Adaptive Finite Element Analysis of the Anisotropic Biphasic Theory of Tissue-Equivalent Mechanics

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Abstract

The nonlinear partial differential equations of the anisotropic biphasic theory of tissue-equivalent mechanics are solved with axial symmetry by an adaptive finite element system. The adaptive procedure operates within a method-of-lines framework using finite elements in space and backward difference software in time. Spatial meshes are automatically refined, coarsened, and relocated in response to error indications and material deformation. Problems with arbitrarily complex two-dimensional regions may be addressed. With meshes graded in high-error regions, the adaptive solutions have fewer degrees of freedom than solutions with comparable accuracy obtained on fixed quasi-uniform meshes. The adaptive software is used to address problems involving an isometric cell traction assay, where a cylindrical tissue equivalent is adhered at its end to fixed circular platens; a prototypical bioartificial artery; and a novel configuration that is intended as an initial step in a study to determine bioartificial arteries having optimal collagen and cell concentrations.

1 Introduction

The mechanical interaction of motile cells with collagen fibers (used generally for both fibrils and fibers) in the surrounding extracellular matrix (ECM) is fundamental to cell behavior in soft tissues and tissue equivalent (TE) systems (highly entangled networks of collagen fibers and, thus, to many biomedical problems and tissue engineering applications (Stopak & Harris, 1982; Madri & Pratt, 1986; Huang et al., 1993; L’Heureux et al., 1993; Hirai et al., 1994; Grinnell, 1994; Wilkins et al., 1994). The anisotropic biphasic theory (ABT) describes the mechanical interactions between cells and the ECM (Barocas & Tranquillo, 1997a). It accounts for the biomechanical feedback loop in which cells deform the surrounding network of ECM fibers, which induces network alignment with inhomogeneous deformation and cell alignment (contact guidance).

Understanding TE mechanics is central to the design and fabrication of bioartificial tissues, including skin (Lopez Valle et al., 1992) and arteries (L’Heureux et al., 1993; Tranquillo et al., 1996). In this investigation, we solve the system of nonlinear partial differential equations governing the ABT theory (§2) by an adaptive finite element software system (§3, (Aiffa, 1997)). To be more specific, solutions are obtained within a method-of-lines framework using finite
element techniques in space and backward difference software in time. The spatial mesh is adaptively refined, coarsened, and relocated (hr-refinement) in response to an error indicator (§3.4) and material deformation. With this technology, we show that solutions of the ABT system and, hopefully, other bio-chemical systems can be obtained with greater efficiency and reliability.

The adaptive finite element software has been applied to three axisymmetric ABT problems in order to demonstrate its advantages relative to more traditional solution techniques (§4). Problems involve a cylindrical isometric cell traction assay (§4.1, (Barocas & Tranquillo, 1997b)), a model bioartificial artery (§4.2, (Tranquillo et al., 1996; L’Heureux et al., 1993)), and a model bioartificial artery with reinforced ends (§4.3). Each problem undergoes extensive material distortion which is accurately tracked by mesh relocation. Two of the problems also have singularities due to discontinuities in the boundary data and the geometry (corners). Sharp solution gradients near these singularities are accurately resolved by automatically placing a graded mesh within these regions. In one example (§4.1), the adaptive method produced a solution using only 16% of the degrees of freedom required by a uniform-mesh solution having comparable accuracy.

2 Anisotropic Biphasic Theory of Tissue-Equivalent Mechanics

The entrapment of cells in a collagen gel to create an in vitro model TE was pioneered in the 1970s (Bell et al., 1979) and quickly emerged as an efficient and easily controllable method for studying cell behavior. TEs have been used extensively to study the contractile behavior of fibroblasts (Ehrlich & Rajaratnam, 1990; Guidry & Grinnell, 1986; Moon & Tranquillo, 1995) because the volume change of the TE (a cell-induced syneresis) provides a quantifiable measure of cell contractility.

In order to facilitate the rational interpretation of in vitro contraction experiments and the design of artificial tissues, Barocas and Tranquillo (Barocas & Tranquillo, 1997a) developed an ABT to describe the dynamic behavior of TEs that accounts for interaction between

- cell growth and migration;
the biphasic nature of the TE, containing a collagen phase and an interstitial water phase;
contractile stress exerted by the entrapped cells, driving the compaction of the TE (Moon & Tranquillo, 1995);
viscoelastic fluid behavior of the collagen matrix (Barocas et al., 1995; Knapp et al., 1997);
defformation-induced anisotropy in the collagen matrix; and
contact guidance (the preferential alignment of cells in the characteristic direction of matrix alignment, which in turn leads to anisotropic cell migration and contractile stress (Dickenson et al., 1994)).

