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Application of a Three-Dimensional Poroelastic BEM to Modeling the Biphasic Mechanics of Cell-Matrix Interactions in Articular Cartilage (REVISION)

Mansoor A. Haider¹ and Farshid Guilak²

¹ Department of Mathematics, North Carolina State University, Raleigh, North Carolina 27695

² Departments of Surgery and Biomedical Engineering, Duke University Medical Center, Durham, North Carolina 27710

Abstract

Articular cartilage exhibits viscoelasticity in response to mechanical loading that is well described using biphasic or poroelastic continuum models. To date, boundary element methods (BEMs) have not been employed in modeling biphasic tissue mechanics. A three dimensional direct poroelastic BEM, formulated in the Laplace transform domain, is applied to modeling stress relaxation in cartilage. Macroscopic stress relaxation of a poroelastic cylinder in uni-axial confined compression is simulated and validated against a theoretical solution. Microscopic cell deformation due to poroelastic stress relaxation is also modeled. An extended Laplace inversion method is employed to accurately represent mechanical responses in the time domain.

Keywords

boundary element method; biphasic theory; poroelasticity; articular cartilage; cells

1. INTRODUCTION

Articular cartilage is the connective tissue lining the surfaces of diarthrodial joints in the body, serving to provide a low-friction bearing surface for the transmission of stresses across joint surfaces. This tissue exhibits significant viscoelastic behavior that arises predominantly from frictional drag due to relative motion between the solid and fluid phases [1]. The unique mechanical properties of this tissue have been attributed to the complex structure and composition of the extracellular matrix, which comprises a fluid phase consisting of water with dissolved ions, and a solid matrix consisting primarily of a fibrous network of type II collagen and aggregating proteoglycans, as well as other proteins, lipids, and cells [2]. With mechanical loading, interstitial fluid is redistributed through the porous, permeable solid matrix, giving rise to significant viscoelastic behavior predominantly due to frictional drag between the solid and fluid phases. The mechanical behavior of cartilage has been shown to be well described by

Corresponding Author Mansoor A. Haider, Ph.D. Department of Mathematics, Box 8205, North Carolina State University, Raleigh, North Carolina 27695, Phone: (919) 515-3100, Fax: (919) 515-3798, m_haider@ncsu.edu.

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biphasic or poroelastic continuum models that account for the mechanical interactions of the different phases [1].

The molecular constituents of the extracellular matrix are maintained in a state of homeostatic turnover by a balance between the biosynthetic and degradative activities of the cells in cartilage, termed chondrocytes. Chondrocytes are surrounded by a narrow tissue region termed the “pericellular matrix” and make up less than 10% of the tissue volume in mature cartilage. In addition to molecular signals and genetic programming, chondrocyte physiology is regulated by mechanical stress and other biophysical factors in the local environment of the cell [3]. However, identification of the role of specific biophysical signals engendered by loading of the joint has been difficult, as many of the mechanical and physicochemical factors that are known to affect chondrocytes are coupled to one another [4,5]. In this respect, theoretical models of the cell-matrix interactions may be particularly valuable by providing information on biophysical parameters that cannot be measured experimentally *in situ* at the cellular level, e.g., the stress-strain, physicochemical, and electrical states in the immediate vicinity of the cell [6,7]. However, the complexity of the governing equations for biphasic or poroelastic materials typically precludes analytical solutions to multi-dimensional problems with complex geometries or boundary conditions.

Numerical simulation of the biphasic mechanics of articular cartilage is most often performed within the framework of the finite element method (FEM). Some common FEM approaches include displacement-velocity (u-v) penalty formulations [8,9], in which the divergence of mixture velocity is related to the pore pressure via a user-specified penalty parameter, and displacement-pressure (u-p) formulations [10,11] that are independent of such a parameter. The versatility of the FEM in simulating biphasic cartilage mechanics has been well-established with sample applications including finite strain deformation of tissue [9] and cells [12,13], diarthrodial joint contact [14], tissue anisotropy [15] and multiscale simulations of cell-matrix mechanics [6,16].

In the case of linear models, an alternative numerical approach to the domain-based FEM is the boundary element method (BEM), which is based on fundamental solutions of the governing partial differential equations and requires discretization on only the domain boundary. To date, the BEM has not been applied to the analysis of linear biphasic mechanics of articular cartilage. The governing equations of linear biphasic theory are mathematically equivalent to those for Biot’s theory of linear quasi-static poroelasticity in the case of incompressible constituents [17]. However, the boundary conditions associated with models of cartilage cell and matrix mechanics are distinct from those typically considered in applications of poroelasticity. Consequently, the goal of this study was to develop a three-dimensional poroelastic BEM for application to modeling biphasic cartilage mechanics. In particular the reduced geometric complexity of the BEM, as compared to the FEM, has the potential to facilitate simulation of *in vivo* biphasic cell-matrix interactions in cartilage where imaging of cell-matrix geometry can be obtained using three-dimensional imaging techniques such as confocal laser scanning microscopy [18].

In the poroelasticity literature, there have been many applications of BEMs based on direct and indirect boundary integral equation formulations in both the time and Laplace transform domains. An excellent review of poroelastic BEMs has been presented by Cheng and Detournay [19]. In the current study, we employ the three dimensional Laplace domain direct BEM formulation of Badmus et al. [20] which we implemented and used to simulate macroscopic and microscopic biphasic mechanics in articular cartilage. In particular, we model the configuration of confined compression and extend the exponential Laplace inversion technique [20] to account for material response typical of articular cartilage under stress

relaxation. Model simulations are validated against a theoretical solution under the assumption of uni-axial deformation.

