilage has received much attention. It is now widely believed that the physical, chemical and functional properties of cartilage are closely related in both the normal and diseased states. However, questions as to the cause and effect nature of these relationships remain. Currently, the pathogenesis and etiology of osteoarthritis are unknown.

There is a growing body of evidence that documents changes in the biochemical structure and composition of the tissue in natural and surgically induced models of osteoarthritis. McDevitt and Muir [10] have found biochemical changes in the articular cartilage of the knees of mature dogs with surgically induced osteoarthritis. They found that the PGs were more easily extracted and had higher ratios of chondroitin
sulfate to keratan sulfate than normal articular cartilage. Shapiro and Glimcher [14] found a diminished amount of GAGs in the menisectomized knee of rabbits used in a surgical animal model of osteoarthritis. Working with a similar model, Moskowitz et al [15] found PGs in the operated joint that were less aggregated and were more easily extracted than the PGs from the control joints. Brandt and Palmoski [16] found less PG aggregation in fibrillated steer cartilage compared to normal steer cartilage.

Changes have also been observed in the mechanical properties of osteoarthritic cartilage. Lane et al [17] performed indentation experiments on rabbit cartilage following medial meniscectomy. Cartilage from the meniscectomized joints had a lower equilibrium shear modulus and required a longer time to reach equilibrium than tissue obtained from unoperated joints. Hoch et al [18] studied both the biochemical and mechanical changes associated with a medial meniscectomy in the rabbit. Changes in the mechanical stiffness of the tissue following surgery were closely correlated with changes in uronic acid content and water content. Kempson et al [19] studied the mechanical response of human articular cartilage to indentation testing. They found a positive correlation between the "two second modulus" and the total GAG content as well as the individual chondroitin and keratan sulfate contents. Armstrong and Mow [20] have studied the relation between the longitudinal bulk modulus of human patellar cartilage in confined compression and GAG content. They report a correlation between the total GAG content of the tissue and the magnitude of the modulus.

These studies suggest a close relationship between changes in
mechanical properties and changes in biochemical composition and structure in natural and surgically induced osteoarthritis. Enzymatic extraction of PG or constituent GAGs of the PG monomer from normal articular cartilage modifies the tissue in a way that mimics certain aspects of osteoarthritis. Mechanical testing of enzymatically modified tissues has provided additional evidence of the importance of tissue composition to mechanical properties. Kempson et al [21] removed a large percentage of the PGs from human cartilage with cathepsin D and cathepsin B1. The treated samples showed reduced compressive stiffness. Harris et al [22] found that tissue depleted of its PG content by enzymatic digestion in trypsin and hyaluronidase compressed more in a 15 second creep deformation than undigested tissues. Similar results were obtained by Olson [23] in oscillatory confined compression and by Stahurski [24] in creep deformation and stress relaxation experiments.

Changes in electromechanical interactions have been implicated as being largely responsible for the observed relation between changes in the mechanical properties of the tissue and changes in chemical composition and structure. The dependence of the material properties on electromechanical interactions can be demonstrated in experiments that alter electromechanical interactions without changing tissue composition. The mechanical stiffness of cartilage has been shown to vary as a function of solution ionic strength. The dependence of the mechanical stiffness on solution ionic strength highlights the importance of electrostatic interactions in determining the material properties of the tissue. This was first demonstrated by Elmore et al [25] in a series of indentation studies using excised human and animal joints. They found that the compressibility of cartilage was increased
when measured in solutions of increased ionic strength. Complete
reswelling of the compressed cartilage following the removal of the load
took longer in solutions of higher ionic strength than in lower ionic
strength solutions. In a series of creep deformation experiments,
Sokoloff [26] also found that the indentability of the tissue was
substantially influenced by the ionic strength of the bath. Maroudas
[27] demonstrated the importance of electrostatic repulsion forces in
determining the compressibility of cartilage. She found that larger
applied loads were required in 0.15 M NaCl to produce a given reduction
in equilibrium water content than were required in 1.0 M NaCl.
Similarly, Lee [12] showed that a major portion of the equilibrium
stress in cartilage in uniaxial confined compression is due to
electrostatic interactions. The contribution of electrostatic forces to
the mechanical behavior of the tissue is also evident when tissue charge
density is altered by changing the pH of the tissue's bathing solution.
Grodzinsky et al [28] observed changes in the tensile force of strips of
cartilage held at constant length in response to changes in either the
hydrogen ion concentration or the salt concentration of the external
bath. The kinetics of the changes in force induced by changes in the
chemical environment appeared to be rate limited by the diffusion of
ions into the tissue.

1.3 Overview of this Research

A general electromechanochemical swelling model is developed to
describe the equilibrium and nonequilibrium swelling behavior of
polyelectrolyte materials. A constitutive relation for the swelling
pressure as a function of tissue deformation and external bath
electrolyte concentration is developed, introducing the concept of the chemical stress. This constitutive relation is then used to describe the mechanical response of a tissue sample in uniaxial confined compression to a change in the salt concentration of the external bath. A coupled set of differential equations describing the chemically induced stress relaxation and creep deformation are derived. The system of equations highlights the importance of the relation between the mechanical properties of the tissue (equilibrium modulus and Darcy permeability) and the ionic diffusivities in determining the mechanical response of the system to a change in the chemical environment. The equilibrium modulus and the Darcy permeability determine the time required for the tissue to change its deformation state ($\tau_m$), while the ionic diffusivity determines the time required to change the tissues ionic content ($\tau_c$). The behavior of the system in the limits $\tau_m \gg \tau_c$ and $\tau_m \ll \tau_c$ is examined. Expressions are derived that clearly show that the system response when the surface displacement is held constant is at least as fast as the shortest of the mechanical and chemical diffusion time constants. When the stress is held constant, the creep deformation proceeds with the longer of the two time constants. When neither of these limits apply, the complete model developed in Chapter II must be solved numerically.

One limiting form of the model has been investigated by Grimshaw [29], and shown to adequately describe the stress relaxation response of cartilage in response to additions of HCl to the tissue's bathing fluid. The change in hydrogen ion concentration alters the tissue's fixed charge density by a nonlinear diffusion – reaction process. The chemical diffusion – reaction of the hydrogen ions into the tissue makes the
effective chemical diffusion time much longer than the mechanical
diffusion time. A limiting form of the more general theory developed in
Chapter II can then be used in conjunction with independently measured
constitutive relations for the dependence of the material properties on
the local chemical environment and strain state to describe the
transient change in the resulting measured stress.

Experiments to test the validity of the model are described in
Chapter III. Because of the sensitivity of the model to the ratio of the
mechanical and chemical time constants, bovine articular cartilage as
well as corneal stroma tissue samples are tested. Corneal stroma is
compositionally very similar to cartilage. Corneal stroma is comprised
of ~ 80% aqueous electrolyte and a solid organic matrix composed
primarily of collagen (~ 70%) and proteoglycans (~ 4.5%) [30,31].
Besides having fewer PGs, the structural organization of cornea is very
different from articular cartilage. In cornea, the collagen fibers form
distinct layers, or lamella, with almost no interconnections between
lamella, as shown in Fig. 1.7. Because of these structural differences,
the material properties of the corneal stroma are quite different from
those of articular cartilage. Specifically, corneal stroma is
approximately 10 - 20 times more compliant than articular cartilage.
This allows the model to be tested experimentally for different values
of the ratio of mechanical and chemical time constants.

In order to solve the system of equations numerically,
constitutive equations relating the swelling pressure to the strain and
salt concentration must be determined. The swelling pressure as a
function of tissue deformation and the salt concentration of the

Section 1.3
Figure 1.7 Electron micrograph of cross section of normal corneal stroma. The collagen fibers in each lamella run parallel to the corneal surface. The axis of the fibrils in adjacent lamella make large angles with each other, causing the different patterns observed in each lamella.
external bath is measured for both cartilage and corneal stroma tissue samples. The data are used to develop empirical constitutive equations that can be used with the model developed in Chapter II to solve the coupled differential equations describing the stress relaxation response induced by changing the salt concentration of the external bath. Also described in Chapter III are experiments to measure the transient stress response induced by changes in the salt concentration of the external bath.

Chapter IV describes the numerical methods used to solve the coupled differential equations developed in Chapter II. Solutions are obtained for the swelling pressure as a function of space and time. From the solution for the swelling pressure, the stress response can be computed. The tissue deformation and the fluid pressure are also determined as a function of space and time from the solution for the swelling pressure. The characteristics of the solution are discussed in terms of the mechanical and chemical fields as a function of space and time.

In Chapter V, the predictions of the model are compared to the data obtained in Chapter III. Good agreement between the theoretical and measured response is obtained for reasonable values of the system and material parameters.

The phenomenological equations of nonequilibrium thermodynamics are introduced in Chapter VI to describe electrokinetic interactions in charged porous materials. A first order electrokinetic micromodel is developed to describe the coupling coefficients in terms of microscopic structural and compositional parameters of the tissue. A unit cell
approach is used where the solid matrix is modeled as an ordered array of electrically insulating cylinders supporting a fixed surface charge density. The double layer is modeled as a Helmholtz capacitor, with all of the mobile double layer charge located one Debye length from the surface of the charged cylinder. The coupling coefficients are developed for flow perpendicular and parallel to the axes of the charged cylinders. The coupling coefficients appropriate for a random assemblage of cylinders are obtained by taking a weighted average of the coefficients for parallel and perpendicular flow. The electrokinetic micromodel predicts values for the coupling coefficients that are the same order of magnitude as coupling coefficients measured by Lee [12] for cartilage for parameter values appropriate for cartilage. Furthermore, the micromodel predicts an initial rise in the effective conductivity of cartilage which has been observed experimentally, and cannot be explained with traditional ion exchange macromodels.
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CHAPTER II
ELECTROMECHANOCHEMICAL SWELLING MODEL

2.1 Introduction

The swelling of connective tissues under a variety of chemical and mechanical conditions has been studied extensively over the last few decades. Most work has focused on equilibrium swelling behavior; that is the final state of the tissue when all rate processes have ceased. Equilibrium swelling behavior has been characterized by the measured tissue swelling pressure at constant hydration (deformation), or the equilibrium tissue thickness for a constant applied load.

It is well known that changes in chemical environment significantly alter the swelling state of a tissue such as articular cartilage. Changes in the pH of the bathing medium alter cartilage fixed charge density, and changes in neutral salt (e.g. NaCl) concentration alter the electrostatic and osmotic forces between matrix macromolecules [1]. Thus, changes in ionic strength and pH can significantly affect the electromechanical and physicochemical forces that determine material properties. The early work of Michaeli and Katchalsky [2] on charged polymethacrylic acid is representative of the equilibrium constitutive laws employed to describe changes in swelling as a function of bath salt concentration and pH. More recently, Maroudas and coworkers [3-6] have studied the equilibrium swelling of cartilaginous tissues as a function of salt concentration and tissue fixed charge density.

Relatively fewer studies have been devoted to the nonequilibrium
swelling of connective tissues induced by mechanical and chemical stimuli. However, an extensive literature exists on the general problem of deformation and fluid flow in chemically inert fluid saturated porous media. The classical model for the mechanics of deformation and acoustic propagation in fluid saturated porous media is attributed to Biot [7-12]. Biot's theory provides a general and powerful technique for understanding the composite elastic properties of fluid saturated porous media. Rice and Cleary [13] have recently recast Biot's constitutive equations relating strain and fluid mass content to stress and pore pressure. They present a new formulation of the Biot linearized quasistatic theory with total stress and pore pressure as basic state variables that may frequently be easier to use than the Navier formulation in terms of fluid and solid displacements given by Biot [9]. However, because the swelling forces and the physicochemical origin and chemical dependence of these swelling forces do not have analogs in the classical poroelastic models, specialized models for connective tissues were developed.

Fatt and Goldstick [14] and Friedman [15,16] modeled the free swelling of corneal stroma in electrolyte baths. The approach used by Fatt and Goldstick was one of the first to recognize and emphasize the role of fluid flow in determining the kinetics of the swelling process in corneal stroma. Unfortunately, the physical origins of the fluid pressure were not accurately accounted for or discussed. This led to the introduction of an arbitrary and artificial constitutive relation between the fluid pressure and the swelling pressure. Friedman used a more general formulation that correctly related the fluid and tissue swelling pressures. Both assumed instantaneous Donnan equilibrium
throughout the tissue and neglected all ionic fluxes.

Mow and coworkers [17-20] have introduced a mixture model to describe the dynamic relationship between stress, strain and fluid velocity fields in articular cartilage. Their model treats cartilage as a binary mixture of interacting continua, where it is assumed that each point within the mixture is simultaneously occupied by each of the constituents. The mixture theory approach incorporates individual stress and strain relationships for the solid matrix phase and the interstitial fluid phase. In contrast, the poroelastic theory of Rice and Cleary [13] uses a single constitutive law to relate the total, measurable stress and the pore pressure to the strain. In its simplest form, the model of Mow et al [17] describes a mixture of an isotropic, incompressible, linear elastic, nondissipative solid, and an incompressible fluid. Chemical gradients, reactions and the effects of ionic constituents were not considered. Although their development uses a different theoretical approach, the end result is closely related to the respective models of Fatt and Goldstick, and Friedman.

The Mow et al [17] model was the first literature to emphasize the role of fluid flow in determining the time dependent relation between stress and strain in cartilage. It has been shown to predict many of the features of stress, strain and fluid flow observed in cartilage during confined uniaxial creep deformation and stress relaxation [17], as well as confined uniaxial oscillatory compression [21]. By quantifying the fluid flow field, it has helped investigators determine that stress generated potentials in cartilage have their origin in the flow of fluid past the charged surfaces of the proteoglycans [21-23].

Section 2.1
Nonequilibrium swelling has also been studied in gels. Tanaka and Filmore [24] have described the free swelling of spherical polyacrylamide gel particles in water. Using the approach of Tanaka, Hocker and Benedek [2], Tanaka and Filmore [24] obtain a diffusion equation in spherical coordinates for the displacement field that is analogous to the equations obtained by Friedman, and Fatt and Goldstick for cornea and by Mow for cartilage. However, Tanaka et al [25] did not incorporate a pore pressure into this model. The effect of the relative motion of the fiber network and the gel fluid on the displacement field is included through a frictional drag term proportional to the time rate of change of the matrix displacement field. The fluid is assumed to be stationary, implying that the porosity $\phi = 1$.

Johnson [26] has recently developed a more general model for gels that treats the displacements of the solid and fluid on an equal footing using Biot's Navier formulation, and avoids introducing specialized approximations about the porosity or the bulk and shear moduli of the polymer frame. Johnson [26] is critical of the approach of Tanaka et al [25], although he concludes that their approach yields correct results for high porosity gels when the bulk moduli of the fluid and the individual polymer chains are each much greater than the bulk and shear moduli of the composite gel. He shows in general that when the bulk moduli of the fluid and the individual polymer chains are each much greater than the bulk and shear moduli of the composite gel, the gel fluid is essentially stationary. However, the general theory shows that the assumption of unity porosity is not required for this to be so. Hence, the model of Tanaka et al [24] is essentially correct even when fluid flows, and does not need to be corrected in order to account for
fluid flow. For this reason, the ad hoc addition of a fluid flow term to the equation of Tanaka et al [24] for the matrix displacement field as described by Geissler and Hecht [27] is unnecessary, and leads to an incorrect diffusivity for the gel.

None of the models discussed have included the possible effects of chemical constituents or chemical gradients on the swelling process. Hence, these models must be modified in order to consider problems where chemical rate processes are important. By including chemical gradients and diffusive fluxes we will be able to describe a more general electromechanochemical theory of swelling for articular cartilage and other connective tissues. This will provide another tool to help investigate the coupling of mechanical, biochemical and physicochemical properties in cartilage and other connective tissues.

There are two experimental paradigms that will be used in the remainder of this chapter. The first is a uniaxial confined compression creep test in which the load is held at a constant level while the resulting tissue deformation is measured as a function of time. The second is a uniaxial confined compression stress relaxation test in which the surface displacement is held constant while the resulting load is measured as a function of time. When equilibrium is reached, the load and displacement remain constant.

In developing an electromechanochemical swelling model, we will be concerned with describing transient tissue behavior that is mediated by tissue fixed charge. Changing the salt concentration of the tissue bathing solution changes the Debye length inside the tissue, thereby altering the electrical repulsive forces between charged constituents.
In an experiment in which the deformation is held constant, the altered electrical repulsive forces will cause a change in the measured load required to keep the deformation constant. Conversely, in a constant load experiment, a change in salt concentration will result in a change in tissue deformation as the charged constituents alter their relative spacing in response to the altered repulsive forces.

2.2 Swelling Pressure

2.2.1 General Considerations

The term swelling pressure has been used in different ways by different authors. In general, the swelling pressure $p$ results from several interactions [28,29]:

a) pressure due to stretching of the polymer chains comprising the interconnected solid matrix. This component opposes swelling and its magnitude increases as swelling increases.

b) pressure due to electrostatic (Donnan osmotic) interactions. This component can be thought of as resulting from double layer repulsive forces between charged constituents of the tissue, or as an osmotic pressure resulting from the increased concentration of counterions that must be present in the tissue to preserve electroneutrality. These are one and the same phenomenon [28]. The magnitude of the pressure decreases as swelling increases, decreases as external salt concentration increases, and decreases as fixed charge density is decreases.

c) pressure due to interactions between the polymer network and the solvent. This component accounts for the affinity between the
polymer and the solvent. For "good" solvents, the polymer network tends to imbibe fluid, and increase swelling. Similarly, the polymer network tends to resist swelling for a "poor" solvent.

d) pressure due to the thermal motion of the polymer segments. This component tends to swell the network, and its magnitude decreases as swelling increases.

As each of these terms can be defined at any point within the tissue, the swelling pressure can be thought of as the stress that an incremental volume element in the tissue exerts on the volume elements surrounding it. Hence, the swelling pressure $p$ everywhere inside an unconstrained tissue sample in equilibrium must always be zero. Similarly, in equilibrium, $p$ must be uniform throughout the sample and equal and opposite to the stress $\sigma$ required to keep the tissue at a given equilibrium thickness in the confined uniaxial configuration of Fig. 2.1. The stress $\sigma$ is defined to be positive in compression. This configuration, then, provides a simple way of measuring the swelling pressure $p$ in equilibrium.

From the definition of the swelling pressure, it is clear that $p$ is a function of the local tissue deformation. Since we are concerned with a confined uniaxial configuration, deformations can occur only in the $z$ direction. Hence, we can measure this deformation as a strain $\varepsilon$, where $\varepsilon$ is defined as the deviation of an incremental volume element from its reference thickness, normalized to that thickness. Since we will be concerned exclusively with compressive strains, we define the compressive strain as being positive for convenience. With the $z$ axis
Figure 2.1 Schematic of confined uniaxial compression chamber for measuring tissue swelling pressure.
defined as shown in Fig. 2.1, \( \varepsilon = -\frac{\partial u}{\partial z} \), where \( u \) is the displacement of a point in the tissue from its reference state. In equilibrium, the local deformation is uniform throughout the tissue. Hence, in equilibrium, \( \varepsilon \) is the deviation of the sample thickness from its reference thickness \( \delta_{\text{ref}} \), normalized to the reference thickness.

Since the tissue's fixed charge density can be changed by titrating the carboxyl groups of the charged proteoglycans, the swelling pressure will be a function of the hydrogen ion concentration of the bath. We can also change the repulsive interactions between the charged constituents of the tissue by changing the salt concentration of the bath. Hence, we can think of the swelling pressure \( p \) as being a function of tissue deformation, bath salt concentration and pH. This functionality is shown qualitatively in Fig. 2.2.

For the swelling pressure to change in response to changes in the chemical composition of the external bath, ions must diffuse into the tissue from the external solution. Each of the individual terms making up the swelling pressure can change on a time scale that is very short compared to the time required for the ions to diffuse into the tissue. The electrical double layer surrounding the charged constituents of the solid tissue matrix can adjust to changes in the local ionic environment within a relaxation time, \( \tau_{\text{rel}} \sim 10^{-9} \text{ sec} \) [1]. The chemical reaction that neutralizes carboxyl groups, thereby changing the tissue's fixed charge density, occurs with a half reaction time on the order of \( 10^{-7} \text{ sec} \) [30]. It is also possible for changes in the local ionic environment to affect the mechanical conformation of the macromolecules and thereby change the tissue swelling pressure. However, as these

Section 2.2.1
Figure 2.2 Schematic representation of the swelling pressure as a function of deformation $\varepsilon$, external bath salt concentration $c_0$ and the pH of the external bath.
mechanical changes occur over molecular distances, they must also occur on a time scale that is short compared to the time required for ions to diffuse from the external solution into the tissue. Since changes in swelling pressure can occur much faster than changes in the local ionic environment, every point within the tissue can be thought of as always being in local equilibrium with the local ionic environment.

Because the tissue is charged, the ionic concentrations are discontinuous at the tissue/solution interface. This discontinuity results in order to preserve electroneutrality within the tissue in face of the tissue's fixed charge density. The coion concentrations are, therefore, depressed and the counterion concentrations elevated compared to their concentrations in the external bath. Hence, a single external salt concentration (say NaCl) in equilibrium with a charged tissue maps to two unequal ionic concentrations inside the tissue. For the case of a single salt, the internal ionic concentrations \( \bar{c}_\pm \) are related to the external salt concentration \( c_o \) and the tissue fixed charge density \( \rho_m \) by the Donnan equilibrium relation

\[
\bar{c}_\pm = \pm \frac{\rho_m}{2} + \left( \frac{\rho_m^2}{2} + c_o^2 \right)^{1/2}
\]  

(2.1)

where \( \rho_m \) and \( \bar{c}_\pm \) are expressed as moles per liter of tissue fluid. We therefore have a choice of three concentrations to use in describing the functionality of the swelling pressure with concentration. It is clear that only one of these is independent, given the tissue fixed charge density and the constraints imposed by eq. 2.1 and quasineutrality. However, since the fixed charge density is in general a function of Section 2.2.1
material deformation, the internal ionic concentrations can be changed by compressing the tissue even though the external salt concentration remains constant. The internal ionic concentrations must adjust in a way that is consistent with the new fixed charge density in the tissue and the salt concentration of the external bath.

Since the swelling pressure is independently a function of both the strain and the ionic concentrations, we require that the concentration used to describe this relationship itself be independent of strain. The internal ionic concentrations are clearly not independent of the strain, and are therefore not convenient to describe the dependence of the swelling pressure on ionic content. However, the external concentration is independent of strain. Hence, chemically induced changes in the swelling pressure will be related to changes in the concentration of the external bath. The change in the swelling pressure that accompanies the strain induced change in the fixed charge density will be included in the relationship between the swelling pressure and strain to be derived below.

The swelling pressure can be unambiguously related to the external bath concentration when the internal concentration is in equilibrium with the external bath. However, we will be interested in describing the swelling pressure transients that occur when the external salt concentration is changed, while the internal ionic concentrations are equilibrating with the new external salt concentration. Since we view the swelling pressure as being mediated by local ionic concentrations, it is clear that the swelling pressure transient must be related to the diffusion of ions inside the tissue. The relationship between the

Section 2.2.1
swelling pressure and the nonequilibrium internal ionic concentrations will be discussed in section 2.5.1.

In what follows, we will primarily be concerned with the interplay between the swelling pressure terms due to chain stretching and electrostatic interactions defined above. In many connective tissues there are distinct tissue components separately responsible for each term. For example, in articular cartilage at physiological pH, it is the repulsive interactions between the charged proteoglycan aggregates that provide the swelling force, and the elastic recoil of the stretched collagen fibrous network that opposes this swelling force and maintains tissue integrity [1,31].

In general, any structural micromodel for the swelling pressure must incorporate both of these features in order to accurately predict the total swelling pressure. Nevertheless, it is possible to succeed with partial models of tissue swelling behavior as long as the limitations of the model are clearly understood. For example, Lee [32] used a cylindrical cell model to describe the electrostatic part of the swelling pressure in cartilage. Because he did not include the constraining effect of the collagen network in the model, the model does not accurately predict the swelling pressure for small compressive uniaxial deformations. For small compressive strains, the collagen network plays a major role in balancing the proteoglycan electrostatic repulsive forces [1,31]. However, at higher strains, the model does well because the tensile strain on the collagen network has been removed, and the swelling pressure is almost entirely due to the electrostatic interactions between the charged proteoglycans [32].

Section 2.2.1
2.2.2 Swelling Pressure Constitutive Equation

To begin the discussion of chemically induced changes in swelling pressure, we consider swelling behavior when the tissue is in mechanical and chemical equilibrium. We imagine testing a tissue disk that is in equilibrium at \((c_1, p_{H_1})\) in confined uniaxial compression as shown in Fig. 2.1. We define zero measured stress and strain when the distance from the bottom of the porous platen to the bottom of the well is the same as the equilibrium thickness of the tissue at \((c_1, p_{H_1})\). We deform the tissue from its equilibrium thickness through a series of strains, measured as the displacement from the original tissue thickness normalized to that same thickness, and trace out the first swelling pressure versus strain curve shown in Fig. 2.3a. For now we assume that the swelling pressure - strain relationship is linear with slope \(M_1\). Next, we go back to the original zero strain state and chemically alter the bath in such a way as to increase the swelling pressure, while holding the thickness constant. After allowing the tissue to equilibrate at \((c_2, p_{H_2})\), we measure a stress at zero strain. We proceed to deform the tissue as before, using the same definition of strain as before, and trace out curve 2 of Fig. 2.3a, which we also assume to be linear with slope \(M_2\). This process can be repeated to generate an entire family of swelling pressure curves. For the simple linear case, we can represent this information as

\[
\begin{align*}
  p_1 &= M_1 \varepsilon \\
  p_2 &= M_2 \varepsilon + b_2 \\
  p_3 &= M_3 \varepsilon + b_3
\end{align*}
\]  

(2.2)
Figure 2.3 Linear swelling pressure - strain relation parameterized by concentration. (a) single reference thickness used for all concentrations. (b) different reference thickness used for each concentration.
where $M_i$ refer to the moduli $M(c_i, \phi H_i)$, and the $\beta_i$ account for the stress measured at zero strain for $(c_i, \phi H_i)$. $\beta_i$ will be referred to as the chemical stress. The origin of the $\beta_i$ can be elucidated by testing the tissue sample using a slightly different protocol.

Imagine that we trace out curve 1 of Fig. 2.3b as previously described. We alter the bath in the same way as before, but this time we allow the sample to equilibrate unconfined, that is, unconstrained by the porous platen. We proceed to deform the sample, but now zero strain is defined when the distance from the bottom of the porous platen to the bottom of the well is exactly the same as the new equilibrium thickness. Doing the experiment this way, we never measure a stress at zero strain, and therefore the chemical stress is always 0. However, we now measure the strain $\varepsilon'$ as the displacement from the new equilibrium thickness, normalized to that thickness. We end up with the family of curves shown in Fig. 2.3b. Note that $M'_1 \neq M'_2$, etc., although curve 1 and 1' are identical since the reference thickness used to determine the strains for 1 and 1' is the same.

While the curves shown in Fig. 2.3a and b are in general different, both sets of experiments were performed on the same material under the same chemical conditions and hence, should embody the same information about the material. The difference between the experiments involves the definition of strain. In the first set of experiments, $\varepsilon$ is the deformation from a single free equilibrium thickness, in this case $\delta_1$, normalized to $\delta_1$. In the second set $\varepsilon'$ is the deformation from the free equilibrium thickness at each concentration normalized to that thickness. Hence, a 25 µm displacement in Fig. 2.3a represents a single
strain, independent of the chemical conditions of the bath, while the same 25 \( \mu \text{m} \) displacement in Fig. 2.3b represents a different strain for each set of chemical conditions. Note that this difference is more important than it might at first seem. In the first set of experiments, the equilibrium \( \epsilon \) is a parameter that the experimenter can control. In this sense it is like external bath pH and salt concentration which can also be controlled independently. In the second set of experiments, \( \epsilon' \) is not an independent parameter. Its value is a function of the chemical state of the tissue. The way we choose to represent the strain will become important when we treat the time course of changes in swelling or swelling pressure caused by changes in the chemical environment.

The slopes of the curves in Fig. 2.3a and 2.3b can be related as follows. For experiment 1, the slope of the \( i \)th curve \( M_i \) is

\[
M_i = \frac{\Delta P_i}{\Delta \epsilon} = \frac{\Delta P_i}{\Delta u} \delta_i
\]  \hspace{1cm} (2.3)

where \( \delta_i \) is the equilibrium thickness of the sample under the reference chemical conditions \((c_1, \text{pH}_1)\). \( M_i' \) is given by

\[
M_i' = \frac{\Delta P_i}{\Delta \epsilon'} = \frac{\Delta P_i}{\Delta u} \delta_i
\]  \hspace{1cm} (2.4)

where \( \delta_i \) is the equilibrium thickness of the sample under the \( i \)th chemical conditions, \((c_i, \text{pH}_i)\). Since the sample was tested under identical chemical conditions in both experiments, we expect a given change in displacement \( \Delta u \) to yield the same change in stress or swelling pressure. Hence
\[ M'_i = M_i \frac{\delta_i}{\delta_1} \tag{2.5} \]

We can now return to the origin of the chemical stress \( \beta \). If we were to back the platen off the sample on curve 2 of Fig. 2.3a, until we measured zero stress corresponding to zero swelling pressure, we would, by definition, be at the equilibrium thickness of the sample consistent with the chemical conditions \((c_2, pH_2)\). Hence, the non-zero swelling pressure measured at zero strain must be due to an effective displacement equal to the difference between the equilibrium thicknesses \( \delta_2 \) and \( \delta_1 \). A similar argument applies to each of the curves in Fig. 2.3a. Therefore, the chemical stress \( \beta \) is described by

\[ \beta_i = \frac{\delta_i - \delta_1}{\delta_1} M_i \tag{2.6} \]

Clearly, the information contained in Fig. 2.3a is equivalent to knowing both the concentration dependence of the sample thickness and the information presented in Fig. 2.3b. This implies that information is lost if only the modulus is reported as a function of concentration. Unfortunately, this has been standard reporting practice in the literature.

From the above discussion, it is clear that the chemical stress \( \beta \) can be defined with respect to any reference thickness. The only effect of changing the reference thickness is to change the concentration at which \( \beta = 0 \). It will be convenient to define \( \beta \) in terms of the tissue thickness attained when the concentration is sufficiently large to effectively shield the electrical interactions between the charged

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constituents of the tissue. This reference thickness corresponds to the minimal free swelling thickness of the sample. By choosing this minimal thickness as the reference thickness, the chemical stress \( \sigma \) can only be greater than or equal to zero.

In general, we do not obtain such ideal, linear constitutive laws for swelling pressure and strain as those depicted in Fig. 2.3. For large strains, nonlinear behavior is observed. However, there may be regions of the curve which are linear. Within these regions it is possible to relate changes in swelling pressure to changes in strain in a linear manner. In such cases it is convenient to define an operating point swelling pressure \( p^*_1(\varepsilon_o) \) at some strain \( \varepsilon_o \) in the linear region that can be used to relate the change in swelling pressure to changes in the chemical environment at constant strain. Hence, in the linear region we represent the swelling pressure as

\[
p = M \Delta \varepsilon + p^*_1(\varepsilon_o) \quad \text{(2.7)}
\]

For experiments performed in a constant chemical environment, we can relate the change in swelling pressure to the change in strain as

\[
\Delta p = M \Delta \varepsilon \quad \text{(2.8)}
\]

To account for changes in the chemical environment from \((c_2, pH_2)\) to \((c_3, pH_3)\) at constant strain \( \varepsilon_o \) (Fig. 2.4a), we would use

\[
\Delta p(\varepsilon_o) = p^*_3(\varepsilon_o) - p^*_2(\varepsilon_o) \quad \text{(2.9)}
\]

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where $\varepsilon_0$ corresponds to the strain at which the $p_i^*$ are measured. If we were to change the strain and chemical environment simultaneously, or change the chemical environment at some strain other than $\varepsilon_0$ (Fig. 2.4b), we would have

$$\Delta p = M_3 \Delta \varepsilon + p_3^*(\varepsilon_0) - p_2^*(\varepsilon_0)$$

$$= M_2 \Delta \varepsilon + p_3^*(\varepsilon_0 + \Delta \varepsilon) - p_2^*(\varepsilon_0 + \Delta \varepsilon)$$

where

$$p_3^*(\varepsilon_0 + \Delta \varepsilon) - p_2^*(\varepsilon_0 + \Delta \varepsilon) = (p_3^*[\varepsilon_0] + M_3 \Delta \varepsilon) - (p_2^*[\varepsilon_0] + M_2 \Delta \varepsilon)$$

(2.11)

For the general nonlinear case it makes little sense to define an M or a $p^*$ in a large signal sense. However, in certain applications it may be appropriate to linearize around an operating point in terms of the mechanical or chemical parameters.

2.2.3 Summary: Definition of Chemical Stress $g(c)$ and Modulus $M(c)$

In the preceding section we have defined the modulus M as the slope of the swelling pressure – strain, or equilibrium stress – strain curve for a tissue sample tested in the uniaxial confined compression configuration depicted in Fig. 2.1. It was argued that for a charged material, the modulus could be altered by changing the chemical composition of the external bath. It was also necessary to define the chemical stress $g$ to account for nonzero equilibrium stresses that could be chemically induced at zero strain. The chemical stress was related to
Figure 2.4 Linear region of nonlinear swelling pressure - strain relation parameterized by concentration: (a) chemically induced change in swelling pressure at constant strain (b) change in swelling pressure due to change in concentration and strain.
chemically induced changes in the balance of the individual swelling pressure terms. In samples allowed to swell freely in the thickness direction in the configuration of Fig. 2.1, the altered balance of the swelling pressure terms is manifested as a change in sample thickness as a function of salt concentration.

The introduction of a concentration dependent modulus and the chemical stress was motivated by using equilibrium arguments in uniaxial confined compression. However, the swelling pressure was defined on a continuum basis, in terms of the local environment. It was further postulated that all concentration dependent terms in the swelling pressure could respond to changes in the local environment on a time scale that was short compared to the time required for ions to diffuse into the sample when the external salt concentration was changed. Hence, \(M\) and \(\beta\) always maintain a local equilibrium with the local environment and \(M(c_i(z,t))\) and \(\beta(c_i(z,t))\) evolve with the local concentrations during a chemical transient. The swelling pressure \(p(z,t)\) can, therefore, be used in a transient analysis with no further assumptions. The relation between the swelling pressure \(p(z,t)\) during a chemical transient and the uniform swelling pressure measured in equilibrium will be discussed in section 2.5.1.

Finally, it is worth while noting that the arguments used to motivate the existence of \(M(c)\) and \(\beta(c)\) are not restricted to a one dimensional analysis. All intrinsic material constants can be treated as functions of concentration in a fully three dimensional analysis.
2.3 Nonequilibrium Stress - Strain Constitutive Equation

In order to characterize the behavior of the tissue in nonequilibrium situations when fluid is flowing, we must include a fluid pressure term in the relation between the stress and the swelling pressure. In what follows we will assume that the fluid is incompressible, and will describe the flow of fluid in the tissue with Darcy's law. However, because the tissue is charged, we must allow for osmotic as well as hydrostatic pressure gradients since fluid flows in response to a gradient in their difference [33]. That this is so can be simply shown by considering water equilibrium between elements in the tissue, or between the tissue and the external bath. Equilibrium between element a and b in the tissue requires

\[
\bar{\nu}_w P_a + RT \ln x_w^a = \bar{\nu}_w P_b + RT \ln x_w^b
\]

where \(P\) is the hydrostatic pressure, \(x_w\) is the water mole fraction, and \(\bar{\nu}_w\) is the partial molar volume of water expressed as liters per mole. This can be rearranged to show for dilute solutions

\[
P_a - P_b = RT(\Sigma c_i^a - \Sigma c_i^b) = \pi^a - \pi^b
\]

where the \(\Sigma c_i\) are the sum of solute concentrations in the respective tissue elements. If \((P_a - \pi_a) \neq (P_b - \pi_b)\), then fluid will flow from the region where \((P - \pi)\) is greater to the region where it is less until they are equal. Therefore, in Darcy's law we require that water flow in response to a gradient in \((P - \pi)\) instead of the usual hydrostatic pressure. This results in
U = - k \nabla (P - \pi) \quad (2.14)

Since in equilibrium there is no flow anywhere inside the tissue or across the tissue/bath interface, the gradient in total fluid pressure vanishes, and \((P - \pi)_{\text{inside}} = (P_0 - \pi_0)\), where \(P_0\) and \(\pi_0\) are the hydrostatic and osmotic pressures in the external bath. Note that we can set \(P_0 = 0\) (free draining) without loss of generality. However, we cannot set \(\pi_0 = 0\). Because of this asymmetry between the hydrostatic pressure \(P\) and the osmotic pressure \(\pi\), it is convenient to define the osmotic pressure difference as

\[
\Delta \pi(z,t) \equiv \pi(z,t) - \pi_0 \quad (2.15)
\]

and to use it in Darcy's law as

\[
U = - k \nabla (P - \Delta \pi) \quad (2.16)
\]

Then, in equilibrium, \((P - \Delta \pi) = 0\) everywhere inside the tissue.