The mathematical statement of the model (Barocas & Tranquillo, 1997a) is:

\[
\frac{1}{2G} \dot{\sigma} + \frac{1}{2\mu} \sigma = \frac{1}{2} [\nabla \mathbf{v} + (\nabla \mathbf{v})^T] + \frac{\nu}{1 - 2\nu} (\nabla \cdot \mathbf{v}) \mathbf{I},
\]

\[
\nabla \cdot [\theta (\sigma + \tau c \Omega_c) - P \mathbf{I}] = 0,
\]

\[
\frac{Dc}{Dt} + c(\nabla \cdot \mathbf{v}) = \nabla \cdot (D_0 \Omega_c \cdot \nabla c) + k_0 c,
\]

\[
\frac{D\theta}{Dt} + \theta (\nabla \cdot \mathbf{v}) = 0,
\]

and

\[
-\nabla \cdot \left[ \frac{(1 - \theta)}{\theta} \nabla P \right] + \varphi_0 \nabla \cdot \mathbf{v} = 0,
\]

where

\[
\dot{\sigma} \equiv \frac{D\sigma}{Dt} - \nabla \mathbf{v} \cdot \mathbf{\sigma} - \mathbf{\sigma} \cdot (\nabla \mathbf{v})^T.
\]

Here, \( D/Dt \) denotes a material derivative, \( \mathbf{I} \) denotes the identity tensor, \( \theta \) denotes the collagen network volume fraction, \( \mathbf{v} \) denotes the network velocity, \( c \) denotes cell concentration, \( \mathbf{\sigma} \) denotes the stress tensor, and \( P \) denotes pressure. Material properties associated with the collagen
network are the modulus $G$, the viscosity $\mu$, Poisson’s ratio $\nu$, and the interstitial flow resistance $\varphi_0$. Cell parameters are the migration (diffusivity) $D_0$, the growth rate constant $k_0$, the cell orientation tensor $\Omega_c$ (Barocas & Tranquillo, 1997a), and the traction parameter $\tau$

$$\tau \equiv \tau_0 \cdot \frac{t^{X_A}}{t^{X_A} + X_B^{X_A} \cdot 1 + \lambda^2},$$

where $\tau_0$, $X_A$, $X_B$, and $\lambda$ are constants. The first fraction in (7) accounts for the lag in cell traction stress due to the time needed to adjust to the change from suspension to tissue-equivalent. The cell traction force during this period has been correlated with cell spreading (Barocas et al., 1995). The second fraction accounts for so-called contact inhibition, the reduction in cell traction observed at high cell densities (Moon & Tranquillo, 1995; Oster et al., 1983).

The viscoelastic fluid momentum equation (5) cannot be eliminated by substitution into the stress balance equation (2); thus, unlike previous work involving elastic solid (Mow et al., 1980) or Newtonian fluid (Dembo & Harlow, 1986) models, the stress remains as a dependent variable.

A variational form of (1)-(5) was developed and solved by a mixed finite element method with piecewise biquadratic velocities and concentrations, piecewise bilinear pressures, and discontinuous piecewise biquadratic stresses (Barocas & Tranquillo, 1997b). Although this formulation was successfully applied to several boundary value problems (Barocas & Tranquillo, 1997a), the associated software lacked the mesh generation and adaptivity capabilities necessary to handle sharp gradients and irregular configurations. This difficulty provides the motivation for the current study.