2. BOUNDARY ELEMENT METHOD

2.1 Biphasic-Poroelastic Equivalence

We consider a material that can be modeled as a continuum mixture of solid and fluid phases based on linear isotropic biphasic theory [1]. For convenience, simplified notation is employed for the linear biphasic model (e.g. [21]) to illustrate correspondence with poroelastic theory. The momentum balance equations for the solid and fluid phases are, respectively,

$$\nabla \cdot \sigma^s + \Pi = \mathbf{0}, \quad \nabla \cdot \sigma^f - \Pi = \mathbf{0}, \quad (1)$$

where σ^s and σ^f are *partial Cauchy stress tensors* for each phase, and the *momentum exchange vector* Π accounts for interphase drag in the mixture. The mixture is assumed to be saturated, and the incompressibility condition is:

$$\varphi \nabla \cdot (\partial_t \mathbf{u}) + (1 - \varphi)(\nabla \cdot \mathbf{v}) = 0, \quad (2)$$

where $\mathbf{u}$ is the *solid displacement*, $\mathbf{v}$ is the *fluid velocity* and φ is the *solid volume fraction*. Under the assumptions that the solid phase is isotropic linear elastic, the fluid phase is inviscid, and the momentum exchange is due to Darcy's Law, the constitutive laws are:

$$\sigma^s = [-\varphi p + \lambda \text{tr}(\mathbf{e})] \mathbf{I} + 2\mu \mathbf{e}, \quad \sigma^f = -(1 - \varphi)p \mathbf{I}, \quad \Pi = \frac{(1 - \varphi)^2}{k} (\mathbf{v} - \partial_t \mathbf{u}), \quad (3)$$

where p is the *pore pressure*, $\mathbf{e} (= 1/2 [\nabla \mathbf{u} + \nabla \mathbf{u}^t])$ is the infinitesimal strain tensor, λ, μ are Lamé coefficients for the solid phase, k is the *permeability* and $\mathbf{I}$ is the identity tensor.

The relationship between the linear biphasic model (Eqs. 1–3) and Biot poroelasticity [17] is now considered. Based on a linear isotropic quasi-static poroelastic model [20,22], the stress equilibrium relation is

$$\nabla \cdot \sigma = \mathbf{0}, \quad (4)$$

where the *total stress tensor* is:

$$\sigma = [-\alpha p + \lambda \text{tr}(\mathbf{e})] \mathbf{I} + 2\mu \mathbf{e}. \quad (5)$$

In Eq. 5, α is the *Biot effective stress coefficient*, and the pore pressure p satisfies:

$$\frac{p}{M} = \zeta - \alpha \text{tr}(\mathbf{e}), \quad (6)$$

where M is an *inverse storage coefficient* and ζ is the *variation of fluid volume per unit reference volume*. The continuity equation is expressed as:

$$\partial_t \zeta + \nabla \cdot \mathbf{q} = 0, \quad (7)$$

where the *specific discharge vector* $\mathbf{q}$ obeys Darcy's law:

$$\mathbf{q} = -\kappa \nabla p, \quad (8)$$

and κ is a *permeability coefficient*.

It is straightforward to show that the linear biphasic model (Eqs. 1–3) is mathematically equivalent to the poroelastic model (Eqs. 4–8) under the following conditions:

$$\sigma = \sigma^s + \sigma^f, \quad \mathbf{q} = (1 - \varphi)(\mathbf{v} - \partial_t \mathbf{u}), \quad \alpha = 1, \quad M = \infty, \quad \kappa = k. \quad (9)$$

In the poroelasticity literature, the choice $M = \infty$, $\alpha = 1$ is referred to as the 'incompressible constituents' model [17].

A common nondimensionalization of the biphasic model involves taking μ as the unit of stress, and $h^2/(k\mu)$ as the unit of time, where h is a characteristic length scale taken as the unit of length. The unit of velocity is then $k\mu/h$. In this case, it is equivalent to solve the dimensional equations with the effective parameters $k_{eff} = 1$ and $\mu_{eff} = 1$ where v , which is already dimensionless, can be specified in the usual manner.

2.2 Boundary Integral Formulation

A three-dimensional boundary integral representation of the poroelastic governing equations (4–8) is formulated in the Laplace transform domain (transform variable s). The resulting formulation and implementation of the spatial solution in a boundary element method are based on the work of Badmus et al. [20]. Employing Green's theorem with point force and point source fundamental solutions, the governing integral equations are, in Cartesian component form:

$$\begin{aligned} \theta \tilde{u}_j(\mathbf{x}; s) = & \sum_{i=1}^3 \int_S [\tilde{u}_{ij}^f(\mathbf{y} - \mathbf{x}; s) \tilde{t}_i(\mathbf{y}; s) - \tilde{t}_{ij}^f(\mathbf{y} - \mathbf{x}; s) \tilde{u}_i(\mathbf{y}; s)] dS(\mathbf{y}) \\ & + \sum_{i=1}^3 \int_S [\tilde{p}_j^f(\mathbf{y} - \mathbf{x}; s) \tilde{q}(\mathbf{y}; s) - \tilde{q}_j^f(\mathbf{y} - \mathbf{x}; s) \tilde{p}(\mathbf{y}; s)] dS(\mathbf{y}) \quad j=1, 2, 3 \end{aligned} \quad (10)$$

$$\begin{aligned} -\theta \tilde{p}(\mathbf{x}; s) = & \sum_{i=1}^3 \int_S s [\tilde{u}_i^s(\mathbf{y} - \mathbf{x}; s) \tilde{t}_i(\mathbf{y}; s) - \tilde{t}_i^s(\mathbf{y} - \mathbf{x}; s) \tilde{u}_i(\mathbf{y}; s)] dS(\mathbf{y}) \\ & + \sum_{i=1}^3 \int_S [\tilde{p}^s(\mathbf{y} - \mathbf{x}; s) \tilde{q}(\mathbf{y}; s) - \tilde{q}^s(\mathbf{y} - \mathbf{x}; s) \tilde{p}(\mathbf{y}; s)] dS(\mathbf{y}), \end{aligned} \quad (11)$$

where S is the domain boundary, $\tilde{t}_i$ are boundary tractions for the total (i.e. mixture) stress, $\tilde{u}_i$

are the boundary displacements, and $\tilde{p}$ and $\tilde{q} = \sum_{i=1}^3 \tilde{q}_i n_i$ are the pore pressure and normal flux, respectively, along the boundary with unit outward normal n_i . The quantity θ is 4π when $\mathbf{x}$ is interior to S , and equal to the interior solid angle when $\mathbf{x} \in S$. In Eqs. 10–11, the fundamental

solutions for boundary traction, displacement, pore pressure and normal flux due to an impulse point force of strength 4π in the j direction are denoted by $\tilde{t}_{ij}^f, \tilde{u}_{ij}^f, \tilde{p}_j^f, \tilde{q}_j^f$, respectively. Similarly, the fundamental solutions for boundary traction, displacement, pore pressure and normal flux due to an impulse fluid source of strength 4π are denoted as $\tilde{t}_i^s, \tilde{u}_i^s, \tilde{p}^s, \tilde{q}^s$, respectively. These fundamental solutions, presented for the poroelastic model in [20], are included in reduced form (Appendix A) for the special case of correspondence between the biphasic and poroelastic models. For the specific integral equations and associated fundamental solutions required to evaluate the stress and flux components in the interior of S , the reader is referred to the original paper [20].