It is worthwhile noting that in any charged tissue where \(\pi_{\text{in}} \neq \pi_0\) in equilibrium, the hydrostatic pressure \(P\) will go through a step jump at the surface of the tissue. This is an important point to keep in mind, as it has not been incorporated into previous swelling models \([14, 15, 16, 17, 24, 34]\). This has led to confusion concerning the meaning of hydrostatic and osmotic pressures \([14, 34]\).

If the compressive stress \(\sigma\) was suddenly increased in the uniaxial configuration of Fig. 2.1, fluid would begin to flow out of the tissue.
Neglecting inertial effects, the divergence of the total stress must be zero. Hence,

\[ \frac{\partial \sigma}{\partial z} = 0 \]  \hspace{1cm} (2.17)

If we assume that the solid is also incompressible, at \( t=0^+ \), just after increasing the compressive force, the hydration of the tissue will not have had time to change, and hence, the swelling pressure \( p \) will also not have changed anywhere in the tissue. The increased stress in the tissue is supported by the frictional interaction of the fluid with the tissue matrix, which is manifest in the fluid pressure \( (P - \Delta \pi) \). As fluid flows out of the tissue, the tissue hydration is reduced, the swelling pressure \( p \) increases and the fluid pressure \( (P - \Delta \pi) \) decreases. Once fluid flow has ceased, the fluid pressure vanishes, and the swelling pressure equals the the applied stress everywhere in the tissue. Hence, the relation between the stress, the swelling pressure and fluid pressure appropriate when fluid is flowing is

\[ \sigma = p + (P - \Delta \pi) \]  \hspace{1cm} (2.18)

The present model can be put into a more general framework by expressing the relationship between total stress, swelling pressure, strain, chemical stress and fluid pressure in a more general tensor form of Hooke's law. The total stress \( \sigma_{ij} \) can be expressed in terms of the strain \( \epsilon_{ij} \), the chemical stress \( \beta \) the Lamé constants \( G \) and \( \lambda \) and the fluid pressure \( (P - \Delta \pi) \) as

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\[ \sigma_{ij} = 2G(c)\varepsilon_{ij} + \lambda(c)\varepsilon_{kk}\delta_{ij} - \beta(c)\delta_{ij} - (P - \Delta\pi)\delta_{ij} \quad (2.19) \]

where \( \delta_{ij} \) is the Kronecker delta function. We note in writing eq. 2.19 that the stress and strain tensors \( \sigma_{ij} \) and \( \varepsilon_{ij} \) are defined with the standard convention of being negative in compression. This is the opposite of the definition used earlier for the strain \( \varepsilon \) and the stress \( \sigma \), and is why the term for the chemical stress \( \beta \) has a negative sign in eq. 2.19. This should not cause any major confusion as the tensor quantities will always be subscripted. This expression is analogous to the general relations given by Rice and Cleary [eq. 7 of 13] and Biot [eq. 3.10 of 12] in the limit of incompressible fluid and solid constituents, although the chemical stress \( \beta \) and the chemical dependence of the material constants \( G \) and \( \lambda \) were not included in those developments. The total stress \( \sigma_{ij} \) is equivalent to the sum of the \( T_{ij}^s \) for the solid and \( T_{ij}^f \) for the fluid in the mixture model used by Mow et al [17], and should not be confused with either of these stresses individually. Writing the general stress-strain constitutive equation in the form of eq. 2.19 clearly shows the analogy between the chemical stress and the thermal stress of thermoelasticity [3].

In confined uniaxial compression, the only nonzero strain is \( \varepsilon_{zz} \) and eq. 2.19 can be written as

\[ -\sigma = \sigma_{zz} = (2G + \lambda)\varepsilon_{zz} - \beta - (P - \Delta\pi) \quad (2.20) \]

Equating the previously defined compressive strain \( \varepsilon \) with \( -\varepsilon_{zz} \) we have

\[ \sigma = (2G + \lambda)\varepsilon + \beta + (P - \Delta\pi) = M\varepsilon + \beta + (P - \Delta\pi) \quad (2.21) \]
where the modulus in confined compression (the bulk longitudinal modulus) \( M = 2G + \lambda \).

Since we have assumed that the solid and fluid constituents of the tissue are incompressible, conservation of mass for confined uniaxial compression can be written simply as

\[
\frac{\partial u}{\partial t} = -U \tag{2.22}
\]

where \( u \) is the displacement of a point in the tissue from its original location in the undeformed sample, and \( U \) is the average velocity of the fluid relative to the solid phase. This, combined with eqs. (2.16), (2.17) and (2.18) yields

\[
\frac{\partial u}{\partial t} = -k \frac{\partial p}{\partial z} \tag{2.23}
\]

For a material with a linear stress – strain curve we had

\[
p = Me + B \tag{2.24}
\]

When a homogeneous tissue (\( M \) and \( B \) independent of position in the tissue) with this constitutive law is subjected to a mechanical stimulus with bath concentrations held fixed we have

\[
\frac{\partial u}{\partial t} = Mk \frac{\partial^2 u}{\partial z^2} \tag{2.25}
\]

where \( \varepsilon = -\frac{\partial u}{\partial z} \) has been used.

Section 2.3
Eq. 2.25 is a diffusion equation for the displacement field $u$ in the tissue resulting from a mechanical stimulus holding external concentration constant. It was derived assuming that the tissue could be modeled as a linear, isotopic porous material comprised of incompressible constituents. This equation is also the end result of the more general poroelastic and mixture theories under similar limiting conditions. However, because we have incorporated the chemical stress into our development, we are now in a position to investigate the mechanical behavior of the tissue as a function of time when the tissue is not in chemical equilibrium. All that is needed is a constitutive relation that specifies the swelling pressure $p$ as a function of the mechanical and chemical variables. If we assume that $p$ is a linear function of the mechanical deformation, all we need is the functional dependence of $M$ and $\beta$ on chemical concentration.

2.4 Mechanically Induced Transients

Before considering the transient response of the tissue to a chemical stimulus, we will solve eq. 2.25 for a tissue sample in confined compression in response to a mechanical stimulus with external chemical variables held fixed. We will consider both constant load and constant displacement experiments.

2.4.1 Stress Relaxation

We will first consider the transient stress in the tissue in response to a step change in displacement. In general, the tissue will have an initial surface displacement $u_0$ with a corresponding linear
displacement field and stress, $\sigma_0$. Hence,

$$ u(z,t<0) = u_0 (1 - \frac{z}{\delta}) $$  

(2.26)

$$ \sigma_0 = p_0 = M \epsilon_0 + \beta $$

where

$$ \epsilon_0 = - \frac{\partial u}{\partial z} = \frac{u_0}{\delta} $$  

(2.27)

At $t=0$, the displacement of the porous platen at $z=0$ is stepped to $u_0 + \Delta u_0$ and held constant for the duration of the experiment. We will determine the transient response of the measured stress, $\sigma_0 + \Delta \sigma(t)$.

The bottom of the sample at $z=\delta$ remains fixed in space and the displacement there is always zero. We therefore have the boundary conditions for $t>0$

$$ \Delta u(0,t) = \Delta u_0 $$  

(2.28)

$$ \Delta u(\delta,t) = 0 $$

Also, since fluid cannot flow out of the bulk of the tissue instantaneously, the displacement in the bulk at $t=0^+$ must be the same as it was at $t=0^-$. Therefore, the initial condition is

$$ \Delta u(z,0) = 0 $$  

(2.29)

Section 2.4.1
The solution to eq. 2.25 satisfying these conditions is

\[ \Delta u(z,t) = \Delta u_0 (1 - \frac{z}{\delta}) - \frac{2\Delta u_0}{\pi} \sum_{n=1}^{\infty} \frac{1}{n} \sin \frac{n\pi z}{\delta} \exp(-\frac{n^2 t}{\tau_m}) \]  

(2.30)

where the mechanical time constant \( \tau_m \) has been introduced,

\[ \tau_m = \frac{\delta^2}{\pi^2 N k} \]  

(2.31)

To determine the stress transient we use eq. (2.21). Since the stimulus was purely mechanical, and since we have assumed a linear equilibrium stress - strain curve, M and \( \beta \) will remain constant throughout the experiment. Hence, for the transient

\[ \Delta \sigma(t) = \sigma(t) - \sigma_0 \]

\[ = M(\varepsilon[z,t] - \varepsilon_0) - (P[z,t] - \Delta \pi[z,t]) \]  

(2.32)

where the fluid pressure is zero for \( t < 0 \). \( \Delta \sigma(t) \) in eq. 2.32 is the total stress everywhere in the bulk. Since we compress the tissue with a porous platen (assumed to be infinitely more permeable than the tissue sample), the fluid pressure (\( P - \Delta \pi \)) at the surface of the tissue must be zero at all times. Hence, the measured change in stress is given by

\[ \Delta \sigma(t) = M(\varepsilon[0,t] - \varepsilon_0) = -M \frac{\partial \Delta u(0,t)}{\partial z} \]  

(2.33)

Differentiating eq. 2.30 we have,
\[ \Delta \sigma(t) = M \frac{\Delta u_0}{\delta} \left( 1 + 2 \sum_{n=1}^{\infty} \exp\left(-\frac{n^2 t}{\tau_m}\right) \right) \]  

(2.34)

Note that this is infinite at \( t=0 \), and decays to its final value with the characteristic time constant \( \tau_m \).

2.4.2 Creep Deformation

For a step change in load \( \Delta \sigma_0 \), the displacement of the tissue surface will change with time until a new equilibrium surface displacement is reached consistent with the new load. Since the fluid pressure is zero at the tissue surface, the change in strain at the surface \( \Delta \varepsilon_0 \) must always equal the increment in stress divided by the modulus. This results in the boundary conditions

\[ \varepsilon(0,t) = -\frac{\partial \Delta u(0,t)}{\partial z} = -\frac{\Delta u_0}{\delta} = \frac{\Delta \sigma_0}{M} \]  

(2.35)

\[ \Delta u(\delta,t) = 0 \]

and the initial condition

\[ \Delta u(z,0) = 0 \]  

(2.36)

The solution to (2.25) satisfying these conditions is

\[ \Delta u(z,t) = \frac{\Delta \sigma_0 \delta}{M} \left( (1 - \frac{z}{\delta}) - \frac{8}{\pi^2} \sum_{\text{odd}} \frac{1}{n^2} \cos \frac{n \pi z}{2 \delta} \exp(-\frac{n^2 t}{4 \tau_m}) \right) \]  

(2.37)

Section 2.4.2
Evaluating $\Delta u$ at $z=0$ for the surface displacement yields

$$
\Delta u_o(t) = \frac{\Delta \sigma_o \delta}{M} \left[ 1 - \frac{8}{\pi^2} \sum_{\text{odd}} \frac{1}{n^2} \exp\left(-\frac{n^2 t}{4\tau_m}\right) \right]
$$

(2.38)

The change in surface displacement $\Delta u_o$ is zero at $t=0$, as required. The surface displacement grows in time for an increase in compressive load, and reaches its final value with a characteristic time $4\tau_m$, where $\tau_m$ is as defined in eq. 2.31. Hence, experiments measuring creep deformation take 4 times longer than stress relaxation experiments done on the same tissue.

2.5 **Chemically Induced Mechanical Transients**

2.5.1 **Chemical Transient**

The goal of this section is to develop a general model to describe the transient mechanical behavior of the tissue in response to a chemical stimulus. In what follows, we imagine the stimulus to be a step change in the salt concentration of the bath.

Because the tissue is charged, it makes no sense to speak of the diffusion of neutral salt into the tissue since a single internal salt concentration cannot be defined. Instead, equations must be written to describe the flux of each ion into the charged tissue. The flux of the ions in the tissue can be described by

$$
\bar{i}_\pm = -D \frac{\partial \bar{c}_\pm}{\partial z} + \bar{c}_\pm \bar{v} \pm \bar{c}_\pm \bar{u}_\pm \bar{E}
$$

(2.39)
where

\( \Gamma_\pm = \text{ion fluxes in the tissue fluid phase} \)

\( \bar{c}_\pm = \text{ion concentrations in the tissue fluid phase} \)

\( D_\pm = \text{intra-tissue diffusivities} \)

\( \bar{\mu}_\pm = \text{intra-tissue mobilities} \)

\( v = \text{local z-directed fluid velocity} \equiv \frac{U}{\phi} \)

\( \phi = \text{tissue porosity} \)

\( E = \text{z-directed electric field} \)

Continuity for each species relates the time rate of change of the ionic concentrations at any point in the tissue to the divergence of the flux,

\[
\frac{\partial \bar{c}_\pm}{\partial t} = -v \cdot \Gamma_\pm \tag{2.40}
\]

where we have assumed that no chemical reactions occur. Charge neutrality within the tissue requires

\[
\bar{\rho}_m(z,t) + \bar{c}_+(z,t) - \bar{c}_-(z,t) = 0 \tag{2.41}
\]

where \( \bar{\rho}_m \) is the tissue fixed charge density expressed as moles of charge per liter of tissue fluid and the electrolyte is assumed to be mono - monovalent. Since the amount of fluid in a tissue element varies with the strain \( \varepsilon \), the fixed charge density also varies with strain:

\[
\bar{\rho}_m(z,t) = \frac{-\bar{\rho}_m(z,t)}{1 - \varepsilon(z,t)/\bar{\nu}_w} \tag{2.42}
\]
where $\bar{v}_w^0$ is the volume fraction of fluid in the tissue corresponding to the initial charge density $\bar{p}_m^0$. Since we have assumed that the solid is incompressible, the strain necessary to squeeze all of the fluid out of the tissue is equal to the original fluid volume fraction.

This system of equations describes the transport of ions into the tissue and the evolution of the internal ionic concentrations. However, in order develop the complimentary mechanical equations, we must describe the effect of the local ionic concentrations on the tissue swelling pressure. In section 2.2.1 it was shown that the concentration dependence of the swelling pressure should be expressed in terms of an external concentration since the external concentration is independent of tissue deformation. Furthermore, the concentration dependence of the swelling pressure is most conveniently measured in terms of external salt concentration. Hence, during the chemical transient when local ion concentrations are not in equilibrium with the external bath, it is convenient to ascribe to each point within the tissue at every point in time an equivalent external equilibrium concentration. In order to transform the internal concentrations $\bar{c}_\pm$ to an effective external concentration, we invoke a pseudo Donnan equilibrium that relates $\bar{c}_\pm$ and $\bar{p}_m$ at each point in space and time to the effective external concentration $c^*$,

$$c^*(z,t) = \bar{c}_\pm(z,t) \left[ 1 \pm \frac{\bar{p}_m(z,t)}{\bar{c}_\pm(z,t)} \right]^{1/2} \quad (2.43)$$

The effective external concentration $c^*(z_o, t_o)$ represents the external
concentration that would be in equilibrium with the ionic concentrations and the tissue fixed charge density at the point $z_o, t_o$. Hence, if the incremental volume of tissue at $z_o, t_o$ with internal ion concentrations $\tilde{c}_\pm(z_o, t_o)$ was excised and placed in a solution with a salt concentration of $c^*(z_o, t_o)$, the incremental volume of tissue would be in Donnan equilibrium with its new environment, as illustrated in Fig. 2.5. The effective external equilibrium concentrations $c^*(z_o, t_o)$ do not actually exist, but can be used in conjunction with a constitutive law for the swelling pressure as a function of external concentration to determine the chemical contribution to the swelling pressure at the point $z_o, t_o$ inside the tissue.

The chemical subsystem is coupled to the mechanics through the fluid velocity $U$ and the strain dependence of the fixed charge density $\rho_m$, while the mechanical subsystem is coupled to the chemical subsystem through the concentration dependence of the swelling pressure $p$. In principle, this coupled system of differential equations can be solved without further approximation given appropriate boundary and initial conditions. However, for the benefit of gaining insight into the behavior of the system, we will make additional approximations and eliminate one of the coupling paths.

We consider an experiment where a change in the measured load is induced by a change in the bath salt concentration for a tissue disk in uniaxial confined compression, holding the applied displacement constant. (Alternatively, the role of load and displacement can be reversed.) The local fluid velocity $\nu$ that appears in the flux eqs. 2.39 is then self generated in the sense that it is due to local tissue
Figure 2.5 Definition of the effective external equilibrium concentrations.
consolidation rather than an imposed trans-tissue flow. This local velocity is small enough in both constant load and constant displacement experiments that the Peclet number is very small. This means that the effect of convection is small compared to diffusion. Hence, in what follows, we will neglect the convective transport of ions in determining the ion concentration profiles within the tissue as a function of space and time. We can always determine $v$ after the fact and check to make sure that this assumption is justified.

The remaining mechanical-to-chemical coupling lies in the strain dependence of the charge density. For experiments in which the surface displacement is held constant, the mechanical consolidation of the tissue at the end of the experiment is the same as it was at the beginning of the experiment. Hence, the net change in the fixed charge density due to mechanical consolidation is zero. While salt diffuses into the tissue there will be local tissue consolidation and redistribution of fluid during the transient. However, it seems reasonable to assume that this consolidation and redistribution will be small. Hence, in displacement control we will neglect this coupling as well.

In load control, the total tissue volume may change significantly. The extent of the volume change will depend on the tissue as well as on the chemical stimulus applied. For the time being, we will restrict ourselves to cases where the total change in normalized displacement resulting from the chemical stimulus is small. Under these circumstances, it is reasonable to neglect the coupling of strain to charge density.
We are left with much simpler chemical transport equations. If we further assume that the charge density in the tissue is uniform in the unstrained tissue, eqs. 2.39, 2.40 and 2.41 can be combined to give

\[
\frac{\partial \bar{c}_\pm}{\partial t} = \frac{1}{a} \frac{\partial}{\partial z} \left( \bar{D}_a \frac{\partial \bar{c}_\pm}{\partial z} \right) \tag{2.47}
\]

where the ambipolar diffusivity \( \bar{D}_a \) is defined in terms of the individual ion diffusivities inside the tissue, \( \bar{D}_+ \) and \( \bar{D}_- \), and the internal ionic concentrations as [36]

\[
\bar{D}_a = \frac{\bar{D}_+ \bar{D}_- \left( \bar{c}_+ + \bar{c}_- \right)}{\bar{D}_+ \bar{c}_+ + \bar{D}_- \bar{c}_-} \tag{2.48}
\]

If we assume an instantaneous Donnan equilibrium at the tissue/electrolyte interface at \( z=0 \), we have

\[
\bar{c}_\pm(0,t) = \pm \frac{m}{2} + \left( \frac{m}{2} + (c_o + \Delta c_o)^2 \right)^{1/2} \equiv \bar{c}_\pm^\infty \tag{2.49}
\]

where \( c_o \) is the concentration of the bath before changing the concentration and \( \Delta c_o \) is the increment in concentration. At the solid wall located at \( z=\delta \) we have

\[
\frac{\partial \bar{c}_\pm}{\partial z} = 0 \tag{2.50}
\]
The initial condition is

\[ \bar{c}_\pm (z,0) = \frac{\rho_m}{2} + \left( \frac{\rho_m^2}{4} + c_o^2 \right)^{1/2} \equiv \bar{c}_o \pm \] (2.51)

If the initial concentration and/or the increment in concentration are such that \( D_a \) remains approximately constant throughout the course of the experiment, eq. 2.47 can be solved analytically. The solution is then [37]

\[ \bar{c}_\pm (z,t) = \bar{c}_o^\pm - \frac{4(c_o^\pm - \bar{c}_o^\pm)}{\pi} \sum_{\text{odd}} \frac{1}{n} \sin \frac{n\pi z}{2d \delta} \exp\left(-\frac{n^2 t}{\tau_c}\right) \] (2.52)

where

\[ \tau_c = \frac{4\delta^2}{\pi^2 D_a} \] (2.53)

2.5.2 Chemically Induced Stress Relaxation

Although we have decoupled the chemical diffusion problem from the mechanics, we have retained the effect of the chemical concentrations on the material properties \( M \) and \( B \), and hence, on the swelling pressure. This coupling is what we originally set out to describe. We will first describe the change in measured stress in response to a step change in concentration, with the displacement held constant.

In general, the measured stress \( \sigma(t) \) is given by
\[ \sigma(t) = p(c^*[z,t], \epsilon[z,t]) - (P[z,t] - \Delta \pi[z,t]) \tag{2.54} \]

where the tissue swelling pressure is a function of the effective external equilibrium concentration and local strain. Taking the \( z \)-derivative of eq. 2.54 twice we have

\[ 0 = \frac{\partial^2 p}{\partial z^2} + \frac{\partial}{\partial z} \left( \frac{\partial}{\partial z} (P - \Delta \pi) \right) \tag{2.55} \]

Taking the \( z \)-derivative of Darcy's law yields

\[ \frac{\partial u}{\partial z} = -k \frac{\partial^2}{\partial z^2} (P - \Delta \pi) \tag{2.56} \]

Recognizing that

\[ \frac{\partial u}{\partial z} = \frac{\partial \epsilon}{\partial t} \tag{2.57} \]

and using eqs. 2.55 and 2.56 in eq. 2.57 yields

\[ \frac{\partial \epsilon}{\partial t} = k \frac{\partial^2 p}{\partial z^2} \tag{2.58} \]

Since \( p(z,t) \) is a function of the independent variables \( c^*(z,t) \) and \( \epsilon(z,t) \), we can use the chain rule to express \( \frac{\partial \epsilon}{\partial t} \) as

\[ \frac{\partial \epsilon}{\partial t} = \frac{\partial p}{\partial t} - \frac{\partial p}{\partial c^*} \frac{\partial c^*}{\partial \epsilon} \tag{2.59} \]

Equations 2.58 and 2.59 can be combined to give
\[ \frac{\partial p}{\partial t} = k \frac{\partial p}{\partial \varepsilon} \frac{\partial^2 p}{\partial z^2} + \frac{\partial p}{\partial \varepsilon^*} \frac{\partial \varepsilon^*}{\partial t} \]  \hspace{1cm} (2.60)

which can be solved if the functionality of \( p \) with \( \varepsilon \) and \( \varepsilon^* \) is known.

The boundary conditions can be found by taking the \( z \)-derivative of eq. 2.54 to yield

\[ \frac{\partial p}{\partial z} = - \frac{3}{2} (P - \Delta \pi) \]  \hspace{1cm} (2.61)

Because of the impermeable wall at \( z=\delta \), \( \frac{\partial}{\partial z} (P - \Delta \pi) \) and therefore \( \frac{\partial p}{\partial z} \), must be zero there. Since the total tissue volume remains constant (surface displacement fixed), we must have no flow boundary condition at \( z=0 \) as well. Hence,

\[ \frac{\partial p}{\partial z} = 0 \quad \text{at} \quad z = 0, \delta \]  \hspace{1cm} (2.62)

The initial condition is simply

\[ p(z,0) = p_0 \]  \hspace{1cm} (2.63)

We assume that the tissue can be described by the linear swelling pressure – strain relation:

\[ p(z,t) = M(c^*[z,t])\varepsilon(z,t) + \varepsilon(c^*[z,t]) \]  \hspace{1cm} (2.64)

where \( M \) and \( \varepsilon \) are functions of the effective external equilibrium concentration alone. With eq. 2.64, eq. 2.60 becomes

Section 2.5.2
\[ \frac{\partial p}{\partial t} = Mk \frac{\partial^2 p}{\partial z^2} + \frac{(P - \beta)}{M} \frac{\partial M}{\partial \bar{c}^*} \frac{\partial \bar{c}^*}{\partial t} + \frac{\partial \bar{g}}{\partial \bar{c}^*} \frac{\partial \bar{c}^*}{\partial t} \]  

(2.65)

Equation 2.65 can be recast in terms of the real internal ionic concentrations in a straightforward manner. Since the transformation from the internal ionic concentrations to the effective external concentration can be written in terms of either of the two internal ionic concentrations, eq. 2.65 can similarly be written in terms of either of the internal ionic concentrations, \( \bar{c}^* \). To avoid confusion, we will explicitly use the positive ion concentration. Since

\[ \frac{\partial M}{\partial \bar{c}^*} \frac{\partial \bar{c}^*}{\partial t} = \frac{\partial M}{\partial \bar{c}^+} \frac{\partial \bar{c}^+}{\partial t} \]  

(2.66)

and

\[ \frac{\partial \bar{g}}{\partial \bar{c}^*} \frac{\partial \bar{c}^*}{\partial t} = \frac{\partial \bar{g}}{\partial \bar{c}^+} \frac{\partial \bar{c}^+}{\partial t} \]

eq. 2.65 can be written as

\[ \frac{\partial p}{\partial t} = Mk \frac{\partial^2 p}{\partial z^2} + \frac{(P - \beta)}{M} \frac{\partial M}{\partial \bar{c}^+} \frac{\partial \bar{c}^+}{\partial t} + \frac{\partial \bar{g}}{\partial \bar{c}^+} \frac{\partial \bar{c}^+}{\partial t} \]  

(2.67)

What we have found is an expression for the swelling pressure \( p \) valid for all \( z,t \). Since the top surface of the tissue is held in place by a porous platen, the pressure \( (P - \Delta \tau) \) is zero there. Hence, if we solve eq. 2.65 for \( p(z,t) \) and evaluate it at the surface, we have \( \sigma(t) \), the transient response of the load signal that would be measured by a

Section 2.5.2
load cell holding the tissue at constant thickness.

Because there are two rate processes, it is instructive to normalize eq. 2.65 in order to explicitly introduce the time constants involved. We will normalize time explicitly to the chemical time constant \( \tau_c \). The modulus \( M(\tilde{c}_+[z,t]) \) will be normalized to a characteristic modulus \( M_0 \), and \( z \) will be normalized to the sample thickness \( \delta \). Hence,

\[
\frac{\tau_m}{\tau_c} \frac{\partial P}{\partial \tilde{c}_+} = \frac{M}{\tau^2} \frac{\partial^2 P}{\partial z^2} + \frac{\tau_m}{\tau_c} \left[ \frac{(p - \delta)}{M} \frac{\partial M}{\partial \tilde{c}_+} + \frac{p \delta}{\partial \tilde{c}_+} \right] \frac{\partial \tilde{c}_+}{\partial t} \tag{2.68}
\]

where

\[
\begin{align*}
\tilde{z} &= \frac{z}{\delta} \\
M &= \frac{M}{M_0} \\
P &= \frac{P}{P_0} \\
p_0 &= \text{initial swelling pressure} \\
\delta &= \frac{\delta}{\tau_c} \\
\tau_m &= \frac{\tau^2 M_0 k}{4 \delta^2 P} \\
\tau_c &= \frac{\tau^2 D_a}{\delta^2}
\end{align*}
\]

The factor of \( 1/\tau^2 \) in eq. 2.68 results from choosing the time constants \( \tau_m \) and \( \tau_c \) that correspond to the \( n=1 \) normal mode solution for the uncoupled mechanical stress relaxation and chemical diffusion equations, respectively. Using these times in the normalization preserves a correspondence between experimental time and normalized theoretical time.
It is instructive to examine eq. 2.68 in the limits $\tau_m \gg \tau_c$ and $\tau_m \ll \tau_c$. When $\tau_m \ll \tau_c$, eq. 2.68 reduces to

\begin{equation}
\frac{\partial^2 p}{\partial z^2} = 0
\end{equation}

(2.69)

Solving eq. 2.69 subject to boundary conditions 2.62 we find that the swelling pressure can only be a function of time:

\begin{equation}
p(z,t) = f(t) = \sigma(t)
\end{equation}

(2.70)

This implies that the fluid pressure $(P[z,t] - \Delta \pi[z,t]) = 0$. Since the surface displacement is held constant at $u_o$, throughout the experiment we have

\begin{equation}
u_o = \int_0^\delta \varepsilon(z,t) \, dz
\end{equation}

(2.71)

The constitutive relation for the swelling pressure $p$ can be solved for $\varepsilon$, and then integrated across the sample thickness. Rearranging the result yields

\begin{equation}
\sigma(t) = \frac{u_o + \int_0^\delta \frac{\delta \bar{c}_+ [z,t]}{M(\bar{c}_+ [z,t])} \, dz}{\int_0^\delta \frac{dz}{M(\bar{c}_+ [z,t])}}
\end{equation}

(2.72)

It is clear from this expression that the time course of the load transient in this limit is determined by the chemical profile $\bar{c}_+(z,t)$. 

Section 2.5.2
If we examine the limit \( \tau_m \gg \tau_c \), eq. 2.68 reduces to

\[
\frac{\partial p}{\partial t} = \left( \frac{p - \beta}{M} \frac{\partial M}{\partial c_c} + \frac{\partial \sigma}{\partial c_c} \right) \frac{\partial c_c}{\partial t} \tag{2.73}
\]

This can be rearranged as

\[
\frac{\partial (p - \beta)}{(p - \beta)} = \frac{\partial M}{M} \tag{2.74}
\]

which has the solution

\[
p(z,t) = A(z) M(c_c(z,t)) + \beta(c_c(z,t)) \tag{2.75}
\]

Since the concentration at the surface reaches its final value instantaneously,

\[
p(0,t) = \sigma(t) = \varepsilon_0 M(c_c) + \beta(c_c) \tag{2.76}
\]

and the stress goes through a step jump to its final value in this limit.

What has been shown is that in a constant displacement experiment, the stress transient will never be slower than the chemical time constant. The longer the mechanical time constant \( \tau_m \) relative to the chemical time constant \( \tau_c \), the faster the stress reaches its final value. This behavior will now be contrasted with tissue behavior in response to the same chemical stimulus when the load is held constant.

Section 2.5.2
2.5.3 Chemically Induced Creep Deformation

When we maintain a constant load on the tissue and change the salt concentration in the external bath, the surface displacement and tissue deformation must change to compensate for changes in the material properties $M$ and $\beta$. We will solve for the displacement field $u(z,t)$ in the tissue. During the transient creep deformation in a constant load experiment, the applied load $\sigma_0$ is always

$$\sigma_0 = p(\bar{c}_+[z,t],\bar{e}[z,t]) + (P[z,t] - \Delta\pi[z,t]) \quad (2.77)$$

Fluid flow and conservation of mass are described by

$$\frac{\partial u}{\partial t} = -U = k \frac{\partial}{\partial z}(P - \Delta\pi) \quad (2.78)$$

Taking the $z$-derivative of eq. 2.77 and subbing in eq. 2.78 for $\frac{\partial}{\partial z}(P - \Delta\pi)$ yields

$$\frac{\partial u}{\partial t} = k \left( \frac{\partial p}{\partial \varepsilon} \frac{\partial^2 u}{\partial z^2} - \frac{\partial p}{\partial \bar{c}} \frac{\partial \bar{c}}{\partial z} \right) \quad (2.79)$$

where $\varepsilon = -\frac{\partial u}{\partial z}$ has been used.

At $z = \delta$, the displacement is always zero. Since the upper surface is free draining, the swelling pressure $p$ at $z=0$ remains constant and equal to the applied stress throughout the transient creep of the tissue. Since the concentration at the surface reaches its final value instantaneously, the strain at the surface must also attain its final value instantaneously. This amounts to a boundary condition on the
z-derivative of the displacement. Hence

\[ p(\bar{c}_+, \varepsilon_0 + \Delta \varepsilon_0) = \sigma_0 \]  

(2.80)

Given the functional dependence of \( p \) on \( \bar{c}_+ \) and \( \varepsilon \), the value of \( \varepsilon = -\frac{\partial u}{\partial z} \) at the surface can be obtained. Finally, the initial condition is given by

\[ u(z,0) = u_0 (1 - \frac{z}{\delta}) \]  

(2.81)

For a material that exhibits a linear relationship between swelling pressure and strain,

\[ p(z,t) = M(\bar{c}_+[z,t]) \varepsilon(z,t) + \beta(\bar{c}_+[z,t]) \]  

(2.82)

Equation 2.79 then becomes

\[ \frac{\partial u}{\partial t} = k \left( \frac{\partial u}{\partial z} \right) \frac{\partial M}{\partial \bar{c}_+} - \frac{\partial \beta}{\partial \bar{c}_+} \frac{\partial \bar{c}_+}{\partial z} + Mk \frac{\partial^2 u}{\partial z^2} \]  

(2.83)

and the boundary conditions become

\[ \frac{\partial u}{\partial z}(0,t) = \frac{\beta(\bar{c}_0) - \sigma_0}{M(\bar{c}_0)} \]  

(2.84)

\[ u(\delta,t) = 0 \]

Section 2.5.3
Introducing normalized variables into eq. 2.83, we have

\[
\frac{\tau_m}{\tau_c} \frac{\partial u}{\partial t} = \left( \frac{\partial u}{\partial z} \frac{\partial M}{\partial \bar{C}_+} - \frac{\partial \beta}{\partial \bar{C}_+} \right) \frac{\partial \bar{C}_+}{\partial z} + M \frac{\partial^2 u}{\partial z^2} \tag{2.85}
\]

where \[ u = \frac{u}{\delta} \]

\[ \beta = \frac{\beta}{M_c} \]

and \( z, t, M, \tau_m, \) and \( \tau_c \) are as previously defined. In the limit \( \tau_m \ll \tau_c \), eq. 2.85 reduces to

\[
\frac{\partial}{\partial z} (M \frac{\partial u}{\partial z} - \beta) = 0 \tag{2.86}
\]

Solving eq. 2.86 subject to boundary conditions (2.84) yields

\[
u(0,t) = \delta \int_0^\infty \frac{\sigma_0([z,t]) - \sigma_1}{M([\bar{C}_+([z,t])])} \, dz \tag{2.87}
\]

In this limit it is clear that the time course of the surface displacement will be determined by the chemical time constant \( \tau_c \), which in this limit is longer than the mechanical time constant \( \tau_m \). For \( \tau_m \gg \tau_c \), the chemical gradient \( \frac{\partial \bar{C}_+}{\partial z} \) goes to zero in short order, and we are left with

\[
\frac{\partial u}{\partial t} = M(\bar{C}_+)k \frac{\partial^2 u}{\partial z^2} \tag{2.88}
\]

Section 2.5.3
Hence, the tissue creep response to a chemical stimulus is determined by the longest of the system time constants.


Bibliography II


Bibliography II


CHAPTER III
EXPERIMENTAL PROCEDURES AND RESULTS

In order to solve eq. 2.68 for the swelling pressure \( p(z,t) \) and the total stress \( \sigma(t) = p(0,t) \), constitutive relations that describe the functionality of the equilibrium modulus \( M \) and the chemical stress \( \beta \) with bath NaCl concentration are required. These constitutive relations were determined experimentally for specimens of bovine cartilage and corneal stroma in confined uniaxial compression. For each specimen, load was measured as a function of compressive thickness at several salt concentrations spanning the range \( 0.005 \text{ M} - 1.0 \text{ M} \). In addition, in order to test the transient model developed in Chapter II, stress transients resulting from larger increments in salt concentration were also measured. Experimental protocols and the experimental apparatus are now described.

3.1 Experimental Apparatus

Uniaxial confined compression experiments were performed in a Dynastat Mechanical Spectrometer fitted with a special testing chamber. The overall experimental apparatus is pictured in Fig. 3.1. The Dynastat was usually operated with the servo mechanism in high range displacement control mode. The Dynastat was interfaced to an LSI 11/03 computer so that stress transients could be sampled and stored for further analysis. An analog chart recording was also made. The testing chamber shown schematically in Fig. 3.2, was securely fastened to the actuator of the Dynastat. The tissue sample was placed in a 1/4" diameter, 1.2 mm deep

Section 3.1
Figure 3.1 Photograph of experimental chamber.
Figure 3.2 Schematic of the experimental setup.
confining well machined into the bottom of the solution reservoir. This was slightly deeper than the thickest tissue samples tested. Tissue samples were compressed in the confining chamber by a porous platen, connected to the Dynastat's load cell through a mechanism that allowed the central axis of the porous platen to be aligned with the center of the confining well. The porous platen assembly (shown in Fig. 3.3) consisted of a 1/4" diameter stainless steel shaft fitted with a porous polyethylene tip. A 1/16" diameter hole was drilled into the center of the shaft that connected to an inlet port drilled into its side, as shown in Fig. 3.2. The bathing solution was recirculated through the porous platen, onto the surface of the specimen. This minimized the influence of stagnant films on the transport of ionic solutes into the specimen.

The temperature of the recirculating solution was controlled by first precooling the solution and then heating it to a desired temperature by means of a submerged Teflon coated chromel heating element built into the walls of the reservoir chamber (Fig. 3.2). Precooling was accomplished by placing a heat exchanger connected to a refrigeration unit in the recirculation path. A thermistor probe located in the reservoir was connected to a proportional temperature controller which controlled the voltage output to the heating element. The temperature of the bath was thereby controlled at 20°C ± 0.5°C.

Before testing could begin, the apparatus was aligned in order to minimize rubbing between the porous platen and the sides of the tissue confining well. This was done by positioning the tip of the porous platen in the well at its approximate working depth, and sinusoidally
Figure 3.3 Photograph of the porous platen showing the recirculation port.
varying this position with a 100 μm peak to peak displacement of the Dynastat's actuator at 1 Hz. The position of the porous platen was adjusted in the plane perpendicular to its axis so as to minimize the load measured with no sample in place. Typically, a minimum of 3-5 gm peak to peak load was observed. This was generally negligible compared to the experimental changes in load produced by compression of the sample.