### 3 Adaptive Finite Element Software

Initial-boundary value problems for the axisymmetric ABT equations (1)-(5) are solved by an extended version of an adaptive finite element software system (Aifia, 1997) that addresses two-dimensional transient partial differential systems of the form

$$g(t, x, u, \partial_t u) + f(t, x, u, \nabla u) = \nabla \cdot a(t, x, u, \nabla u), \quad x \in \Omega, \quad t > 0. \quad (8)$$

Here, $x$ denotes position, $t$ denotes time, $\partial_t$ denotes partial differentiation with respect to $t$, and $u$ is an $m$-vector of dependent variables. The software is generic and specific problems are addressed by supplying procedures to evaluate the $m$-dimensional functions $a$, $f$, and $g$; defining
the initial and boundary conditions; describing the domain $\Omega$; and generating an initial mesh. For the ABT system (1)-(5), $\mathbf{u}$ contains

$$
\mathbf{u} = [\sigma_{rr}, \sigma_{\phi \phi}, \sigma_{zz}, \sigma_{rz}, v_r, v_z, e, \theta, P]^T
$$

where $\sigma_{rr}$, $\sigma_{\phi \phi}$, $\sigma_{zz}$, and $\sigma_{rz}$ are the axisymmetric components of $\mathbf{\sigma}$, and $v_r$ and $v_z$ are components of $\mathbf{v}$.

A spatially-discrete Galerkin form of (8) is solved by a method-of-lines formulation ($\S$3.3) with a hierarchical finite element basis ($\S$3.2) of arbitrary degree. The software has capabilities to

- perform arbitrary combinations of adaptive mesh refinement and coarsening ($h$-refinement), order variation ($p$-refinement), and mesh motion ($r$-refinement) ($\S$3.5);
- construct meshes of triangular elements on complex two-dimensional regions using an octree spatial decomposition (Shephard & Georges, 1991) ($\S$3.1);
- provide a high-order representation of $\Omega$ ($\S$3.1);
- handle combinations of Dirichlet, Neumann, and Robin boundary conditions for different solution components on stationary and moving boundaries; and
- address mixed finite element formulations.

Herein, only combinations of adaptive $h$- and $r$-refinement have been used. Similar analyses have been performed on the oxidation of ceramic-matrix composites (Adjerid et al., 1997) and ceramic fiber coating by chemical vapor deposition (Adjerid et al., 1998b). Aiffa (Aiffa, 1997) presents results using adaptive $p$- and $hp$-refinement.

### 3.1 Mesh Structures

Prior to solution, the domain $\Omega$ is discretized by an octree spatial decomposition (Shephard & Georges, 1991) and partitioned into triangular elements $\Omega_i$, $i = 1, 2, \ldots, N$. Exact representation of curved regions is possible with elements having curved sides; thus, $\Omega = \bigcup_{i=1}^{N} \Omega_i$. Polygonal representations of boundaries are also possible for use with low-order finite element approximation. Even in this case, adaptive $h$-refinement is performed on the curved boundary
rather than its polygonal approximation. With an octree decomposition, the mesh will naturally be finer near curved boundaries.

Maintaining an exact representation of $\Omega$ when its boundary evolves in time is no longer possible. In this case, the moving boundary is approximated by a piecewise polynomial of degree $q$. Interpolating a curved boundary to degree $q$ introduces an $O(h^{q+1/2})$ error in the $H^1$-norm of the finite element solution (Wait & Mitchell, 1985), where $h$ is the length of the longest edge in the mesh and the $H^1$-norm of a scalar function $f$ on $\Omega$ is

$$\|f\|_1 \equiv \left( \int_{\Omega} [(\nabla f)^T (\nabla f) + f^2] \, dV \right)^{\frac{1}{2}}. \quad (10)$$

Without such an approximation, the error of the finite element solution with a piecewise polynomial basis of degree $p$ is $O(h^p)$ in the $H^1$-norm (Brenner & Scott, 1994). Thus, the choice $q = p$ ensures that the solution accuracy is not diminished by the approximation of the boundary.

The mesh is stored in a data structure called the SCOREC Mesh Database (Beall & Shephard, 1997) with data divided into entities that are element vertices, edges, and faces (finite elements in two dimensions). The representation is hierarchical with faces having pointers to their bounding edges which, in turn, have pointers to their bounding vertices. Entities of a given dimension are linked to facilitate traversals. Operators (functions) exist to find bounding entities, such as the vertices bounding a face, and to create and delete elements. Solution and other data is stored with the mesh entities with a goal of facilitating the development and maintenance of finite element software, particularly when using $p$-refinement. Entities may be queried for the solution or mesh data that they contain. Mesh data may be altered for use with $h$ and $r$-refinement. The operators that create and delete elements eliminate most of the complex programming effort associated with adaptive $h$-refinement (§3.5).