2.3 Boundary Element Discretization

The boundary S is partitioned into M 6-node isoparametric, triangular quadratic boundary elements S_k ($k = 1, \dots, M$). Within each element, local coordinates (ξ, η) are adopted where $S_k = \{(\xi, \eta) : 0 \leq \xi \leq 1, 0 \leq \eta \leq 1 - \xi\}$. Within each boundary element, approximations of the boundary surface $\mathbf{y}^k(\xi, \eta) \in S_k$ and the dependent variables $(\bullet)^k(\xi, \eta)$ are then given by:

$$\mathbf{y}^k(\xi, \eta) = \sum_{\beta=1}^6 \mathbf{y}_{\beta}^k N^{\beta}(\xi, \eta), \quad (\bullet)^k(\xi, \eta) = \sum_{\beta=1}^6 (\bullet)_{\beta}^k N^{\beta}(\xi, \eta), \quad \text{for } (\xi, \eta) \in S_k, \quad (12)$$

where $(\bullet)_{\beta}^k$ denotes the value of a quantity at local node β of element k , and the quadratic shape functions are:

$$\begin{aligned} N^{(1)}(\xi, \eta) &= \xi(2\xi - 1), & N^{(2)}(\xi, \eta) &= 4\xi\eta, \\ N^{(3)}(\xi, \eta) &= \eta(2\eta - 1), & N^{(4)}(\xi, \eta) &= 4\eta(1 - \xi - \eta), \\ N^{(5)}(\xi, \eta) &= (1 - \xi - \eta)(1 - 2\xi - 2\eta), & N^{(6)}(\xi, \eta) &= 4\xi(1 - \xi - \eta) \end{aligned} \quad (13)$$

Discretizing Eqs. 10–11 along the boundary elements, and evaluating at the mesh node $\mathbf{x}^l$ ($l = 1, \dots, n$), leads to a discrete system of equations of the following form:

$$\sum_{k=1}^M \sum_{\beta=1}^6 \mathbf{T}^{k,\beta}(\mathbf{x}^l) \omega^{k,\beta} - \sum_{k=1}^M \sum_{\beta=1}^6 \mathbf{U}^{k,\beta}(\mathbf{x}^l) \tau^{k,\beta} = 0, \quad l = 1, \dots, n, \quad (14)$$

where $\omega = [\tilde{u}_1, \tilde{u}_2, \tilde{u}_3, \tilde{p}]$, $\tau = [\tilde{t}_1, \tilde{t}_2, \tilde{t}_3, \tilde{q}]$

$$\mathbf{T}^{k,\beta}(\mathbf{x}^l) = \int_0^{1-\xi} \int_0^{1-\xi} N^{(\beta)}(\xi, \eta) \tau_k^*(\mathbf{x}^l, \xi, \eta) J_k(\xi, \eta) d\xi d\eta + \theta \mathbf{I}^*, \quad (15)$$

$$\mathbf{U}^{k,\beta}(\mathbf{x}^l) = \int_0^{1-\xi} \int_0^{1-\xi} N^{(\beta)}(\xi, \eta) \omega_k^*(\mathbf{x}^l, \xi, \eta) J_k(\xi, \eta) d\xi d\eta, \quad (16)$$

$$\tau_k^* = \begin{bmatrix} \tilde{t}_{11}^f & \tilde{t}_{21}^f & \tilde{t}_{31}^f & s^{-1}\tilde{q}_1^f \\ \tilde{t}_{12}^f & \tilde{t}_{22}^f & \tilde{t}_{32}^f & s^{-1}\tilde{q}_2^f \\ \tilde{t}_{13}^f & \tilde{t}_{23}^f & \tilde{t}_{33}^f & s^{-1}\tilde{q}_3^f \\ s\tilde{t}_1^s & s\tilde{t}_2^s & s\tilde{t}_3^s & \tilde{q}^s \end{bmatrix}, \quad \omega_k^* = \begin{bmatrix} \tilde{u}_{11}^f & \tilde{u}_{21}^f & \tilde{u}_{31}^f & s^{-1}\tilde{p}_1^f \\ \tilde{u}_{12}^f & \tilde{u}_{22}^f & \tilde{u}_{32}^f & s^{-1}\tilde{p}_2^f \\ \tilde{u}_{13}^f & \tilde{u}_{23}^f & \tilde{u}_{33}^f & s^{-1}\tilde{p}_3^f \\ s\tilde{u}_1^s & s\tilde{u}_2^s & s\tilde{u}_3^s & \tilde{p}^s \end{bmatrix}, \quad (17)$$

$$\mathbf{I}^* = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & -1 \end{bmatrix} \text{ if } \mathbf{x}^l = \mathbf{x}^{k,\beta}, \text{ otherwise } \mathbf{I}^* = \mathbf{0}. \quad (18)$$

In Eqs. 15–16, the Jacobian of the transformation to element coordinates is $J_k(\xi, \eta) = |\partial_{\xi} \mathbf{y}^k \times \partial_{\eta} \mathbf{y}^k|$, and can also be used to determine the unit outward normal vector along the element. Once all integrals in Eqs 15–16 are determined, relationships between element-level and global nodes are used to assemble a system of linear algebraic equations of the form:

$$\sum_{m=1}^n \mathbf{F}^{lm} \mathbf{w}^m - \sum_{m=1}^n \mathbf{G}^{lm} \mathbf{t}^m = \mathbf{0}, \quad l=1, \dots, n, \quad (19)$$

where the matrices $\mathbf{F}, \mathbf{G}$ are the nodal sums of element integrals in $\mathbf{T}^{k,\beta}, \mathbf{U}^{k,\beta}$, respectively, and $\mathbf{w}, \mathbf{t}$ are the nodal boundary values corresponding to $\omega^{k,\beta}, \tau^{k,\beta}$, respectively. By specifying a consistent set of boundary conditions at the nodes of the boundary element mesh, Eq. 19 is then assembled into a linear algebraic system of equations for the unknown nodal variables.