With the alignment optimized, the location of the bottom of the confining well with respect to the porous platen was determined by placing a 1.1 mm sintered steel 1/4" diameter disk in the sample well and lowering the porous platen until a rapid rise in load was observed. This allowed the absolute jaw to jaw distance to be determined at all times over the course of an experiment, and hence the compressed thickness of the sample for any applied displacement. 10 ml of saline solution of predetermined ionic strength was added to the reservoir at this time and bath recirculation was begun. The temperature was adjusted to 20°C and maintained for the duration of the experiment.

3.2 Sample Preparation

3.2.1 Cartilage

Intact knee joints from freshly slaughtered 2 year old cattle were obtained from City Packing Co., Boston MA. The femoropatellar region was removed from each femur, sealed and frozen. Samples were thawed as needed for testing. Cartilage plugs were cut from the medial facet of the femoropatellar groove. The joint surface was aligned perpendicular to the cutting tool using a method and an apparatus similar to that
described by Lipshitz et al [1] (Fig. 3.4). The cartilage was first scored with a sharp 1/4" die cutter through the full thickness of the cartilage. Then, a concentric .354" plug of cartilage and subchondral bone was drilled. Ringer's solution was used as a lubricating fluid during the coring process. Three samples were typically taken from a single joint surface. The cored samples that could not be tested immediately were sealed in 100% humidity vessels and refrigerated for no more than three days before testing. Special care was taken to assure that the cartilage was never in direct contact with fluid during storage, so as to minimize potential leaching of proteoglycans out of the specimen before testing.

Immediately before testing, the cartilage/bone plug was mounted in a sledge microtome. The most superficial 100 μm was taken off the top to eliminate any effect of surface curvature. 600 μm samples of cartilage were then microtomed off the bone. This yielded a 1/4" diameter plane parallel disk of cartilage for mechanical testing and an annular ring of cartilage of equal area, as shown in Fig. 3.5a. The annular ring served as a biochemical control and was used to infer the composition of the tested samples prior to testing. This ring was immediately refrozen. The thickness of the sample was determined after microtoming with a current sensing micrometer. The thickness, measured as the average of three separate sites on each cartilage disk, was generally slightly larger than 600 μm.
Figure 3.4 Photograph of tools used to core cartilage samples.
Figure 3.5 (a) Photograph of cored cartilage sample before microtoming together with microtomed sample and control ring. (b) Photograph of corneal stroma sample, control ring, and remaining portion of excised cornea.
3.2.2 Cornea

Bovine eyes were obtained fresh from J.T. Trelegan & Co., Cambridge, MA. The cornea were dissected from the eyes and the epithelial and endothelial cell layers removed by gently scraping the corneal surfaces with a scalpel. A 1/4" diameter disk was punched out of the central region of the corneal stroma with a sharp die cutter. An annular ring around the 1/4" diameter disk was also excised for use in biochemical control assays (Fig. 3.5b). The thickness of the 1/4" diameter corneal stroma samples was measured immediately after excision as described for bovine cartilage samples, and ranged from 750 - 850 µm. Each tissue sample was then sealed together with its control ring in a vial at 100% humidity, again taking special care to assure that the tissue sample did not come in direct contact with fluid during storage. Samples were stored at 4°C until testing. All samples were tested within 4 days of preparation.

3.3 Equilibrium Experimental Protocol

The prepared tissue sample was then placed in the testing chamber. The distance between the bottom of the confining well and the bottom of the porous platen was immediately adjusted (within 1 minute of sample contact with solution) to correspond to the previously measured thickness of the sample. The sample was then allowed to equilibrate with the bathing solution approximately 1 hour. After equilibrium was reached, the load was recorded and the sample was compressed. For cartilage, the applied displacement was typically 2 - 3% of the initial sample thickness per deformation. For cornea, typically a 5 - 7%
displacement was applied per deformation. These respective deformations were reached in a staircase fashion by applying a number of 5 μm step displacements of the actuator. This corresponded to the smallest increment the Dynastat servo mechanism could make in the high range control mode. Applying the platen displacement as a sequence of small steps rather than one large step minimized the time required for stress relaxation, and hence the time required between successive increments in applied displacement. This dependence of the stress relaxation time on the magnitude of the applied step in deformation results from the nonlinear relation between tissue permeability and local strain [2]. Load equilibrium was generally reached within 10 - 15 minutes for cartilage and 50 - 60 minutes for cornea. The measured load was recorded and another series of small step displacements applied. The entire sequence was repeated 3 - 5 times at a single concentration allowing the relationship between load and the compressed thickness of the sample to be determined at that concentration.

After the equilibrium load had been recorded for a sufficient number of compressive displacements at a single concentration, a small increment of concentrated NaCl was added to the solution reservoir with an adjustable microliter automatic pipette. This rapidly increased the NaCl concentration of the bath to a predetermined value. It is important to note that the concentration was changed while holding the compressed thickness of the sample constant. After the addition of NaCl, the stress decreased monotonically. The load was recorded when it reached equilibrium, and the deformation - relaxation sequence was repeated. In this way an entire family of load - compressed thickness curves was obtained as a function of the bath NaCl concentration. Upon completion

Section 3.3
of the experiment, tissue samples were refrozen and sent together with the control rings to Children's Hospital Medical Center for uronic acid analysis.

Fig. 3.6 shows a typical sequence of applied displacements and changes in salt concentration that was used to characterize the load-displacement response for a single cartilage sample. Because all of the samples employed in this study were 1/4" in diameter, the conversion factor between load and stress is the same for all samples. All loads are plotted as stresses by normalizing the measured load in newtons to the sample area of $3.17 \times 10^{-5}$ m$^2$.

The protocol used in these experiments is similar to that used by Lee [3] in previous studies on the effect of bath salt concentration on the compressive bulk modulus of cartilage in confined compression. The distinctive features of the specific protocol used here are that:

1) Load is measured as a function of the sample's compressed thickness (i.e. jaw to jaw separation distance) rather than strain. This method circumvented the ambiguity involved in deciding which sample thickness to use in the definition of strain, and preserved a meaningful relation between all data measured for a single plug at different salt concentrations. More importantly, it makes it clear that the ultimate determination of strain should not involve renormalization to the free equilibrium thickness of the sample at each new salt concentration, as discussed in Chapter II.

2) All changes in concentration are performed in situ, keeping the specimen's state of compression constant when the salt
concentration is altered.

3) The sample thickness is constrained during the initial equilibration with the bathing solution and is never allowed to swell freely while in solution. This protocol eliminates the "toe region" in the load - displacement curves generally ascribed to confinement problems [3,4] by assuring that good confinement is obtained at "zero" displacement.

3.4 Equilibrium Data

3.4.1 Cartilage

Four cartilage samples were tested in this way. As a consistency check on the experimental method, one additional sample (sample SP106) was tested in a similar manner with the Dynastat servo mechanism in load control mode. The protocol was identical except that steps in load were applied and the resulting compressed thickness measured. Because the tissue response was creep deformation instead of stress relaxation, a substantially longer time was required for the sample to reach equilibrium (as shown in Chapter II). The equilibrium data for the five cartilage samples are shown in Figs. 3.6 - 3.10. The data are presented as plots of equilibrium stress vs compressed thickness parameterized by bath concentration.

3.4.2 Cornea

Four cornea samples were also tested as described. From preliminary experiments it became clear that there were complicated processes occurring in cornea which affected the equilibrium load —
Figure 3.6 Equilibrium stress - compressed thickness data parameterized by concentration for sample SP103.
Figure 3.7 Equilibrium stress - compressed thickness data parameterized by concentration for sample SP104.
Figure 3.8 Equilibrium stress - compressed thickness data parameterized by concentration for sample SP106.
Figure 3.9 Equilibrium stress - compressed thickness data parameterized by concentration for sample SP111.
Figure 3.10 Equilibrium stress - compressed thickness data parameterized by concentration for sample SP112.
displacement behavior over the concentration range of .005 M - 1.0 M. It was found that the slopes of the load-compressed thickness curves were not monotonically decreasing functions of salt concentration, as was observed in cartilage and as Debye shielding would predict. This behavior can perhaps be explained by including the solvent/polymer interactions described in section 2.2.1, and may be similar to the so-called salting in and salting out behavior observed by Rajagh et al [5] in gelatin and collagen solutions as a function of salt concentration. While this behavior is interesting and important, it is tangential to the main thrust here. Hence, for convenience, we focus our attention on a range of concentrations over which the observed tissue behavior appeared monotonic. Such a region was found between .01 M and .05 M NaCl. The corresponding data from the four cornea samples tested are shown in Figs. 3.11 - 3.14.
Figure 3.11 Equilibrium stress - compressed thickness data parameterized by concentration sample CRN20.
Figure 3.12 Equilibrium stress - compressed thickness data parameterized by concentration for sample CRN21.
Figure 3.13 Equilibrium stress - compressed thickness data parameterized by concentration for sample CRN22.
Figure 3.14 Equilibrium stress - compressed thickness data parameterized by concentration for sample CRN23.
3.5 Equilibrium Data Analysis

The ultimate goal in this section is to extract constitutive laws for the modulus $M$ and the chemical stress $\beta$ for both cartilage and cornea from the raw data of Figs. 3.6 - 3.14. In reducing the data, all of the data for a single tissue was assumed to be representative of the general population of that tissue. This approach is based on the premise that both $M$ and $\beta$ are intrinsic material properties of a given tissue that vary with concentration, but do not vary significantly from sample to sample given normal populations of cartilage and cornea. We will, therefore, require that a single constitutive law be used to represent the concentration and deformation dependence of all of the plugs tested for a single tissue.

In order to derive material constants from the data of Figs. 3.6 - 3.14 the data must be transformed from stress vs compressive thickness to stress vs strain. In order to do this in a meaningful way, we must decide on a reference thickness from which to measure compressive deformations. Once this is done, we can define the absolute strain as being the difference between the reference thickness and the sample's current compressed thickness, normalized to the reference thickness. We are free to choose this reference thickness as we see fit. However, from our previous discussion of the chemical stress (section 2.2.2), we require that $\beta = 0$ at the chosen reference thickness. It is convenient to choose as the reference thickness the free thickness of the tissue sample attained when the salt concentration is sufficiently large to effectively shield the electrical interactions between the charged constituents of the tissue. This thickness is the minimal free swelling
thickness of the sample. By choosing this as the reference thickness, we restrict \( g \) to the range of positive definite values.

This definition makes sense when the tissue in question is able to attain an unconstrained equilibrium thickness. Corneal stroma lacks the cohesive structure necessary to provide elastic recoil forces capable of competing with the electrical repulsion forces. Hence, unlike cartilage, cornea does not attain an unconstrained equilibrium thickness. Studies have shown [6,7,8] that cornea samples that are allowed to swell freely in saline solutions never reach swelling equilibrium. In fact, even cornea \textit{in vivo} is not in static swelling equilibrium. Active transport by the endothelial and epithelial cells is required to keep the tissue from swelling beyond its normal hydration [9]. Any disruption of this active process leads to corneal edema and consequent impairment of vision.

The fact that cornea samples do not reach an equilibrium thickness complicates the issue of exactly how to define the reference thickness for cornea. However, although the tissue never reaches swelling equilibrium, there exists a thickness beyond which it requires an infinitesimal compressive restraint to keep the tissue from swelling further. We can, therefore, operationally define the reference thickness as the sample thickness at which the swelling pressure becomes smaller than our ability to measure it. In the Dynastat, this corresponds to a swelling pressure of approximately 300 Pa (1 gm load on 1/4" area sample).

Having chosen an appropriate reference thickness for each tissue, we can transform the equilibrium stress - compressive thickness data...
into stress - strain space and extract constitutive relations that
describe the way the intrinsic material properties vary with bath salt
concentration. It is apparent from the data that the stress varies
linearly with compressed thickness over the range of compression applied
at each concentration. This suggests that we cast the stress -
compressed thickness relationship at each concentration in the form

$$\sigma = m(c) \delta + b(c)$$

(3.1)

This relationship can be transformed into a stress - strain constitutive
law in terms of intrinsic material parameters, of the form

$$\sigma = M(c) \varepsilon + \beta(c)$$

(3.2)

where the modulus M and chemical stress $\beta$ have been defined previously,
and the strain in terms of the reference thickness of the ith plug at
infinite concentration $\delta_{i}^{\text{ref}}$ is

$$\varepsilon = \frac{\delta_{i}^{\text{ref}} - \delta}{\delta_{i}^{\text{ref}}}$$

(3.3)

3.5.1 Cartilage

From the cartilage data of Figs. 3.6 - 3.10, it can be clearly
seen that the modulus as a function of concentration decreases
monotonically towards a constant modulus that describes the material in
the absence of electrical interactions. A simple function that is consistent with the observed behavior is

\[ M(c) = M_\infty + (M_0 - M_\infty) e^{-c/c_M^{\text{ref}}} \]  

(3.4)

This function is described by the three parameters:

- \( M_\infty \) - the modulus as \( c \to \infty \)
- \( M_0 \) - the modulus at \( c = 0 \)
- \( c_M^{\text{ref}} \) - a concentration constant that describes the decay of the modulus with concentration from \( M(c=0) \) to \( M(c=\infty) \).

It can also be seen from the data of Figs. 3.6 - 3.10 that the stress at a given compressed thickness always decreases with concentration, and that it does so by a proportionately lesser amount as concentration increases. This suggests that the chemical stress can be described by a function of the form

\[ \beta(c) = \beta_0 e^{-c/c^{\text{ref}}_{\beta}} \]  

(3.5)

where \( \beta_0 \) is the chemical stress when \( c = 0 \), and \( c^{\text{ref}}_{\beta} \) describes the decay of the chemical stress to 0.

Eqs. 3.4 and 3.5 are advanced as convenient analytical representations of the concentration dependence of the material parameters \( M \) and \( \beta \) for cartilage. The stress - compressed thickness data was fit to the system of eqs. 3.4 - 3.5 in order to compute the five material parameters \( (M_0, M_\infty, c_M^{\text{ref}}, \beta_0, c^{\text{ref}}_{\beta}) \) in these equations as well as the reference thickness \( \delta^{\text{ref}} \) for each tissue specimen. A standard

Section 3.5.1
nonlinear regression analysis employing the method of Marquardt [10] was used. The five parameters of eqs. 3.4 and 3.5 are common to all of the data, while each of the sample reference thickness is assigned to a single sample. The fit to the data is shown for each sample in Figs. 3.15 - 3.19. The combined data from all samples can also be shown grouped by concentration. These plots are shown in Figs. 3.20 - 3.27.

3.5.2 Cornea

The stress vs compressed thickness cornea data was treated in a similar way. The slopes of the stress - compressed thickness data for the cornea samples are somewhat scattered. However, Figs. 3.11 - 3.14 suggest that the slope of the stress - compressed thickness data tends to increase over the early portion of the .01 M - .05 M concentration range, and then level off and remain approximately constant over the remainder of the this concentration range. Preliminary experiments with cornea over a wider concentration range (using coarser concentration increments) showed an initial increase in slope, followed by a gradual decrease at concentrations above .05 M, which is consistent with the behavior observed in Figs. 3.11 - 3.14. The data suggest that the modulus can be approximated over the narrow concentration range presented in Figs. 3.11 - 3.14 by a function of the form

\[
M = \begin{cases} 
M_0 + (M_\infty - M_0) & \frac{c_{\text{ref}}}{c_M} c < c_M^{\text{ref}} \\
M_\infty & c > c_M^{\text{ref}}
\end{cases}
\]  

(3.6)
Figure 3.15 Superposition of fit and data parameterized by concentration for sample SP103.
Figure 3.16 Superposition of fit and data parameterized by concentration for sample SP104.
Figure 3.17 Superposition of fit and data parameterized by concentration for sample SP106.
Figure 3.18 Superposition of fit and data parameterized by concentration for sample SP111.
Figure 3.19 Superposition of fit and data parameterized by concentration for sample SP112.
Figure 3.20 Superposition of fit and data for all cartilage samples at $c = 0.005$. 

- $M_\infty = 0.270$ MPa
- $M_0 = 1.17$ MPa
- $c_{\text{ref}} = 0.128$ M
- $\beta_0 = 0.031$ MPa
- $c_{\beta_{\text{ref}}} = 0.032$ M
Figure 3.21 Superposition of fit and data for all cartilage samples at $c = 0.010$. 

Symbols:
- SP103
- SP112
- SP104
- SP106
- SP111

Equations:
- $M_\infty = 0.270$ MPa
- $M_o = 1.17$ MPa
- $c_{\text{ref}} = 0.128$ M
- $\beta_o = 0.031$ MPa
- $c_{\beta} = 0.032$ M
Figure 3.22 Superposition of fit and data for all cartilage samples at c = 0.025.

- $M_0 = 1.17$ MPa
- $C_{ref} = 0.128$ MPa
- $M_{0c} = 0.270$ MPa
- $C_{ref} = 0.032$ MPa
- $C_{ref} = 0.031$ MPa

Parameter $c = 0.025$. 

Stress, kPa

Compressive Strain
Figure 3.23 Superposition of fit and data for all cartilage samples at \( c = 0.050 \).
Figure 3.24: Superposition of fit and data for all cartilage samples at $c = 0.10$. 

- $M = 0.270$ MPa
- $M_0 = 1.17$ MPa
- $c_M \text{ ref} = 0.128 M$
- $b_0 \text{ ref} = 0.031 M$
- $c_8 \text{ ref} = 0.032 M$
Figure 3.25 Superposition of fit and data for all cartilage samples at c = 0.15.
Figure 3.26 Superposition of fit and data for all cartilage samples at $c = 0.50$. 

- $M_\infty = 0.270$ MPa
- $M_O = 1.17$ MPa
- $c_M^{\text{ref}} = 0.128$ M
- $\beta_O = 0.031$ MPa
- $c_\beta^{\text{ref}} = 0.032$ M
Figure 3.27 Superposition of fit and data for all cartilage samples at \( c = 1.0 \).
where we expect \( c_{M}^{\text{ref}} < 0.05 \text{ M} \) and \( M_0 < M_w \).

The chemical stress for cornea appears to be a monotonically decreasing function of concentration. As for cartilage, changes in \( \beta \) appear largest at the lowest concentrations, and get smaller as concentration increases. Hence, eq. 3.5 was also used to describe the variation of the chemical stress in cornea as a function of concentration.

As with cartilage, the individual sample reference thickness must be determined in the fitting routines. The cornea data was fit to the system of equations 3.5 - 3.6 using the same nonlinear regression analysis as before. The fit to the data are shown in Figs. 3.28 - 3.31, grouped by sample, and in Figs. 3.32 - 3.37 grouped by concentration.

3.6 Consistency with Previous Findings

The moduli of cartilage and cornea can be determined from the fitted parameters and the constitutive relations as a function of concentration. The modulus predicted for cartilage in \( 0.15 \text{ M NaCl} \) is \( 0.55 \text{ MPa} \), with a value of \( 1.1 \text{ MPa} \) in \( 0.005 \text{ M NaCl} \) and \( 0.27 \text{ MPa} \) in \( 1 \text{ M NaCl} \). For cornea, the modulus ranges between \( 34 \text{ kPa} \) in \( 0.01 \text{ M NaCl} \) and \( 59 \text{ kPa} \) in \( 0.05 \text{ M NaCl} \). These values are in good agreement with values reported in the literature for bovine cartilage [5,11] and cornea [12]. Since the concept of the chemical stress \( \beta \) has been introduced in this study for the first time, there are no data to directly compare with \( \beta \).

However, from the fitted parameters of the constitutive relations, it is possible to calculate the unconstrained free swelling thickness of
Figure 3.28 Superposition of fit and data parameterized by concentration for sample CRN20.
Figure 3.29 Superposition of fit and data parameterized by concentration for sample CRN21.
Figure 3.30 Superposition of fit and data parameterized by concentration for sample CRW22.
Figure 3.31 Superposition of fit and data parameterized by concentration for sample CRN23.
Figure 3.32 Superposition of fit and data for all cornea samples at $c = 0.010 \text{ M}$.
Figure 3.33 Superposition of fit and data for all cornea samples at \( c = 0.015 \) M.
Figure 3.34 Superposition of fit and data for all cornea samples at σ = 0.02 M.
Figure 3.35 Superposition of fit and data for all cornea samples at $c = 0.03$ M.
Figure 3.36 Superposition of fit and data for all cornea samples at $c = 0.04 \text{ M}$. 

$M_o = 58.7 \text{ kPa}$

$M_c = 34.0 \text{ kPa}$

$c_{ref}^M = 0.043 \text{ M}$

$b_o = 30.2 \text{ kPa}$

$c_{ref}^B = 0.018 \text{ M}$
Figure 3.37 Superposition of fit and data for all cornea samples at $c = 0.05\, \text{M}$. 
a tissue sample normalized to its thickness at infinite salt concentration as a function of concentration. These calculations can be compared to the free swelling thickness at different concentrations measured independently by other investigators, providing an opportunity to check the fitted parameters for the chemical stress $\tilde{\beta}$ for consistency with data in the literature.

For a freely swelling sample, the applied stress is by definition 0. Hence,

$$\sigma = 0 = M(c) \varepsilon + \tilde{\beta}(c) \quad (3.7)$$

where the strain related to the free swelling reference thickness at infinite concentration, $\delta^{\text{ref}}$, is given by

$$\varepsilon = \frac{\delta^{\text{ref}} - \delta(c)}{\delta^{\text{ref}}} \quad (3.8)$$

This can be solved for the normalized thickness $\delta(c)/\delta^{\text{ref}}$ to give

$$\frac{\delta(c)}{\delta^{\text{ref}}} = 1 + \frac{\tilde{\beta}(c)}{M(c)} \quad (3.9)$$

Plots of the calculated normalized thickness vs salt concentration are presented in Fig. 3.38 for cartilage and in Fig. 3.39 for cornea.

For cartilage, Maroudas has found that normal cartilage swells in the range of 1.5 – 3% in hypotonic (.015 M) saline compared with physiological saline (.15 M) [13]. To our knowledge there have not been any other studies of the variation of free equilibrium thickness Section 3.6
Figure 3.38 Computed normalized thickness of cartilage as a function of concentration from fit parameters.
Figure 3.39 Computed normalized thickness of cornea as a function of concentration from fit parameters.
performed for cartilage. The calculated normalized thickness compares favorably with Maroudas' observations, and decays monotonically with concentration as expected. With a fixed charge density for cartilage of approximately -.15 M [13], it is reasonable for the variation of normalized thickness with concentration to be less pronounced for concentrations above .15 M. These observations suggest that the analytical representation of the constitutive laws (eqs. 3.4 and 3.5) for M and β are reasonable predictors of cartilage behavior as a function of concentration.

For corneal stroma, free swelling thicknesses have been measured as a function of time by several investigators [7,8]. However, as previously discussed, corneal stroma do not attain swelling equilibrium. This fact has been attributed to the lack of adequate structural restraints in the form of interlamellar crosslinks. The existence or nonexistence of crosslinks between lamella in vivo has been debated over the years [14,15]. Whether these crosslinks exist or not, it is clear that irreversible changes occur over time in stroma that are allowed to swell freely for long periods of time. Given enough time, the tissue will hydrolyze and eventually dissolve.

For these reasons, it is difficult to relate the results of free swelling experiments conducted over long periods of time to the results presented here. Nevertheless, the hydration data of Hedbys [8] and Elliot et al [7] for corneal stroma allowed to swell freely for 24 hours in solutions of varying ionic strength show that the stroma swells less as the solution ionic strength increases. This agrees with the trends observed in the calculated normalized thickness as a function of salt
concentration. Finally, given that the charge density of cornea has been reported by Hodson [15] to be approximately \(-0.05\) M, it is reasonable that the variation of normalized thickness with concentration flatten out as salt concentration exceeds \(0.05\) M.

3.7 Transient Experimental Protocol

In order to test the chemical transient model developed in Chapter II, additional experiments were performed to measure the transient in stress that occurred when the tissue was subjected to a rapid change in the NaCl concentration of the external bath. The experimental apparatus, sample preparation and sample placement in the confining chamber were as described above for the equilibrium experiments. With the tissue sample in place, the stress - compressed thickness relation was measured at the initial salt concentration as previously described. After determining the load at four compressed thicknesses at the initial concentration, an increment of concentrated NaCl was added to the reservoir as before. The difference here was the size of the increment in salt concentration. Where before we focused on small increments in order to determine the constitutive laws as a function of bath concentration, here we were interested in larger increments in concentration in order to test the transient swelling model developed in Chapter II. After the load had reached equilibrium, the stress - compressed thickness relationship was measured at the new concentration. These equilibrium stress - compressed thickness relationships were measured to assure that the samples used in the transient experiments were adequately described by the constitutive laws fit to the equilibrium data. Upon completion of the experiment, the
tissue sample was refrozen and sent together with its control ring to Children's Hospital for uronic acid analysis.

Equilibrium stress vs compressed thickness was measured for seven cartilage samples in .005 M NaCl. The stress transient was recorded, and the bath salt concentration was then increased to .1 M NaCl (by adding concentrated NaCl to the reservoir) with the sample thickness constrained to approximately 92% of its original thickness. The stress relaxed monotonically to approximately 46% of its value in .005 M NaCl just prior to the addition of salt. After the sample equilibrated at .1 M NaCl, the sample was compressed further and the stress recorded at several compressed thicknesses as previously described. With the sample confined to approximately 85% of its original thickness, the concentration was increased in a stepwise fashion to .15 M NaCl. The equilibrium stress attained was approximately 82% of its value in .1 M NaCl at the same compressed thickness. Six samples went through the second transition in concentration. (An equipment malfunction aborted the second transition for the seventh cartilage sample.) After reaching load equilibrium at .15 M NaCl, the equilibrium stress - compressed thickness relation was measured.

Transient measurements of salt induced stress relaxation behavior were made with cornea in a similar fashion. However, because the cornea equilibrium behavior was determined over a much smaller range in concentration, data was obtained for a single chemical transition from .01 M to .05 M NaCl. The equilibrium stress - compressed thickness relation was measured for six cornea samples at the initial concentration as previously described. The bath concentration was then

Section 3.7
increased to .05 M by a step addition of concentrated NaCl, with the samples constrained to approximately 83% of their original thicknesses. The stress decreased monotonically with the addition of salt to approximately 49% of its value in .01 M NaCl at the same thickness.

3.8 Transient Data

When comparing the stress transient data between experiments performed on different tissue samples, it is important to account for differences in the constrained sample thickness just prior to the addition of salt. As shown in Chapter II, the equations governing the stress transient are diffusion equations. Hence, the rate at which the transient occurs is proportional to the square of the sample thickness at the time the bath concentration is changed. In order to compare the transient data between samples in a meaningful way, time must be normalized to a single thickness. A thickness of 600 μm was arbitrarily chosen as the reference thickness for this purpose. Hence, time was normalized to the square of the ratio of the sample thickness at the time the concentration transition occurred and the 600 μm reference thickness. Time for all transient data has been normalized in this way. The computer sampled transient data are shown in Appendix A. Figs. A.1 - A.7 show the transient in stress resulting from the .005 M → .1 M NaCl transition for cartilage, Figs. A.8 - A.14 show the results for the cartilage .1 M → .15 M NaCl transition, and Figs. A.15 - A.19 show the results for the cornea .01 M → .05 M transition. The data are presented as plots of normalized load vs normalized time, where the load has been normalized to the equilibrium load prior to the addition of NaCl.
It should be noted that the absolute strain in these tissue samples is not known, since we do not know for certain the reference thickness at infinite concentration for each sample. This can account for the scatter in the final equilibrium stress after the concentration transition, as we expect the $M$ and $\beta$ of each sample to change in the same way for a given change in salt concentration. This sensitivity to the exact strain state can be partially eliminated by plotting the transient data in a slightly different form. Instead of normalized load we plot one minus the normalized change in load, where we define the normalized change in load $\Delta \sigma(t)$ as

$$\Delta \sigma(t) = \frac{\sigma_0 - \sigma(t)}{\sigma_0 - \sigma_\infty}$$  \hspace{1cm} (3.10)

where

$\sigma_0$ = load just prior to addition of salt

$\sigma_\infty$ = final equilibrium load

This normalizes the transient to its magnitude and stretches all of the transient plots between 1 (at $t = 0$) and 0 (as $t \to \infty$). This allows us to focus on the kinetics of the transition in the load resulting from the increase in salt concentration, removing the absolute magnitude of the final load from further consideration.

With the transient data in this form, we can proceed to combine all of the data for a single transition into a single graph. This will facilitate comparing the data to the model. We can combine the transient experiments for a single transition by averaging the data from all the plugs for a particular transition at discrete points in time. Before averaging between specimens, we first smooth the sampled transient data.
for a single specimen in order to reduce the effect of sampling noise on the overall specimen average. After smoothing all of the transient data for each transition, the smoothed data is averaged at a specified number of points in time. The result is the mean and standard deviation at the specified time points.

The transient data were sampled asynchronously. When the load was changing rapidly the sampling rate was higher. This makes the smoothing and averaging algorithms slightly more complicated than if all data had been sampled at the same rate. The smoothing algorithm and a listing of the program used to smooth the data are presented in Appendix B, along with the individual sample results of the smoothing operation. A listing of the interpolation and averaging program is presented in Appendix C. The average of the smoothed plots for each of the three salt transitions performed are presented in Figs. 3.40 - 3.42.

3.9 Uronic Acid Analysis

All of the tested samples and control rings were analyzed for uronic acid content by Dr. Koob at Children's Hospital Medical Center. The cartilage specimens were dried, weighed and then solubilized by papain digestion at 60°C. The uronic acid content of the solutions was determined by the carbazole - H₂SO₄ procedure adapted for the auto analyzer [16]. The uronic acid contents for the cartilage samples and controls are presented in Table 3.1, divided into equilibrium and transient subgroups.

Although the test sequence at any single concentration was identical for both the equilibrium and transient subgroups, each
Figure 3.40 Averaged transient normalized change in stress for cartilage 0.005 \( \rightarrow \) 0.1 M NaCl concentration transition. Time normalized to 600 \( \mu \)m thickness.
Figure 3.41 Averaged transient normalized change in stress for cartilage 0.1 $\rightarrow$ 0.15 M NaCl concentration transition. Time normalized to 600 $\mu$m thickness.
Figure 3.42 Averaged transient normalized change in stress for cornea 0.01 → 0.05 M NaCl concentration transition. Time normalized to 600 μm thickness.
### EQUILIBRIUM SAMPLES

<table>
<thead>
<tr>
<th>SAMPLE</th>
<th>URONIC ACID (%) dry wt. TESTED</th>
<th>URONIC ACID (%) dry wt. CONTROL</th>
<th>U.A. RATIO ( \frac{\text{test}}{\text{control}} )</th>
<th>HOURS TESTED TOTAL</th>
<th>ABOVE .15 M</th>
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<tr>
<td>SP103</td>
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<td>5.68</td>
<td>.84</td>
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<td>SP111</td>
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<td>.64</td>
<td>7</td>
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<tr>
<td>SP112</td>
<td>2.41</td>
<td>3.65</td>
<td>.66</td>
<td>13</td>
<td>5.5</td>
</tr>
</tbody>
</table>

### TRANSIENT SAMPLES

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<th>SAMPLE</th>
<th>URONIC ACID (%) dry wt. TESTED</th>
<th>URONIC ACID (%) dry wt. CONTROL</th>
<th>U.A. RATIO ( \frac{\text{test}}{\text{control}} )</th>
<th>HOURS TESTED TOTAL</th>
<th>ABOVE .15 M</th>
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<td>3.66</td>
<td>.91</td>
<td>13</td>
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</tbody>
</table>

**TABLE 3.1**

Uronic Acid Content of Experimental and Control Samples
transient sample was subjected to fewer tests than each of the equilibrium samples. As a result, the equilibrium samples soaked longer in solution during a single experiment. The transient group was also tested over a more restricted concentration range. It is known that uronic acid loss due to leach out of proteoglycans from cartilage increases as the time a tissue sample is immersed in solution during testing. It has also been established that proteoglycan loss is accelerated in solutions of higher ionic strength [17]. It is for these reasons that the transient and equilibrium samples are grouped separately.

It is evident from Table 3.1 that the equilibrium samples lost a significant amount of proteoglycans, as measured by uronic acid loss, with the mean of the tested sample being 70% ± 9% of the uronic acid content of the control ring. The loss from the transient samples was less pronounced, with the tested samples being 98% ± 17% of the control ring. It is noteworthy that two of the transient samples actually showed a higher uronic acid content than the corresponding control ring of approximately 19%. It is highly unlikely that the control ring actually had less uronic acid in it, and we regard this scatter as giving some indication of the absolute accuracy of the method used to assess uronic acid content. However, even without considering these samples, the transient samples still show substantially less loss than the equilibrium group.

Since one of the major differences between the equilibrium and transient samples was the amount of time spent in contact with solution, an attempt was made to correlate the uronic acid loss with the total

Section 3.9
sample immersion time. The uronic acid loss did not correlate well with the immersion time, with $r = .36$, $p > .15$. This lack of correlation may be due to the added influence of bath salt concentration on the rate of proteoglycan loss.

It is generally accepted that uronic acid loss from cartilage can alter the material properties of the tissue [13, 17 – 21]. The fact that the equilibrium samples as a group lost approximately 30% of their uronic acid content raises some questions about the significance of the constitutive relations for the concentration dependence of the material properties $M$ and $B$ presented earlier. It is significant in this context to note that the material exhibited a characteristic stress transient similar to the large signal stress transients reported previously for each addition of concentrated NaCl to the bath. Since the stress transient is caused by salt induced changes in the material properties, the fact that the stress changed with each addition of salt suggests that the measured variation in the material properties $M$ and $B$ with concentration is not solely due to the cumulative effect of proteoglycan loss from the tissue. Further, the fact that the transient samples showed a much smaller loss than the equilibrium samples suggests that the equilibrium samples lost most of their proteoglycans at the higher concentrations tested (above .15 M), since the duration of the tests at lower concentrations as well as the range of concentrations tested for the equilibrium samples were similar to those for the transient samples. Hence, if the uronic acid loss introduced error into the determination of the constitutive relations for cartilage, it would appear that this error is most significant for the higher concentrations. For these reasons, despite the long term loss of proteoglycans from the samples,
we are satisfied that these relations provide an adequate characterization of the salt concentration dependence of the material properties for cartilage.

The amount of uronic acid present in the cornea samples as measured by the same automated carbazole - \( \text{H}_2\text{SO}_4 \) procedure was low enough to be within the noise level of the measurement method. Hence, we were not able to accurately assess the amount of uronic acid lost during testing of the cornea samples. However, Hedbys [22] has reported a 30% loss in the hexosamine content of corneal stroma allowed to swell freely for 48 hours in \( .15 \text{ M NaCl} \) solution at 37°C. Hexosamine content is a measure of the total amount of chondroitin and keratin sulfate present in the tissue. The cornea samples in this study were immersed in saline solution of lower ionic strength at a lower temperature and for less time than Hedbys' cornea samples. Further, the thickness of our samples was constrained, whereas Hedbys' samples were allowed to swell freely. This suggests that the proteoglycan loss reported by Hedbys is greater than the loss incurred during testing in this study. Hence, as with the cartilage samples, the equilibrium data used to determine the relationship between the material properties and solution ionic strength may suffer from a long term baseline drift due to the gradual loss of proteoglycans during the testing procedure. This appears to be the unavoidable consequence of immersing the samples in solution for the long periods of time required to determine the mechanical behavior of the tissue as a function of salt concentration. However, as with cartilage, the stress transients observed in response to increases in the salt concentration of the bathing solution occurred in times that were short compared to the duration of an entire experiment. This again
suggests that the apparent concentration dependence of the material properties is real, and is not due solely to the cumulative effects of proteoglycan loss.


CHAPTER IV
NUMERICAL METHODS AND RESULTS

The goal of this chapter is to solve the coupled diffusion equation developed in Chapter II for the transient in the swelling pressure \( p(z,t) \) produced by a rapid change in the concentration of the bathing solution. We wish to do this for arbitrary values of the ratio of the mechanical and chemical time constants, \( \tau_m / \tau_c \). This chapter will describe the numerical methods used to solve the system of equations. In the process of developing the solution method we will discuss the details of applying the empirically determined constitutive relations measured in section 3.5 of Chapter III, the various approximations introduced and their impact on the solution obtained. Solutions for the stress transient will be presented parameterized by the ratio \( \tau_m / \tau_c \), together with graphs of the normalized swelling pressure \( p(z,t) \) for a range of \( \tau_m / \tau_c \) values. To help visualize the underlying physics of the swelling pressure transient and to help explain the dependence of the stress transient on the ratio \( \tau_m / \tau_c \), graphs of the change in compressive strain \( \Delta \varepsilon \) and the normalized fluid pressure \( (p - \Delta \pi) \) as a function of space and time will be presented.