### 3.2 Piecewise Polynomial Basis

The finite element basis is a modification of the classical (Szabo & Babuška, 1991) hierarchical basis on a triangle. Thus, polynomial shape functions of degree $p + 1$ are obtained as corrections to shape functions of degree $p$. Elements of the basis are associated with vertices (for $p \geq 1$), edges (for $p \geq 2$), and faces (for $p \geq 3$); thus, complementing the structure of the SCOREC mesh database. The new basis (Aiffa, 1997; Adjerid et al., 1998a) differs from the classical (Szabo &
Babuška, 1991) one in that face functions (internal modes) satisfy an orthogonality condition in strain energy. When applied to the Laplacian operator, the new basis reduces the growth of the condition number of the stiffness matrix from exponential to nearly linear in $p$ (Aiffa, 1997; Adjerid et al., 1998a). Similar savings were recorded on problems with more complex stiffness matrices (Adjerid et al., 1998a) relative to other hierarchical bases (Carnevali et al., 1993). These hierarchical bases can be constructed to arbitrarily high orders; thus, facilitating adaptive $p$-refinement and $a$ posteriori error estimation through adaptive $p$-refinement (§3.4).

Mixed methods, where different components of $u$ have different order approximations, are permitted. A traditional reason for using a mixed finite element method is the satisfaction of the Babuška-Brezzi stability condition (Brezzi & Fortin, 1991). For an incompressible medium, this condition requires that the approximation space of the pressure be a subspace of that used for the velocity. This is often achieved by using a lower-order basis for the pressure than for the velocity. The pressure space may further be selected relative to a patch of elements (macro-elements) used for the velocity or made discontinuous relative to a continuous velocity space (Brezzi & Fortin, 1991). Our software has no capabilities for macro-elements. While discontinuous spaces are possible, the computations of §4 used a piecewise quadratic polynomial for pressure and a piecewise cubic for all other variables in $u$. This choice produced solutions without the spurious oscillations associated with a failure to satisfy the Babuška-Brezzi condition.

Elemental integrals associated with Galerkin inner products are evaluated by Gaussian quadrature of order $2p$ for a basis of degree $p$ (Dunavant, 1985). If the element has a curved edge corresponding to a piecewise polynomial approximation of the boundary to order $q$ (§3.1), then quadrature is performed to order $2(p + q - 1)$. This prescription maintains quadrature errors at a higher order than finite element interpolation errors (Ciarlet & Raviart, 1972; Fix, 1972; Strang, 1972; Strang & Fix, 1973).

3.3 Temporal Solution Techniques

Approximating (8) by the finite element-Galerkin technique in space gives rise to a large system of either ordinary differential equations (ODEs) or, when the Jacobian of $g$ with respect to $\partial_t u$ is singular, differential-algebraic equations (DAEs), which must be solved in time. Solving this system using ODE/DAE software is known as the method of lines and it is the approach used
by our adaptive software. Separating the spatial and temporal discretization has the advantage that time integration procedures may be changed without affecting the larger finite element portion of the software.

We use the variable-order, variable-time-step, backward-difference formula package DASPK (described in (Brenan et al., 1996)) to solve the ODE/DAE system. Nonlinear problems are solved by a damped Newton’s method, and the linear system introduced at each Newton step is solved by sparse Gaussian elimination with a minimum degree reordering (Gursky & Sherman, 1977). After each successful time step, solution coefficients are stored with the geometric entities corresponding to their basis elements.

3.4 Error Indication

A posteriori error estimates provide a measure of solution accuracy and a means of guiding the adaptive enrichment process. The hierarchical basis (§3.2) supplies an inexpensive (relative to the solution cost) way of estimating spatial discretization errors as the correction terms of the next polynomial in the sequence. Thus, if the finite element approximation has degree $p$, a spatial error estimate can be obtained from the hierarchical correction of degree $p + 1$. The effectiveness of this strategy depends on several factors including mesh uniformity and structure, the PDE system, and the computational procedure used to determine the error (Strouboulis & Haque, 1992; Verfürth, 1996). The technique performs best on diffusion-dominated problems. Procedures typically localize the error computation to an element or a patch of elements (Verfürth, 1996) to further reduce the cost of obtaining estimates. These local finite element problems are closed by prescribing fluxes on element or patch boundaries. Performance differs greatly with flux prescriptions (Ainsworth & Oden, 1993; Strouboulis & Haque, 1992). A strategy of this type is offered within our software with fluxes at element boundaries prescribed as the average numerical flux across an edge (Aiffa, 1997).