2.4 Numerical Integration and Treatment of Singular Integrals

In assembling Eq. 19, the underlying integrals of Eqs. 15–16 are non-singular when $l \neq m$. In the case $l = m$, the associated integrals are weakly singular for $\mathbf{G}^{ll}$ and

$F_{14}^{ll}, F_{24}^{ll}, F_{34}^{ll}, F_{41}^{ll}, F_{42}^{ll}, F_{43}^{ll}$, and strongly singular for the remaining components of $\mathbf{F}^{ll}$. The large majority of integrals, which are non-singular, are evaluated using a standard 7-point Gaussian quadrature formula for a triangular element [23]. The weakly singular integrals have a $1/r$ singularity that, as indicated in [20], can be removed via a transformation to local polar coordinates along each node of the element containing the weakly singular integral. The resulting regular integrals are then evaluated using standard Gaussian quadrature integration for a double integral. The details of this integration procedure, for the 6-node triangular element employed in this study, are summarized in Appendix B. The remaining integrals are strongly singular ($1/r^2$). Their evaluation is by-passed via substitution, into Eq. 19, of constant rigid

body solutions ($\tilde{u}_{\gamma}^l = s^{-1}, \tilde{\mathbf{t}}^l = \mathbf{0}, \tilde{q} = \tilde{p} = 0; \gamma = 1, 2, 3$), and a constant compressive stress solution ($\tilde{u}_{\gamma}^l = 0, \tilde{t}_{\gamma}^l = -s^{-1}n_{\gamma}, \tilde{q} = 0, \tilde{p} = s^{-1}; \gamma = 1, 2, 3$), which provide the following relations for the remaining components of $\mathbf{F}^{ll}$ ($l = 1, \dots, n$) (e.g. [24]):

$$F_{\delta\gamma}^{ll} = - \sum_{m=1}^n F_{\delta\gamma}^{lm}, \text{ for } (\delta, \gamma) = (1, 1), (1, 2), (1, 3), (2, 1), (2, 2), (2, 3), (3, 1), (3, 2), (3, 3) \quad (20)$$

$$F_{44}^{ll} = - \sum_{\substack{m=1 \\ m \neq l}}^n F_{44}^{lm} - \sum_{m=1}^n (G_{41}^{lm} n_1 + G_{42}^{lm} n_2 + G_{43}^{lm} n_3). \quad (21)$$

2.5 Numerical Inversion of Laplace Transforms

Application of the boundary element method presented above yields solutions in the Laplace transform domain that must be numerically inverted to obtain time domain representations. For a specific boundary value problem, the linear algebraic system of governing equations (19) must be solved for multiple values of the Laplace transform parameter s . The original

poroelastic BEM [20] employed an exponential series approximation $f(t) = \sum_{i=1}^{\tilde{n}} c_i e^{-\alpha_i t}$ for the quantity of interest, combined with a least-squares collocation procedure in the Laplace domain, to determine the unknown coefficients in the exponential series, assuming specification of the relaxation times α_i . However, for several boundary value problems in biphasic mixture mechanics (e.g. stress relaxation, dynamic loading), a simple exponential series will not accurately approximate time dependence in the quantities of interest. Hence, we choose a more general representation:

$$g(t) = \sum_{i=1}^{\tilde{n}} d_i \phi_i(t), \quad (22)$$

to model the quantity of interest in the time domain. The time series should be chosen such that the functions $\phi_i(t)$ admit explicit representations $\tilde{\phi}_i(s)$ in the Laplace domain. Numerical optimization is then used to determine the coefficients d_i , as well as any additional coefficients in the functions $\phi_i(t)$, via minimization of a least-squares cost function relating the analytical representation in the Laplace domain:

$$\tilde{g}(s) = \sum_{i=1}^{\tilde{n}} d_i \tilde{\phi}_i(s), \quad (23)$$

to BEM computations at multiple value of s . Some knowledge of the material response, based on analytical solutions in simpler configurations or experiments, will be beneficial in choosing appropriate functions $\phi_i(t)$ in Eq. 22. The asymptotic behavior of the analytical Laplace domain representation for large and small values of s can also be used to facilitate solution of the numerical optimization problem. As illustrated in the next section, for the biphasic problems considered in the current study, BEM computations at less than 20 values of s are sufficient for accurate representation of the material response with a small number of terms $\tilde{n}$ in Eq. 22.

3. NUMERICAL EXAMPLES

The BEM described in the previous section was implemented in MATLAB 7.0 on a dual-2.3GHz Power Macintosh. To evaluate potential capability of the poroelastic BEM in modeling biphasic cartilage mechanics, two problems were considered. The first problem simulated stress relaxation of a biphasic cylinder on the macroscopic scale of a cartilage layer, and accuracy of the BEM was evaluated by comparison to an associated theoretical solution (Appendix C). The second problem simulated deformation on the microscopic scale of a single

cartilage cell, motivated by our ultimate goal to employ the poroelastic BEM in modeling three-dimensional cell-matrix interactions in situ. For the purposes of the current study, axisymmetric geometries were used. Thus, while the BEM method and mesh were three-dimensional, the governing equations were assembled only at a set of primary nodes in one half-plane of three-dimensional space. However, at each such primary node, influence integrals were calculated over all elements in the three dimensional mesh. Unknown variables at non-primary nodes were determined, as appropriate, to be equivalent to primary values, or as simple rotations of the associated variables at primary nodes on the same circle of symmetry.