4.1 System of Equations

4.1.1 Differential Equation for Swelling Pressure

The equation to be solved and its associated boundary and initial conditions were developed in section 2.5.1 of Chapter II (eqs. 2.68, 2.62 and 2.63). They are duplicated here for convenience:
\[
\tau_m \frac{\partial P}{\partial t} = \frac{M}{\tau_c} \frac{\partial^2 P}{\partial z^2} + \tau_m \left( \left( \frac{P - \beta}{M(c)} \right) \frac{\partial M}{\partial c^+} + \frac{\partial \beta}{\partial c^+} \right) \frac{\partial c^+}{\partial t}
\]

(4.1)

where

\[\tau = t / \tau_c \]
\[z = z / \delta \]
\[M = \frac{M(z,t)}{M(c_0)} \]
\[P = \frac{p(z,t)}{p_0} \]
\[\beta = \frac{\beta(z,t)}{p_0} \]
\[\bar{c}_+ = \text{internal positive ion concentration} \]
\[\tau_m = \frac{\delta^2}{\pi^2 M(c_0) k} \]
\[\tau_c = \frac{\frac{4}{3}\delta^2}{\pi^2 D} \]
\[D = \text{ion diffusion coefficient in the tissue} \]
\[c_0 = \text{initial salt concentration in the external bath} \]
\[p_0 = \text{initial swelling pressure} \]

We recall from Chapter II that the factor \(1 / \pi^2\) in eq. 4.1 results from defining the time constants \(\tau_m\) and \(\tau_c\) in terms of the decay constant of the \(n=1\) normal mode solution of the uncoupled mechanical and chemical diffusion equations, respectively. This was done in order to clarify the relation between experimentally determined times and the normalized theoretical time. We note that the normalized material properties \(M\) and \(\beta\) are expressed as functions of normalized space and time. The transformation from the internal concentration of the positive ion \(\bar{c}_+\) to the effective external concentration \(c^*\) defined in section 2.5.1 is discussed in section 4.1.3.

Section 4.1.1
The boundary conditions on the swelling pressure $p$ appropriate for a change in the salt concentration of the external bath while holding the sample volume constant are

$$\frac{\partial p}{\partial z}(0, t) = \frac{\partial p}{\partial z}(1, t) = 0 \quad (4.2)$$

with the initial condition

$$p(z, 0) = 1 \quad (4.3)$$

4.1.2 Analytical Solutions for Internal Concentration

Eq. 4.1 is driven by concentration induced changes in the material properties. In order to determine the time and space variations of the material properties, an expression for concentration as a function of space and time must be determined. Because the tissue is charged, the concentration of the positive and negative ions inside the tissue are unequal. For this reason, a single internal salt concentration cannot be defined. However, as discussed in Chapter II, because of the quasineutrality condition, the internal ionic concentrations as a function of space and time are not independent. When the charge density is decoupled from the tissue deformation, the internal concentrations are described by a single diffusion equation. It is the relationship between the internal ionic concentrations that allows us to focus on only one of the two ionic species. We have arbitrarily chosen to use the internal positive ion concentration in eq. 4.1. In Chapter II, an analytical solution for the internal concentration $c_+(z, t)$ resulting

Section 4.1.2
from a step change in the salt concentration of the external bath was presented (eq. 2.52). However, since it is impossible to impose a step change in concentration in a real system, we will use a boundary condition that exponentially raises the boundary concentration (just inside the tissue) from $c^0_+$ to its new value, $c^\infty_+$. Hence,

$$\overline{c}_+ (0, t) = c^0_+ + (c^\infty_+ - c^0_+) \left(1 - e^{-t/\tau_S}\right)$$

(4.4)

where we define the normalized surface time constant $\tau_S = \tau_S/\tau_0$, and the internal concentrations $c^0_+$, $c^\infty_+$ are related to the initial and final concentrations $c_0$, $c_\infty = c_0 + \Delta c_0$, of the external bath through the Donnan equilibrium condition of eqs. 2.49 and 2.51. This boundary condition is introduced to account for the effects of finite mixing time and the stagnant film layer which is known to exist at the surface of the sample. Boundary conditions of this form are noted by Crank [1] and Carslaw and Jaeger [2] as being of practical interest in cases where an instantaneous change in the surface concentration is attempted in an experiment.

Fortunately, the concentration diffusion equation subject to boundary condition 4.4 at $z = 0$ and a no flow condition at $z = 1$ can be solved analytically. The separable solution can be shown to be [2]

$$\overline{c}_+ (z, t) = c^0_+ + (c^\infty_+ - c^0_+) G(z, t)$$

(4.5)

where
\[ G(z, t) = 1 - e^{-t/\tau_s} \left\{ \tan \frac{\pi}{2\sqrt{\tau_s}} \sin \frac{\pi z}{2\sqrt{\tau_s}} + \cos \frac{\pi z}{2\sqrt{\tau_s}} \right\} \]

\[ - \frac{u}{\pi} \sum_{n \text{ odd}} \frac{\sin \frac{n\pi}{2} z e^{-n^2 t}}{n(1 - n^2 \tau_s)} \]

This solution is valid provided that \( n^2 \tau_s \neq 1 \) for \( n \) odd. Note that in the limit \( \tau_s \to 0 \), eq. 4.6 becomes the same as the solution for a step change in concentration given in eq. 2.52.

In the solution of eq. 4.1, we will need to evaluate \( G(z, t) \) for both short and long time. Unfortunately, the Fourier series in eq. 4.6 does not converge rapidly for small values of normalized time. We, therefore, introduce an equivalent solution for the concentration transient in terms of a series of complex error functions, that converges rapidly for small values of normalized time. It is derived by the method of Laplace transforms in Appendix D. The resulting solution has the same form as eq. 4.5, with \( G(z, t) \) given by

\[ G(z, t) = \sum_{i=1}^{2} \left\{ \sum_{n=0}^{\infty} (-1)^n \text{erfc} \ a_i \right\} \]

\[ - \frac{1}{2} e^{-t/\tau_s} \sum_{n=0}^{\infty} (-1)^n \left\{ \cos \frac{f_i}{\sqrt{\tau_s}} \Re\{\text{erfc}[a_i - j \sqrt{t/\tau_s}]\} \right\} \]

\[ + \sin \frac{f_i}{\sqrt{\tau_s}} \Im\{\text{erfc}[a_i - j \sqrt{t/\tau_s}]\} \]

where

Section 4.1.2
\[ f_1 = \frac{\pi}{2} [2(n+1) - z] \]

\[ f_2 = \frac{\pi}{2} [2n + z] \]

\[ \alpha_i = \frac{f_i}{\sqrt{t}} \tag{4.8} \]

The time derivatives of eqs. 4.6 and 4.7 can be evaluated in a straightforward manner. For completeness, they are:

\[ \frac{\partial \bar{c}^+}{\partial t} = (\bar{c}_+^\infty - \bar{c}_+^0) G'(z, t-_) \tag{4.9} \]

where, for the Fourier series solution

\[ G'(z, t) = \frac{e^{-t/\tau}}{\tau} \left[ \tan \frac{\pi}{2\sqrt{\tau/s}} \sin \frac{\pi z}{2\sqrt{\tau/s}} + \cos \frac{\pi z}{2\sqrt{\tau/s}} \right] \tag{4.10} \]

\[ + \frac{4}{\pi} \sum_{n \text{ odd}} \frac{n \sin \frac{n\pi}{2} \frac{z}{s} e^{-n^2t}}{1 - n^2\frac{\tau}{s}} \]

and for the error function series solution

\[ G'(z, t) = \sum_{i=1}^{2} \frac{e^{-t/\tau}}{\tau} \sum_{n=0}^{\infty} (-1)^n \left[ \cos \frac{f_i}{\sqrt{\tau/s}} \text{Re}(\text{erfc}[\alpha_i - j \sqrt{t/\tau}]) \right. \]

\[ + \sin \frac{f_i}{\sqrt{\tau/s}} \text{Im}(\text{erfc}[\alpha_i - j \sqrt{t/\tau}]) \right] \tag{4.11} \]
4.1.3 Transformation from Internal to Effective External Concentration

We now have analytical solutions for the internal ionic concentration and its derivative with respect to time appropriate for both short and long times. However, the constitutive laws determined in Chapter III were measured as a function of the salt concentration of the external bath. In order to make use of the constitutive relations, we must map the actual internal ionic concentration at every point in space and time to the effective external equilibrium bath concentration, $c^*$, defined in section 2.5.1. This effective external equilibrium concentration (which is a function of space and time) at the point $z_0$, $t_0$ represents the external concentration that would be in Donnan equilibrium with the internal ionic concentrations at $z_0$, $t_0$, given the tissue fixed charge density $\bar{\rho}_m$ at $z_0$, $t_0$. The expression relating the internal ionic concentration $\bar{c}_+(z,t)$ to the effective external concentration $c^*(z,t)$, can be found by inverting the Donnan equilibrium relation to give

$$c^*(z,t) = \bar{c}_+(z,t) \left[ 1 + \frac{\bar{\rho}_m}{\bar{c}_+(z,t)} \right]^{1/2} \quad (4.12)$$

In order to use this expression (or its inverse), we need values for the fixed charge density of the respective tissues. Experiments to determine the fixed charge density of cornea and cartilage tissue samples have been reported in the literature. Otori [3] calculated a value of $-0.036$ M for the fixed charge density in fresh corneal stroma.

Section 4.1.3
utilizing the biochemical data of Laurent and Anseth [4]. However, Hodson [5] stated that Otori left out the carboxyl groups of the chondroitin sulfates in his tally. When all the charge groups are included, the estimated value is approximately -.05 M. Hodson [5] experimentally determined the fixed charge density to be .047 M using the Donnan exclusion method of Maroudas and Thomas [6]. For our purposes, we will adopt the value of -.05 M for the fixed charge density of corneal stroma.

Maroudas has reported a range of values for the fixed charge density of human articular cartilage, with a mean of approximately -.15 M [7]. Detailed measurements of the fixed charge density of bovine cartilage have not been reported. However, Grimshaw [8] recently estimated the fixed charge density of cartilage as a function of pH from biochemical data in the literature [9 - 13]. His result for neutral pH was ~ -.125 M. Phillips [14] has titrated intact bovine articular cartilage in our laboratory. Her data, taken together with independent determinations of the pH at which bovine cartilage is isoelectric [15, 16, 17], allow the fixed charge density of the intact tissue to be determined. At neutral pH, the fixed charge density determined by this method is ~ -.2 M. We will adopt the value of -.15 M as a reasonable compromise for the purposes of this study.

Using eq. 4.12, $M(z,t)$ and $\beta(z,t)$ can be determined from the analytical solution for $c_+(z,t)$, and the empirical relations for $M(c)$ and $\beta(c)$ developed in Chapter III. The derivatives of $M$ and $\beta$ with respect to the internal concentration $c_+$ can be determined in a straightforward manner from the constitutive relations developed in

Section 4.1.3
Chapter III using the chain rule

\[
\frac{\partial M}{\partial c_+} = \frac{\partial M}{\partial c^*} \frac{\partial c^*}{\partial c_+}
\]  \hspace{1cm} (4.13)

where, from eq. 4.12

\[
\frac{\partial c^*}{\partial c_+} = \frac{c_+ + \rho_m/2}{c_+ \left[ 1 + \rho_m/c_+ \right]^{1/2}}
\]  \hspace{1cm} (4.14)

4.2 Crank-Nicolson Solution Method

We now have expressions to evaluate every function in eq. 4.1 and can proceed to cast it into a form suitable for numerical solution. The Crank-Nicolson implicit finite difference numerical method was used to solve eq. 4.1. In implementing a finite difference method, space and time are divided into discrete intervals, and the differential equation is approximated by a finite difference equation written in terms of the value of the solution variable at the discrete space and time points. The Crank-Nicolson method uses the finite difference molecule shown in Fig. 4.1. The differential equation is approximated at the artificial grid point \( i, n+1/2 \) in terms of the six surrounding grid points. Three of these grid points are at the time level \( n \) and three are at the time level \( n+1 \). The method is termed implicit because we must implicitly solve for the three unknown values of the solution at the time level \( n+1 \) in order to advance the solution one step forward in time.

The time derivative of the swelling pressure at \( i,n+1/2 \) is
Figure 4.1 Finite difference molecule used in Crank Nicolson implicit finite difference method.
approximated by

\[ \frac{\partial P}{\partial t} \bigg|_{i,n+1/2} = \frac{P_i^{n+1} - P_i^n}{\Delta t} \]  

(4.15)

where we adopt the convention that the subscript \( i \) refers to the spatial grid and the superscript \( n \) refers to the temporal grid.

The second derivative of the swelling pressure at \( i,n+1/2 \) is approximated by the mean of the finite difference representation of the second derivatives at \( i,n \) and \( i,n+1 \) as

\[ \frac{\partial^2 P}{\partial z^2} \bigg|_{i,n+1/2} = \frac{1}{2} \left( \frac{P_i^{n+1} - 2P_i^n + P_i^{n-1}}{\Delta z^2} \right) \]  

\[ + \frac{P_i^{n+1} - 2P_i^n + P_i^{n-1}}{\Delta z^2} \]  

(4.16)

Similarly, the value of the swelling pressure at \( i,n+1/2 \) is approximated as

\[ P_i^{n+1/2} = \frac{1}{2} (P_i^{n+1} + P_i^n) \]  

(4.17)

To be consistent with the finite difference approximation employed in writing the derivatives at \( i,n+1/2 \), the functions that can be evaluated analytically must be evaluated at the \( x, t \) values that correspond to the grid point \( i, n+1/2 \).

Combining the results of the preceding development, eq. 4.1 can be

Section 4.2
approximated as

\[
\frac{p_i^{n+1} - p_i^n}{\Delta t} = \frac{\tau_c}{\tau_m} \frac{1}{\pi^2} \frac{M_i^{n+1/2}}{2 \Delta z} \left\{ \left( p_{i+1}^{n+1} - 2p_i^{n+1} + p_{i-1}^{n+1} \right) + \left( p_{i+1}^n - 2p_i^n + p_{i-1}^n \right) \right\}
\]

\[+ \frac{1}{2} \left( \frac{1}{M} \frac{\partial M}{\partial c^+} \frac{\partial c^+}{\partial t} \right)_i^{n+1/2} \left( p_i^{n+1} + p_i^n \right)
\]

\[+ \left\{ \left( \frac{\partial b}{\partial c^+} - \frac{\beta}{M} \frac{\partial M}{\partial c^+} \right) \frac{\partial c^+}{\partial t} \right\}_i^{n+1/2}
\]  
(4.18)

We can rewrite eq. 4.18 in the form

\[
p_i^{n+1} - a_i \left( p_{i+1}^{n+1} - 2p_i^{n+1} + p_{i-1}^{n+1} \right) - \gamma_i p_i^{n+1}
\]

\[= p_i^n + a_i \left( p_{i+1}^n - 2p_i^n + p_{i-1}^n \right) + \gamma_i p_i^n + \lambda_i
\]  
(4.19)

where we have introduced the definitions

\[
a_i = \frac{\tau_c}{\tau_m} \frac{\Delta t}{2\Delta z} \frac{1}{\pi^2} M_i^{n+1/2}
\]

\[
\gamma_i = \frac{\Delta t}{2} \left( \frac{1}{M} \frac{\partial M}{\partial c^+} \frac{\partial c^+}{\partial t} \right)_i^{n+1/2}
\]  
(4.20)

\[
\lambda_i = \Delta t \left\{ \left( \frac{\partial b}{\partial c^+} - \frac{\beta}{M} \frac{\partial M}{\partial c^+} \right) \frac{\partial c^+}{\partial t} \right\}_i^{n+1/2}
\]

The left hand side of eq. 4.19 contains three values of the

Section 4.2
swelling pressure at the time level \( n+1 \) (which we do not know), while the right hand side has three known values of \( p \) at the \( n^{th} \) time level. For \( N \) discrete space intervals, there are \( N+1 \) spatial grid points, and we can write eq. 4.19 at each of these grid points with the exception of the two grid points coincident with the boundaries. At both boundaries we have the condition

\[
\frac{\partial p}{\partial z} = 0 \tag{4.21}
\]

To incorporate the boundary conditions into the finite difference equations, Crank [1] and Carslaw and Jaeger[2] introduce fictitious grid points located one spatial increment past each boundary. At the left hand \((z = 0)\) boundary, the finite difference approximation of eq. 4.21 becomes

\[
\frac{p_{n}^{n} - p_{1}^{n}}{\Delta z} = 0 \quad \rightarrow \quad p_{-1}^{n} = p_{1}^{n} \tag{4.22}
\]

where \( p_{-1}^{n} \) represents the fictitious grid point located just to the left of the boundary. We can now write eq. 4.19 at the \( i=0 \) grid point corresponding to the left hand boundary. Making use of the fact that \( p_{n}^{n} = p_{1}^{n} \), we eliminate the fictitious grid point to give

\[
p_{0}^{n+1} - 2a_0 \left( p_{1}^{n+1} - p_{0}^{n+1} \right) - \gamma_0 p_{0}^{n+1}
\]

\[
= p_{0}^{n} + 2a_0 \left( p_{1}^{n} - p_{0}^{n} \right) + \gamma_0 p_{0}^{n} + \lambda_0 \tag{4.23}
\]

A similar equation can be written at the right hand boundary. This
leaves us \( N+1 \) equations in terms of the \( N+1 \) unknowns \( p_{i}^{n+1} \), which must be solved simultaneously in order to advance the solution forward one increment in time.

This system of equations can be conveniently cast in matrix form as

\[
[ A ] \hspace{0.5em} p^{n+1} = [ B ] \hspace{0.5em} p^n + \lambda \tag{4.24}
\]

where the matrices \( A \) and \( B \) are given by

\[
A = \begin{bmatrix}
1 + \alpha_0 - \gamma_0 & -2\alpha_0 \\
-\alpha_1 & 1 + \alpha_1 - \gamma_1 & -\alpha_1 \\
& \ddots & \ddots & \ddots \\
& -\alpha_{N-1} & 1 + \alpha_{N-1} - \gamma_{N-1} & -\alpha_{N-1} \\
& & -2\alpha_{N} & 1 + \alpha_{N} - \gamma_{N}
\end{bmatrix}
\tag{4.25}
\]

\[
B = \begin{bmatrix}
1 - \alpha_0 + \gamma_0 & 2\alpha_0 \\
\alpha_1 & 1 - \alpha_1 + \gamma_1 & \alpha_1 \\
& \ddots & \ddots & \ddots \\
& \alpha_{N-1} & 1 - \alpha_{N-1} + \gamma_{N-1} & \alpha_{N-1} \\
& & 2\alpha_{N} & 1 - \alpha_{N} + \gamma_{N}
\end{bmatrix}
\tag{4.26}
\]

and the vectors \( p^{n+1}, p^n \) and \( \lambda \) are
\[
\begin{bmatrix}
p_0^{n+1} \\
p_0^{n+1} \\
p_1^{n+1} \\
\vdots \\
p_N^{n+1}
\end{bmatrix}
= (4.27)
\]

\[
\begin{bmatrix}
p_0^n \\
p_0^n \\
p_1^n \\
\vdots \\
p_{N-1}^n
\end{bmatrix}
= (4.28)
\]

\[
\begin{bmatrix}
\lambda_0 \\
\lambda_1 \\
\vdots \\
\lambda_{N-1} \\
\lambda_N
\end{bmatrix}
= (4.29)
\]

To solve for \( \hat{p}^{n+1} \) we need only invert \( A \). Since \( A \) is tridiagonal, this matrix inversion can be done very efficiently in a computer program.

The Crank-Nicolson method of solving eq. 4.1 was implemented in the computer program listed in Appendix E. Because we were interested in solving eq. 4.1 for arbitrary values of the ratio \( \tau_m/\tau_c \), the implementation was made flexible enough to deal with sharp spatial
variations in the swelling pressure \( p \) encountered when \( \tau_m/\tau_c \gg 1 \), and still efficient enough to handle the more gradual spatial variations encountered for \( \tau_m/\tau_c \ll 1 \). To accomplish this, a self adjusting spatial grid was employed in the implementation. The program also allowed the time increment to be adjusted, allowing smaller time increments to be used when \( p \) varied rapidly in time, and larger time increments when \( p \) varied slowly in time. Specific details on how this was implemented are presented in Appendix E.

The stress transient is computed from the solution for the swelling pressure in a straightforward manner. Because the surface of the tissue is held in place by a porous platen, the fluid pressure there is 0. As a consequence, the total stress at the surface is due solely to the swelling pressure \( p \), and the normalized stress transient can be determined directly from the time dependence of the normalized swelling pressure at the surface of the tissue as

\[
\sigma(t) = p(0,t)
\]  

(4.30)

4.3 Checks of the Numerical Method

It is prudent to treat numerical results cautiously. Hence, before accepting the results of our implementation of the Crank-Nicolson method, other methods were used to determine the stress transient for several test cases. The primary test method employed was the use of generalized prepackaged numerical routines from the Numerical Algorithms Group (NAG) library on the Multics time sharing system. The NAG library routine D03PBF was used to solve eq. 4.1 using Gear's method and the
method of lines. The routine allowed the use of a nonuniform distribution of spatial mesh points. As swelling pressure variations were sharpest at the left hand boundary, corresponding to the surface of the tissue, the NAG subroutine was instructed to automatically cluster mesh points in the vicinity of the left hand boundary. Eq. 4.1 was solved for several $\tau_m/\tau_c$ ratios with $\tau_s$ values of .01 and .1. In all cases examined, the solution obtained by the NAG routine could not be distinguished from the solution obtained by the Crank–Nicolson method previously described.

An additional method was used to calculate the stress transient in the limit $\tau_m/\tau_c \ll 1$. We recall from Chapter II that in this limit, eq. 4.1 reduces to a much simpler equation (eq 2.69) that can be solved for the stress $\sigma(t)$ to give

$$\sigma(t) = \frac{u_o + \int_0^\delta \frac{\beta}{M} dz}{\int_0^\delta \frac{dz}{M}}$$

(4.31)

This can be evaluated using the analytical solution for $\bar{c}_+$, the internal to external transform of eq. 4.12, and the constitutive relations developed in Chapter III. The integrals were evaluated using Simpson's 1/3 rule with end corrections [18]. The limiting behavior was always approximately the same as that observed for the case $\tau_m/\tau_c = .01$ in the numerical solution of eq. 4.1. This implies that for $\tau_m/\tau_c = .01$, the mechanical time constant is small enough that the deformation does not lag behind the diffusion of ions into the sample (see below).

Section 4.3
4.4 Numerical Results

The swelling pressure $p(z,t)$ was computed for an exponential change in the surface concentration from $0.1$ M to $0.15$ M. The resulting stress transient, plotted as normalized change in stress $(1 - 10)$ vs normalized time $(t/\tau_c)$, is shown in Fig. 4.2, parameterized by the ratio $\tau_m/\tau_c$. The spatial variation of the normalized swelling pressure at several points in time is shown in Figs. 4.3 - 4.5 for $\tau_m/\tau_c = 0.1$, $1.0$, and $10.0$, respectively. The swelling pressure has been computed for a normalized surface time constant $\tau_s = v$, using the constitutive relations developed in Chapter III for cartilage. The relevant parameters used in the calculation are listed in Table 4.1. Since the numerical solution presents a number of interesting features that merit further discussion, we defer comparing the numerical solution to the results of the transient experiments until Chapter V.

It is clear from Fig. 4.2 that the stress decreases more quickly for early time as the ratio of the mechanical to chemical time constants increases. This is consistent with the trends suggested from the discussion presented in Chapter II of the stress transient in the limiting cases $\tau_m/\tau_c = 0$ and $\tau_m/\tau_c = \infty$. However, the crossing of the curves by definition cannot be explained from the limiting behavior and, in fact, contradicts the notion that the larger $\tau_m/\tau_c$, the faster the stress falls and reaches its final equilibrium value.

The crossing can be understood by considering the strain profile in the tissue for different $\tau_m/\tau_c$ ratios. The spatial variation of the strain can be easily computed from the unnormalized solution for the swelling pressure $p(z,t)$, the solution for the internal concentration
Figure 4.2 Computed stress transient parameterized by $\tau_m/\tau_c$ for 0.1 $\rightarrow$ 0.15 M NaCl concentration transition with $I_s = 0.1$. The material parameters used in the model are summarized in Table 4.1.
Figure 4.3 Computed spatial variation of normalized swelling pressure parameterized by time for $\tau_m/\tau_c = 0.1$ resulting from the $0.1 \rightarrow 0.15$ M NaCl concentration transition with $\tau_s = 0.1$. The material parameters are summarized in Table 4.1.
Figure 4.4 Computed spatial variation of normalized swelling pressure parameterized by time for $\frac{\tau_m}{\tau_c} = 1.0$ resulting from the 0.1 → 0.15 M NaCl concentration transition with $\tau_s = 0.1$. The material parameters are summarized in Table 4.1.
Figure 4.5 Computed spatial variation of normalized swelling pressure parameterized by time for $\tau_m/\tau_c = 10.0$ resulting from the 0.1 $\rightarrow$ 0.15 M NaCl concentration transition with $z_s = 0.1$. The material parameters are summarized in Table 4.1.
Constitutive Relations:  \[ M_\infty = 0.27 \text{ MPa} \]
\[ M_0 = 1.17 \text{ MPa} \]
\[ c_{\text{M \, ref}} = 0.128 \text{ M} \]
\[ \beta_0 = 0.031 \text{ MPa} \]
\[ c_{\text{B \, ref}} = 0.032 \text{ M} \]

Charge Density:  \[ \rho_m = -0.15 \text{ M} \]

Applied Strain:  \[ \varepsilon_0 = 0.10 \]

Concentration:

Initial:  \[ 0.1 \text{ M} \]
Final:  \[ 0.15 \text{ M} \]

**TABLE 4.1**

NUMERICAL PARAMETERS FOR
STRESS TRANSIENT SIMULATION
(Figs. 4.2 and 4.12)
and the constitutive relations to give

\[ \varepsilon(z,t) = \frac{p(z,t) - \beta(z,t)}{M(z,t)} \]  \hspace{1cm} (4.32)

Since the initial and final compressive strains are equal, it is convenient to define the change in compressive strain \( \Delta \varepsilon(z,t) \) as the deviation of the strain from its initial (and final) value \( \varepsilon_0 \) as

\[ \Delta \varepsilon(z,t) = \varepsilon(z,t) - \varepsilon_0 \]  \hspace{1cm} (4.33)

Because the sample is held at constant volume, the integral of the deviation in strain over the sample thickness must be zero, implying that positive deviations in strain must be balanced by negative deviations. It is helpful to look at the spatial and temporal variation of the strain because it represents the purely mechanical rearrangement of the tissue that occurs as the salt diffuses into the sample, while the swelling pressure \( p(z,t) \) contains both mechanical and chemical effects. The spatial variation of the change in compressive strain parameterized by time is shown in Figs. 4.6 - 4.8 for \( \frac{\tau_m}{\tau_c} = .1, 1., \) and 10., respectively. Since the change in compressive strain is plotted, positive changes represent larger compressive deformations in the tissue. It will also be helpful to refer to the fluid pressure distribution in space and time. Since the total stress is given by

\[ \sigma(t) = p(0,t) = p(z,t) + (P(z,t) - \Delta \pi(z,t)) \]  \hspace{1cm} (4.34)

the fluid pressure is

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Figure 4.6 Computed spatial variation of change in compressive strain parameterized by time for $\frac{\tau_m}{\tau_c} = 0.1$ resulting from $0.1 \rightarrow 0.15$ M NaCl concentration transition with $\frac{\tau_c}{\tau_s} = 0.1$. The material parameters are summarized in Table 4.1.
Figure 4.7 Computed spatial variation of change in compressive strain parameterized by time for $\frac{t_m}{t_c} = 1.0$ resulting from 0.1 → 0.15 M NaCl concentration transition with $\lambda_0 = 0.1$. The material parameters are summarized in Table 4.1.
Figure 4.8 Computed spatial variation of change in compressive strain parameterized by time for $\tau_m/\tau_c = 10.0$ resulting from 0.1 $\rightarrow$ 0.15 M NaCl concentration transition with $\tau_s = 0.1$. The material parameters are summarized in Table 4.1.
\[(P[z,t] - \Delta \tau[z,t]) = p(0,t) - p(z,t)\]  \hspace{1cm} (4.35)

The spatial variation of the normalized fluid pressure \((P - \Delta \tau)\) parameterized by time is shown in Figs. 4.9 - 4.11 for \(\tau_m/\tau_c = .1, 1.0,\) and 10., respectively.

We can see by comparing Figs. 4.6 - 4.8 that changes in deformation extend further into the sample at a given time as the ratio \(\tau_m/\tau_c\) decreases. Further, it is evident that the amplitude of the change in strain is largest when \(\tau_m/\tau_c\) is smallest. The most striking feature of Figs. 4.9 - 4.11 is the increase in the magnitude of the fluid pressure as the ratio \(\tau_m/\tau_c\) increases.

These observations can be explained by considering the meaning of the ratio of \(\tau_m/\tau_c\). The mechanical time constant characterizes the time required for a fluid saturated elastic material to change its fluid content, while the chemical time constant characterizes the rate that ions diffuse into the tissue and change the material properties. When \(\tau_m/\tau_c\) is small, changes in the fluid content of a tissue element can occur rapidly compared to the rate that ions diffuse into the tissue. When \(\tau_m/\tau_c\) is large, these changes occur more slowly.

When salt is added to the external bath, the driving force that forces the tissue to rearrange its fluid content is the diffusion of ions into the sample. Since the ionic concentrations in the tissue are spatially nonuniform during the transient, the material properties of the tissue are spatially nonuniform. This spatial variation of material properties causes the regions where there are fewer ions to push on the regions where there are more ions. Since fluid must flow before

Section 4.4
Figure 4.9 Computed spatial variation of normalized fluid pressure parameterized by time for $\tau_m/\tau_c = 0.1$ resulting from $0.1 \rightarrow 0.15$ M NaCl concentration transition with $\bar{\tau} = 0.1$. The material parameters are summarized in Table 4.1.
Figure 4.10 Computed spatial variation of normalized fluid pressure parameterized by time for $\tau/\tau_c = 1.0$ resulting from $0.1 \rightarrow 0.15$ M NaCl concentration transition with $\tau_s = 0.1$. The material parameters are summarized in Table 4.1.
Figure 4.11 Computed spatial variation of normalized fluid pressure parameterized by time for $\tau_m/\tau_c = 10.0$ resulting from $0.1 \rightarrow 0.15$ M NaCl concentration transition with $\tau_s = 0.1$. The material parameters are summarized in Table 4.1.
deformations can change, this pushing causes fluid to flow out of the regions of higher ionic concentration to regions of lower ionic concentration. When the mechanical time is short compared to the rate that ions move into the bulk \( \tau_m/\tau_c < 1 \), fluid has time to redistribute itself throughout the sample. This minimizes fluid pressures (Fig. 4.9) and results in larger deformations that are distributed throughout the sample, as observed in Fig. 4.6. The material deformation maintains a quasi-equilibrium with the spatially nonuniform, ion induced changes in the material properties. Because the sample is held at constant volume, the net result is a decrease in the stress.

As the ratio \( \tau_m/\tau_c \) increases, the fluid takes longer to redistribute itself throughout the sample compared to the rate that ions move in. Hence, larger pressures develop as less fluid has a chance to flow (Figs. 4.10 and 4.11). Less fluid flow results in smaller deviations in strain that tend to be confined more towards the surface of the sample as \( \tau_m/\tau_c \) increases, as observed in Figs. 4.7 and 4.8.

The stress decreases faster for early time as \( \tau_m/\tau_c \) increases because the deviations in strain fall further behind the ion induced changes in the material properties. Since the change in strain lags behind the ionic gradient, a spatially varying residual deviation in strain remains after the ions have equilibrated throughout the sample, whose magnitude decreases as \( \tau_m/\tau_c \) increases. This residual strain must diffuse before the stress can reach its final equilibrium value. Since the magnitude of the residual strain decreases as \( \tau_m/\tau_c \) increases, the deviation of the stress from its final equilibrium value likewise

Section 4.4
decreases as $\tau_m/\tau_c$ increases. However, since the mechanical diffusion occurs with the characteristic mechanical time $\tau_m$, the normalized time required for the stress to reach equilibrium increases as $\tau_m/\tau_c$ increases. This explains the crossing observed in Fig. 4.2. It further suggests that each curve crosses every other curve exactly once.

The surface time constant was introduced to partially account for the effects of mixing time and stagnant films on the actual time dependence of the concentration at the surface of the tissue sample. While there is no way to theoretically determine the correct value for this time, we can set reasonable bounds on it. The lower bound on $\tau_s$ is the mixing time, which was estimated to be approximately 10 - 20 seconds based on the time required for fluid to complete one circuit in the recirculation loop. The upper bound can be estimated by considering the diffusion of salt to the surface of the tissue sample through the stagnant film. It is not uncommon to encounter stagnant films as large as 40 - 50 $\mu$m in membrane diffusion experiments even when the solution at the surface of the membrane is vigorously stirred [19]. In our experimental apparatus, the solution is recirculated through the porous platen to minimize the effect of the stagnant film. However, this can hardly mix the solution close to the sample surface as effectively as stirring in free solution. Hence, it is not difficult to imagine a stagnant film of 100 - 200 $\mu$m thick. This thickness is equivalent to a nontrivial percentage of the sample thickness. Since the salt diffusivity in the polyethylene plug is similar to the salt diffusivity in the tissue sample (within a factor of 2), it would not be unreasonable for the surface time constant to be as large as .1 - .2 times time chemical time constant based on the 600 $\mu$m reference

Section 4.4
thickness. It is for this reason that a normalized surface time constant of .1 was chosen in computing the stress transients shown in Fig. 4.1. In order to see the effect of varying $\tau_s$ on the numerical solution for the stress transient, stress transients were also computed for several ratios of $\tau_m/\tau_c$ with $\tau_s = .01$, using the same material parameters and conditions as used to obtain Fig. 4.2 (Table 4.1). The results are shown in Fig. 4.12.

It is clear from comparing Fig. 4.12 and Fig. 4.2 that varying $\tau_s$ from .1 to .01 has a marked effect on the stress. For $\tau_m/\tau_c > 1$, decreasing $\tau_s$ appears only to make the stress transient fall faster. However, for some values of $\tau_m/\tau_c < 1$, the effect of decreasing $\tau_s$ is to sharpen the inflection in the stress transient at $t = .2$, while for other values of $\tau_m/\tau_c < 1$ there appears to be no effect on the stress.

The inflections in the stress transient and their dependence on the value of $\tau_m/\tau_c$ can be interpreted using the same concepts used to elucidate the dependence of the rate of stress decay and the magnitude of the residual strain on the ratio of $\tau_m/\tau_c$. As $\tau_s$ is decreased, ion induced changes in the material properties occur more quickly and may begin to change faster than deformations at the surface can change. The value of $\tau_s$ at which this happens will depend on the value of the ratio $\tau_m/\tau_c$. If we require that $\tau_s$ be less than $\tau_c$, three orderings for the relevant time constants $\tau_s$, $\tau_m$ and $\tau_c$ are possible, as shown in Fig. 4.13. If $\tau_m$ is less than $\tau_s$ (Fig. 4.13a), then fluid can leave the surface of the sample and redistribute itself throughout the sample on a time scale that is short compared to the time scale of ion induced changes in the material properties of the surface. Hence, as long as $\tau_m$

Section 4.4
Figure 4.12 Computed stress transient parameterized by $\frac{T_m}{T_0}$ for $0.1 \rightarrow 0.15$ M NaCl concentration transition with $T_L = 0.01$. The material parameters used in the model are summarized in Table 4.1.
Figure 4.13 Possible orderings of the time constraints $\tau_s$, $\tau_m$ and $\tau_c$ when $\tau_s$ is restricted to be less than $\tau_c$. 
remains less than \( \tau_s \), decreasing \( \tau_s \) will have a negligible effect on the stress transient. The small effect that it does have can be attributed to the fact that the surface concentration attains its final equilibrium value at an earlier time.

When \( \tau_m > \tau_s \), the surface deformation lags behind the ion induced changes in the material properties of the surface. This causes an increasingly rapid initial stress decay as the ratio of \( \tau_m/\tau_s \) increases. The spatial distribution of strain for early times in this case is similar to that encountered for long times when \( \tau_m/\tau_c > 1 \). However, once the surface concentration reaches its final value, the deformation in the material has a chance to catch up with the evolution of the concentration profile in the bulk. This can happen only if the ions diffuse into the bulk more slowly than the time it takes the fluid to redistribute itself, i.e. if \( \tau_m/\tau_c < 1 \) (Fig. 4.13b). During the catch up phase, the stress transient goes through a transition region from the early, fast response induced by the rapid change in the material properties of the surface, and the more gradual stress relaxation characteristic of the particular \( \tau_m/\tau_c \) ratio. When \( \tau_m/\tau_c > 1 \) (Fig. 4.13c), the spatial distribution of the strain induced by the rapid change in material properties at the surface is consistent with the spatial distribution attained throughout the stress transient, and, hence, no transition occurs.
BIBLIOGRAPHY - CHAPTER IV


Bibliography IV


CHAPTER V
COMPARISON OF THEORY AND EXPERIMENT

5.1 Numerical Parameters

In order to compare the stress transient predicted by the model to the experimental stress data presented in Chapter III, appropriate values for material parameters must be determined for each tissue appropriate to the conditions of each experimental concentration transition. Most of the parameters required by the model have either been determined independently in this study, or are set by the particular conditions of the transient experiment to be modeled.