Local finite element problems for the spatial error estimate consist of contributions from the element or patch of elements and from the fluxes across the element or patch boundary. Error estimates have been shown to converge under $h$-refinement in exactly the same manner as the true error for linear elliptic (Yu, 1991a; Yu, 1991b) and parabolic (Adjerid et al., 1998c; Adjerid et al., 1998d) problems on uniform rectangular-element meshes. These results further
demonstrate that the elemental contribution dominates the flux contribution of the error for even-order finite element computations, while the opposite is true for odd-order finite element solutions. This, and the uncertainty of estimating errors of nonlinear mixed problems such as (1)-(5), motivates us to adapt a simpler alternative. Instead of computing an error estimate, we compute an error indicator $E_i$ on $\Omega_i$ as

$$E_i = E_i^1 + E_i^2 + E_i^3$$

where

$$E_i^j = \left| \partial \Omega_i^j \right| \int_{\partial \Omega_i^j} \left| \frac{\partial C^+}{\partial \mathbf{n}} - \frac{\partial C^-}{\partial \mathbf{n}} \right| dS, \quad j = 1, 2, 3. \tag{12}$$

Here, $\partial \Omega_i^j$ is the $j$th edge of the boundary $\partial \Omega_i$ of $\Omega_i$, $\mathbf{n}$ is the unit outward normal vector to $\partial \Omega_i$, $E_i^j$ is the error indicator on edge $j$, $\left| \partial \Omega_i^j \right|$ is the length of $\partial \Omega_i^j$, $C(t, \mathbf{x})$ is the finite element approximation of the concentration $c(t, \mathbf{x})$, and superscripts + and − denote values on the exterior and interior of $\Omega_i$. Thus, the error indicator on $\Omega_i$ is the absolute jump in the concentration gradient across the boundary of $\Omega_i$ scaled by the length of the boundary. The concentration gradient was chosen to control adaptivity because $c$ varies significantly (relative to other components of $\mathbf{u}$) and high gradients in $\mathbf{u}$ are reflected by a high gradient in $c$.

Theoretical results (Adjerid et al., 1998c; Adjerid et al., 1998d) implying that the spatial error of odd-order finite element solutions are proportional to flux jumps are only available for rectangular-element meshes. Nevertheless, computational evidence (Ilin et al., 1997) suggests that they hold on triangles. With the concentration approximated by a piecewise cubic polynomial, the error indicator (11)-(12) might be proportional to the true error; however, with the complexities of the ABT system, this remains unverified.

Control of local temporal errors is done by procedures within DASPK. Strategies for controlling global errors by maintaining the local temporal error at a small fraction of global spatial error have been described for stiff differential systems arising from the discretization of parabolic problems (Lawson et al., 1991). If the error indicator (11)-(12) were a true error estimate, this strategy might give an appraisal of the global discretization error; however, once again, the ABT system is too involved to characterize as either being stiff or parabolic.
3.5 Adaptivity

When choosing adaptive $hr$-refinement to solve the ABT system (1)-(5), our aims were accurate resolutions of moving boundaries by $r$-refinement and of sharp gradients by $h$-refinement. Mesh coarsening is needed in addition to refinement since high-gradient locations may move with time.

Adaptive $r$-refinement can concentrate a mesh within high-error regions and follow these regions as they evolve. This mesh motion is often far less expensive than $h$-refinement (Adjerid & Flaherty, 1986) for a given accuracy. With parallel computation, $r$-refinement avoids the need for dynamic load balancing which must be done with $h$-refinement. Unfortunately, two- and three-dimensional meshes tend to tangle with $r$-refinement and there is no effective way of controlling the discretization error.