3.1 Confined Compression of a Biphasic Cylinder – Macroscopic Stress Relaxation

The macroscopic problem of confined compression of a biphasic cylinder was first considered (Fig. 1). A cylinder of depth $h = 1$ and radius $R = 4$ was represented using a boundary element mesh with 64 6-node quadratic boundary elements (Fig. 2). Computation of an axisymmetric solution was facilitated by arranging nodes along concentric circles parallel to the x_1 - x_2 plane with centers along the rotational axis of symmetry. For this cylindrical mesh, there are 130 nodes, and 19 of these are primary nodes that are located on the surface $x_1 \geq 0, x_2 = 0$.

Biphasic stress relaxation was simulated by applying a ramp-and-hold compressive displacement at the upper surface:

$$u_3(x_1, x_2, h, t) = \begin{cases} -\gamma t & 0 \leq t \leq t_0 \\ -\gamma t_0 & t > t_0 \end{cases} \quad \text{for } x_1^2 + x_2^2 \leq R^2, t > 0, \quad (24)$$

where $\gamma = 0.1$ and the ramp time was taken as $t_0 = 0.1$. In the associated BEM simulation, the primary quantities of interest were chosen as the normal traction t_3 and normal flux q on the upper surface ($x_3 = h$) at the axis of symmetry ($x_1 = x_2 = 0$). These quantities were represented in the time domain as a function of the form:

$$g(t) = H(t_0 - t) \left[g_0 t + \sum_{i=1}^{\tilde{n}} g_i (1 - e^{-\delta_i t}) \right] + H(t - t_0) \left[d_0 t_0 + \sum_{i=1}^{\tilde{n}} d_i e^{-\delta_i t} \right], \quad (25)$$

where $H(t)$ is the Heaviside step function. Continuity of $g(t)$ at $t = t_0$ yields the relations $g_0 = d_0$ and $g_i = e^{-\delta_i t_0} (1 - e^{-\delta_i t_0})^{-1} d_i$ for $i = 1, \dots, \tilde{n}$. The corresponding representation in the Laplace domain is:

$$\tilde{g}(s) = d_0 \left[\frac{1 - e^{-s t_0}}{s^2} \right] + \sum_{i=1}^{\tilde{n}} d_i \left[\frac{\delta_i}{e^{\delta_i t_0} - 1} \frac{1 - e^{-s t_0}}{s(s + \delta_i)} \right]. \quad (26)$$

The BEM was run for 15 values of s generated as e^{s_j} with $s_j = -3 + (j - 1)/2$ for $j = 1, \dots, 15$, and data for curve-fitting was generated for the quantities of interest. Eq. 26 was then fit to the logarithm of the BEM data via minimization of a least squares cost function at the 15 points using the “fminsearch” function in MATLAB, which employs a Nelder-Mead simplex (direct search) method. The first relaxation time δ_1 was included as an optimization parameter, and the remaining parameters were distributed as $\delta_i = i^2 \delta_1$ for $i = 2, \dots, \tilde{n}$. Via an asymptotic analysis of Eq. 26 for small s , it is straightforward to show that

$$\tilde{g}(s) \sim \frac{d_0 t_0}{s} \quad \text{as } s \rightarrow 0. \quad (27)$$

This relation was verified by examining the product of s and the BEM data at several small values of s , since this product was observed to be roughly constant. The optimization was conducted with $\tilde{n} = 4$ and Eq. 27 was used to estimate the initial value of d_0 . Initial values of the remaining parameters d_1, d_2, d_3, d_4 were chosen as $-\gamma 10^0, -\gamma 10^2, -\gamma 10^{10}, -\gamma 10^{20}$, respectively. There was little sensitivity to the initial value of δ_1 , when chosen in the range 1–100.

Using this optimization method, excellent fits were obtained for Laplace domain representations (i.e. Eq. 26) of the normal traction and the normal flux at the surface (Fig. 3). The optimal values of the parameters δ_1 and d_1-d_4 , were then substituted into Eq. 25 to obtain time domain representations of the surface stress relaxation (Fig. 4-dashed) and the surface normal flux (Fig. 5). Accuracy of these variables was evaluated by comparison to an associated theoretical solution (Appendix C) for several values of the Poisson's ratio in a range that is representative of cartilage extracellular matrix [25]. BEM simulations were found to be in very good agreement for the surface normal flux, whose theoretical value is zero, and for the surface normal traction, whose theoretical value is determined from Eq. C1 (Fig. 4-solid). In particular, the BEM provides excellent approximations of the peak-to-equilibrium stress ratio which is, typically, a feature of the response that is of interest to the experimentalist. Sources of error in the BEM computations include the number of terms employed in the representation (25), as well as the presence of corner nodes in the mesh, where boundary conditions must be associated with one of the two bounding surfaces.

3.2 Microscopic Cell Deformation in Confined Compression

The microscopic problem of biphasic cell deformation within a macroscopic cylinder under confined compression, due to boundary condition (24), was also considered. Taking the typical depth of a cartilage layer ($\sim 1\text{mm}$) as the unit of length, the undeformed cell was assumed to be spherical and its nondimensional radius was taken as 0.007, corresponding to $7\mu\text{m}$. The cell was centered along the symmetry axis at depths that were 50% and 75% through the depth the layer. For the 75% depth case, the corresponding boundary element mesh is shown in Fig. 6 and has 16 elements and 34 nodes, with 7 of these being primary nodes located on the surface $x_1 \geq 0, x_2 = 0$.

Microscopic cell deformation due to confined compression of a cartilage layer was modeled as a boundary value problem on the sphere, with boundary conditions prescribed using the associated theoretical solution (Appendix C). Cells of articular cartilage are surrounded by a stiff pericellular matrix [26] with a Young's modulus that is roughly 50 times that of the cell [27]. To approximate the local stress environment of the cell, the macroscopic theoretical solution was used to apply boundary conditions in the Laplace domain for traction (Eqs. C5–8) and pressure (Eq. C4) along all but one of the primary nodes of the spherical mesh. The exceptional node was the lower pole of the sphere (II in Fig. 6), where displacements were prescribed (Eq. C3) to avoid non-uniqueness due to rigid body solutions. The nondimensional pericellular permeability and the nondimensional shear modulus were taken as 1 and the pericellular Poisson's ratio was set at 0.05 [25]. The Laplace inversion technique of the previous section was employed with $\tilde{n} = 2$ terms in Eq. 25.