The material parameters $M_0$, $M_m$, $c^\text{ref}_M$, $\beta_0$, and $c^\text{ref}_\beta$ used in the constitutive relations that specify the modulus $M$ and chemical stress $\beta$ as a function of concentration (eqs. 3.4 and 3.5 for cartilage, eqs. 3.5 and 3.6 for cornea) were fit to data from independent equilibrium swelling pressure–strain experiments as described in Chapter III. For the purposes of modeling the transient experiments, these parameters and constitutive relations will be assumed to adequately describe the concentration dependence of the swelling pressure. No attempt will be made to refit these parameters here.

The tissue charge densities were not measured in this study. These values were estimated from the literature as discussed in section 4.1.3. The values $\bar{\rho}_m = -0.05$ M for cornea and $\bar{\rho}_m = -0.15$ M for cartilage were used in the model. It is worthwhile to note that the model is quite insensitive to the exact value of the charge density, provided the value

Section 5.1
is the right order of magnitude. This insensitivity is due to the fact that the Donnan equilibrium condition (eq. 2.1) is used to relate \( \bar{\rho}_m \) and the actual external concentration to the internal concentration at the boundary, as well as to relate \( \bar{\rho}_m \) and the internal concentration (as a function of space and time) to the effective external equilibrium concentrations (eq. 2.43) used to determine the spatial and temporal evolution of the material properties \( M \) and \( \beta \). If the internal to external mapping was linear, the value of \( \bar{\rho}_m \) would not affect the transient at all.

Similarly, the model is rather insensitive to changes in the applied strain \( \varepsilon_0 \), when the transient is presented as the normalized change in stress \( (1 - \Delta \sigma(t)) \), with \( \Delta \sigma(t) \) defined as

\[
\Delta \sigma(t) = \frac{\sigma(t) - \sigma_0}{\sigma_\infty - \sigma_0}
\]  

(5.1)

where \( \sigma_0 \) is the stress just prior to the addition of salt, and \( \sigma_\infty \) is the stress reached after the sample has reached equilibrium with its new environment. However, the absolute values of the initial and final stresses are affected by the magnitude of the applied strain. Hence, by comparing the actual stress values to the values predicted by the model (eq. 3.2 with constitutive eqs 3.4 and 3.5 for cartilage, and eqs. 3.5 and 3.6 for cornea), an \( \varepsilon_0 \) can be chosen that gives initial and final stress values in close agreement with the average experimental initial and final stress values, as shown in Table 5.1.

The only additional parameters that are yet to be determined are the ratio of \( \tau_m/\tau_c \) and the normalized surface time constant \( \tau_s \). Finally,
<table>
<thead>
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<th>CONCENTRATION TRANSITION</th>
<th>EXPERIMENTAL</th>
<th>PREDICTED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AVG INITIAL STRESS</td>
<td>AVG NORMALIZED FINAL STRESS</td>
</tr>
<tr>
<td></td>
<td>(\sigma_{\text{initial}}) (kPa)</td>
<td>(\frac{\sigma_{\text{final}}}{\sigma_{\text{initial}}})</td>
</tr>
<tr>
<td>Cartilage 0.005 M -&gt; 0.1 M</td>
<td>109 ± 48</td>
<td>0.46 ± 0.07</td>
</tr>
<tr>
<td>Cartilage 0.1 M -&gt; 0.15 M</td>
<td>98.5 ± 44</td>
<td>0.83 ± 0.02</td>
</tr>
<tr>
<td>Cornea 0.1 M -&gt; 0.15 M</td>
<td>18.5 ± 6.7</td>
<td>0.51 ± 0.09</td>
</tr>
</tbody>
</table>

Comparison of Average Experimental Stress Values and Predicted Stress Values for Estimated Strain

Table 5.1
to compare theory and experiment, we must additionally relate the theoretical time axis, which is normalized to the chemical time $\tau_c$, to the experimental time axis, which is expressed in seconds for a 600 $\mu$m sample thickness (see section 3.8). To do this we must evaluate $\tau_c$ for a 600 $\mu$m sample.

5.1.1 Mechanical Diffusivity $M_k (\tau_m)$

Since we have already determined the modulus $M$ as a function of concentration, all that is required to determine the mechanical time constants $\tau_m$ for cartilage and cornea are values for the permeability $k$. The permeabilities were not measured independently in this study. However, several investigators have measured the permeability of bovine articular cartilage and cornea. McCutchen [1] was the first to measure the Darcy permeability of cartilage, obtaining a value of $0.58 \times 10^{-15} \text{ m}^4/\text{N}\cdot\text{s}$. More recently, Mow and Monsour [2] have reported on the strain dependence of the permeability, measured using static pressure drop experiments. Lai and Mow [3] report an intrinsic permeability at zero applied strain of $2 \times 10^{-15} \text{ m}^4/\text{N}\cdot\text{s}$, and $1.4 \times 10^{-15} \text{ m}^4/\text{N}\cdot\text{s}$ for a 10% applied compressive strain. Measurements of the permeability from transient and dynamic experiments give values that are generally larger than those measured in static pressure drop experiments. Mow and Lai [4] report an estimated average apparent permeability of $1 \times 10^{-14}$ for cartilage in confined uniaxial creep. Lee et al [5] determined a value of $3.45 \times 10^{-15} \text{ m}^4/\text{N}\cdot\text{s}$ for $k$ from a simultaneous, nonlinear regression analysis of the dynamic streaming potential and the dynamic stiffness of bovine cartilage in oscillatory confined compression. Using a value for $k$ of $1 \times 10^{-15} \text{ m}^4/\text{N}\cdot\text{s}$ and an approximate value for the modulus of 1 MPa,
the $M_{\theta}k$ product characterizing the mechanical diffusivity is \(-2 \times 10^{-9}\). It is understood that this value is a rather rough approximation, in view of the scatter in the reported values for $k$. However, it does provide an estimate of the correct order of magnitude for the mechanical diffusivity for cartilage.

Hedbys and Mishima [6] determined the permeability of corneal stroma from studies on the flow of water in the tissue resulting from an applied pressure gradient. They report a flow conductivity $k$ of $1.5 \times 10^{-15}$ m$^4$/N·s for corneal stroma at normal hydration. However, as mentioned above, static pressure drop experiments have been shown in cartilage to underestimate the tissue permeability by as much as a factor of 5 - 10 compared to transient creep or stress relaxation experiments [3]. Hence, these tissue permeabilities will be treated as only approximate values. Nevertheless, it is apparent that the tissue permeability, when combined with the modulus for cornea measured in this study ($M = 40$ kPa), yields an $M_{\theta}k$ product for cornea that is at least one order of magnitude less than the $M_{\theta}k$ product of cartilage.

5.1.2 Intratissue Ion Diffusivities ($\tau_0$)

The ions diffusing in the tissue are considered to be small compared to the distances between polymer chains in the tissue. Hence, their individual diffusivities at any point in the aqueous phase of the tissue are assumed to be the same as their diffusivities in free solution [7]; that is, ion binding and other specific short range interactions between ions and the tissue are assumed negligible, as has been previously observed [8]. However, since the ions diffuse inside the
tissue, they must meander around the macromolecular chains of the solid matrix. Thus, the average distance an individual ion inside the tissue travels in diffusing across a distance \( \Delta x \) is longer than it would be in diffusing across the same distance in free solution. This results in apparent ion diffusivities in the tissue that are less than their values in free solution by a so-called tortuosity factor.

Mackie and Meares [7] have proposed a model for solute diffusion in polymer solutions applicable to lightly and moderately crosslinked polymer networks. Their model relates the apparent diffusion coefficient in the polymer network \( D_i^p \) to the diffusion coefficient in free solution \( D_i^\infty \). They use a lattice model for the polymer network as the basis for a statistical derivation based solely on geometrical considerations. They obtain:

\[
\frac{D_i^p}{D_i^\infty} = \left( \frac{1 - \bar{V}_S}{1 + \bar{V}_S} \right)^2 = \left( \frac{\bar{V}_W}{2 - \bar{V}_W} \right)^2
\]

(5.2)

where \( \bar{V}_S \) is the solid volume fraction, \( \bar{V}_W \) is the water volume fraction, and \( \bar{V}_S + \bar{V}_W = 1 \).

This relation has been shown to be a good approximation for the diffusion of nonelectrolytes and cations in lightly and moderately crosslinked resins where the homogeneous gel model is appropriate [9]. Maroudas has successfully used this relationship to describe self diffusion coefficients of small ionic solutes (including \( Na^+ \) and \( Cl^- \)) in cartilage [8]. Hence, each of the ion diffusivities \( D_+ \) and \( D_- \) in the ambipolar diffusivity \( D_a \) must be scaled by the factor of eq. 5.2,
resulting in

$$D_a = \left( \frac{D^+ \, D^- \, (\bar{c}_+ + \bar{c}_-)}{D^+ \, \bar{c}_+ + D^- \, \bar{c}_-} \right) \left( \frac{\bar{v}_W}{2 - \bar{v}_W} \right)^2$$

(5.3)

where $D^\pm_\pm$ are the ionic diffusivities in free solution. For the case of infinitely dilute solutions (activity coefficients approximated as unity) $D^\infty_{\text{Na}^+} = 1.33 \times 10^{-9}$ m$^2$/s and $D^\infty_{\text{Cl}^-} = 2.03 \times 10^{-9}$ m$^2$/s.

Both cartilage and cornea have fractional water contents of approximately 0.8 [10,11]. Therefore, the effect of the increased diffusional path length on the effective ion diffusivities in the tissue is to make them approximately 0.4 - 0.5 times their value in free solution.

The fractional water content $\bar{v}_W$ in the tissue varies as a function of the applied strain, $\varepsilon$ as

$$\bar{v}_W = \frac{\bar{v}_W^0 - \varepsilon}{1 - \varepsilon}$$

(5.4)

where $\bar{v}_W^0$ is the fractional water content with no applied strain. Hence, the effect of the tortuosity on the ion diffusivities will be more pronounced in the samples with the larger strain. Since the strain for the cartilage 0.1 $\rightarrow$ 0.15 M and the cornea 0.01 $\rightarrow$ 0.05 M concentration transitions are larger than the Acartilage 0.005 $\rightarrow$ 0.1 M concentration transition, the chemical time constant will be slightly larger for these experiments. Furthermore, the ambipolar diffusivity is closer to the diffusivity of the chloride coion (which is the faster ion) for the

Section 5.1.2
0.005 → 0.1 M cartilage concentration transition. This also tends to decrease the chemical time constant of the 0.005 → 0.1 M cartilage concentration transition compared to the other concentration transitions. With internal ion diffusivities in the range \(0.7 - 0.8 \times 10^{-9}\) m²/s, the chemical time constant \(\frac{4\delta^2}{\pi^2D}\) for a 600 µm sample is on the order of 200 seconds.

5.1.3 Normalized Surface Time Constant

The normalized surface time \(\tau_s\) was introduced as an ad hoc way of accounting for the stagnant film which is known to exist between the surface of the tissue and the well mixed region in the porous polyethylene platen. Hence, the introduction of \(\tau_s\) allows the concentration at the surface of the tissue to change gradually to its final value in response to a step change in the concentration of the external bath. However, by considering diffusion across the stagnant film – tissue combination, it is apparent that the stagnant film can also affect the time required for the entire sample and stagnant film region to equilibrate with the external bath. However, this effect cannot be accounted for entirely in the surface time constant \(\tau_s\). Hence, the existence of the stagnant film may also affect the apparent chemical time constant \(\tau_c\), because the ions must diffuse across a distance that is greater than the actual sample thickness. A stagnant film of 200 µm will make the chemical time based on the total thickness of the film and sample approximately twice as large as the chemical time based only on the 600 µm sample thickness, where it has been assumed that the ion diffusivities in the film and in the sample are roughly equal. While the diffusivity in the porous polyethylene is actually slightly larger than
the diffusivity in the tissue sample itself (no tortuosity because pores are large), this calculation points out the sensitivity of the actual experimental time constant to the extent of the stagnant film. This sensitivity is manifest in factors of order unity, as long as the sample remains the rate limiting step in the diffusion of ions into the tissue. Further, since the introduction of $\tau_s$ is ad hoc, it is impossible to determine a value for $\tau_s$, or the effect of the stagnant film on $\tau_C$ from a theoretical framework. However, it is clear that the stagnant film will tend to lengthen the apparent chemical time constant. It is also clear that the ad hoc surface time will always be less than the apparent chemical time constant. Hence, $\tau_s$ will always be less than 1.

5.1.4 Summary

The values of the material parameters cited from the literature are tabulated in Table 5.2. These values were used together with the material parameters measured in this study to approximate the chemical and mechanical time constants appropriate for the cartilage and cornea concentration transitions.

The chemical time constant for a 600 μm sample was shown to be on the order of 200 seconds. It was also argued that the chemical time constant for the 0.005 $\rightarrow$ 0.1 M concentration transition should be slightly less than the chemical time constant for the 0.1 $\rightarrow$ 0.15 M and 0.01 $\rightarrow$ 0.05 M concentration transitions for cartilage and cornea, respectively, because of the strain dependence of the tortuosity and the concentration dependence of the ambipolar diffusivity. The $M_o k$ product for cartilage was determined to be approximately $2 \times 10^{-9}$ m$^2$/s. This

Section 5.1.4
<table>
<thead>
<tr>
<th>MATERIAL PARAMETER</th>
<th>CARTILAGE</th>
<th>CORNEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$</td>
<td>$\sim 1 \times 10^{-15} \ \text{m}^4/\text{N}\cdot\text{s}$</td>
<td>$\sim 1.5 \times 10^{-15} \ \text{m}^4/\text{N}\cdot\text{s}$</td>
</tr>
<tr>
<td>$D_{Na^+}^\infty$</td>
<td>$1.33 \times 10^{-9} \ \text{m}^2/\text{s}$</td>
<td>$1.33 \times 10^{-9} \ \text{m}^2/\text{s}$</td>
</tr>
<tr>
<td>$D_{Cl^-}^\infty$</td>
<td>$2.03 \times 10^{-9} \ \text{m}^2/\text{s}$</td>
<td>$2.03 \times 10^{-9} \ \text{m}^2/\text{s}$</td>
</tr>
<tr>
<td>$\frac{\bar{D}}{D_{Na^+}^\infty}$</td>
<td>$0.4 - 0.5$</td>
<td>$0.4 - 0.5$</td>
</tr>
<tr>
<td>$\bar{\rho}_m$</td>
<td>$-0.15 \ \text{M}$</td>
<td>$-0.05 \ \text{M}$</td>
</tr>
</tbody>
</table>

Material Parameters Cited From the Literature

Table 5.2
results in a $\tau_m/\tau_c$ ratio of approximately 0.1 for cartilage.

The $\tau_m/\tau_c$ ratios for both cartilage concentration transitions are approximately the same, with the decrease in the modulus from 0.005 M to 0.1 M being offset by the decrease in the internal diffusivity caused by the increased tortuosity and the increase in the internal ionic concentrations (higher external bath concentration). The corresponding $\tau_m/\tau_c$ ratio for cornea is at least one order of magnitude larger. Because of the scatter in the reported values of the Darcy permeability $k$, these values should be treated as first order estimates only.

Because of the difficulty inherent in determining a value for $I_s$, and because of the possible effect of the stagnant film on $\tau_c$, these values cannot be determined a priori. However, it is reasonable to expect similar values of $I_s$ to apply for each experiment, as the experimental setup and the sample thicknesses at the time of each chemical transition were always similar. Furthermore, for the same reason, it is expected that the effect of the stagnant film on $\tau_c$ will be approximately the same for each experiment.

All that can be said about $I_s$ is that it is reasonable to expect that it be less than 1. Furthermore, since no inflections were seen in the stress transient data, it would appear that $I_s$ is bounded as to how much less than 1 it can be (see discussion in section 4.3). For want of any better criteria, a value of 0.1 will be used for $I_s$ initially to compare the theoretical stress transient to the data. It will then be shown that the model is not particularly sensitive to the exact value of the normalized surface time for a reasonable range of values. In comparing the data to the theoretical model, we will require a set of

Section 5.1.4
\( I_s, \tau_a, \) and \( \tau_m/\tau_c \) values that are consistent with the conclusions of this discussion, and that adequately describe the data for all three concentration transitions with reasonable values for each of the parameters.

5.2 Results and Discussion

5.2.1 Superposition of Data and Theory

Theoretical curves were computed for the conditions of each of the concentration transitions. The parameters used in the calculation for each concentration transition are summarized in Table 5.3.

The normalized swelling pressure as a function of normalized space and normalized time was computed for \( \tau_m/\tau_c \) ratios from 0.01 to 100 for the conditions of the cartilage 0.1 \( \rightarrow \) 0.15 M concentration transition. The normalized stress as a function of normalized time was computed from the solution for the normalized swelling pressure as described in section 4.3. These theoretical stress transient curves were then superimposed on the experimental data for several values of the chemical time constant \( \tau_c \) in the range of 200 seconds. A good match was found for the cartilage 0.1 \( \rightarrow \) 0.15 M concentration transition for \( \tau_m/\tau_c = .1 \) with \( \tau_c = 400 \) s. The stress transients parameterized by \( \tau_m/\tau_c \) are shown in Fig. 5.1 superimposed on the the data for the 0.1 \( \rightarrow \) 0.15 M concentration transition for cartilage with \( \tau_c = 400 \) s (i.e. \( 5\tau_c = 2000 \) s). It is worth noting that the particular shape of the stress transient curve varies markedly from one value of \( \tau_m/\tau_c \) to another (Fig. 5.1). Hence, the reasonable fit to the data obtained for the \( \tau_m/\tau_c = 0.1 \) curve could not be obtained by some other arbitrary choice of \( \tau_c \). Conversely,
<table>
<thead>
<tr>
<th>MATERIAL PARAMETERS</th>
<th>CARTILAGE 0.005 → 0.1 M</th>
<th>CARTILAGE 0.1 → 0.15 M</th>
<th>CORNEA 0.01 → 0.05 M</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_\infty$</td>
<td>0.27 MPa</td>
<td>0.27 MPa</td>
<td>58.7 kPa</td>
</tr>
<tr>
<td>$M_0$</td>
<td>1.17 MPa</td>
<td>1.17 MPa</td>
<td>34 kPa</td>
</tr>
<tr>
<td>$c_{\text{ref}}^{M}$</td>
<td>0.128 M</td>
<td>0.128 M</td>
<td>0.043 M</td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>0.031 MPa</td>
<td>0.031 MPa</td>
<td>30.2 kPa</td>
</tr>
<tr>
<td>$c_{\text{ref}}^{\beta}$</td>
<td>0.032 M</td>
<td>0.032 M</td>
<td>0.018 M</td>
</tr>
<tr>
<td>$\bar{p}_m$</td>
<td>-0.15 M</td>
<td>-0.15 M</td>
<td>-0.05 M</td>
</tr>
<tr>
<td>$\tau_s$</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>$\varepsilon_0$</td>
<td>0.075</td>
<td>0.15</td>
<td>0.17</td>
</tr>
<tr>
<td>$c_{\text{initial}}$</td>
<td>0.005 M</td>
<td>0.1 M</td>
<td>0.01 M</td>
</tr>
<tr>
<td>$c_{\text{final}}$</td>
<td>0.1 M</td>
<td>0.15 M</td>
<td>0.05 M</td>
</tr>
</tbody>
</table>

Summary of Material Parameters
Input to Model

Table 5.3
CARTILAGE
C: .1 --> .15 M
AVERAGE ± SD
N = 6
τ_c = 400 sec

Figure 5.1 Superposition of data (●) and theoretical stress transient for 0.1 -> 0.15 M NaCl concentration transition for cartilage. Theoretical curves were computed for material parameters summarized in Table 5.3, parameterized by τ_m/τ_c.
adjustment of $\tau_c$ did not yield a satisfactory fit with any other $\tau_m/\tau_c$ curve in Fig. 5.1.

It was argued previously that the value of $\tau_c$ for the cornea concentration transition $0.01 \rightarrow 0.05$ M should be approximately the same as the $0.1 \rightarrow 0.15$ M concentration transition for cartilage. The theoretical stress transient curves for the cornea $0.01 \rightarrow 0.05$ M concentration transition parameterized by $\tau_m/\tau_c$ are shown superimposed on the cornea stress transient data in Fig. 5.2, again with $\tau_c = 400$ s. It is clear from Fig. 5.2 that the stress transient resulting from the $0.01 \rightarrow 0.05$ M concentration transition is fit well by the prediction of the model for $\tau_m/\tau_c = 1$. We observed previously that the ratio of $\tau_m/\tau_c$ for the cornea samples should be approximately ten times the $\tau_m/\tau_c$ ratios for cartilage. The results of the numerical calculation are consistent with this observation.

The stress transient data for the cartilage $0.005 \rightarrow 0.1$ M concentration transition are shown in Fig. 5.3 with the computed stress transients for a range of $\tau_m/\tau_c$ values. Here the chemical time constant required to obtain a reasonable fit to the shape of any of the theoretical curves is $200$ s, i.e. $10\tau_c = 2000$ s. The discussion in section 5.1.2 concluded that the apparent chemical diffusivity of the ions in the tissue would be greater for the cartilage $0.005 \rightarrow 0.1$ M concentration transition than either of the other two concentration transitions. However, it can be shown that the factor relating the ion diffusivities is in the range of $1.2 - 1.3$. A factor as large as 2 cannot be justified solely by changes in diffusivity or tortuosity. Nevertheless, the fit for this stress transient is reasonably good for

Section 5.2.1
Figure 5.2 Superposition of data (●) and theoretical stress transient for 0.01 → 0.05 M NaCl concentration transition for cornea. Theoretical curves were computed for material parameters summarized in Table 5.3, parameterized by $\tau_m/\tau_c$. 

CORNEA
C: .01 → .05 M
AVERAGE ± SD
N = 6
$\tau_c = 400$ sec
Figure 5.3 Superposition of data (●) and theoretical stress transient for 0.005 → 0.1 M NaCl concentration transition for cartilage. Theoretical curves were computed for material parameters summarized in Table 5.3, parameterized by $\tau_m/\tau_c$. 

CARTILAGE 

C: .005 --> .1 M 

AVERAGE ± SD 

N = 7 

$\tau_c = 200$ sec
\( \tau_m / \tau_C = 0.1 \), which is the same \( \tau_m / \tau_C \) ratio that fit the other cartilage transition. As noted previously, the \( \tau_m / \tau_C \) ratio should be approximately the same for both cartilage concentration transitions. The predictions of the model are consistent with this observation. Furthermore, although the factor of two difference in the chemical time constants cannot be supported by the model, the trend of a shorter chemical time constant for the 0.005 \( \rightarrow \) 0.1 M concentration transition is.

5.2.2 Estimation of Convective Transport of Ions

The model was developed under the assumption that the Peclet number was small. This assumption allowed the transport of ions in the tissue to be decoupled from the fluid flow caused by the chemically induced changes in the material properties of the tissue. It was mentioned at that time that the Peclet number could be evaluated after the fact to assure that the results obtained were self consistent with the assumption made. That is to say, the fluid velocity calculated from the solution for the swelling pressure obtained assuming no convective transport of ions in the tissue in fact should satisfy the relation

\[
\text{Pe} = \frac{UL}{D} \ll 1
\]  

(5.4)

where \( \text{Pe} \) is the Peclet number, \( U \) is the fluid velocity, \( L \) is a characteristic length, and \( D \) is the diffusivity of the ions in the tissue.

The Peclet number can in fact be estimated rather simply. Since the gradient in the swelling pressure must be equal and opposite to the
gradient in the fluid pressure, the normalized z-derivative of the fluid pressure can be calculated directly from the solution vector for the normalized swelling pressure by using a finite difference approximation of the derivative. This normalized derivative must be multiplied by the ratio $p_0/\delta$ where $p_0$ is the initial swelling pressure and $\delta$ the sample thickness, in order to unnormalize the derivative of the fluid pressure. The fluid velocity can be found by multiplying the unnormalized fluid pressure gradient by the Darcy permeability of the tissue. Eq. 5.4 can then be used together with the effective ionic diffusivity and the thickness of the sample to determine the Peclet number in the tissue. In all cases, the maximum Peclet number was less than 0.1. However, the Peclet number for the 0.005 → 0.1 M cartilage concentration transient was $-7 \times 10^{-2}$, approximately 3 times larger than the next largest Peclet number resulting from the other concentration transitions. Furthermore, the fluid velocity is largest in the early stages of the stress transient and directed from the upper regions of the tissue to the lower. This fluid flow would tend to accelerate the ionic transport in the tissue. This would tend to make the apparent chemical time constant smaller than it would be in the absence of fluid flow. While the Peclet number resulting from the 0.005 → 0.1 M concentration transition is still less than 0.1, this effect coupled with the nonlinear dependence of the material properties on concentration could be partially responsible for the experimentally observed rapid stress transient. This could help explain part of the factor of two difference between the chemical time constant for the cartilage 0.005 → 0.1 M concentration transition and the chemical time constant that describes the cartilage 0.1 → 0.15 M and the cornea 0.01

Section 5.2.2
-> 0.05 M concentration transitions.

5.2.3 Variation of the Normalized Surface Time

The effect of varying the normalized surface time constant by a factor of two in either direction is shown in Fig. 5.4 for the parameters for the cartilage 0.1 \(\rightarrow\) 0.15 M concentration transition. It can be seen that the predicted stress transient is affected primarily for early time, and that the effect is not large provided that \(\tau_s\) and \(\tau_m/\tau_c\) are such that large inflections in the stress transients are not introduced (see section 4.3). Similar results are obtained for the cartilage 0.005 \(\rightarrow\) 0.1 M and the cornea 0.01 \(\rightarrow\) 0.05 M concentration transitions. It is also worth pointing out that within this range, the normalized surface time constant does not affect the chemical time constant required to relate the normalized experimental time to the normalized time of the theoretical model, \((t/\tau_c)\).

5.2.4 Summary

The model developed in Chapter II for chemically induced stress relaxation has been shown to adequately describe the experimental stress transients with a self-consistent set of reasonable values for the relevant physical and chemical parameters. In the final analysis, the model is seen to contain two semi-adjustable parameters, the chemical time constant \(\tau_c\) and the normalized surface time \(\tau_s\). The normalized surface time constant cannot be estimated with any accuracy as it represents an ad hoc attempt to account for the effects of the stagnant film layer in the porous polyethylene platen at the surface of the

Section 5.2.4
Figure 5.4 Variation in theoretical stress transient for 0.1 \( \rightarrow 0.15 \) M NaCl concentration of transition for cartilage as \( \tau_0 \) is varied, with \( \tau_m / \tau_c = 0.1 \). Material parameters are summarized in Table 5.3.
tissue sample. However, rather tight bounds can be placed on the value of the normalized surface time constant $\tau_s$. It was also shown that the particular choice of the normalized surface time was not particularly critical within this small range of values. The chemical time constant $\tau_c$ appears to be mildly affected by the stagnant film, but only by a factor of order unity compared to theoretical estimates of the chemical time constant based on the ion diffusivities in the tissue and the 600 $\mu$m reference thickness.


6.1 Introduction

6.1.1 Phenomenological Equations

In the electromechanochemical swelling model developed in Chapter II, the effect of fluid flow on the mechanical behavior of the tissue was included through Darcy's law, which linearly relates the average local fluid velocity to the local fluid pressure gradient in the tissue. When Darcy's law is applied to charged porous materials, the Darcy permeability $k$ implicitly includes the electromechanical interactions between the fixed charge and the ions in the fluid, in addition to the fluid/solid frictional interactions generally thought of as being included in $k$. Electromechanical effects that have their origin in the relative motion of charged solids and electrolytes are generally termed electrokinetic.

Electrokinetic transduction in charged tissues and membranes has been modeled by the phenomenological equations of nonequilibrium thermodynamics. Assuming that there are negligible macroscopic ionic concentration gradients, these can be written in one dimensional form as \[1,2\]
\[
\begin{bmatrix}
U \\
J
\end{bmatrix} =
\begin{bmatrix}
-k_{11} & k_{12} \\
-k_{21} & -k_{22}
\end{bmatrix}
\begin{bmatrix}
\frac{\partial}{\partial z}(P - \Delta \pi) \\
\frac{\partial V}{\partial z}
\end{bmatrix}
\] (6.1)

where

\begin{align*}
U &= \text{average } z - \text{directed fluid flow w.r.t solid} \\
J &= z - \text{directed current density} \\
\frac{\partial}{\partial z}(P - \Delta \pi) &= \text{fluid pressure gradient} \\
\frac{\partial V}{\partial z} &= \text{electrical potential gradient}
\end{align*}

and the \(k_{ij}\) are called phenomenological coupling coefficients.

Since eqs. 6.1 apply to systems having negligible macroscopic ionic concentration gradients, the macroscopic gradient in \(\Delta \pi\) vanishes. However, there is still a step jump in \(\Delta \pi\) from inside the tissue to outside, as discussed in section 2.3. For this reason it is convenient to use the fluid pressure \((P - \Delta \pi)\) in eqs. 6.1. In this form, fluid flow ceases when \(\nabla(P - \Delta \pi)\) is zero everywhere.

Darcy's law is consistent with the more general formulation of eqs. 6.1 in two limiting cases. When the tissue is uncharged, or when a short circuit constraint is imposed such that there is no potential gradient \((\frac{\partial V}{\partial z} = 0)\), the Darcy permeability \(k\) relating fluid flow to the fluid pressure gradient is

\[
k = k_{11}
\] (6.2)

However, if an open circuit constraint is imposed such that \(J = 0\), then

Section 6.1.1
the Darcy permeability is given by

\[ k = \left\{ k_{11} - \frac{k_{12}k_{21}}{k_{22}} \right\} \quad (6.3) \]

and the presence of the tissue fixed charge density affects the fluid flow resulting from an applied fluid pressure gradient.

In order to include the effect of macroscopic gradients in the ionic concentrations, a more general form of eqs. 6.1 is required. This form would have a $3 \times 3$ $k_{ij}$ matrix, and would include a chemical gradient as an additional driving force [2,3]. However, since the ionic transport was uncoupled from the fluid flow in the electromechanochemical model developed in Chapter II, eqs. 6.1 can be used to approximate the electrokinetic interactions during a chemically induced mechanical transient.

The chemically induced stress relaxation experiments described in Chapter III were performed under open circuit constraints. Hence, during the chemically induced stress transients, fluid pressure gradients induced gradients in the electrical potential $V$. From eqs. 6.1 with $J = 0$, the gradient in the electrical potential $V$ can be shown to be

\[ \frac{\partial V}{\partial z} = \frac{k_{21}}{k_{22}} \frac{\partial}{\partial z} (P - \Delta \pi) \quad (6.4) \]

The potential that would be measured by electrodes located at $z = 0$ and $z = \delta$ in the confined uniaxial configuration of Fig. 6.1 due to the streaming of fluid past the charged surfaces of the solid, is obtained by integrating the potential gradient of eq. 6.4 from the reference Section 6.1.1
Figure 6.1 Schematic for measuring streaming potential in uniaxial confined compression.
electrode at \( z = \delta \), to the porous electrode at the surface of the sample \( z = 0 \). Recalling that the gradient in the fluid pressure is equal and opposite to the gradient in the swelling pressure, we have

\[
V(t) = \int_{\delta}^{0} \frac{\partial V}{\partial z} \, dz = \int_{\delta}^{0} \frac{k_{21}}{k_{22}} \frac{\partial}{\partial z} \left( P - \Delta \tau \right) \, dz
\]

\[
= \frac{k_{21}}{k_{22}} \int_{\delta}^{0} \frac{\partial P}{\partial z} \, dz = \frac{k_{21}}{k_{22}} \left( p[\delta,t] - p[0,t] \right)
\]

(6.5)

where the sign convention for the voltage is defined in Fig. 6.1, and the \( k_{ij} \) are assumed to be constant in performing the integration in eq. 6.5. The streaming potential that accompanies the chemically induced stress relaxation can be computed directly from the solution for the swelling pressure. The computed streaming potential is shown as a function of normalized time \((t/\tau_0)\) in Fig. 6.2 for the cartilage 0.1 \( \rightarrow \) 0.15 M concentration transition with \( \tau_m/\tau_c = 0.1 \). The value of \(-4 \times 10^{-8} \) V/Pa has been used for \( k_{21}/k_{22} \) [4]. Since this value for \( k_{21}/k_{22} \) was determined for a cartilage specimen equilibrated in 0.0001 M NaCl, it substantially overestimates the streaming potential that would be induced by the chemical stress relaxation transient. Nevertheless, the shape of the streaming potential transient is unaffected by the choice of \( k_{21}/k_{22} \). The general shape of the streaming potential response shown in Fig. 6.2 can be understood by considering the flow of fluid in the tissue. The fluid flow as a function of space and time can be computed from the solution for the swelling pressure in a straightforward manner by differentiating the swelling pressure once with respect to space. Recalling that the gradient in the swelling pressure is equal and opposite to the gradient in the fluid pressure, the fluid velocity \( \mathbf{U} \) can
Figure 6.2 Computed streaming potential response for 0.1 → 0.15 M NaCl concentration transition for cartilage. Computed for material parameters summarized in Table 5.3 with $\frac{\tau_m}{\tau_c} = 0.1$ and $k_{21}/k_{22} = -4 \times 10^8$ V/Pa.
be determined directly from Darcy's law. The fluid velocity $U$ is shown in Fig. 6.3 for the cartilage $0.1 \rightarrow 0.15$ M concentration transition with $\tau_m/\tau_c = 0.1$. The value of $\tau \times 10^{-15}$ was used for the Darcy permeability.

The large negative streaming potential peak results from the large fluid pressure gradients that force fluid from the upper regions of the tissue to the lower in response to the concentration induced change in the material properties. Fluid flow in the positive $z$ direction pulls the mobile positively charged counterions in the direction of fluid flow, causing an electric field in the minus $z$ direction, which in turn tends to pull the counterions back to their original, unperturbed position. The zero crossing of the streaming potential response results when the space averaged fluid velocity is zero. The positive peak results from the return flow of fluid from the lower regions back into the upper layers of the tissue.

The potential that would actually be measured by Ag/AgCl electrodes located at $z = 0$ and $z = \delta$ during a chemically induced stress relaxation experiment would result from the sum of the streaming potential, the diffusion potential, and the difference between the two electrode/electrolyte potentials that would result from the unequal electrolyte concentrations at the surface of the two electrodes during the chemical transient. Each of these terms would be time dependent. This would clearly complicate the interpretation of the experimental results. However, the observation of a bimodal potential would provide compelling evidence of the streaming potential component, since both the diffusion potential and the electrode potentials would be monotonic.

Section 6.1.1
Figure 6.3 Spatial variation of fluid velocity parameterized by time for 0.1 → 0.15 M NaCl concentration transition for cartilage. Computed for material parameters summarized in Table 5.3 with $\tau_m/\tau_c = 0.1$ and a sample thickness of 600 $\mu$m. Darcy permeability is $1 \times 10^{-15}$. 
during a single chemical transient experiment.

Streaming potentials have successfully been measured in cartilage for statically applied trans-tissue pressure gradients [5], as well as deformation induced streaming potentials in stress relaxation [6], and in oscillatory confined compression [4], where the measurement problems associated with the chemical transient are not present. The phenomenological representation embodied in eq. 6.1 has recently been used in conjunction with a macroscopic biphasic tissue model to account for time varying electrokinetic coupling in cartilage [4,7,8]. A similar approach has been used to account for streaming potentials measured in porous rocks [9].

6.1.2 Macroscopic versus Microscopic Modeling

Macroscopic (ion exchange) continuum theories have typically been used to model electromechanical and electrokinetic coupling in cartilage and other connective tissues [10-15]. The swelling model developed in Chapter II is another example of a macrocontinuum model employed to relate macroscopically measured constitutive relations to macroscopic tissue behavior. In these macrocontinuum models, the parameters ascribed to a point within the tissue represent a local average over an incremental volume that is large enough to smooth over microstructural features of the tissue. Hence, the tissue is viewed as having a smoothed out volume charge density. The accompanying potential profile and mobile ion concentration profiles are also smooth in the tissue volume (Fig. 6.4a), and experience rapid changes only at the tissue/electrolyte interfaces. Characteristic dimensions include many macromolecular
Figure 6.4 Schematic of structural level associated with macro and microcontinuum models of electromechanics.

a) Macromodel - electrical potential, charge and ion concentrations are uniform within the tissue and are discontinuous at the boundaries.

b) Micromodel - space varying potential and ion concentrations exist between charged macromolecules.
constituents, and are assumed to be sufficiently large compared to a Debye length to justify the assumption of quasielectroneutrality everywhere in the tissue. In equilibrium, mobile ion concentrations are assumed to satisfy the Donnan equilibrium relation throughout the tissue. By design, macrocontinuum models do not incorporate structural or detailed compositional information about the tissue.