$R$-refinement may be regarded as a dynamic coordinate transform and, as such, the software permits mappings from the physical $x$-plane to a computational $\xi$-plane of the form

$$\mathbf{x} = \mathbf{x}(t, \xi, u)$$ (13)

to be prescribed. Typically, only the vertices of the triangular elements are mapped by this transformation. Element edges remain straight, at least for those elements that are not on a moving curved boundary or interface. In this analysis, we follow a simpler course and move mesh vertices according to their material positions, i.e.,

$$\frac{d\mathbf{x}_j}{dt} = \mathbf{v}(t, \mathbf{x}_j), \quad j = 1, 2, \ldots, N_V,$$ (14)

where $\mathbf{x}_j$ is the coordinate of vertex $j$ and $N_V$ is the number of vertices. Curved element sections on moving boundaries are tracked with greater precision. If, as described in §3.1, a curved element edge is approximated by a polynomial of degree $q$, then the $q + 1$ interpolation points describing the segment are moved according to (14). The ODE system (14) may either be coupled with the finite element system for integration by DASPK or, with less precision, solved separately in an explicit manner. The former course was taken in this application.

The temporal integration is halted after each time step, error indicators are calculated according to (12), and adaptive $h$-refinement is performed, if necessary. In particular, edge $j$ of element $i$ is marked for refinement when $E_{ij} \geq \alpha_R \overline{E}$ and marked for coarsening when $E_{ij} \leq \alpha_C \overline{E}$, where $\alpha_R$ and $\alpha_C$ are, prescribed refinement and coarsening tolerances, respectively, and $\overline{E}$ is the average of $E_{ij}$ over the edges of the mesh. Normally, error indicators would be checked after
four to five time steps (Aiffa, 1997); however, these error indicators are so inexpensive that checking after each time step incurs a negligible cost and provides additional reliability. Given the uncertainties of the initial mesh, backtracking is performed to ensure its adequacy. Thus, the initial time step is repeated until every edge of the mesh satisfies $E_i^j \in (\alpha_R, \alpha_C)E$.

Elements having edges that are marked for refinement are refined by templates as shown in Figure 3.5. Dashed lines indicates the edges created by refinement. Marked edges scheduled for bisection are shown as darker lines. The choice of the refinement that is performed when three edges are marked (right two templates in Figure 3.5) is determined to minimize the difference in the angles of the resulting four triangles. This decision is based on a desire to avoid elements with small or large angles for accuracy considerations.

![Figure 1: Refinement templates for a triangle with one (left), two (center left), and three (center right and right) marked edges.](image1)

![Figure 2: An edge (shown dark on the left) is removed by collapsing its upper vertex to the lower one (right).](image2)

Coarsening is done by edge collapsing, *i.e.*, one of the vertices bounding an edge is moved to the other to remove the edge. An edge marked for removal on a patch of elements is shown dark on the left of Figure 3.5. This edge is removed by collapsing the upper vertex to the lower one as shown on the right of Figure 3.5. The dashed lines indicate the new elements of the patch. Other complications arise, particularly with simultaneous $h$- and $r$-refinement. The major problem is ensuring that the angles of elements remain bounded away from zero and $\pi$ radians during enrichment. Failure to do so renders the coordinate transform between the physical and canonical elements singular. Techniques used to address these and other $h$-refinement issues are described elsewhere (Aiffa, 1997).
Finite element solutions must be available on the newly refined or coarsened elements before the time integration can continue and we obtain these by a local $L^2$ projection. Consider an element or patch of elements that have been affected by refinement (Figure 3.5) or coarsening (Figure 3.5) and construct a finite element basis relative to the new mesh. The finite element solution $\mathbf{U}_{new}$ is determined on the new element or patch $\Omega_{new}$ by solving the $L^2$ problem

$$
\int_{\Omega_{new}} (\nabla^T K^new) [\nabla^T U_{new} - \nabla^T U] dV = 0, \quad \forall \nabla^T U_{new} \in S(\Omega_{new}),
$$

(15)

where $\nabla^T U$ is the finite element solution prior to $h$-refinement and $\nabla^T U_{new}$ is a test function relative to the finite element space $S_{new}$ on the new mesh. Structures within the SCOREC mesh database (§3.1) facilitate the solution of (15) since all solution and shape function data are stored with the appropriate mesh entities.

4 Simulations

We apply the adaptive finite element software to three initial-boundary value problems for the ABT system (1)-(5): an isometric cell traction assay (ICTA) (Barocas & Tranquillo, 1997b), a prototypical bioartificial artery (BAA) (L’Heureux et al., 1993; Tranquillo et al., 1996), and a BAA with thicker ends. Collagen parameter values (Barocas & Tranquillo, 1997a) and cell parameter values for the ICTA (Barocas & Tranquillo, 1997b) and BAA (L’Heureux et al., 1993; Tranquillo et al., 1996) problems were obtained from the literature.