The cell BEM model was first validated by equating the cellular and pericellular parameters. Displacements normal to the surface were simulated at nodes corresponding to the upper pole (III) and the equator (I) of the cell (Fig. 7) and were in excellent agreement with corresponding

displacements obtained using the theoretical solution (Eq. C2). Next, the effect of the pericellular stress environment on the cell was modeled by taking the cell Young's modulus to be 1/50 of the pericellular Young's modulus [27]. Cell permeability was taken to be 4.2 times the pericellular permeability [28] and the cell Poisson's ratio was varied in the range 0.35–0.45 [12]. These parameters correspond to a nondimensional cell shear modulus in the range 0.0145–0.0156. The BEM was used to simulate displacements at the two poles and the equator of the cell for a cell centered at depths of 50% (Fig. 8a) and 75% (Fig. 8b) within the tissue layer. Based on these results, and an ellipsoidal approximation of cell volume, the ratio between deformed and undeformed cell volume was also evaluated at the two depths (Fig. 8c, d). Simulations of cell volume ratios suggest that the cell volumetric deformation may be highly sensitive to small changes in the microscopic material parameters. A previous finite element study of chondrocyte recovery subsequent to complete micropipette aspiration reported a Poisson's ratio of 0.38 for cells harvested from healthy cartilage, and increasing sensitivity to Poisson's ratio near the incompressible limit. In combination with our simulations of cell volumetric deformation (e.g. Fig. 8c), these findings suggest that care must be taken in interpreting computational models as the Poisson's ratio approaches $\nu=0.5$ in the case of nearly incompressible cells. The relative contrast between cellular and pericellular stiffness also contributes to significant variations in cell volumetric deformation over the time course of the loading, even at depths in the tissue layer that are far removed from the loading surface (Fig. 8d).

4. CONCLUSIONS AND FUTURE WORK

In this study, the three-dimensional poroelastic direct boundary element method of Badmus et al. [20] has been applied to modeling the biphasic mixture mechanics of articular cartilage. The original Laplace inversion method was extended to account for more general time-varying responses, such as those associated with stress relaxation in articular cartilage, and accuracy was established via comparison to an associated theoretical solution.

To date, most numerical simulations of biphasic cartilage mechanics have employed the finite element method (FEM). While the FEM approach is highly versatile in its capability to simulate finite strain and anisotropy, it requires discretization on the full three-dimensional domain with conforming meshes along internal material interfaces. The BEM approach, while limited to linear models, reduces the three dimensional problem to an analysis on two dimensional bounding surfaces, and can also be readily extended to handle internal interfaces. The treatment of time dependence via a Laplace domain formulation makes these particular BEM methods suitable for parallelization where, for large scale problems, BEM computations at each value of s can be distributed over multiple processors. The foundation of the BEM methodology is in fundamental solutions (Green's functions) for the governing partial differential equations. This has several advantages. First, it avoids the need for a penalty formulation (e.g. [8]) in which the mixture continuity Eq. 2 is modified to include a penalty term of the form p/β , where β is a large, user-specified parameter. Second, the analytical forms of the underlying fundamental solutions are amenable to a detailed analysis of near and far-field interactions in the influence integrals that has the potential to significantly accelerate BEM computations. The primary limitation of the BEM is the restriction to small strain and, for the current formulation, material isotropy. In the context of modeling chondrocyte mechanics in cartilage, care must be taken to ensure that the method is employed in only regions of the tissue (e.g. mid-zone) and at loading levels that are consistent with these restrictions.

The simulations of cell-matrix interactions in this study are consistent with previous experimental studies measuring three-dimensional chondrocyte shape and volume during compression of the extracellular matrix [29], which showed that spherical cells become ellipsoidal with compression and exhibit significant changes in volume. Furthermore,

volumetric changes in the cells were found to be sensitive to the relative material properties of the cell, pericellular matrix, and extracellular matrix [6]. Our primary interest in future applications of the poroelastic BEM is the simulation of interface problems associated with biphasic deformation of the chondron, a term used to describe the chondrocyte and its surrounding pericellular matrix [26,27]. Three-dimensional images of the micromechanical environment of cells in cartilage can be obtained using confocal scanning laser microscopy both before and after application of loading. Analysis of these images using the poroelastic BEM will contribute to our understanding of the complex relationships between mechanical variables at the microscale and the metabolic response of cells in cartilage to their surroundings.

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Appendix A – Fundamental Solutions

In the formulas presented below, all free indices range over 1,2,3 and the Einstein summation convention is assumed for all repeated indices.

A.1 Impulse point force solution

$$\tilde{u}_{ij}^f = \frac{1}{2\mu r} \delta_{ij} + \frac{1}{2\mu} \frac{r_{,i} r_{,j}}{r} + \kappa \frac{1}{sr^3} \left\{ \delta_{ij} (1 - (1+\zeta)e^{-\zeta}) + r_{,i} r_{,j} \left[(3+3\zeta+\zeta^2)e^{-\zeta} - 3 \right] \right\} \quad (\text{A1})$$

$$\begin{aligned} \tilde{t}_{ij}^f = & -\frac{3}{r^2} r_{,i} r_{,j} r_{,k} n_k + 2\mu \kappa \frac{1}{sr^4} \left\{ \left(\delta_{ij} r_{,k} n_k + n_j r_{,i} \right) \left[(3+3\zeta+\zeta^2)e^{-\zeta} - 3 \right] \right. \\ & \left. + n_i r_{,j} \left[(3+3\zeta+2\zeta^2+\zeta^3)e^{-\zeta} - 3 \right] + r_{,i} r_{,j} r_{,k} n_k \left[15 - (15+15\zeta+6\zeta^2+\zeta^3)e^{-\zeta} \right] \right\} \end{aligned} \quad (\text{A2})$$

$$\tilde{p}_j^f = \frac{r_{,j}}{r^2} \left[1 - (1+\zeta)e^{-\zeta} \right] \quad (\text{A3})$$

$$\tilde{q}_j^f = \kappa \frac{1}{r^3} \{ n_j [(1+\zeta)e^{-\zeta} - 1] + r_{,j} r_{,k} n_k [3 - (3+3\zeta+\zeta^2)e^{-\zeta}] \} \quad (\text{A4})$$

where:

$$\zeta = r \sqrt{\frac{s}{\kappa(\lambda+2\mu)}}, \quad r_{,i} = \partial_{y_i} r = \frac{y_i - x_i}{r}, \quad r = \|\mathbf{x} - \mathbf{y}\|, \quad \kappa = k \quad (\text{A5})$$