Microscopic models attempt to incorporate molecular level structural and compositional features to describe macroscopically measurable phenomena. In so doing, they attempt to get inside the phenomenological constitutive relations to provide a more fundamental view of the governing physical interactions between material components that ultimately determine macroscopic behavior. Since micromodels focus on length scales that are on the order of a Debye length, the space varying potential profile depicted in Fig. 6.4b must be accounted for in the modeling approach. Such models will be an essential aid in determining the specific roles played by individual tissue components, and in attempting to understand the physical basis of various disease states. They may also help to delineate cause and effect relationships involved in the process of tissue degeneration.

In constructing a tissue micromodel, a major problem is to strike an appropriate balance between mathematical complexity and mathematical tractability. Ideally, the micromodel should incorporate the complex structure and composition of the tissue as a whole. However, to be useful, the micromodel must remain simple enough to allow for the mathematical modeling of the interactions of primary importance. In the following, the tissue will be modeled as an ordered array of charged
polyelectrolyte rods. Our goal will be to derive expressions for the $k_{ij}$ in terms of structural and compositional parameters.

Lee [16] began formulating the coupling coefficients in terms of microscopic parameters. His model developed an electrokinetic micromodel for fluid flow parallel to the axes of an ordered array of cylinders, accounting for electrokinetic interactions on a length scale the order of a Debye length. In the following, the $k_{ij}$ for the flow perpendicular to the axis of the cylindrical molecules will be developed. In the general case of random cylindrical assemblages, it is necessary to employ a weighted average. Since there are two orthogonal orientations for the case of perpendicular flow, twice the weight is given to the cross flow coefficients as to those obtained for parallel flow in determining the average $k_{ij}$.

6.2 Cell Model

In deriving the $k_{ij}$, we will make use of the unit cell technique as employed by Happel [17], shown in Fig. 6.5. The development proceeds on the assumption that two concentric cylinders can serve as a model for fluid flowing through the entire assemblage of cylinders. The inner cylinder of radius $a$ represents a single rod in the total assemblage, while the outer cylinder of radius $b$ represents the fluid surrounding the solid cylinder. The solid volume fraction in the cell, $(a/b)^2$, is taken as the solid volume fraction of the entire assemblage of cylinders. The radius $a$ of the solid is related to the structural parameters of the proteoglycan aggregates. In adopting a cell model it is assumed that at a distance from the solid cylinder, the flow will not
Figure 6.5 Unit cell model depicting the solid cylinder of radius a and the cylinder of fluid of radius b surrounding the solid.
be greatly affected by the exact shape of the outer boundary, provided suitable boundary conditions are chosen. The boundary conditions will be considered in greater detail below.

6.2.1 Bulk Relations

In the presence of electrical forces the Navier Stokes equation governing fluid flow can be written in the creep flow limit as

\[ \nabla P = \eta \nabla^2 \mathbf{v} + \mathbf{v} \cdot T^e \]  

(6.6)

where

- \( P \) = hydrostatic pressure
- \( \mathbf{v} \) = fluid velocity
- \( \eta \) = fluid viscosity
- \( T^e \) = electric stress tensor

We note that in equilibrium, for the general case of a diffuse double layer (\( (\mathbf{v} \cdot T^e)_r \neq 0 \)), there is an \( r \)-directed gradient in the hydrostatic pressure \( P \) in the double layer region when \( \mathbf{v} = 0 \) everywhere. This nonzero gradient in \( P \) results in order to keep the local gradient in the fluid pressure \( (P - \Delta \pi) \) equal to zero in face of the steep ionic concentration gradients in the double layer region resulting from the balance of the drift and diffusional fluxes. Eq. 6.6 can be cast in terms of the fluid pressure \( (P - \Delta \pi) \) as

\[ \nabla(P - \Delta \pi) = \eta \nabla^2 \mathbf{v} + \mathbf{v} \cdot T^e - \mathbf{v}(\Delta \pi) \]  

(6.7)

In this form, fluid will always flow in response to gradients in the

Section 6.2.1
fluid pressure \((P - \Delta p)\), and the nonzero divergence of the electrical stress tensor is explicitly balanced by the local gradient in \(\Delta p\) (e.g. in radial component at equilibrium with \(\nabla \cdot \nabla = 0\)).

The electromechanical coupling will be considered in the limit where the double layer thickness \(d\) is small compared to the fluid region \((b-a)\) of the unit cell. This treatment puts all of the electromechanical coupling into the boundary region \(a < r < a+d\), and allows fluid flow in the bulk to be treated in the absence of electrical forces \([18,19]\). The effect of the double layer will be included in the boundary conditions imposed at \(r=a+d=a\). While these approximations are not rigorously true for cartilage, treating all of the electromechanical coupling in the boundary greatly simplifies the mathematical problem, yet retains salient features of the real situation in the tissue. In this context, the model can be viewed as a first order approximation of the complete coupling in the bulk.

With all of the electrical forces confined to the boundary region, eq. 6.6 simplifies to

\[
\nabla P = \eta \nabla^2 \nabla
\]  
(6.8)

Making use of the vector identity

\[
\nabla \times \nabla \times \nabla = \nabla (\nabla \cdot \nabla) - \nabla^2 \nabla
\]  
(6.9)

together with the fluid incompressibility condition
\[ \nabla \cdot \vec{V} = 0 \quad (6.10) \]

eq 6.8 can be rewritten as

\[ \nabla P = -\eta (\nabla \times \vec{v} \times \vec{V}) \quad (6.11) \]

Because the flow is incompressible, it is convenient to use a vector stream function \( \vec{C} \) defined as

\[ \vec{V} = \nabla \times \vec{C} \quad (6.12) \]

\[ \nabla \cdot \vec{C} = 0 \]

Taking the curl of eq. 6.11, together with eqs. 6.12 and vector identity 6.9 yields

\[ \nabla^2 \vec{C} = 0 \quad (6.13) \]

Because we are considering a two dimensional flow perpendicular to the axis of the cylinder, \( \vec{C} \) has a single component, which is in the direction of the cylinder axis:

\[ \vec{C} = C(r, \theta) \hat{r}_z = \hat{c}(r) \sin \theta \hat{r}_z \quad (6.14) \]

The velocities \( v_r \) and \( v_\theta \) can be evaluated from eq. 6.12a and are given by

Section 6.2.1
\[ v_r = \frac{1}{r} \frac{\partial C}{\partial \theta} = \hat{v}_r \cos \theta \]  

(6.15)

\[ v_\theta = -\frac{\partial C}{\partial r} = \hat{v}_\theta \sin \theta \]

Substituting eq. 6.14 into eqs. 6.15, we have

\[ \hat{v}_r = \frac{\psi}{r} \]  

(6.16)

\[ \hat{v}_\theta = -\frac{d\psi}{dr} \]

Substituting the assumed form of C (eq. 6.14) into eq. 6.13 yields

\[ \left( \frac{d^2}{dr^2} + \frac{1}{r} \frac{d}{dr} - \frac{1}{r^2} \right) 2 \hat{\psi} = 0 \]  

(6.17)

which has as a general solution

\[ \hat{\psi} = A(r/a)^3 + B \frac{r}{a} + C \frac{a}{r} + D \frac{r}{a} (\ln r - \frac{1}{2}) \]  

(6.18)

where the constant 1/2 has been included in eq. 6.18 for convenience. With this solution for \( \hat{\psi} \), eqs. 6.16 give us

\[ \hat{v}_r = \frac{Ar^2}{a^3} + \frac{B}{a} + \frac{Ca}{r^2} + \frac{D}{a} (\ln r - \frac{1}{2}) \]  

(6.19)

\[ \hat{v}_\theta = \frac{3Ar^2}{a^3} - \frac{B}{a} + \frac{Ca}{r^2} - \frac{D}{a} (\ln r + \frac{1}{2}) \]

The drag per unit length on the cylinder can be found by integrating the stress over the cylinder surface:
\[ f_z = \int_0^{2\pi} (S_r^d(\theta) \cos \theta - S_\theta^d(\theta) \sin \theta) \, d\theta \]  

(6.20)

where

\[ S_r^d = S_r \cos \theta = (2\pi \frac{3v_r}{3r} - P)|_r = a \]  

(6.21)

\[ S_\theta^d = S_\theta \sin \theta = \pi (\frac{a}{\theta} \frac{v_\theta}{r^2} + \frac{1}{r} \frac{3v_r}{3\theta})|_r = a \]

Plugging the \( \theta \) dependence of \( S_r^d \) and \( S_\theta^d \) into eq. 6.20 gives

\[ f_z = \int_0^{2\pi} (S_r^d \cos^2 \theta - S_\theta^d \sin^2 \theta) \, d\theta \]  

(6.22)

\[ = \pi a (\hat{S}_r - \hat{S}_\theta) \]

In order to get an expression for \( \hat{S}_r \) in terms of the stream function \( \hat{v} \), we must solve

\[ \nabla P = \eta \nabla^2 \hat{v} \]  

(6.23)

to relate the hydrostatic pressure to the velocities \( v_r \) and \( v_\theta \). With \( P = \hat{P} \cos \theta \) we have

\[ \frac{d\hat{P}}{dr} = \eta \left( \frac{d}{dr} \frac{1}{r} \frac{d}{dr} (r \hat{v}_r) - \frac{\hat{v}_r}{r^2} - \frac{2\hat{v}_\theta}{r^2} \right) \]  

(6.24)

\[ \hat{P} = -r \eta \left( \frac{d}{dr} \frac{1}{r} \frac{d}{dr} (r \hat{v}_\theta) - \frac{\hat{v}_\theta}{r^2} - \frac{2\hat{v}_r}{r^2} \right) \]

Using eqs. 6.19 in either of eqs. 6.24 yields
\[ \hat{P} = \eta \left( \frac{8A}{a^3} r - \frac{2D}{ar} \right) \]  

(6.25)

Substituting eq. 6.25 and eqs. 6.19 into eqs. 6.21 gives us

\[ \hat{S}_r = -4\eta \left( \frac{A}{a^3} r + \frac{Ca}{r^3} - \frac{D}{ar} \right) \]  

(6.26)

\[ \hat{S}_\theta = -4\eta \left( \frac{A}{a^3} r + \frac{Ca}{r^3} \right) \]

Finally, evaluating eqs. 6.26 at \( r=a \) and substituting the result into eq. 6.22, we have

\[ f_z = \frac{4\eta \pi D}{a} \]  

(6.27)

as the force per unit length on the cylinder due to fluid flow. In order to evaluate the drag we need only solve for \( D \). To evaluate \( S_r \) and \( S_\theta \) individually we must also solve for \( A \) and \( C \).

6.2.2 **Boundary Conditions**

As mentioned earlier, we will consider all electromechanical coupling in the boundary conditions at the surface of the solid cylinder. In addition, we will assume that the Debye length is small compared to the radius of the solid cylinder, i.e. \( d/a \ll 1 \). This allows us to unwrap the surface of the cylinder in order to determine the appropriate relationship between viscous and electrical forces in the boundary region \( a < r < a+d \).

We will work in the frame of the solid cylinder, and will assume
that the solid cylinder is at rest, while the velocity of the fluid at 
\( r = a + d \) is \( v^d_0 \), as shown in Fig. 6.6. We must now include the electrical 
stress term in eq. 6.6. However, because \( d/a \ll 1 \), we can use a planar 
approximation of eq. 6.6. Furthermore, because the double layer region 
is so thin, large viscous stresses develop for small velocities. These 
viscous shears are balanced by electrical forces in the double layer, 
and the pressure gradient in the double layer can be ignored. Hence, eq. 
6.6 can be approximated as

\[
\eta \frac{a^2 v_\theta}{a r^2} + \frac{a}{a r} (T_{\theta r}) = 0 \tag{6.28}
\]

In what follows, the double layer will be modeled as a Helmholtz 
capacitor. In the Helmholtz capacitor model, all of the mobile charge in 
the double layer is assumed to be located one Debye length from the 
surface charge on the solid. In determining the electrokinetic coupling, 
it will be assumed that the double layer remains unperturbed in the face 
of the fluid flow. This allows the electrical potential to be split into 
two components, \( \psi \) and \( \phi \). The potential \( \psi \) represents the potential drop 
across the double layer which is assumed to remain constant in the face 
of the fluid flow. We note that \( \psi \) gives rise to a radially directed 
field which is confined to the region between \( r = a \) and \( r = a + d \). \( \phi \) is 
responsible for the electric field that is either induced by the fluid 
flow, or results from the combined effects of an applied field and the 
field generated by fluid flow. With these definitions, \( T_{\theta r} \) is given by

\[
T_{\theta r} = -\varepsilon \frac{\partial \psi}{\partial r} E_\theta \tag{6.29}
\]
Figure 6.6 Schematic of solid cylinder surface with Helmholtz capacitor model of double layer.
Eq. 6.28 can be integrated across the region \( a < r < a+d \) subject to the conditions

\[
v_\theta(a) = 0
\]
\[
v_\theta(a+d) = v_\theta^d
\]
\[
\psi(a) = \zeta
\]
\[
\psi(a+d) = 0
\]

The first integration results in

\[
\eta \frac{\partial v_\theta}{\partial r} - \varepsilon \frac{\partial \psi}{\partial r} E_\theta = C_1
\]

Since the potential \( \psi \) is confined to the double layer region, its derivative vanishes at the outer edge of the outer Helmholtz plane at \( r=a+d \). Hence, the constant \( C_1 \) can be evaluated as

\[
C_1 = \eta \frac{\partial v_\theta}{\partial r} \bigg|_{d+a} = S_\theta^d
\]

and eq. 6.31 becomes

\[
\eta \frac{\partial v_\theta}{\partial r} - \varepsilon \frac{\partial \psi}{\partial r} E_\theta = S_\theta^d
\]

in the double layer region. Integrating a second time from \( r=a \) to \( r=a+d \), subject to boundary conditions 6.30 yields

Section 6.2.2
\[ S^d_\theta = \frac{n}{d} v^d_\theta + \frac{\varepsilon E_\theta \tau}{d} \] (6.34)

This relates the tangential electric field \( E_\theta \) resulting from an externally applied field or flow, the change in velocity across the double layer and the shear stress at the outer edge of the Helmholtz double layer. We will require that the shear stress calculated from the bulk flow represented by eq. 6.26b be continuous with the shear stress at the double layer boundary.

The second boundary condition at the cylinder surface results from conservation of charge. If we consider a control volume that cuts through the double layer and the particle surface as shown in Fig. 6.7, we require that the normal current in the fluid balance the surface divergence of the surface current. Because there is no net charge in the bulk, the current there can only result from a conduction process. However, because of the net charge in the mobile region of the double layer, the surface current results from the combined effects of a tangential fluid velocity and a tangential electric field. Hence,

\[ n^0 \cdot (J_1 - J_2) + \nabla \cdot K = 0 \] (6.35)

where \[ K = \frac{\sigma_m}{\mu} E_\theta (a + d) - \sigma_m v^d_\theta \]

\[ \sigma_m \equiv \text{surface charge} = \varepsilon \tau / d \]

\[ J_1 = -\sigma_0 \frac{\partial \phi}{\partial r} \bigg|_{r=d+a} \]

\( \mu = \text{mobility of the counter ion} \)

\( \sigma_0 = \text{conductivity of the bulk} \)
Figure 6.7 Schematic of charge conservation boundary condition.
The magnitude of the surface charge \( \sigma_m \) must be used in the surface current conduction term because the current resulting from the conduction of the mobile charge by an electric field depends only on the sign of the field and not the sign of the charge. The sign of the current carried by convection depends both on the sign of the convected charge and the direction of fluid flow. The term \( |\sigma_m|\mu \) is a surface conductivity due to the presence of a charge singularity at \( r = a+d \). Implicit to defining the surface conductivity is the assumption that the ions in the mobile part of the double layer (which are represented in the Helmholtz approximation by the charge singularity at \( r = a+d \)) are in fact mobile.

In cylindrical coordinates, boundary condition 6.35 becomes

\[
- \sigma_o \frac{\partial \Phi}{\partial r} \bigg|_{r=d+a} - \frac{1}{a} \frac{\partial}{\partial \theta} \left( |\sigma_m|\mu \frac{\partial \Phi}{\partial \theta} + \sigma_m v^d \right) = 0
\]

(6.36)

where \( -\frac{\partial \Phi}{\partial \theta} \bigg|_{r=d+a} \) has been substituted for \( E_\theta(a+d) \). With

\[
v^a_\theta = \hat{v}^a \sin \theta
\]

\[
v^d_\theta = \hat{v}^d \sin \theta
\]

\[
\Phi = \hat{\Phi} \cos \theta
\]

we have

\[
- \frac{\partial \hat{\Phi}}{\partial r} \bigg|_{r=d+a} = - \frac{a}{a \sigma_o} \hat{v}^d + \frac{|\sigma_m|\mu}{a^2 \sigma_o} \hat{\Phi}^d
\]

(6.37)

where \( \hat{\Phi}^d \) is the potential evaluated at the outer Helmholtz plane.
(r = a+d).

We now turn to the fluid boundary conditions to be applied at the outer edge of the cell. We will consider a frame where the solid cylinders are at rest and the fluid is moving far from the assemblage of cylinders with a velocity \( u_0 \). Referring back to Fig. 6.5, it is evident that when considering the entire assemblage, symmetry requires that the fluid velocity be continuous across the walls separating the square cells in the array. This is equivalent to saying that there is no shear stress at the walls separating the cells. Hence, in the cylindrical approximation of the square cell we require zero shear stress at \( r=b \). Hence,

\[
\frac{\partial v_\theta}{\partial r} + \frac{1}{r} \frac{\partial v_r}{\partial \theta} - \frac{v_\theta}{r} = 0
\]  

(6.38)

With the solid cylinder fixed and an average imposed fluid velocity \( u_0 \), the second boundary condition at \( r=b \) is

\[
v_r(b) = u_0 \cos \theta
\]

(6.39)

In light of eqs. 6.16, these conditions can be written as

\[
\hat{v}_r(b) = u_0
\]

(6.40)

\[
\frac{\partial \hat{v}_\theta}{\partial r} \bigg|_{r=b} - \frac{\hat{v}_\theta}{b} = \frac{u_0}{b}
\]

The boundary conditions 6.40 were used by Happel [17] to solve the fluid
mechanical problem in the absence of electrokinetic coupling. Because of the undefined nature of the imagined boundary at the outer edge of the unit cell, these boundary conditions are not necessarily unique in the sense that different conditions can be applied which do not violate the spirit of the model. It can be shown that the nature of the solution is not radically altered by a different choice of boundary conditions. Conditions 6.40 are used in order to be consistent with Happel's approach, with the understanding that other conditions would give similar, although not identical, results.

Finally, at the boundary \( r = a + d = a \) we have

\[
\hat{v}_r(a+d) = 0
\]

(6.41)

\[
\hat{v}_\theta(a+d) = \hat{v}_\theta^d
\]

where we allow for a non-zero \( \hat{v}_\theta^d \) because of the electrical shear stress at the outer Helmholtz plane.

Using eqs. 6.19 for \( \hat{v}_r \) and \( \hat{v}_\theta \), eqs. 6.40 and 6.41 can be written as

\[
\frac{A}{a} + \frac{B}{a} + \frac{C}{a} + \frac{D}{a} (\ln a - \frac{1}{2}) = 0
\]

\[
\frac{3A}{a} + \frac{B}{a} - \frac{C}{a} + \frac{D}{a} (\ln a + \frac{1}{2}) = -\hat{v}_\theta^d
\]

(6.42)

\[
\frac{A}{a^3} + \frac{B}{a} + \frac{C}{b^2} + \frac{D}{a} (\ln b - \frac{1}{2}) = u_0
\]

Section 6.2.2
\[
\frac{3Ab^2}{a^3} - \frac{B}{a} + \frac{3Ca}{b^2} - \frac{D}{a} (\ln b - \frac{1}{2}) = - u_o
\]

This gives four equations which can be solved in terms of the as yet unknown velocity \( \hat{v}_d^d \). To evaluate the shear stress \( S^d_\theta \) the constants \( A, C, D \) are required. However, as noted previously, to evaluate the drag per unit length, only \( D \) is required. Solving eqs. 6.42 gives us

\[
\begin{align*}
\frac{A}{a} &= \frac{-a^*(u_o + \hat{v}_d^d \ln b)}{b^*} \\
\frac{B}{a} &= \frac{2u_o a^* - (1 + a^*) \ln a - \hat{v}_d^d (1 - a^*) (\ln b - \frac{1}{2})}{\text{det}} \\
\frac{C}{a} &= \frac{u_o + \hat{v}_d^d \ln b}{\text{det}} \\
\frac{D}{a} &= \frac{2u_o (1 + a^*) + \hat{v}_d^d (1 - a^*)}{\text{det}} \quad (6.43)
\end{align*}
\]

\[
\text{det} = 2(1 + \frac{a^*}{b^*})(\ln \frac{b}{a} - \frac{1}{2} \frac{b^*}{b^*} - \frac{a^*}{b^*})
\]

6.3 Derivation of \( k_{ij} \) for Perpendicular Flow

6.3.1 Derivation of \( k_{11} \)

The coefficient \( k_{11} \) represents the permeability of the matrix to fluid flow when the macroscopic voltage drop is constrained to zero. In the following, the \( z \) direction will be taken as the direction perpendicular to the cylinder axis, and will be used to describe the macroscopic gradients in the fluid pressure \( (P - \Delta F) \) and the electrical potential \( V \). It should not be confused with the axis of the cylindrical
cell. With \( \frac{\partial V}{\partial z} = 0 \), there is no uniform electric field and the potential \( \phi \) takes the form

\[
\phi = \hat{\phi}(r) \cos \theta = \frac{F}{r} \cos \theta
\]  

(6.44)

Using eq. 6.44 in boundary condition 6.42 we have

\[
-\frac{F}{a^2} = -\frac{\sigma_m \hat{v}_\theta}{a\sigma_o} + \frac{|\sigma_m|\mu F}{a^3\sigma_o}
\]  

(6.45)

\[
F = \frac{\hat{v}_\theta \sigma_m a^2}{a\sigma_o + |\sigma_m|\mu}
\]

Given \( F \) we can evaluate the tangential electric field at the cylinder surface as

\[
E_\theta = -\frac{1}{a} \frac{\partial \phi}{\partial \theta} = \frac{\hat{v}_\theta \sigma_m}{a\sigma_o + |\sigma_m|\mu} \sin \theta
\]  

(6.46)

Combining eq. 6.46 with eq. 6.34 yields

\[
S^d_\theta = S^d_\theta \sin \theta = \frac{n}{d} \left( 1 + \frac{\epsilon \sigma_m}{\eta(a\sigma_o + |\sigma_m|\mu)} \right) \hat{v}_\theta \sin \theta
\]  

(6.47)

\[
\hat{S}^d_\theta = \frac{n}{d} \left( 1 + \frac{\epsilon \sigma_m}{\eta(a\sigma_o + |\sigma_m|\mu)} \right) \hat{v}_\theta
\]

which we equate with the shear stress 6.26b, evaluated at \( r=a \):

\[
\hat{S}^d_\theta = \frac{-2n (1 - \frac{a^*}{b^*})(\frac{1}{a} + \frac{\hat{v}^d \ln \frac{b}{a}}{d} \frac{\beta}{\gamma})}{a(1 + \frac{a^*}{b^*})(\ln \frac{b}{a} - \frac{1}{2} \frac{b^* - a^*}{b^* + a^*})}
\]  

(6.48)
where eqs. 6.43 have been used in eq. 6.26b to obtain eq. 6.48

From eqs. 6.47 and 6.48 we can solve for \( \hat{v}_d^d \) in terms of \( u_o \):

\[
\hat{v}_d^d = \frac{-2u_o \frac{d}{a} G_1}{1 + \frac{\epsilon \sigma_m}{\eta(a\sigma_o + |\sigma_m|\mu)} + 2 \frac{d}{a} G_1 \ln \frac{b}{a}} 
\]

(6.49)

where

\[
G_1 = \frac{(1 - \frac{a^*}{b^*})}{(1 + \frac{a^*}{b^*})(\ln \frac{b}{a} - \frac{1}{2} \frac{a^*}{b^*} - \frac{a^*}{b^*})} 
\]

(6.50)

Finally, we can relate \( u_o \) to the drag force, which in turn can be related to the macroscopic fluid pressure gradient. From eq. 6.27 and eq. 6.38 we have the force per unit length

\[
f_z = \frac{4\pi \eta D}{a} = \frac{4\pi \eta u_o}{\ln \frac{b}{a} - \frac{1}{2} \frac{b^*}{b^*} - \frac{a^*}{a^*}} 
\]

(6.51)

where we have dropped \( \hat{v}_d^d \) compared to \( u_o \) because we have assumed \( d/a \ll 1 \). Eq. 6.51 represents the force per unit length that the fluid in the unit cell exerts on the solid cylinder. The cylinder therefore exerts a force per unit length \(-f_z\) on the fluid. In the macroscopic view, this force per unit length is spread out over the cell volume per unit length, which is the cross sectional area of the cell, \( \pi b^2 \), and must be balanced by the applied fluid pressure gradient in order to maintain the macroscopic fluid velocity. Following Happel, we convert the force per
unit length to a force density by dividing by the cell cross sectional area. The macroscopic fluid pressure gradient necessary to keep the fluid flowing with the macroscopic average velocity \( u_o \) is then given by

\[
\frac{3}{\partial z} (P - \Delta \pi) = \frac{-f_z}{\pi b^2} = \frac{-4\eta u_o}{b^2 \left( \ln \frac{b}{a} - \frac{1}{2} \frac{b^*}{b^* + a^*} \right)}
\]  

(6.52)

where the macroscopic fluid pressure \((P - \Delta \pi)\) is used in eq. 6.52 to be consistent with the formulation of the phenomenological equations given in eq. 6.1. We note here that the gradients in \( \Delta \pi \) within the tissue are zero. The phenomenological coefficient \( k_{11} \) is given by

\[
k_{11} = \frac{u_o}{\left\{- \left[ \frac{3}{\partial z} (P - \Delta \pi) \right]\right\}} = \frac{b^2 \left( \ln \frac{b}{a} - \frac{1}{2} \frac{b^*}{b^* + a^*} \right)}{4\eta}
\]

(6.53)

6.3.2 Derivation of \( k_{12} \)

In order to find an expression for \( k_{12} \) we must determine the fluid velocity resulting from an applied field \( \frac{3V}{\partial z} = -E_0 \frac{\partial r}{\partial z} \), with \( \frac{3}{\partial z} (P - \Delta \pi) = 0 \). Because of the applied field, the potential \( \phi \) takes the form

\[
\phi = -E_0 r \cos \theta + \frac{F}{r} \cos \theta
\]

(6.54)

Boundary condition 6.37 gives
\[-(\frac{F}{a^2} + E_o) = -\left(\frac{\sigma_m v^d}{a\sigma_o} + \frac{\mid\sigma_m\mid\mu}{a\sigma_o} (E_o - \frac{F}{a^2})\right)\]

(6.55)

\[F = a^2 \left(\frac{\sigma_m v^d - E_o (a\sigma_o - \mid\sigma_m\mid\mu)}{a\sigma_o + \mid\sigma_m\mid\mu}\right)\]

The tangential field is then given by

\[E_\theta = -\frac{1}{a} \frac{\partial \phi}{\partial \theta} = \left(\frac{\sigma_m v^d - 2E_o a\sigma_o}{a\sigma_o + \mid\sigma_m\mid\mu}\right) \sin \theta\]

(6.56)

Combining eqs. 6.55 and 6.34 yields

\[\hat{\sigma}_\theta = \frac{n}{d} \left[1 + \frac{\epsilon \tau \sigma_m}{\eta (a\sigma_o + \mid\sigma_m\mid\mu)}\right] \frac{2a\sigma_o \epsilon \tau E_o}{d(a\sigma_o + \mid\sigma_m\mid\mu)}\]

(6.57)

which must equal the shear stress given by 6.26b evaluated at \(r=a\):

\[\hat{\sigma}_\theta = -\frac{2n}{a(1 + \frac{a^*}{b^*})(\ln \frac{b}{a} - \frac{1}{2} \frac{b^* - a^*}{b^*})} \left(u_o + \frac{v^d}{a} \ln \frac{b}{a}\right)\]

(6.58)

where eqs. 6.43 have been used in eq. 6.26 to obtain eq. 6.58. Solving for \(v^d\) in terms of \(u_o\) and \(E_o\) we have

\[\hat{v}^d_\theta = 2 \left[\frac{\epsilon \tau a\sigma_o E_o}{\eta (a\sigma_o + \mid\sigma_m\mid\mu)} - u_o \frac{d}{a} G_1\right]\]

(6.59)

\[1 + \frac{\epsilon \tau \sigma_m}{\eta (a\sigma_o + \mid\sigma_m\mid\mu)} + 2 \frac{d}{a} G_1 \ln \frac{b}{a}\]

Section 6.3.2
where $G_1$ is given in eq. 6.50.

To determine $k_{12}$, we must determine the flow resulting from an applied field with the macroscopic fluid pressure gradient constrained to zero. Force equilibrium requires that the drag on the cylinder vanish. From eq. 6.27 we therefore require that $D$ vanish. Hence, eq. 6.43c yields

$$
\hat{v}_d = - \frac{2u_o(1 + \frac{a^*}{b^*})}{1 - \frac{a^*}{b^*}}
$$

(6.60)

Taken together with eq. 6.59 we have

$$
u_o = \frac{-\frac{\varepsilon \varepsilon}{\eta} \left( \frac{b^*}{b^* + a^*} \right) E_o}{1 + \frac{\varepsilon \varepsilon \sigma_m}{\eta \sigma_o} + \frac{|\sigma_m| \mu}{\sigma_o} + 2 \frac{d}{a \frac{b^*}{a b^* + a^*}}(1 + \frac{|\sigma_m| \mu}{\sigma_o})}
$$

(6.61)

Therefore

$$
k_{12} = \frac{u_o}{\hat{v}} = \frac{u_o}{(-E_o)}
$$

(6.62)

$$
= \frac{\frac{\varepsilon \varepsilon}{\eta} \left( \frac{b^*}{b^* + a^*} \right)}{1 + \frac{\varepsilon \varepsilon \sigma_m}{\eta \sigma_o} + \frac{|\sigma_m| \mu}{\sigma_o} + 2 \frac{d}{a \frac{b^*}{a b^* + a^*}}(1 + \frac{|\sigma_m| \mu}{\sigma_o})}
$$

Section 6.3.2
6.3.3 Derivation of $k_{21}$

To determine $k_{21}$, we must find the current $J$ that results from an applied macroscopic fluid pressure gradient $\frac{\partial}{\partial z}(P - \Delta P)$ when the macroscopic potential gradient $\frac{\partial V}{\partial z}$ is constrained to zero. With $\frac{\partial V}{\partial z} = 0$, the potential $\phi$ takes the form

$$\phi = \frac{F}{r} \cos \theta$$  \hspace{1cm} (6.63)

The analysis proceeds along the same lines leading from eq. 6.43 to 6.49 and will not be repeated here. We now ask for the current resulting from the fluid motion. We will assume that the rods are sufficiently dilute that the current dipoles do not interact, and proceed in a manner analogous to that used in deriving the polarization vector $\hat{P}$ from a number of non-interacting little dipoles $\hat{p}$ [20]. The problem is sketched in Fig. 6.8.

For a current line dipole $I_\Delta$, the potential in cylindrical coordinates is given by

$$\phi = \frac{I_\Delta}{2\pi \sigma r} \cos \theta$$  \hspace{1cm} (6.64)

Equating eqs. 6.63 and 6.64 we have

$$F = \frac{I_\Delta}{2\pi \sigma_0}$$  \hspace{1cm} (6.65)

Substituting eq. 6.43 in eq. 6.65 yields in eq. 6.45 for $F$ yields

Section 6.3.3
Figure 6.8 Current dipoles induced by convection of charge in the mobile region of the double layer.
\[ I_\Delta = \frac{2\pi \sigma_m a^2 \sigma \hat{V}_d}{a \sigma \theta + |\sigma_m| \mu} \]  
(6.66)

We require that

\[ \nabla \cdot (J_f + \mathcal{J}) = 0 \]  
(6.67)

\[ J_f + \mathcal{J} = J \]

where

- \( J_f \) = conduction current
- \( J \) = total current in circuit
- \( \mathcal{J} = N I \Delta \)

and \( N \) is the number density per unit length of current dipoles. In the cell model

\[ N = \frac{1}{\pi b^2} \]  
(6.68)

Further, because we have constrained the macroscopic potential gradient

\[ \frac{\partial V}{\partial z} = 0, \]

the macroscopic conduction current \( J_f = 0 \). Hence

\[ J = N I \Delta = \frac{2\sigma_m a^2 \sigma \hat{V}_d}{b^2 (a \sigma \theta + |\sigma_m| \mu)} \]

\[ = \frac{-4 u \sigma_m a \sigma \phi}{b^2 (a \sigma \theta + |\sigma_m| \mu)} \left( 1 + \frac{\epsilon \tau \sigma_m}{\eta (a \sigma \theta + |\sigma_m| \mu)} + 2 \frac{d}{a} G_1 \ln \frac{b}{a} \right) \]  
(6.69)

where eq. 6.49 has been used for \( \hat{V}_d \). Note that here we are required to keep terms that are first order in \( d/a \).

Section 6.3.3
To complete the derivation of $k_{21}$, we must evaluate the drag on the cylinder. From eqs. 6.27 and 6.43c we have

$$f_z = \frac{4\pi a}{a} = \frac{2\pi a}{a} \left( 2u_o (1 + \frac{a^*}{b^*}) + \frac{c}{d}(1 - \frac{a^*}{b^*}) \right) \left( 1 + \frac{a^*}{b^*} \right)^{(\ln \frac{b}{a} - 1) / \left( \frac{b^*}{a} + a^* \right)}$$  \hspace{1cm} (6.70)

Substituting eq. 6.49 for $\frac{c}{d}$ in eq. 6.70 yields, after some manipulation

$$\frac{a}{\Delta}(P - \Delta) = -\frac{f_z}{b^2}$$

(6.71)

$$= -\frac{4\pi u_o}{b^2} \left[ \frac{\epsilon c \sigma_m}{\sigma_m |a| + \frac{\sigma_m}{a}} + 2 \frac{d}{a} \frac{b^* - a^*}{b^* + a^*} \right]
\left[ \frac{\epsilon c \sigma_m}{\sigma_m |a| + \frac{\sigma_m}{a}} + 2 \frac{d}{a} \ln \frac{b}{a} \right]
\left[ \ln \frac{b}{a} - \frac{1}{2} \frac{b^* - a^*}{b^* + a^*} \right]$$

Dividing eq. 6.69 by 6.71 gives

$$k_{21} = \frac{\epsilon c}{a \Delta(Z - \Delta)}$$

(6.72)

$$= \frac{\sigma_m d}{\epsilon c \sigma_m (b^* - a^*)}
\frac{1}{1 + \frac{\epsilon c \sigma_m}{\sigma_m |a| + \frac{\sigma_m}{a}} + 2 \frac{d}{a} \frac{b^* - a^*}{b^* + a^*} (1 + \frac{\sigma_m |a|}{a_o})}$$

With $\sigma_m = \epsilon c/d$ we have

$$k_{21} = \frac{\epsilon c (b^* - a^*)}{\epsilon c \sigma_m (b^* - a^*)}
\frac{1}{1 + \frac{\epsilon c \sigma_m}{\sigma_m |a| + \frac{\sigma_m}{a}} + 2 \frac{d}{a} \frac{b^* - a^*}{b^* + a^*} (1 + \frac{\sigma_m |a|}{a_o})}$$  \hspace{1cm} (6.73)
We note that the expressions for \( k_{21} \) and \( k_{12} \) are identical as required by the Onsager relations [2]. This implies that the order of approximation used in deriving \( k_{12} \) was the same as that used to derive \( k_{21} \).

6.3.4 Derivation of \( k_{22} \)

To complete the \( k_{ij} \) we must find an expression for the current \( J \) that flows in response to an applied \( \frac{\partial V}{\partial z} \) when the macroscopic fluid pressure gradient \( \frac{\partial}{\partial z}(P - \Delta \pi) \) is set to zero. With an applied \( \frac{\partial V}{\partial z} \) the potential takes the form

\[
\phi = -E_o r \cos \theta + \frac{F}{r} \cos \theta
\]

(6.74)

The derivation proceeds exactly as for \( k_{12} \) in eqs. 6.54 through 6.62. Hence, from eq. 6.55

\[
F = a^2 \left[ \frac{\sigma_m \hat{v}_d^d - E_o (a\sigma_o - |\sigma_m|\mu)}{a\sigma_o + |\sigma_m|\mu} \right]
\]

(6.75)

Eqs. 6.59 and 6.50 can be combined to express \( \hat{v}_d^d \) as a function of the applied electric field \( E_o \)

\[
\hat{v}_d^d = \frac{2\varepsilon \varepsilon_0 E_o}{n\sigma_o + |\sigma_m|\mu + 2 \frac{d}{a^*} (b^* - a^*) (1 + \frac{|\sigma_m|\mu}{a\sigma_o})}
\]

(6.76)

Section 6.3.4
To complete the derivation of $k_{22}$ we use an approach that parallels the approach used by Maxwell [21] in determining the conductivity of a heterogeneous medium. While Maxwell worked with spheres, we shall continue here in cylindrical coordinates.