The types of boundary conditions involved with each problem are:

- A free surface where the pressure, the normal component of the total stress, and the diffusive cell flux vanish, i.e.,

$$
P = 0, \quad (\sigma + c\Omega_c) \cdot \mathbf{n} = 0, \quad (\Omega_c \cdot \nabla c) \cdot \mathbf{n} = 0.
$$

(16)

- A plane of symmetry or a free-slip surface where the tangential component of the total stress, the interstitial flow, the diffusive cell flux, and the velocity of the network normal to the surface vanish, i.e.,

$$
\mathbf{n} \cdot (\sigma + c\Omega_c) \cdot \mathbf{t} = 0, \quad \nabla P \cdot \mathbf{n} = 0, \quad (\Omega_c \cdot \nabla c) \cdot \mathbf{n} = 0, \quad \mathbf{v} \cdot \mathbf{n} = 0,
$$

(17)

where $\mathbf{t}$ is a unit tangent vector. A free-slip surface represents a surface that is impenetrable but does not adhere to the TE. It is functionally equivalent to a plane of symmetry.
A no-slip surface has the impenetrability conditions of the free-slip surface, but the tangential component of the velocity vanishes instead of the tangential stress, i.e.,

\[ \nabla P \cdot \mathbf{n} = 0, \quad (\Omega_c \cdot \nabla c) \cdot \mathbf{n} = 0, \quad \mathbf{v} = 0. \quad (18) \]

In all experiments, the initial solution vector \( \mathbf{u}(0, \mathbf{x}), \mathbf{x} \in \Omega \), is zero except \( c = \theta = 1 \). These conditions correspond to a stress-free state of equilibrium with the domain filled with a collagen network having a unit concentration and no solution phase volume.

### 4.1 Isometric Cell Traction Assay

The ICTA has been used in various forms (Kolodney & Elson, 1993) to measure the force generated by cells in a TE. ICTA problems have been solved on a slab (Kolodney & Elson, 1993); however, we solve axisymmetric problems on the cylinder \( \{(r, \phi, z) \mid 0 < r < 1, \ 0 \leq \phi < 2\pi, \ 0 < z < 1\} \). Symmetry conditions (17) are imposed on \( r = 0; \ z = 0 \) is a plane of symmetry (17); \( r = 1 \) is a free surface (16); and \( z = 1 \) represents a no-slip surface (18).

As the cells contract, the force to maintain a constant length increases, and the circumference at the midplane \( (z = 0) \) decreases. The prior analysis of this problem (Barocas & Tranquillo, 1997b), without adaptivity, had difficulty resolving sharp gradients where the free and free-slip surfaces meet. We show that the adaptive \( hr \)-refinement procedure will alleviate this.

Concentration and the axial stress contours are shown in Figures 3 and 4, respectively, at four times with the computational meshes superimposed. Here, and in all similar illustrations, the radial \( (r) \) direction is shown horizontal and the axial \( (z) \) direction is vertical. There is a singularity, at the juncture of the no-slip and free-surface boundaries. This singularity strengthens as time increases. The mesh is concentrated in this region and graded to resolve the solution adequately. The axial stress obtained in a prior study (Barocas & Tranquillo, 1997b) had an anomalous oscillatory behavior that disappeared with (uniform) mesh refinement. Axial stress components obtained by adaptive \( hr \)-refinement (Figure 4) have no spurious behavior, presumably because the singularity is being adequately resolved on the graded mesh.

As an indication of the convergence rate, we generated a sequence of solutions on meshes obtained by uniform refinement of an initial mesh. In Figure 5, we show \( \|e(t, \cdot)\|_1 \) for these solutions at \( t = 80 \) as a function of the average mesh spacing \( h \) and the total degrees of freedom
Figure 3: ICTA concentration at four times with adaptive meshes superimposed.
Figure 4: ICTA axial stress at four times with adaptive meshes superimposed.
Figure 5: ICTA convergence as a function of the total DOF or $h$ for uniform (solid curve) and adaptive ($\diamond$) mesh refinement.