A.2 Impulse fluid source solution

$$\tilde{u}_i^s = \frac{r_{,i}}{sr^2} \left[1 - (1+\zeta)e^{-\zeta} \right] \quad (\text{A6})$$

$$\tilde{t}_i^s = \frac{2\mu}{sr^2} \left\{ n_i \left[1 - (1+\zeta+\zeta^2)e^{-\zeta} \right] + r_{,i} r_{,j} n_j \left[(3+3\zeta+\zeta^2)e^{-\zeta} - 3 \right] \right\} \quad (\text{A7})$$

$$\tilde{p}^s = \frac{1}{\kappa} \frac{e^{-\zeta}}{r} \quad (\text{A8})$$

$$\tilde{q}^s = \frac{r_{,i} n_i}{r^2} (1+\zeta)e^{-\zeta} \quad (\text{A9})$$

Appendix B – Polar Integration for Weakly Singular Integrals

Nodes 1,3,5

$$\int_0^1 \int_0^{1-\xi} f(\xi, \eta) d\eta d\xi = \int_{\alpha_1}^{\beta_1 g_1(\theta)} \int_0^{\beta_1 g_1(\theta)} f(\xi(r, \theta), \eta(r, \theta)) r dr d\theta \quad (B1)$$

where:

$$\text{For } \beta=1: \xi=1+r\cos\theta, \eta=r\sin\theta, \alpha_1=\frac{3\pi}{4}, \beta_1=\pi, g_1(\theta)=-\frac{1}{\cos\theta} \quad (B2)$$

$$\text{For } \beta=3: \xi=r\cos\theta, \eta=1+r\sin\theta, \alpha_1=\frac{3\pi}{2}, \beta_1=\frac{7\pi}{4}, g_1(\theta)=-\frac{1}{\sin\theta} \quad (B3)$$

$$\text{For } \beta=5: \xi=r\cos\theta, \eta=r\sin\theta, \alpha_1=0, \beta_1=\frac{\pi}{2}, g_1(\theta)=\frac{1}{\sin\theta+\cos\theta} \quad (B4)$$

Nodes 2,4,6

$$\int_0^1 \int_0^{1-\xi} f(\xi, \eta) d\eta d\xi = \int_{\alpha_1}^{\beta_1 g_1(\theta)} \int_0^{\beta_1 g_1(\theta)} f(\xi(r, \theta), \eta(r, \theta)) r dr d\theta + \int_{\beta_1}^{\beta_2 g_2(\theta)} \int_0^{\beta_2 g_2(\theta)} f(\xi(r, \theta), \eta(r, \theta)) r dr d\theta \quad (B5)$$

where:

For $\beta=2$:

$$\xi = \frac{1}{2} + r \cos \theta, \quad \eta = \frac{1}{2} + r \sin \theta \quad (\text{B6})$$

$$\alpha_1 = \frac{3\pi}{4}, \beta_1 = \frac{5\pi}{4}, \beta_2 = \frac{7\pi}{4}, g_1(\theta) = -\frac{1}{2\cos\theta}, g_2(\theta) = -\frac{1}{2\sin\theta} \quad (\text{B7})$$

For $\beta = 4$:

$$\xi = r \cos \theta, \quad \eta = \frac{1}{2} + r \sin \theta \quad (\text{B8})$$

$$\alpha_1 = -\frac{\pi}{2}, \beta_1 = -\tan^{-1}\left(\frac{1}{2}\right), \beta_2 = \frac{\pi}{2}, g_1(\theta) = -\frac{1}{2\sin\theta}, g_2(\theta) = \frac{1}{2(\sin\theta + \cos\theta)} \quad (\text{B9})$$

For $\beta = 6$:

$$\xi = \frac{1}{2} + r \cos \theta, \quad \eta = r \sin \theta \quad (\text{B10})$$

$$\alpha_1 = 0, \beta_1 = \pi - \tan^{-1}(2), \beta_2 = \pi, g_1(\theta) = \frac{1}{2(\sin\theta + \cos\theta)}, g_2(\theta) = -\frac{1}{2\cos\theta} \quad (\text{B11})$$

The integrals (e.g. Eq. B1) are evaluated using regular Gaussian quadrature applied in succession via the following transformation:

$$\int_{\alpha_1}^{\beta_1} \int_0^{g_1(\theta)} f(\xi(r, \theta), \eta(r, \theta)) r dr d\theta = \frac{\beta_1 - \alpha_1}{4} \int_{-1}^1 g_1(\bar{\theta}) \int_{-1}^1 f(\bar{\xi}(\bar{r}, \bar{\theta}), \bar{\eta}(\bar{r}, \bar{\theta})) \bar{r} d\bar{r} d\bar{\theta} \quad (\text{B12})$$

where:

$$r = \frac{g_1(\theta)}{2}(1 + \bar{r}), \quad \theta = \frac{\alpha_1 + \beta_1}{2} + \frac{\beta_1 - \alpha_1}{2}\bar{\theta} \quad (\text{B13})$$

Appendix C – Theoretical Solution for Uni-axial Confined Compression Stress Relaxation