In a cylindrical region of radius $b$ we have $n$ little cylinders of radius $a$ and conductivity $\sigma_i$, as shown in Fig. 6.9. The bathing medium has conductivity $\sigma_o$. We would like to determine the effective conductivity of the mixture in the cylinder of radius $b$ when placed in a uniform field $E_o$.

We first solve the field problem for each little cylinder assuming that the little cylinders do not interact. The potentials inside and outside the cylinder of radius $a$ are given by

$$\phi_o = -E_o r \cos \theta + \frac{G}{r} \cos \theta$$

$$\phi_i = -H r \cos \theta$$

With the boundary conditions that $\phi$ and $J$ be continuous at $r=a$ we have

$$G = a^2 \left( \frac{\sigma_i - \sigma_o}{\sigma_i + \sigma_o} \right) E_o$$

$$H = -\frac{2\sigma_o}{\sigma_i + \sigma_o} E_o$$

Under the assumption of noninteracting dipoles, the potential $\phi'$ for $r>b$ away from the little cylinders is
Figure 6.9 Maxwell model to determine the effective conductivity of a heterogeneous material.
\[ \phi' = -E_0 r \cos \theta + \frac{nG}{r} \cos \theta \]  

(6.79)

where we have simply added the dipole terms in a manner analogous to that used in deriving \( k_{21} \). With the density of little cylinders per unit length defined as

\[ \bar{v}_s = \frac{n \pi a^2}{\pi b^2} \quad \rightarrow \quad n = \frac{b^2 v_s}{a^2} \]  

(6.80)

we have

\[ \phi' = -E_0 r \cos \theta + \frac{b^2 v_s G}{a^2} \frac{r}{r} \cos \theta \]  

(6.81)

If we were to treat the large cylinder of radius \( b \) as a uniform conductor with conductivity \( \sigma' \) placed in a uniform field \( E_0 \), the potential \( \phi' \) for \( r > b \) would be by analogy to eqs. 6.77 and 6.78,

\[ \phi' = -E_0 r \cos \theta + \left( \frac{\sigma' - \sigma_o}{\sigma' + \sigma_o} \right) \frac{E_0 b^2}{r} \cos \theta \]  

(6.82)

Equating eqs. 6.81 and 6.82 yields

\[ \frac{\bar{v}_s G}{a^2} = E_o \left( \frac{\sigma' - \sigma_o}{\sigma' + \sigma_o} \right) \]

(6.83)

With \( G \) given by eq. 6.78a, we could solve for \( \sigma' \) in terms of \( \bar{v}_s \), \( \sigma_o \), \( \sigma_i \) and geometry.
The problem here is slightly different than the classical problem solved by Maxwell. Instead of little conducting cylinders we have insulating cylinders with a boundary condition that balances normal conduction currents in the bulk with current carried along the surface of the cylinders by conduction and convection of charge in the mobile region of the double layer. Hence, instead of $G$ from eq. 6.78, we use $F$ from eq. 6.75 in eq. 6.83 to arrive at the effective conductivity $\sigma'$. We take the solid content of the cylindrical assemblage $\nu_s = (a/b)^2$. Making these substitutions in eq. 6.83, and taking $\nu_d^d$ from eq. 6.76, we have

\[
E_o \left[ \frac{\sigma' - \sigma_o}{\sigma' + \sigma_o} \right]
\]

(6.84)

\[
= E_o \frac{a^2}{b^2} \left\{ -1 + \frac{\varepsilon \sigma_m}{\varepsilon \sigma_o} + \frac{\sigma_m \mu}{a \sigma_o} - 2 \frac{d}{a} \left( \frac{b^* - a^*}{b^* + a^*} \right) \left( 1 - \frac{\sigma_m \mu}{a \sigma_o} \right) \right\} \left( 1 + \frac{\varepsilon \sigma_m}{\varepsilon \sigma_o} + \frac{\sigma_m \mu}{a \sigma_o} + 2 \frac{d}{a} \left( \frac{b^* - a^*}{b^* + a^*} \right) \left( 1 + \frac{\sigma_m \mu}{a \sigma_o} \right) \right)
\]

Solving for $\sigma'$ gives

\[
\sigma' = \sigma_o \left( 1 - \frac{a}{1 + a} \right)
\]

(6.85)

where

\[
a = \frac{a^2}{b^2} \left\{ -1 + \frac{\varepsilon \sigma_m}{\varepsilon \sigma_o} + \frac{\sigma_m \mu}{a \sigma_o} - 2 \frac{d}{a} \left( \frac{b^* - a^*}{b^* + a^*} \right) \left( 1 - \frac{\sigma_m \mu}{a \sigma_o} \right) \right\} \left( 1 + \frac{\varepsilon \sigma_m}{\varepsilon \sigma_o} + \frac{\sigma_m \mu}{a \sigma_o} + 2 \frac{d}{a} \left( \frac{b^* - a^*}{b^* + a^*} \right) \left( 1 + \frac{\sigma_m \mu}{a \sigma_o} \right) \right)
\]

(6.86)

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The current $J$ that flows through the region for an applied macroscopic $\frac{\partial V}{\partial z}$ is then

$$J = \sigma' E_0 = -\sigma' \frac{\partial V}{\partial z} \tag{6.87}$$

Hence,

$$k_{22} = \sigma_o \left( \frac{1 - a}{1 + a} \right) \tag{6.88}$$

This completes the derivation of the $k_{ij}$ for flow perpendicular to the cylinder axis. In order to determine the $k_{ij}$ for a random matrix, we require the $k_{ij}$ for flow parallel to the cylinder axis.

6.4 Summary of $k_{ij}$ for Axial Flow

The phenomenological coefficients for axial flow were derived by Lee [16]. Lee determined the $L_{ij}$ coefficients relating macroscopic flows to macroscopic differences in potentials. The $k_{ij}$ relate the flows to gradients in potentials. Hence, the $L_{ij}$ are related to the $k_{ij}$ by the sample thickness for linear gradients in the potentials. In his derivation, Lee used a different sign convention for the $L_{ij}$ than that used in eq. 6.1. Additionally, Lee used the Mackie and Meares [22] tortuosity factor to relate ion mobilities in the tissue to ion mobilities in free solution. The Mackie and Meares correction factor was derived from a statistical model for the diffusion of solutes in a polymer matrix under the assumption that the solute mobilities in the fluid phase of the matrix are equal to their values in free solution. The relationship between the effective mobility in the matrix and the
mobility in free solution results from considering the extra distance traveled by the solute in finding its way around the solid constituents that form the matrix. Hence, the correction factor is based solely on geometrical considerations. In a micromodel, the effects of the geometry on measurable macroscopic properties of the matrix are included directly in the model. Hence, the use of the Mackie and Meares correction factor in a micromodel is inappropriate, and amounts to double counting. For these reasons, the $k_{ij}$ for axial flow will be reviewed here briefly. In the axial flow model, it is much simpler to derive the $k_{ij}$ for the general case of a diffuse double layer. Since the $k_{ij}$ for perpendicular flow were derived using the Helmholtz approximation, we must use a similar limit for the axial flow coefficients.

We begin with the Navier Stokes equation in the creep flow limit (eq. 6.6), including the the electrical stress tensor $T^e$. We are now interested in axial flow, and will relate macroscopic fluid pressure gradients $\frac{3}{aZ}(P - \Delta \pi)$ and potential gradients $\frac{3V}{aZ}$ to the average fluid flow $U$ and the average current density $J$ in the axial direction. Since we assume that there are no macroscopic gradients in the ionic concentration, the $z$ directed gradient in the osmotic pressure $\Delta \pi$ is zero. However, we include the osmotic pressure in the fluid pressure to be consistent with eqs. 6.1. The comments made in section 6.2 concerning the equilibrium ionic distribution and the fluid pressure are applicable here as well. The $z$ component of eq. 6.6 can then be written as

$$\frac{3}{aZ}(P - \Delta \pi) = \eta \frac{1}{r} \frac{3}{aR} \left( r \frac{3}{aR} v_z(r) \right) + \frac{1}{r} \frac{3}{aR} \left( r_c \frac{3\psi}{\theta} \frac{3V}{aZ} \right)$$

(6.89)

where $\psi$ represents the potential in the double layer region, and $v_z(r)$

Section 6.4
is the local $z$ directed fluid velocity that in general varies as a function of $r$.

Eq. 6.89 can be integrated with respect to $r$ from the outer cell boundary at $r = b$ to any radial position inside the cell. Because of the symmetry at the outer boundary of the cell, the radial derivative of the fluid velocity and the derivative of the double layer potential $\psi$ must be zero at $r = b$. At the surface of the solid charged cylinder ($r = a$), the no-slip condition requires that the axial velocity $v_z(a) = 0$. The double layer potential $\psi(a)$ at the surface of the cylinder is defined as the zeta potential, $\zeta$. The first integration then results in

$$\frac{1}{2} \frac{d}{dz} (P - \Delta \pi) (r^2 - b^2) = \eta r \frac{\partial v_z}{\partial r} + \varepsilon \frac{\partial \psi}{\partial r} \frac{\partial V}{\partial z}$$

(6.90)

Eq. 6.90 is integrated a second time from the cylinder surface $r = a$ to an arbitrary point in the cell volume to yield a relation for the local velocity $v_z(r)$ as a function of the gradient in the fluid pressure $(P - \Delta \pi)$ and the gradient in the electrical potential $V$:

$$v_z(r) = \frac{1}{4\pi} \frac{d}{dz} (P - \Delta \pi) \left( r^2 - a^2 - 2b^2 \ln \frac{b}{a} \right)$$

$$+ \frac{\varepsilon}{\eta} \frac{dV}{dz} \left( \zeta - \psi(r) \right)$$

(6.91)

The phenomenological coefficients $k_{11}$ and $k_{12}$ relate the average fluid velocity $U$ to the gradients in fluid pressure and electrical potential. To determine the average velocity $U$, $v_z(r)$ must be averaged over the cell cross sectional area.
\[ U = \frac{2}{b^2} \int_a^b v_z(r) \, rdr = \]
\[ -\frac{1}{8\pi b^2} \frac{\partial}{\partial z} \left( r - \Delta r \right) \left\{ 4b^* \ln \frac{b}{a} - 3b^* + 4a^2 b^* - a^* \right\} \quad (6.92) \]
\[ + \frac{\varepsilon \kappa}{\eta} \left( 1 - \frac{a^2}{b^2} \right) \frac{\partial V}{\partial z} - \frac{2\varepsilon}{\eta b^2} \frac{\partial V}{\partial z} a \int_a^b \psi(r) \, rdr \]

From eq. 6.92, it is clear that \( k_{11} \) is
\[ k_{11} = \frac{1}{8\pi b^2} \left\{ 4b^* \ln \frac{b}{a} - 3b^* + 4a^2 b^* - a^* \right\} \quad (6.93) \]
where we note that \( k_{11} > 0 \) for \( b > a \). In order to evaluate \( k_{12} \), we must determine an expression for the double layer potential \( \psi(r) \). For the Helmholtz approximation in cylindrical coordinates, the double layer potential can be expressed as
\[ \psi(r) = \begin{cases} 
\zeta \left( \ln \frac{r}{a+d} \right) & a < r < a+d \\
\ln \frac{a}{a+d} & \\
0 & a+d < r 
\end{cases} \quad (6.94) \]

Using eq. 6.94 for \( \psi \), the integral in eq. 6.92 can be evaluated, and \( k_{12} \) can be shown to be
\[ k_{12} = \frac{\varepsilon \kappa}{\eta} \left( 1 - \frac{a^2}{b^2} - \frac{1}{2} \frac{d}{a} \frac{a^2}{b^2} \right) \quad (6.95) \]

The remaining \( k_{ij} \) can be determined by considering current flow in Section 6.4.
response to an applied fluid pressure gradient and an applied potential gradient. The fluid velocity profile resulting from an applied fluid pressure gradient with the potential gradient constrained to zero can be evaluated from eq. 6.91. The current density \( J(r) \) carried by this fluid velocity is

\[
J(r) = \rho_f(r) v_z(r) \quad (6.96)
\]

The average current density can be determined by averaging the total current over the cell cross section. Hence,

\[
J = \frac{2}{b^2} \int_a^b \rho_f(r) v_z(r) \, r \, dr \quad (6.97)
\]

Since we have modeled the double layer as a Helmholtz capacitor, all of the mobile double layer charge is located one Debye length into the fluid phase, at \( r = a + d \). Hence, \( \rho_f \) can be represented as an impulse in charge of magnitude \(-\sigma_m(a/a+d)\) located at \( r = a + d \). The integral in eq. 6.97 can be evaluated in a straightforward manner to show

\[
k_{21} = \frac{\varepsilon \kappa}{\eta} \left[ 1 - \frac{a^2}{b^2} - \frac{1}{2} \frac{d}{a} \frac{a^2}{b^2} \right] \quad (6.98)
\]

The equivalence of \( k_{12} \) and \( k_{21} \) shows that the same order of approximation has been used in the derivation.

To complete the axial flow \( k_{ij} \) we must determine the average current that would flow in response to a gradient in the macroscopic potential \( V \) when the fluid pressure gradient is constrained to zero. From eq. 6.92 it is clear that fluid flow results in response to an
applied potential gradient, in the absence of fluid pressure gradients. Hence, the current that would flow in response to an applied potential gradient will have both convective and conductive terms. The convective term can be determined as in eq. 6.97, were \( v_z(r) \) can be evaluated from eq. 6.91 with the fluid pressure gradient constrained to zero, and \( \rho_f(r) \) is the same charge singularity used in determining \( k_{21} \). The average convective current can be shown to be

\[
J_{\text{conv}} = -2 \frac{a^2}{b^2} \left( \frac{\varepsilon \sigma_m}{\eta a} \right) \tag{6.99}
\]

The average conduction current can be determined from

\[
J_{\text{cond}} = -\frac{2}{b^2} \int_a^b \sigma(r) \frac{\partial V}{\partial z} r dr \tag{6.100}
\]

where \( \sigma(r) \) is the spatially varying conductivity of the fluid. In the Helmholtz approximation of the double layer, and for a mono-monovalent electrolyte, this spatially varying conductivity is given by

\[
\sigma(r) = F c_0 (\mu_+ + \mu_-) + \left( \frac{|\sigma_m| a\mu}{a + d} \right) \delta(r - a - d) \tag{6.101}
\]

where

- \( F \) = Faraday's constant
- \( \mu_{\pm} \) = ionic mobilities
- \( c_0 \) = bulk concentration
- \( \mu \) = mobility of the counterion
- \( \delta \) = delta function = 1 when its argument is 0, 0 otherwise

We note that in this approximation, the effect of the increased ion concentrations in the double layer on the conductivity is included.
through the singularity in the conductivity at the outer edge of the Helmholtz plate. Using eq. 6.101 in eq. 6.100 yields

$$J_{\text{cond}} = - \left[ \sigma_o \left( 1 - \frac{a^2}{b^2} \right) + \frac{2|\sigma_m|\mu a}{b^2} \right] \frac{aV}{az} \quad (6.102)$$

combining eqs. 6.99 and 6.102 and dividing by the macroscopic potential gradient yields

$$k_{22} = \sigma_o \left[ \left( 1 - \frac{a^2}{b^2} \right) + 2 \frac{a^2}{b^2} \left( \frac{\epsilon \sigma_m}{\eta a \sigma_o} + \frac{|\sigma_m|\mu}{a \sigma_o} \right) \right] \quad (6.103)$$

This completes the derivation of the $k_{ij}$ for the axial flow case.

6.5 Structural Parameters of the Model

The $k_{ij}$ for a randomly oriented assemblage of cylinders can be determined by taking a weighted average of the $k_{ij}$ coefficients developed in sections 6.4 and 6.5. It is reasonable to expect this model to apply to a monodisperse solution of charged, rod like macromolecules where the Debye length is small compared to the radius of the rod. Unfortunately, there are few situations where these conditions apply. Under appropriate circumstances it may be possible to meet these conditions in collagen membranes or in proteoglycan gels. However, the problem of determining the appropriate structural length to equate with the rod radius $a$ remains.

In spite of the fact that proteoglycans account for only - 20% of the solid phase of the tissue, there is much experimental evidence to suggest that the proteoglycans play a major role in restricting fluid
flow through the tissue. Experiments by Maroudas [23,24] linking decreased permeability with increased proteoglycan content tend to support this view. Similarly, Lee [16] showed that increasing electrolyte ionic strength at constant strain (implying constant mechanical configuration) increased tissue permeability markedly. It therefore seems appropriate to focus on the proteoglycans as the flow limiting component in cartilage.

We can approach the question of which proteoglycan structural dimension to use in the cell model by computing the charge density from data on proteoglycans and proteoglycan aggregates available in the literature. We can compare the computed charge density to the measured charge density reported for cartilage. This will help determine the solution domain available to the charged GAG chains.

Each proteoglycan monomer is composed of ~ 100 chondroitin sulfate (CS) chains and ~ 50 keratan sulfate (KS) chains. The CS chains have ~ 25 - 30 disaccharide repeat units, with ~ 2 charge groups per repeat unit. The KS chains have ~ 13 disaccharide repeat units with ~ 1 charge group per repeat unit [25]. Summing up all the charge groups gives ~ 5.6 - 6.6x10^3 charge groups per proteoglycan monomer. From the dimensions of the monomer given in Fig. 6.10 (radius ~ 40 nm and length of ~ 350 nm), we can calculate the effective monomer volume as 1.76x10^-18 dm^3. If we assume that the charge on the monomer is distributed over this volume, we get a charge density of 6 - 7 mmole per liter. Maroudas has reported values of cartilage fixed charge density in the range of 150 mmole per liter [26]. The proteoglycan aggregates are clearly more tightly packed in cartilage than in free solution.

Section 6.5
Figure 6.10 Model of the proteoglycan aggregate: PG - proteoglycan; HA - hyaluronic acid; CS - chondroitin sulfate; KS - keratan sulfate (from Muir [ ])

PG mol. wt $2.5 \times 10^6$
HA mol. wt $0.5 \times 10^6$

CS and KS chains

Length of PG 300-400 nm
40 nm

20-50 nm

1200 nm length of HA
If we consider the charge as being distributed over the effective volume occupied by the GAGs alone, we get a charge density in close agreement with the charge density measured by Maroudas. For example, if we neglect the KS chains and divided the ~350 nm proteoglycan monomer length by ~100 chains, we get a domain for each GAG chain of ~3.5 nm. Taking this as the diameter of a cylinder ~40 nm long yields a domain volume of ~3.85x10^{-22} dm^3 per chain. With ~60 charge groups per chain we have 9.6x10^{-18} coulombs per chain. Dividing chain charge by chain volume gives 2.3x10^4 coulombs per liter = 0.25 mole per liter, which is close to the 0.15 mole per liter reported.

These calculations imply that the proteoglycan aggregates are so tightly packed in cartilage that the GAG chains are approximately uniformly distributed over the volume throughout the tissue, approximately as close together as they are on the proteoglycan monomer. This argues strongly in favor of using the radius of a single GAG chain as the effective radius of the cylinder in the micromodel. This results in a rod radius of ~1 nm. Unfortunately, this dimension is not much smaller than the Debye length in cartilage and the assumptions concerning the ratios of the structural length scales to the Debye length do not strictly apply. Nevertheless, the trends predicted by the model can serve as a thought model for transport in charged tissues and membranes.

Since the fluid volume fraction of cartilage is approximately 0.8, the ratio of (a/b)^2 must equal the solid volume fraction of 0.2. This gives a cell radius b of approximately 2.2 nm. The surface charge density used in the model must be consistent with volume charge.

Section 6.5
densities reported in the literature. Hence, the surface charge density can be determined from reported volume charge densities in the literature, the rod radius $a$ and the cell radius $b$ as

$$\rho_m = \frac{2a\sigma_m}{F(b^2 - a^2)}$$

$\sigma_m = \frac{F\rho_m(b^2 - a^2)}{2a}$

(6.104)

where $\sigma_m$ is expressed as coulombs per square meter, $\rho_m$ is expressed as moles per liter, and $F$ is the Faraday constant. Using a charge density of 0.15 M, a value of $-0.03$ C/m$^2$ is obtained.

6.6 Results of Model

Since the phenomenological coefficients determined in sections 6.4 and 6.5 are in closed form, the $k_{ij}$ for a random assemblage of charged cylinders can be evaluated quite simply. A weighted average of 1/3 of the axial flow $k_{ij}$ and 2/3 of the perpendicular flow $k_{ij}$ was used. A listing of the computer program used to calculate the $k_{ij}$ coefficients can be found in Appendix F. We note that the model requires that four values be specified. These are: the concentration of the external bath $c_0$, the initial fractional volume of water $\nu_w^0$, the solid rod radius $a$, and the surface charge density $\sigma_m$. The values for the solid rod radius and the surface charge density were estimated in section 6.5. The water volume fraction of cartilage used in Chapter V was 0.8 [27]. The concentration of the external bath was assumed to be 0.15 M. These values and the values of the derived parameters are summarized in Table 6.1. The $k_{ij}$ were computed as a function of compressive strain for these

Section 6.6
Input Parameters:

\[ a = 1 \text{ nm} \]
\[ \sigma_m = 0.03 \text{ C/m}^2 \]
\[ \nu_w^0 = 0.8 \]
\[ c_o = 0.15 \text{ M} \]

Physical Constants:

\[ \varepsilon = 8.85 \times 10^{-10} \text{ F/m} \]
\[ \mu_+ = 5.19 \times 10^{-8} \text{ m}^2/\text{V} \cdot \text{s} \]
\[ \mu_- = 7.91 \times 10^{-8} \text{ m}^2/\text{V} \cdot \text{s} \]
\[ F = 96,500 \text{ C/mole} \]
\[ \frac{RT}{F} = 25 \text{ mV} \]

Derived Constants:

\[ d = \left( \frac{\varepsilon RT}{2F^2c_o} \right)^{1/2} = 0.87 \text{ nm} \]
\[ \zeta = \frac{\sigma_md}{\varepsilon} = 29.5 \text{ mV} \]
\[ b(\varepsilon=0) = \left( \frac{a^2}{1 - \frac{c_o}{\nu_w^0}} \right)^{1/2} = 2.24 \text{ nm} \]
parameter values. The results are shown in Figs. 6.11 - 6.13. Figs 6.12 and 6.13 also show the $k_{12}$ and $k_{22}$ obtained at different surface charge densities superimposed on the plots determined for the parameter values of Table 6.1. Since $k_{11}$ is independent of charge density, Fig 6.11 results for all values of the charge density.

The model predicts values for each of the coupling coefficients that are in line with the order of magnitude of values reported in the literature. For reference, the value of $-1 \times 10^{-15}$ m$^4$/N·s was used in Chapter V for the Darcy permeability. The value for $k_{12}/k_{22}$ used in computing the streaming potential in section 6.1 was $-4 \times 10^{-8}$. The values of $k_{12}$ and $k_{22}$ in Figs. 6.12 and 6.13 are reasonably consistent with this value. Lee measured the strain dependence of the effective conductivity of cartilage in 0.15 M NaCl [16]. Measured values of conductivity were in the range 0.8 mho/m. His data is shown in Fig. 6.14. The value predicted by the model is a factor of 2 - 3 larger. However, given the assumptions of the model and the questionable validity of those assumptions to the real tissue, the model does surprising well at predicting the values of the $k_{ij}$ for parameter values appropriate to cartilage. Lee found that the conductance initially increased with increasing strain, plateaued in the 25% - 30% strain region and monotonically decreased with additional increase in strain. Similar bimodal behavior was observed by Jakubovic et al [28] in measurements of the effective conductivity of phenolsulfonic acid ion exchange resins as a function of water content. A plot of their data is shown in Fig. 6.15.

The microscopic cell model shows an initial rise in the effective
Figure 6.11 $k_{11}$ determined from micromodel for $a = 1$ mm, $\phi = 0.8$ and $c_0 = 0.15$ M.

$\sigma'_{11} \times 10^{15} \text{ N/m}^2$ vs. compressive strain.
Figure 6.12 $k_{12}$ (or $k_{21}$) determined from micromodel as a function of surface charge for $a = 1$ nm, $\nu_w = 0.8$ and $c_o = 0.15$ M.
Figure 6.13 $k_{22}$ determined from micromodel as a function of surface charge for $a = 1$ nm, $\nu_w = 0.8$ and $c_o = 0.15$ M.
Figure 6.14 The measured dependence of the effective conductivity of cartilage with strain. (From Lee [16]).
Figure 6.15 The measured dependence of the effective conductivity of phenosulfonic acid resin rods as a function of the solid resin volume fraction. (From Jakubovic [26]).
conductivity $k_{22}$ that is in basic agreement with the increase in the effective conductivity seen in the experimental results of Figs. 6.14 and 6.15 for a cartilage surface charge density of 0.03 C/m$^2$. The ability of the micromodel to predict this early rise in $k_{22}$ for reasonable values of the model parameters without introducing any ad hoc assumptions about ionic mobilities represents a major success of the modeling approach. However, the model does not predict the maximum in the effective conductivity nor the eventual monotonic decrease in $k_{22}$. This failure can be understood by considering the assumptions of the model. The Helmholtz model of the double layer assumes that all of the charge in the mobile region of the double layer is located one Debye length from the surface of the charged cylinder. This amounts to there being a singularity in charge located at $r = a + d$. In considering current flow in the fluid phase of the tissue, we accounted for the effect of the singularity in ionic concentrations by including a spatial singularity in the conductivity of the fluid. The conductance of the singular region is unaffected by straining the sample. However, the extent of the bulk conductivity region decreases as strain increases. Hence, more of the volume is occupied by the surface conducting region, and the parallel combination of the conductances determining the overall effective conductivity of the matrix increases as strain increases. However, because the spatially singular region is unaffected by strain, the model predicts a finite conductivity even when 100% of the fluid has been squeezed out of the tissue. This is clearly unreasonable since logic dictates that an insulating solid with no fluid content should have an effective conductivity of zero. This also explains the dependence of the $k_{22} -$ strain relation on the value of the cylinder

Section 6.6
surface charge, since the magnitude of the spatial singularity in conductivity is directly proportional to the magnitude of the surface charge. Also, as strain increases and the solid cylinders get closer together, the ionic mobilities would decrease due to enhanced frictional interactions between the ions, and between the ions and the solid cylinder. This effect is not included in the model, but would eventually cause the conductivity to decrease as strain increased. Hence, the model as posed is not capable of predicting the monotonic decrease in the effective conductivity observed at higher strains.

In order to successfully describe the strain dependence of $k_{22}$, a model accounting for electrokinetic coupling in the bulk must be derived. Such a model would apply when the double layer space charge region extends into the region of bulk fluid flow. In this development the electrical force density would necessarily be included in the Navier Stokes equation for the fluid flow. Similarly, the spatial variation of the ionic concentrations would be coupled to the fluid flow in the bulk regions. Perturbation models have been developed that include this two way coupling for single particles in electrolytes of infinite extent [29]. However, these developments were primarily concerned with electrophoresis and only determined the $k_{12}$ type of coupling. The challenge is to incorporate similar perturbation formulations to describe the electrokinetic coupling for systems of particles that form a single cohesive unit like a tissue or a membrane.


Bibliography VI
APPENDIX A

TRANSIENT STRESS DATA

The normalized transient stress data are shown plotted against normalized time for each sample and each concentration transition. Time has been normalized to a 600 \( \mu \text{m} \) sample reference thickness.
Figure A.1 Normalized stress transient - sample SP115, c = 0.005 → 0.1 M NaCl.
SAMPLE: SP116

C: .005 -> .1 M

σ₀ = 76.9 kPa

Figure A.2 Normalized stress transient - sample SP116, c = 0.005 -> 0.1 M NaCl.
Figure A.3 Normalized stress transient - sample SP117, c = 0.005 → 0.1 M NaCl.
Figure A.4. Normalized stress transient – sample SP118, c = 0.005 → 0.1 M NaCl.
Figure A.5 Normalized stress transient - sample SP19, c = 0.005 → 0.1 M NaCl.
Figure A.6. Normalized stress transient - sample SP133, C = 0.005 → 0.1 M NaCl.

Sample: SP133

C: 0.005 → 0.1 M

$\sigma_0 = 77.9$ kPa

Normalized stress $\sigma(t)/\sigma_0$
Sample: SP134

C: 0.005 → 0.1 M

σ₀ = 72.0 kPa

Normalized stress transient – sample SP134, c = 0.005 → 0.1 M NaCl.

Figure A.7
Figure A.8 Normalized stress transient – sample SP115, c = 0.10 → 0.15 M NaCl.
Figure A.9  Normalized stress transient - sample SP116, c = 0.10 → 0.15 M NaCl.
Figure A.10 Normalized stress transient - sample SP117, $c = 0.10 \rightarrow 0.15$ M NaCl.
Figure A.11 Normalized stress transient - sample SP118, c = 0.10 → 0.15 M NaCl.
SAMPLE: SP119

\[ C : 0.1 \rightarrow 0.15 \text{ M} \]

\[ \sigma_0 = 81.3 \text{ kPa} \]

Figure A.12 Normalized stress transient - sample SP119, \( c = 0.10 \rightarrow 0.15 \) M NaCl.
Figure A.13 Normalized stress transient - sample SP134, c = 0.10 \rightarrow 0.15 M NaCl.
SAMPLE: CRN01

C: .01 → .05 M

σ₀ = 17.0 kPa

Figure A.14 Normalized stress transient - sample CRN01, c = 0.01 → 0.05 M NaCl.
Figure A.16 Normalized stress transient - sample CRN07, c = 0.01 → 0.05 M NaCl.
Figure A.18 Normalized stress transient - sample CRN11, c = 0.01 → 0.05 M NaCl.
Figure A.19 Normalized stress transient - sample CRN13, $c = 0.01 \rightarrow 0.05$ M NaCl.
APPENDIX B

SMOOTHING ALGORITHM AND SMOOTHED DATA

The transient experiments for a single transition were combined by averaging the data from all the samples for a particular transition at discrete points in time. Before averaging between specimens, the sampled transient data for a single specimen was first smoothed in order to reduce the effect of sampling noise on the overall specimen average.

The data was smoothed by averaging over adjacent time points with a modified binomial distribution spanning two time intervals and incorporating three discrete points in time. Because the data was sampled asynchronously, more weight is given to the value of the stress that is closer in time. Hence, the smoothed value of the stress at the time increment \( n \), \( \sigma'(n) \), corresponding to the time \( t(n) \), is given by

\[
\sigma'(n) = \frac{1}{2} \left[ \left( \frac{dt_1}{dt_1+dt_2} \right) \sigma(n+1) + \sigma(n) + \left( \frac{dt_2}{dt_1+dt_2} \right) \sigma(n-1) \right]
\]  

(B.1)

where

\[
\begin{align*}
dt_1 &= t(n) - t(n-1) \\
dt_2 &= t(n+1) - t(n)
\end{align*}
\]

and \( n \) is the index into the time vector \( t \) and the stress vector \( \sigma \).

This algorithm is implemented in the following subroutine. The subroutine allows the user to smooth the data within a window between a minimum and maximum value of time. The stress and time vectors are passed to the subroutine SMOOTH, together with the the vector length,
the minimum and maximum value of time for the window and the number of times to successively apply the algorithm to the data. The results of applying this algorithm to the data presented in Appendix A are shown for each sample and each chemical transition in Figs. B.1 - B.38.
subroutine smooth(y, time, npts, tmin, tmax, nsmooth)

subroutine to smooth data taken at random values of
time between tmin and tmax

real y(1), time(1), tmin, tmax
integer npts, nsmooth

do 40 k = 1, nsmooth
   if (time(1).ge.tmin) goto 10

   do 5 i = 2, npts
      nst = i
      yi = y(i-1)
      if (time(i).ge.tmin) goto 20
      continue
   go to 100

   nst = 2
   yi = y(1)
   y(1) = (3.*yi+y(2))/4.

5          do 30 i = nst, npts-1
            if (time(i).gt.tmax) goto 40

            dt1 = time(i) - time(i-1)
            dt2 = time(i+1) - time(i)
            ynew = .5*( dt1*y(i+1)+dt2*yi)/(dt1+dt2) + y(i) )
            yi = y(i)
            y(i) = ynew

30          y(npts) = (yi+3.*y(npts))/4.

40          continue

50          return

100         type *, ' error in smooth: tmin > all time '
            go to 50

end
Figure B.1 Smoothed transient in normalized change in stress - Sample SP115, c = 0.005 → 0.1 M NaCl. Smoothed 10 times.
Figure B.2 Smoothed transient in normalized change in stress - sample SP16, c = 0.005 → 0.1 M HCl. Smoothed 10 times.
Figure B.3 Smoothed transient in normalized change in stress – sample SP117, c = 0.005 → 0.1 M NaCl. Smoothed 50 times.
Figure B.4 Smoothed transient in normalized change in stress - sample SP118, c = 0.005 -> 0.1 M NaCl. Smoothed 10 times.
Figure B.5 Smoothed transient in normalized change in stress - sample SP119, c = 0.005 → 0.1 M NaCl. Smoothed 10 times.
Figure B.6 Smoothed transient in normalized change in stress - sample SP133, c = 0.005 → 0.1 M NaCl. Smoothed 10 times.
Figure B.7  Smoothed transient in normalized change in stress - sample SP134, c = 0.005 → 0.1 M NaCl. Smoothed 10 times.
Figure B.8 Smoothed transient in normalized change in stress - sample SP115, c = 0.10 → 0.15 M NaCl. Smoothed 10 times.
Figure B.9 Smoothed transient in normalized change in stress - sample SP116, $c = 0.10 \rightarrow 0.15$ M NaCl. Smoothed 100 times.
Figure B.10 Smoothed transient in normalized change in stress - sample SP117, c = 0.10 -> 0.15 M NaCl, Smoothed 500 times.
Figure B.11 Smoothed transient in normalized change in stress - sample SP118, c = 0.10 → 0.15 M NaCl. Smoothed 100 times.
SAMPLE: SP119
C: .1 \rightarrow .15 M

Figure B.12 Smoothed transient in normalized change in stress – sample SP119, c = 0.10 \rightarrow 0.15 M NaCl. Smoothed 500 times.
Figure B.13 Smoothed transient in normalized change in stress - sample SP134, c = 0.10 -> 0.15 M NaCl. Smoothed 100 times.
Figure B.14 Smoothed transient in normalized change in stress - sample CRN01, c = 0.01 → 0.05 M NaCl. Smoothed 100 times.
Figure B.15 Smoothed transient in normalized change in stress – sample CRN05, c = 0.01 → 0.05 M NaCl. Smoothed 100 times.
SAMPLE: CRNO7
C: .01 $\rightarrow$ .05 M

Figure B.16 Smoothed transient in normalized change in stress - sample CRNO7, c = 0.01 $\rightarrow$ 0.05 M NaCl. Smoothed 100 times.
Figure B.17 Smoothed transient in normalized change in stress - sample CRN08, c = 0.01 → 0.05 M NaCl. Smoothed 500 times.
Figure B.18 Smoothed transient in normalized change in stress - sample CRN11, c = 0.01 → 0.05 M NaCl. Smoothed 100 times.
Figure B.19 Smoothed transient in normalized change in stress - sample CRN13, c = 0.01 \rightarrow 0.05 M NaCl, Smoothened 100 times.
APPENDIX C

AVERAGING ALGORITHM

The smoothed transient data for each group of concentration transitions was averaged at a specified number of points in time. If the specified point in time did not correspond to one of the sampled times, the stress at the specified time was obtained by linearly interpolating between the stress values corresponding to the two sampled times straddling the specified time. The averaging program then computes the mean and standard deviation at the specified points in time. A listing of the program follows.
program averag

program averages smoothed data files and
computes mean and standard deviation at specified
time points. Since data is sampled asynchronously,
program interpolates between sampled time points
to obtain value at desired time for averaging.

can handle up to 10 data files of 2000 points each
produces averaged data at up to 200 points

real yvec(2000), timobs(2000), yint(10,200), timavg(200)
real stdev(200)
integer avglen(10), navg(200), maxlen
byte filnam(15), cmnt(64,10), prgnam(10)

common /pltav/ nfil,filnam,cmnt,prgnam

type 1000
accept *, tstart,tstop,nptavg

dtavg = (tstop-tstart)/nptavg
time = 0
do 10 i=1,nptavg
time = time + dtavg
10                 timavg(i) = time

nfil = 0
type 1010
accept 1050, filnam
if (filnam(1).eq.' ' ) goto 290
nfil = nfil + 1
open (unit=2,name=filnam,type='OLD',form='UNFORMATTED')
read(2) prgnam
if (prgnam(10).ne.'3' ) goto 2000
read(2) (cmnt(j,nfil), j=1,64)
read(2) tfact, toff

nobs = 1
read(2,end=40) timobs(nobs), yvec(nobs)
nobs = nobs+1
goto 20

40 nobs = nobs-1
c c interpolate
c

avglen(nfil) = 0
nextj = 1

Appendix C
do 250 i=1,nptavg

  do 200 j = nextj, nobs
  if (timobs(j).gt.timavg(i)) goto 210
  continue
  goto 250

  nextj = j+1
  dyobs = yvec(j) - yvec(j-1)
  dtobs = timobs(j) - timobs(j-1)
  yint(nfil,i) = (dyobs/dtobs)*(timavg(i)-timobs(j-1)) + yvec(j-1)
  avglen(nfil) = avglen(nfil) + 1
  continue

  read next file
  close (unit=2)
  goto 15

average data

  do 300 i=1, nptavg
  navg(i) = 0
  stdev(i) = 0.
  300

  sum

  do 310 i = 1, nptavg
  do 310 j = 1, nfil
  if (i.gt.avglen(j)) goto 310
  yvec(i) = yvec(i) + yint(j,i)
  navg(i) = navg(i) + 1
  continue

  find mean

  do 350 i = 1, nptavg
  if (navg(i).eq.0) goto 350
  yvec(i) = yvec(i)/navg(i)
  continue

  find std. dev.

  do 360 i = 1, nptavg
  do 360 j = 1, nfil
  if(i.gt.avglen(j)) goto 360
  ydif = yint(j,i) - yvec(i)
  stdev(i) = stdev(i) + ydif*ydif
  continue

Appendix C
maxlen = 0
do 365 i = 1, nfil
  maxlen = max(maxlen, avglen(i))
  continue
365
  c
  do 370 i = 1, maxlen
  if (navig(i).le.1) goto 380
  stdev(i) = sqrt(stdev(i)/(navig(i)-1))
370
  continue
  goto 390
  c
  maxlen = i-1
380
  c
  call avgplt(timavg, yvec, maxlen, stdev)
  stop
390
  format (' average from t=? to t=? at ?pts: ',$)
1000
  format (' enter filename: ',$)
1050
  format (15a)
  c
2000
  stop 'illegal file'
end
APPENDIX D

ERROR FUNCTION SOLUTION FOR CONCENTRATION

The diffusion equation

\[ \frac{\partial \Delta c}{\partial t} = \frac{4}{\pi^2} \frac{\partial^2 \Delta c}{\partial z^2} \] (D.1)

is to be solved. For convenience, eq. D.1 has been written in terms of the excess concentration \( \Delta c(z, t) = [c(z, t) - c_o] \), where \( c_o \) is the initial concentration. Eq. D.1 is to be solved subject to the boundary conditions

\[ \Delta c(0, t) = \Delta c_o \left( 1 - e^{-t/\tau_s} \right) \] (D.2)

\[ \frac{\partial \Delta c}{\partial z} \bigg|_{z=1, t} = 0 \]

and the initial condition

\[ \Delta c(z, 0) = 0 \] (D.3)

We will solve eq. D.1 by the method of Laplace transforms. The Laplace transform of the concentration difference \( \Delta c \) is defined as

\[ \overline{\Delta c} = \int_0^\infty \Delta c \ e^{-pt} \ dt \] (D.4)

Taking the Laplace transform of eq. D.1 gives
\[
\frac{4}{\pi^2} \frac{\partial^2 \Delta C}{\partial z^2} = p \Delta C
\]  
(D.5)

The transformed boundary conditions are given by

\[
\Delta C(0) = \Delta C_0 \left( \frac{1}{p} - \frac{1}{p + 1/\tau_s} \right)
\]
(D.6)

\[
\left. \frac{\partial \Delta C}{\partial z} \right|_1 = 0
\]

The solution to eq. D.5 satisfying boundary conditions D.6 is

\[
\Delta C(z) = \Delta C_0 \left( \frac{1}{p} - \frac{1}{p + 1/\tau_s} \right) \left[ \frac{\cosh q(z - 1)}{\cosh q} \right]
\]

\[
= \Delta C_0 \left( \frac{1}{p} - \frac{1}{p + 1/\tau_s} \right) \left[ \frac{e^q(z - 1) + e^{-q(z - 1)}}{e^q(1 + e^{-2q})} \right]
\]

\[
= \Delta C_0 \left( \frac{1}{p} - \frac{1}{p + 1/\tau_s} \right) \left[ e^{q(z-2)} + e^{-qz} \right] \sum_{n=0}^{\infty} (-1)^n e^{-2qn}
\]
(D.7)

\[
= \Delta C_0 \left( \frac{1}{p} - \frac{1}{p + 1/\tau_s} \right) \left[ \sum_{n=0}^{\infty} (-1)^n e^{q(z - 2(n+1))} \right.