(DOF), which is the time integral of the spatial DOF. This sequence indicates that the concentration is converging at an approximate rate of $h^{1.2}$. This is less than the $O(h^2)$ rate for smooth problems because of the singularity at the intersection of the no-slip and free-slip surfaces. The adaptive computation of Figures 3 and 4 is indicated by a $\diamond$ on Figure 5. For comparable accuracy, the solution by adaptive $hr$-refinement required approximately 16% of the total DOF of that with a uniform mesh. The improvement is largely due to the greater resolution of sharp gradients near the singularity provided by adaptivity. The excellent performance of the adaptive method further suggests that the error indicator (12) is a good measure of solution accuracy.

4.2 Bioartificial Artery

A prototypical BAA may be formed by allowing a tubular TE to contract on a rigid, impermeable, free-slip mandrel (Tranquillo et al., 1996; L’Heureux et al., 1993). Using the initial geometry of the cylinder $\{(r, \phi, z) \mid 2 < r < 3, 0 \leq \phi < 2\pi, 0 < z < 1\}$, this axisymmetric study features free surface conditions (16) at $z = 1$ and $r = 3$; a plane of symmetry (17) at $z = 0$; and a free-slip surface (17) at $r = 2$. Concentration contours are shown at four times in Figure 6. These adaptive results compare well with prior results (Barocas & Tranquillo, 1997b; Barocas
et al., 1998) obtained by standard finite element techniques. Since there are no sharp gradients, adaptive $hr$-refinement is needed less than with the ICTA problem. Mesh refinement is fairly uniform and is redistributed as the medium contracts.

4.3 Reinforced Bioartificial Artery

Although we have not identified an appropriate objective function for optimal BAA design, we know that the initial shape of the BAA is an important (and controllable) design parameter. As a preliminary study, we analyze a BAA with reinforced ends and boundary conditions as shown in Figure 7. The volume of the reinforced BAA has been selected to be the same as that of the standard BAA (§4.2). Our hope was that this design will lead to a BAA with significantly higher collagen and cell content near the ends, which could facilitate suturing the BAA at the implant site. The geometry also provides a demanding test of the finite element software because of the singularity at the reentrant corner.

The parameters are the same as in the standard BAA problem (§4.2). Once again, concentration contours are shown at four times in Figure 8. As conjectured, the mesh is refined near the reentrant corner to maintain accuracy in the presence of a singularity. The mesh does not change significantly after some initial refinement. This is likely due to the self-similar behavior of the solution near the singularity.

4.4 Discussion

An adaptive finite element software system has been used to solve the ABT system (1)-(5). Solutions of ICTA and BAA problems duplicate prior results (Barocas & Tranquillo, 1997b); however, the adaptive solutions have comparable accuracy with fewer total DOF. With adaptive $hr$-refinement, we were able to locate singularities and automatically refine the mesh in their vicinity. No a priori solution knowledge was necessary. The software is able to solve problems on arbitrary two-dimensional regions; hence, it should provide a useful tool for the investigation of optimal design and other problems involving complex geometry.

Several computational research issues remain unanswered.

- A posteriori error estimation procedures must replace the error indicators of this study. They will enhance both reliability and efficiency.
Figure 6: Concentration in a BAA at four times with adaptive meshes superimposed.
Adaptive $p$- and $hp$-refinement offer the possibility of exponential convergence rates and, as such, they should be explored. Optimal enrichment strategies are needed to decide when and where to alter the mesh and vary the order.

In this study, linear algebra was performed by a sparse direct procedure. Preconditioned Krylov iteration has been effective on the ABT system (Barocas & Tranquillo, 1997b) and this should be tried within the adaptive system.

Backward difference software in a method-of-lines setting would typically return to a first-order method after each $h$- or $p$-refinement. This can be avoided by projecting the solution in the enriched space backwards in time to supply the necessary history to the backward difference software (Wang, 1991). This strategy is being added to the software system.

For complex PDEs, a substantial effort is needed to calculate the elemental Galerkin inner products. A strategy of interpolation of the nonlinear terms in the inner products with exact integration (Dey et al., 1998) should enhance efficiency relative to the traditional use of Gaussian quadrature.

An object-oriented framework is being written (Beall & Shephard, 1998) to simplify the creation of three-dimensional finite element software. Software having the capabilities described herein will be developed to operate within this environment.
Figure 8: Concentration in a reinforced BAA at four times with adaptive meshes superimposed.
• The reinforced ABT study (§4.3) was only the initial step in an optimal design study. A combination of the adaptive solution and optimization software would be necessary for a more thorough investigation.

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