The sample is assumed to deform in only the axial direction, and depend only on the axial coordinate and time so that $\mathbf{u} = \langle 0, 0, u_3(x_3, t) \rangle$. For the ramp-and-hold displacement boundary condition (24), the solution for the surface normal stress in the time domain is given by:

$$\sigma_{33}(t)|_{x_3=h} = \frac{\gamma H_A}{h} [tH(t_0 - t) + t_0 H(t - t_0)] + \frac{2\gamma h}{k} \sum_{n=1}^{\infty} \frac{1}{n^2 \pi^2} \left[H(t_0 - t)(1 - e^{-a_n t}) + H(t - t_0)(e^{-a_n(t-t_0)} - e^{-a_n t}) \right] \quad (C1)$$

The axial displacement in the layer is

$$u_3(x_3, t) = \frac{\gamma x_3}{h} [tH(t_0 - t) + t_0 H(t - t_0)] + \frac{2\gamma h^2}{k H_A} \sum_{n=1}^N \frac{(-1)^n}{n^3 \pi^3} \left[H(t - t_0)(e^{-a_n(t-t_0)} - e^{-a_n t}) + H(t_0 - t)(1 - e^{-a_n t}) \right] \sin\left(\frac{n\pi x_3}{h}\right) \quad (C2)$$

In the Laplace transform domain, the displacement solution in the layer is given by:

$$\tilde{u}_3(x_3, s) = \frac{\gamma x_3}{h} \frac{1 - e^{-st_0}}{s^2} \frac{2\gamma h^2}{k H_A} \sum_{n=1}^{\infty} \frac{(-1)^n a_n}{n^3 \pi^3} \frac{1 - e^{-st_0}}{s(s+a_n)} \sin\left(\frac{n\pi x_3}{h}\right), \quad (C3)$$

The pore pressure is

$$\tilde{p}(x_3, s) = \frac{2\gamma h}{k} \sum_{n=1}^{\infty} \frac{a_n}{n^2 \pi^2} \frac{1 - e^{-st_0}}{s(s+a_n)} \left[(-1)^n \cos\left(\frac{n\pi x_3}{h}\right) - 1 \right] \quad (C4)$$

and the total (mixture) stress components are given by

$$\tilde{\sigma}_{11}(x_3, s) = \frac{\lambda \gamma}{h} \frac{1 - e^{-st_0}}{s^2} + \frac{2\gamma h}{k} \sum_{n=1}^{\infty} \frac{a_n}{n^2 \pi^2} \frac{1 - e^{-st_0}}{s(s+a_n)} \left[(-1)^{n+1} \frac{2\mu}{H_A} \cos\left(\frac{n\pi x_3}{h}\right) + 1 \right] \quad (C5)$$

$$\tilde{\sigma}_{22}(x_3, s) = \tilde{\sigma}_{11}(x_3, s) \quad (C6)$$

$$\tilde{\sigma}_{33}(x_3, s) = \frac{H_A \gamma}{h} \frac{1 - e^{-st_0}}{s^2} + \frac{2\gamma h}{k} \sum_{n=1}^{\infty} \frac{a_n}{n^2 \pi^2} \frac{1 - e^{-st_0}}{s(s+a_n)} \left[(-1)^{n+1} \cos\left(\frac{n\pi x_3}{h}\right) + 1 \right] \quad (C7)$$

$$\tilde{\sigma}_{12} = \tilde{\sigma}_{21} = \tilde{\sigma}_{13} = \tilde{\sigma}_{31} = \tilde{\sigma}_{23} = \tilde{\sigma}_{32} = 0 \quad (C8)$$

where $H_A = \lambda + 2\mu$ and $a_n = n^2 \pi^2 k H_A / h^2$.

Figure 1.

Confined compression of a biphasic cylinder. The sample is restrained by rigid impermeable boundaries at the bottom and peripheral surfaces. A time-varying compressive displacement is applied at the upper surface via a rigid porous platen. The entire apparatus is maintained in a hydrated chamber.

Figure 2(a)

Figure 2(b)

Figure 2. Boundary element mesh for a cylinder with $h=1$ and $R=4$: (a) Three-dimensional view; (b) Top view.

Figure 3.

Least-squares curve fitting of the Laplace domain representation (26) to values generated using the BEM at 15 values of s . Fits are shown for the surface stress (solid) and normal flux (dashed) at $(0,0,h)$ as compared to the corresponding BEM data (circles).

Figure 4(a)

Figure 4(b)

Figure 4(c)

Figure 4.

BEM simulations of surface stress relaxation at $(0,0,h)$ in response to application of a compressive ramp-and-hold displacement. Numerical solutions (dashed) are compared to a theoretical solution (Eq. C1) for the cases: (a) $\nu = 0.05$; (b) $\nu = 0.15$; (c) $\nu = 0.25$. The unit of time for the layer is the gel diffusion time $h^2/(k\mu)$ and the unit of stress is the layer shear modulus μ .

Figure 5.

BEM simulations of the normal flux at $(0,0,h)$ in response to application of a compressive ramp-and-hold displacement which, in the theoretical solution, is zero. Numerical simulations are shown for the cases $v = 0.05, 0.15, 0.25$. The unit of velocity for the layer is $k\mu/h$.

Figure 6.

Boundary element mesh for a spherical cell placed at 75% depth in the tissue layer with a radius equivalent to 0.007 times the depth of the layer. Normal displacements at the equator (I), lower pole (II) and upper pole (III) were used to estimate the deformed cell volume. The unit of length is taken as the depth h of a cartilage layer.

Figure 7.

BEM simulations of cell displacements at the equator (I) and upper pole (III) of the cell. Numerical solutions (dashed) are compared to the theoretical solution (solid) in the case where the cell has the same biphasic material properties as its pericellular surroundings.

Figure 8(a)

Figure 8(b)

Figure 8(c)

Figure 8(d)

Figure 8.

BEM simulations of microscopic cell deformation in a configuration of confined compression stress relaxation for typical parameter values of the cell and pericellular microenvironment in articular cartilage. Cell displacements normal to the surface are shown at the equator (I), lower pole (II) and upper pole (III) for a cell located at: (a) 50% depth; (b) 75% depth. Cell volume response, normalized to its value in the undeformed state, is shown at: (a) 50% depth; (b) 75% depth.