\left. + \sum_{n=0}^{\infty} (-1)^n e^{-q(z + 2n)} \right]
\]

where \( q \equiv (\pi \sqrt{p})/2 \). From the table of transforms in Carslaw and Jaeger (§'s 8 and 19) [1], we obtain

Appendix D
\[ \Delta c(z, t) = \Delta c_0 \sum_{i=1}^{2} \left\{ \sum_{n=0}^{\infty} (-1)^n \text{erfc} a_i \right. \\
- \frac{1}{2} e^{-t/\tau_s} \sum_{n=0}^{\infty} (-1)^n \left[ \cos \frac{f_1}{\sqrt{\tau_s}} \text{Re} \left( \text{erfc}[a_i - j \sqrt{t/\tau_s}] \right) \\
+ \sin \frac{f_1}{\sqrt{\tau_s}} \text{Im} \left( \text{erfc}[a_i - j \sqrt{t/\tau_s}] \right) \right] \right\} \] (D.8)

where

\[ f_1 = \frac{\pi}{2} \left[ 2(n+1) - z \right] \]
\[ f_2 = \frac{\pi}{2} \left[ 2n + 2 \right] \] (D.9)
\[ a_i = \frac{f_1}{2\sqrt{t}} \]

The relations

\[ \text{erfc} z^* = (\text{erfc} z)^* \]
\[ A + A^* = 2 \text{Re} A \] (D.10)
\[ A - A^* = -2j \text{Im} A \]

were used in writing simplifying eq. D.7. Re and Im have their usual meanings as the real and imaginary parts respectively, and the star (*) denotes the complex conjugate.
BIBLIOGRAPHY - APPENDIX D

APPENDIX E

IMPLEMENTATION OF CRANK - NICOLSON NUMERICAL METHOD

The Crank - Nicolson numerical method outlined in Chapter IV was used to solve the differential equation (eq. 4.1) for the swelling pressure. The Fortran programs that implements this solution method is presented here. The numerical system consists of the main program (SWPRS6) and 8 subroutines. SWPRS6 is responsible for getting input parameters from the user, initializing all variables and performing the main integration loop. In order to solve eq. 4.1 efficiently and accurately for a wide range of $\tau_m/\tau_c$ values, an expanding spatial grid was implemented. The details of how the expanding grid was implemented follow. The time increment was also variable, although the user specified at run time how the time increment was to be varied.

The change in concentration in the tissue begins at the left hand boundary. For early time, changes in swelling pressure are confined to the vicinity of the left hand boundary, and the swelling pressure deep in the tissue remains at its initial value. Hence, for early times, the diffusion of the swelling pressure into the tissue proceeds as if the tissue extended to infinity in the positive z direction. Hence, the right hand boundary has no effect on the solution until the swelling pressure $p$ has had time to change in the vicinity of the boundary.

Since the right hand boundary is unimportant for early time, a finer spatial grid is established for early time that extends from the left hand boundary to a point inside the tissue instead of to the right hand boundary. A pseudo boundary and a pseudo boundary condition are
established at the internal point requiring that the swelling pressure there remain at its initial value. There clearly comes a time when this pseudo boundary condition begins to constrain the solution. To guarantee that this does not affect the solution, the pseudo boundary is moved further towards the actual right hand boundary when the swelling pressure four grid points towards the left hand boundary changes from its initial value. When the result of the next time step makes the swelling pressure at this grid point deviate from the initial swelling pressure by 0.05%, the solution is backed up one time step, the pseudo boundary is moved to the right, and the solution is restarted. When the pseudo boundary coincides with the actual boundary, the correct no flux boundary condition is automatically imposed.

The initial number of spatial increments ($N_{init}$) and the final number of spatial increments ($N_{fin}$) were chosen to be integer powers of two. The size of the final spatial increment is $1/N_{fin}$, while the size of the initial spatial increment was arbitrarily chosen to be $1/(8N_{init})$. Typically, $N_{init}$ was chosen such that $N_{init} = 2N_{fin}$. Hence, the initial spatial resolution was 16 times finer than the final spatial resolution. This increase in resolution was obtained without increasing the number of spatial points used in any calculation and with a minimal amount of computational overhead. Nine of these finer grid points used were initially used, and the pseudo boundary was, therefore, initially located at $1/N_{init}$. When the condition to move the pseudo boundary was reached, the number of grid points was increased by 4, moving the pseudo boundary 4 grid points to the right. This procedure was continued until the pseudo boundary coincided with $x = 0.125$. At this time the number of grid points was $N_{init} + 1$. The next time the condition to move the pseudo
condition to move the pseudo boundary was reached, the size of the spatial increment was doubled, and the number of grid points was set to $N_{\text{init}}/2 + 5$. This put the pseudo boundary at $x = 0.125 + 1/N_{\text{init}}$. The entire procedure was repeated until the pseudo boundary coincided with the real boundary, and the spatial increment coincided with the final spatial increment requested.

SWPRS6 calls the subroutine CRANK once for each time step. CRANK sets up the individual matrices and intermediate results required to determine $p^{n+1}$ from $p^n$. CRANK calls either CONCEX or CNERF to determine the concentration and the derivatives of concentration at each grid point, depending on the value of the normalized time. CONCEX implements the Fourier series solution for the concentration while CNERF implements the error function series solution. Since system routines to determine the required error functions were not available, the routines ERF, ERFC, and CERFC were written to evaluate the error function, complementary error function and complex error function. These routines are based on series approximations found in Abromowitz and Stegun [1]. CRANK calls the subroutines MOD and BETC to determine the material properties $M$ and $B$ at each grid point. After setting up all of the required matrices, CRANK calls TRIDI to perform the required inversion of the tridiagonal matrix. CRANK returns the swelling pressure at the time increment $n+1$ to the main program SWPRS6. To advance another step in time the entire sequence is repeated.
program swprs6

numerical solution for swelling pressure of (z,t) in
response to a change in external bath concentration
with surface displacement held constant
includes influence of M(c) & Bet(c). Solution uses
Crank-Nicholson method, allowing up to 10
different time increments to be used in the solution.
Also allows iterations on time constant ratios keeping all
else constant. Uses mech and chem times with the factor of pi**2.
Also implements variable mesh that automatically grows with time
to final selected mesh. Concentrates on region near x=0 boundary.

____________________________________________________

define storage

____________________________________________________

byte prgnam(10), filnam(11), pflnam(15)
integer norder, nlay, filnum, nruns, ngrid
integer nstep, ncomp(10), nstpst(10)
integer tt, xd, od, dk
real tstop(10), tstart
real cinit, cfin, cinfin, cinint
real dt, dx, dxo, x, rr, taurat, time
real cmref, mrat, minfin, b0, cbref
real rhom, eps0, pi, p0, tausrf, M0
real pvecn(129), pvec0(129), taur(10)
real mdls, dmdls, bet, dbet
logical*1 yesno, filflg
logical tglflg

common /param/ pi,cinint,cinfin,tausrf,nlay
common /modbet/ rhom,cmref,mrat,minfin,cbref,b0,mode
common /cranks/ p0,M0,dxf,tgflg

____________________________________________________

set constants

____________________________________________________

data tt/7/, xd/6/, dk/2/
data prgnam/'S','W','L','P','R','S','.'','V','0','6'/
pi = 3.141592654

____________________________________________________

get parameters from user

Appendix E
c

type  500
accept 513, nstep

type 506

do 10, i = 1, nstep
    type  501, i
    accept 511, tstop(i)
    type  503, i
    accept 515, nstpst(i)
    type  505, i
    accept 513, ncomp(i)

10

type  502
accept 512, nlay

type  509
accept 512, ngrid

type  530
accept 511, cinit

type  535
accept 511, cf in

type  517
accept *, mode

type  507
accept 516, pflnam

open (unit=dk, name=pflnam, type='OLD', form='FORMATTED')


type  508
accept *, eps0
read (dk,*) rhom
read (dk,*) cmref
read (dk,*) mrat
read (dk,*) minfin
read (dk,*) b0
read (dk,*) cb ref


close (unit=dk)

type  544
accept 511, taur f

type  545
filflg = yesno(dum)

if (filflg) goto 20


type  504
accept 514, fnam

type  520
accept 511, taur(1)
nruns = 1


goto 30

20

type  548
accept 512, nruns

type  546
accept 514, fnam

type  547, nruns
accept *, (taur(i), i=1,nruns)

c

format (' enter number of different time step sizes: ','$

501

format (1x, 'enter stop time for interval ',i2, ':(r) ','$

502

format (1x, ' (2**n<128) of space increments? (i): ','$

Appendix E
format  (1x,'enter # of steps to store for interval',i2, >':(i) ',$,)
format  (1x,'name of output file? : ',$)
format  (1x,'enter # of computations per time in interval',i2,':(i) ',$,)
format  (1x,'total number of time increments stored >must not exceed 100')
format  (' enter parameter file name: ',$)
format  (' enter initial strain: ',$)
format  (' initial # of grid points inside .125 (2**n&> >=nlay): ',$,)
format  (g12.3)
format  (g12.3)
format  (i2)
format  (i5)
format  (I1a)
format  (i4)
format  (i5a)
format  (' modes for constitutive laws:'/ 1 - cartilage' >/ 2 - cornea'/ enter mode: ',$)
format  (' ratio of time constants (mech/chem)? (r): ',$,)
format  (' tissue charge density (moles/liter)? (r): ',$,)
format  (' initial salt concentration? (r): ',$,)
format  (' final salt concentration? (r): ',$,)
format  (' enter beta(c=0) for beta constitutive law: ',$)
format  (' enter cref for beta constitutive law: ',$)
format  (' enter M(c=oo) for modulus constitutive law: ',$)
format  (' enter cref for modulus constitutive law: ',$)
format  (' enter ratio of M(c=0) to M(c=oo) >for modulus constitutive law: ',$)
format  (' final norm. swelling pressure will be: ',f5.3)
format  (' enter surface concentration time constant: ',$)
format  (' do you want to run the same parameters for several >different tau ratios? ',$
format  (' enter upto six letter filename.A'/(the ext will be >incremented automatically): ',$)
format  (' enter ',i2,' time constant ratios >(mech/chem): ',$)
format  (' enter number of separate runs to make: ',$

---

calculate internal initial and final concentrations for the given charge density and external concentrations

---

fac = rhom/2.
cinint = -fac + sqrt(fac**2 + cinit**2)
cinfin = -fac + sqrt(fac**2 + cfin**2)
call mod(cinint,MO,dmdl5)
call betc(cinint,bet,dbet)
p0 = M0*eps0 + bet
filnum = 0
open output file and write header

filnum = filnum+1
taurat = taur(filnum)
tgflg = .false.
od = tt
open (unit=dk,name=filnam,type='NEW',form='UNFORMATTED')
write (dk) prgnam
write (dk) eps0,cinit,cfin,rhom,taurat,nlay,ngrid,tausrf,nstep
write (dk) minfin,mrat,cmref,b0,cbref
write (dk) (tstop(i),ncomp(i),nstpst(i), i=1,nstep)
write (dk) mode
write (od,61) prgnam
write (od,62) cinit,cfin, p0

format (/1x,'calculated by ',10a)
format (/1x,' initial concentration: ',1pg10.3,/, ' final
>concentration: ',1pg10.3, '
>pressure: ',1pg10.3/)

call mod(cinin,mxls,dmls)
call betc(cinin,bet,dbet)
type 542, (mdls*eps0+bet)/p0
norder = ngrid + 1

do 70 i=1, norder
pvectn(i) = 1.
pvecto(i) = 1.

calculate n + 1st swelling pressure vector from nth

index = 0
time = 0.
tstart = 0.
dxf = 1.0 / float(nlay)
dxc = 1.0/(8.*ngrid)
nord = 9
do 310 i = 1,nstep
dt = (tstop(i)-tstart)/(ncomp(i)*nstpst(i))
do 300 j = 1, nstpst(i)
do 275 k = 1, ncomp(i)
    rr = dt/(2.*taurat*(pi*dxc)**2)
    if (time=dt/2 .gt. .01) tgflg=.true.
    call crank(time, dt, dxc, rr, nord, pvectn)
    if (abs(dxc-dxf).lt.1e-2) goto 270

Appendix E
if artificial b.c. has constrained solution, backup & change mesh

    if (pvecln(nord-3) .ge. .9995) goto 270
    if (nord.eq.norder) goto 108

add on more layers

    nord = nord + 4
    do 105 nn = 1,nord
         pvecln(nn) = pvecln(nn)
    goto 101

signal terminal that pseudo boundary has been moved

    type *, '**********'
    write (od,551) time, dxc, nord
    write (od,550) (pveclnn(l), l=1,nord)
    type *, '**********'

backup & change mesh

    index = index + 1
    goto (110,110,110,130), index

double mesh size

    do 120, nn=1,(norder-1)/2+1
         pveclnn(nn) = pvecln(2*nn-1)
         pvecln(nn) = pvecln(nn)
    do 125
         mm = (norder-1)/2+2, norder
         pveclnn(mm) = 1.
         pvecln(mm) = 1.
    dxc = 2.*dxc
    nord = (nord-1)/2 + 5
    goto 250

change number of layers from ngrid to nlay

    nrat = ngrid/nlay
    do 140 nn = 1,norder,nrat
         mm = (nn+nrat-1)/nrat
         pveclnn(mm) = pvecln(nn)
    goto 250

write out solution vector after moving pseudo boundary

    type *, '$$$$',
    write (od,551) time, dxc, nord
    write (od,550) (pveclnn(l), l=1,nord)
    type *, '$$$$',
    goto 100
continue with next time increment

do 272 nn = 1, nord
    pvecto(nn) = pvectn(nn)
    time = time + dt
    write (od,552) nruns,filnum
    write (od,551) time, dxc, nord
    write (od,550) (pvectn(l), l=1,nord)
write (dk) dxc,nord
nskp = 1
if ((nord-1)/nskp.1e32 ) goto 300
write (dk) (pvectn(k), k=1,nord,nskp)
tstart = time

format (10(1x,f6.4)/10(1x,f6.4)/10(1x,f6.4))
format (' t = ',g11.4,' current dx = ',g11.4,' nord = > ',i4)
format (' nruns = ',i2,' this run = ',i2)
endfile dk
close (unit=dk)
if (.not.filflg) goto 1000
if (filnum.eq.nrums) goto 1000
do 600 i=1,10
if (filnam(i).eq.'.') goto 610
continue
goto 1000
filnam(i+1) = filnam(i+1)+1
go 35

stop
end
subroutine crank(time, dt, dx, rr, norder, pvect)

implements crank-nicolson method
routine sets up matrices and does the necessary
manipulations to determine p(t+dt) from p(t)

real time, dt, dx, rr, pvect(1), p0, M0
real c, dcdx, dcdt, mdls, dmdls, bet, dbet
real M, dMdc, B, dBdc, dxf
real alpha, gamma, savect(201), dvec(201)
real ofdi1(201), ofdi2(201), diag(201)

logical tgflg
integer norder

common /cranvs/ p0,M0,dxf,tgflg

calculate c(x), dcdt(x), M(x), dMdc(x), B(x) and dBdc(x)
at t=time+dt/2
put intermediate result in save vector and build matrix to invert

if (.not.tgflg) goto 5
call conc(time+dt/2., 0., c, dcdx, dcdt)
goto 10

5
call cncrf(time+dt/2., 0., c, dcdx, dcdt)
call mod(c,mdls,dmdls)
call betc(c,bet,dbet)
M = mdls/M0
dMdc = dmdls/M0
B = bet/p0
dBdc = dbet/p0
alpha = rr*M
gamma = dt*dMdc*dcdt/(2.*M)
savect(1) = pvect(1)*(1.-2.*alpha+gamma) + 2.*alpha*pvect(2)
diag(1) = (1 + 2.*alpha - gamma)
ofdi1(1) = 0.
ofdi2(1) = -2.*alpha
dvec(1) = dt*dcdt*(dBdc - B*dMdc/M)
do 210  
  i = 2,norder-1
  x = float(i-1)*dx
if (.not.tgflg) goto 201
  call conc(time+dt/2., x, c, dcdx, dcdt)
goto 205

201
205

if (.not.tgflg) goto 201
  call conc(time+dt/2., x, c, dcdx, dcdt)
goto 205

205


ofdi2(i) = -alpha
    dvec(i) = dt*dcdt*(dBdc - B*dMdc/M)

i = norder
x = float(i-1)*dx
if (.not.tgflg) goto 212
call conc(time+dt/2., x, c, dcdx, dcdt)
goto 214

212 call onceref(time+dt/2., x, c, dcdx, dcdt)
call mod(c,mdls,dmdls)
call betc(c,bet,dbet)
M = mdls/M0
dMdc = dmdls/M0
B = bet/p0
dBdc = dbet/p0
if ( abs(x-1.).gt. 1e-3 ) goto 215
alpha = rr*M
gamma = dt*dMdc*dcdt/(2.*M)
savect(i) = pvect(i)*(1.+alpha-gamma)
    + 2.*alpha*pvect(i-1)
diag(i) = (1 + 2.*alpha - gamma)
ofdi1(i) = -2.*alpha
ofdi2(i) = 0.
goto 218

use psuedo b.c.

215 savect(i) = pvect(i)
diag(i) = 1.
ofdi1(i) = 0.
ofdi2(i) = 0.

218 dvec(i) = dt*dcdt*(dBdc - B*dMdc/M)
do 220 i = 1, norder
    savect(i) = savect(i) + dvec(i)
find new vector from tridi
    call tridi(ofdi1,diag,ofdi2,savect,pvect,norder)
return
end
subroutine tridi (a, b, c, r, x, norder)

solves tridiagonal matrix equation for unknown vector x
of order norder given the left and right off-diagonal
coefficients (a & b), the diagonal coefficients (b), and
the constant vector r. Solution vector returned in x.

real a(1), b(1), c(1), r(1), x(1), temp
integer norder

a(norder) = a(norder)/b(norder)
r(norder) = r(norder)/b(norder)

do 100 i = 2, norder
   j = norder - i + 2
   k = j-1
   temp = 1./( b(k) - a(j)*c(k) )
   a(k) = a(k)*temp
   r(k) = ( r(k) - c(k)*r(j) )*temp
100

x(1) = r(1)
do 110 i = 2, norder
   x(i) = r(i) - a(i)*x(i-1)
110

return
end
subroutine mod(cin,mmds,dmdls)
real cin, mmds, dmdls, fc
real rhom, cmref, mrat, minfin, cbref, b0
common /modbet/ rhom,cmref,mrat,minfin,cbref,b0,mode

fc = sqrt(cin**2 + rhom*cincin)
goto (5,10), mode

mmds = minfin * (1. + (mrat - 1.)*exp(-fc/cmref))
dmdls = (minfin - mmds) * (cin + rhom/2.)/(cmref*fc)
goto 20

mmds = minfin*(mrat+(1.-mrat)*fc/cmref)
dmdls = minfin*(1.- mrat)*(cin + rhom/2.)/(cmref*fc)

return
end

subroutine betc(cin,bet,dbet)
real cin, bet, dbet, fc
real rhom, cmref, mrat, minfin, cbref, b0
common /modbet/ rhom,cmref,mrat,minfin,cbref,b0,mode

fc = sqrt(cin**2 + rhom*cincin)

bet = b0*exp(-fc/cbref)
dbet = -b0*exp(-fc/cbref)*(cin+rhom/2.)/(cbref*fc)

return
end
subroutine conc(time,x,c,dcdx,dcdt)
  compute concentration for exponential change in boundary concentration using fourier series
  real    time, x, c, dcdx, dcdt
  real    pi, cinint, cinf, tau
  integer nlay
  common  /param/ pi, cinint, cinf, tau, nlay
  set minimum terms (mntrms) to guarantee that n*pi*x/2 falls within a multiple of 2*pi
  mntrms = 4*nlay
  delc = cinf - cinint
  rttau = sqrt(tau)
  arg1 = pi/(2*rttau)
  tan = sin(arg1)/cos(arg1)
  sum1 = 0.
  sum2 = 0.
  sum3 = 0.
  expt = exp(-time/tau)
  do 150 n = 1,mntrms,2
    fltn = float(n)
    tfac = fltn*fltn*time
    if (tfac.gt.50.) goto 160
    arg2 = fltn*pi / 2.
    sinpix = sin( x*arg2 )
    expn2t = exp( -tfac )
    denom = (1. - tau*fltn*fltn)
    cospix= cos( x*arg2 )
    sum1 = sum1 + sinpix*expn2t/( fltn*denom )
    sum3 = sum3 + cospix*expn2t/denom
    sum2 = sum2 + sinpix*expn2t*fltn/denom
  continue
  cpart = expt*(tan*sin(x*arg1)+cos(x*arg1))
  c = cinint + delc*(1. - cpart - 4*sum1/pi)
  dcdt = delc*(cpart/tau + 4.*sum2/pi)
  cpart = arg1*expt*(tan*cos(x*arg1)-sin(x*arg1))
  dcdx = delc*(-cpart -2*sum3)
return
end

Appendix E
subroutine cncerf(time,x,cc,dcdx,dcdt)

calculates c(x,t) for exponential rise in boundary
concentration using error function formulation
made to be interchangeable with conex

real    time, x, c, dcdx, dcdt
real    pi, cinint, cinfin, tau
real    rerfc, ierfc
integer nterms

common /param/ pi, cinint, cinfin, tau, nterms

sum1 = 0.
sum2 = 0.
sum3 = 0.\nrtpi = sqrt(pi)
rttime = sqrt(time)
rttau = sqrt(tau)
timtau = rttime/rttau
expt = exp(-time/tau)
delc = cinfin-cinint
chgsin = 1

do 100 i = 1,2
min1 = -1
chgsin = -1*chgsin
do 100 j = 1, nterms
n = j-1
min1 = -1*min1
goto (10,20), i
f = (2*(n+1)-x)*pi/2
10 goto 30
f = (2*n+x)*pi/2
20 alph = f/(2*rttime)
30 bet = f/rttau
rerfc = erfc(alph)
call cerfc(alph,-timtau,rerfc,ierfc)
cosft = cos(bet)
sinft = sin(bet)

sum1 = sum1 + min1*erfca
sum2 = sum2 + min1*(cosft*rerfc+sinft*ierfc)
sum3 = sum3 + chgsin*min1*(sinft*rerfc - cosft*ierfc)
100 continue

cc = cinint + delc*(sum1-expt*sum2)
dcdt = delc*(expt*sum2/tau)
dcdx = delc*(.5*pi*expt*sum3/rttau)
return
end
function erfc(z)

function computes the value of the complementary error function of argument z via an approximation taken from Abromovitz and Stegun, p. 299, 7.1.26
|error(z)| < 1.5e-7

real z
erfc = 1. - erf(z)
return
end

function erf(z)

function computes the value of the error function of argument z via an approximation taken from Abromovitz and Stegun, p. 299, 7.1.26
|error(z)| < 1.5e-7

real z
double precision p, a1, a2, a3, a4, a5, x
double precision t1 t2, t3, t4, t5, sum
if (z.ne.0.) goto 5
erf = 0.
goto 15
fac = 1.
if (z.gt.0.) goto 7
fac = -1.
x = dble(fac*z)
if (x.lt.9.3) goto 8
erf = fac
goto 15
p = .3275911
a1 = .254329592
a2 = -.284496736
a3 = 1.421413741
a4 = -1.453152027
a5 = 1.061405429
t1 = 1./((1.+ p * x)
t2 = t1*t1
t3 = t2 * t1
t4 = t3 * t1
t5 = t4 * t1
sum = a1*t1 + a2*t2 + a3*t3 +a4*t4 + a5*t5
erf = fac*(1.- sum * dexp(-x*x))
return
end
subroutine cerfc(x,y,rcerfc,icerfc)
computes real and imaginary parts of complex error function
using series approximation from Abromovitz & Stegun
p. 299, 7.1.29
written 3-Sep-82 by SE
corrected 12-Sep-82 by SE
real x,y,rcerfc,icerfc
real ilst, rlst, ismprt, rsmprt, pi
real isum, rsum, n24
logical rflg, iflg

pi = 3.141592654
rflg = .false.
iflg = .false.
isum = 0.
rsum = 0.
if (x.eq.0.) goto 5
x2 = x*x
erfx = erf(x)
if (x2.lt.87.) goto 3
exp2 = 0.
goto 110
exp2 = exp(-x2)
cos2xy = cos(2*x*y)
sin2xy = sin(2*x*y)
goto 10
5
x2 = 0.
erfx = 0.
cos2xy = 1.
sin2xy = 0.
do 100 n = 1,100
if (y.eq.0.) goto 130
expnyp = exp(n*y)
expnym = exp(-n*y)
coshny = (expnyp+expnym)/2.
sinhny = (expnyp-expnym)/2.
n24 = n*n/4.
10
rsmprt = exp(-n24)*(2*x*(1-coshny*cos2xy)
   +n*sinhny*sin2xy)/(n24+x2)
ismprt = exp(-n24)*(2*x*coshny*sin2xy
   +n*sinhny*cos2xy)/(n24+x2)
if (n.eq.1) goto 60
if (rsmprt.eq.0) goto 25
if (abs(rsmprt).lt.1e-2*abs(rsum)) goto 25
goto 30
rflg = .true.

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c
30 if (ismprt.eq.0) goto 40
    if (abs(ismprt).lt.1e-2*abs(isum)) goto 40
    goto 50
40 iflg = .true.
50 if (iflg.and.rflg) goto 110
60 rsum = rsum + rsmprt
100 isum = isum + ismprt
  c
110 if (x.eq.0.) goto 120
    rcerfc = 1-erfx-expx2/(2*pi)*((1-cos2xy)/x + rsum)
    icerfc = -expx2/(2*pi)*(sin2xy/x + isum)
    goto 150
  c
120 rcerfc = 1.
    icerfc = -(2.*y+isum)/(2*pi)
    goto 150
  c
130 rcerfc = 1. - erfx
    icerfc = 0.
150 return
end
APPENDIX F

COMPUTATION OF PHENOMENOLOGICAL COEFFICIENTS

The phenomenological coefficients resulting from the electrokinetic micromodel developed in Chapter VI are computed in the following Fortran program. The computer program requires four parameters as input. These are: the cylinder radius $a$; the initial water volume fraction $\bar{v}_w$; the cylinder surface charge $\sigma_m$; the concentration of the bath $c_o$. The program works internally in units of nanometers, kilograms and seconds to avoid underflow problems. The input parameters are assumed to be in this system of units. The program converts the $k_{ij}$ to standard MKS units prior to output.
program kij

program computes the kij matrix for the micro model as functions of compressive strain eps.

plots the respective kij as f(eps)

real zeta, sigm, debye, arad, brad, rhom
real cndct, eta, prmeps, vw, mupls, mumin, mu
real k11c(101), k12c(101), k22c(101), eps(101)
real k11p(101), k12p(101), k22p(101), k(101)
integer mode
logical*1 yesno, flg, flgsgm
byte title(64), xlab(64), ylab(64), plab(64)

common /xdlab/ title,xlab,ylab,plab
common /label/ c0,vw0,arad,sigm,rhom0,drcyk0,debye,epsfac,flg

set constants
eta = 1e-3
farad = 9.65e4
vth = 25.e-3

micro model - works internally in nMKS units to avoid underflow converts to MKS on output input assumed in nMKS

100 open(unit=2,name='KIJPRM.MIC',type='OLD')
read(2,*) c0,vw0,arad,sigm
close(unit=2)
101 type 12
flg = yesno(dum)
12 format (' compute kij including surface conductance? ',$)

set internal constants in nMKS units
mupls = 5.19e10
mumin = 7.91e10
prmeps = 8.85e-19

compute derived constants

debye = sqrt(prmeps*vth/(2.*farad*c0))
zeta = debye*sigm/prmeps
cndct = farad*(mupls+mumin)*c0
a2 = arad*arad
a4 = a2*a2
da = debye/arad

Appendix F
if(.not.flg) goto 105
mu = mupls
if (sigm.gt.0.) mu = mumin
cndsfc = abs(sigm)*mu/(arad*cndct)
goto 110
c
105
c
epszet = 1e27*prmeps*zeta/eta
zefac = epszet*sigm/(arad*cndct)
c
13
type 13
format (' compute to epsmax = ',$)
accept *, epsmax
epsiln = 0.
deps = epsmax/100.
do 120 i = 1,101
c
vw = (vw0-epsiln)/(1.-epsiln)
brad = arad/sqrt(1.-vw)
b2 = brad*brad
b4 = b2*b2
b4a4 = (b4-a4)/(b4+a4)
lnba = alog(brad/arad)
c
k12c(i) = 1e-18*b2*(lnba - b4a4/2.)/(4.*eta)
sfac = 1.+cndsfc
denom1 = 1.+zefac+cndsfc+2.*da*b4a4*sfac
k12c(i) = 1e-18*epszet*b4a4/denom1
alph = (a2/b2)*(-zefac-cndsfc+2.*da*b4a4*(1.-cndsfc))
k22c(i) = 1e9*cndct*(1.-alph)/(1.+alph)
c
k11p(i) = 1e-18*(4.*(a2*b2+b4*lnba)-3.*b4-a4)/(8.*eta*b2)
k12p(i) = 1e-18*epszet*(1 - (a2/b2)*(1 - .5*da))
k22p(i) = 1e9*cndct*(1.-a2/b2 + 2.*(cndsfc+zefac)*a2/b2)
c
eps(i) = epsiln
epsiln = epsiln+deps
continue

c
plot micro model

c
encode(64,300,xlab)
type 310
if(.not.yesno(dum)) goto 130
encode(64,301,ylab)
encode(64,320,title)
call kijplt(eps,k11c)
c
130
type 311
if(.not.yesno(dum)) goto 140
encode(64,302,ylab)
encode(64,321,title)
call kijplt(eps,k12c)

140
type 312
if(.not.yesno(dum)) goto 150
encode(64,303,ylab)
encode(64,322,title)
call kijplt(eps,k22c)

150
type 313
if(.not.yesno(dum)) goto 160
encode(64,301,ylab)
encode(64,323,title)
call kijplt(eps,k11p)

160
type 314
if(.not.yesno(dum)) goto 170
encode(64,302,ylab)
encode(64,324,title)
call kijplt(eps,k12p)

170
type 315
if(.not.yesno(dum)) goto 180
encode(64,303,ylab)
encode(64,325,title)
call kijplt(eps,k22p)

180
type 316
if(.not.yesno(dum)) goto 190
encode(64,301,ylab)
encode(64,326,title)
      do 185 i = 1, 101
185    k(i) = (2.*k11c(i)+k11p(i))/3.
call kijplt(eps,k)

190
type 317
if(.not.yesno(dum)) goto 200
encode(64,302,ylab)
encode(64,327,title)
      do 195 i = 1, 101
195    k(i) = (2.*k12c(i)+k12p(i))/3.
call kijplt(eps,k)

200
type 318
if(.not.yesno(dum)) goto 210
encode(64,303,ylab)
encode(64,328,title)
      do 205 i = 1, 101
205    k(i) = (2.*k22c(i)+k22p(i))/3.
call kijplt(eps,k)
210 type 319
if(.not.yesno(dum)) goto 220
encode(64,301,ylab)
encode(64,329,title)
do 215 i = 1, 101
k11 = (2.*k11c(i)+k11p(i))/3.
k12 = (2.*k12c(i)+k12p(i))/3.
k22 = (2.*k22c(i)+k22p(i))/3.
k(i) = k11 - k12**2/k22
call kijplt(eps,k)
220 type 309
if(.not.yesno(dum)) goto 230
encode(64,301,ylab)
encode(64,331,title)
do 225 i = 1, 101
k12 = (2.*k12c(i)+k12p(i))/3.
k22 = (2.*k22c(i)+k22p(i))/3.
k(i) = k12**2/k22
call kijplt(eps,k)
230 type 308
if(.not.yesno(dum)) goto 240
encode(64,304,ylab)
encode(64,332,title)
do 235 i = 1, 101
k12 = (2.*k12c(i)+k12p(i))/3.
k22 = (2.*k22c(i)+k22p(i))/3.
k(i) = k12/k22
call kijplt(eps,k)
240 type 330
if(.not.yesno(dum)) goto 250
type 299, sigm
accept *, dum
if (dum.ne.0) sigm = dum
goto 101
250 stop
c
299 format (' surface charge currently = ',g11.4/' enter new surface charge: ',$)
300 format (' compressive strain ') 
301 format (' m**2 / Pa*sec ') 
302 format (' m**2 / V*sec ') 
303 format (' mhos / m ') 
304 format (' V / Pa ') 
c
308 format (' plot ke? ',$)
309 format (' plot backflow? ',$)
310 format (' plot k11 for perpendicular flow? ',$)
311 format (' plot k12 for perpendicular flow? ',$)
312 format (' plot k22 for perpendicular flow? ',$)

Appendix F