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A nonlinear biphasic model of flow-controlled infusion in brain: Fluid transport and tissue deformation analyses

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ABSTRACT

A biphasic nonlinear mathematical model is proposed for the concomitant fluid transport and tissue deformation that occurs during constant flow rate infusions into brain tissue. The model takes into account material and geometrical nonlinearities, a hydraulic conductivity dependent on strain, and nonlinear boundary conditions at the infusion cavity. The biphasic equations were implemented in a custom written code assuming spherical symmetry and using an updated Lagrangian finite element algorithm. Results of the model showed that both geometric and material nonlinearities play an important role in the physics of infusions, yielding important differences from infinitesimal analyses. Geometrical nonlinearities were mainly due to the significant enlargement of the infusion cavity, while variations of the parameters that describe the degree of nonlinearity of the stress–strain curve yielded significant differences in all distributions. For example, a parameter set showing stiffening under tension yielded maximum values of radial displacement and porosity not localized at the infusion cavity. On the other hand, a parameter set showing softening under tension yielded a slight decrease in the fluid velocity for a three-fold increase in the flow rate, which can be explained by the substantial increase of the infusion cavity, not considered in linear analyses. This study strongly suggests that significant enlargement of the infusion cavity is a real phenomenon during infusions that may produce collateral damage to brain tissue. Our results indicate that more experimental tests have to be undertaken in order to determine material nonlinearities of brain tissue over a range of strains. With better understanding of these nonlinear effects, clinicians may be able to develop protocols that can minimize the damage to surrounding tissue.

1. Introduction

The delivery of therapeutic agents into the brain is impeded by the blood–brain barrier, preventing adequate treatment of tumors and other diseases of the central nervous system. Convection-enhanced delivery was developed as a means to deliver therapeutic agents directly into brain tissue and to transport the drugs in the extracellular space using convective flow.

To study the efficacy of convection-enhanced delivery as a treatment protocol, it is necessary to determine the convective flow that results from the infusion. Because measuring interstitial fluid pressure and fluid velocities in vivo is very difficult, researchers have developed mathematical models of convection-enhanced delivery. Poroelastic or biphasic models of brain tissue have been used to study the concomitant fluid transport and tissue deformation that occurs during infusion (Barry and Aldis, 1992; Basser, 1992; Smith and Humphrey, 2007), however each of these studies is limited by the assumption of linear elasticity of the solid phase. Simultaneous tissue deformation and mass transport during infusion has only been recently studied by Netti et al. (2003) and Chen and Sarntinoranont (2007), both of whom assume linear elasticity of the solid phase.

While rigidity or linear elasticity is a common assumption of the aforementioned studies, nonlinear stress–strain curves under finite deformations have been documented for brain tissue (Miller and Chinzei, 1997, 2002; Franceschini et al., 2006). In addition, the nonlinear variation of hydraulic conductivity with strain has also been taken into account in recent studies of hydrocephalus, and this effect has been deemed to play an important role in both the mechanics of the tissue and the associated fluid transport (Sobey and Wirth, 2006; Wirth and Sobey, 2006).

Recently, we proposed a spherical, biphasic model for constant pressure infusion into brain tissue that considers simultaneously nonlinear stress–strain curves under finite deformation and nonlinear variation of hydraulic conductivity (García and Smith, 2009). In practice, however, most experimental or clinical

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infusions are conducted under constant flow rate conditions, in which case the pressure to which the brain is exposed is not controlled and varies to sustain the applied flow rate.

We present a spherical model of flow-controlled infusions, implemented in a custom code written by the authors, to study the physics that occur and to determine the importance of using a nonlinear material model for brain tissue and of including a deformation-dependent hydraulic conductivity. This geometry simplification allowed for an efficient implementation of the nonlinear iterative scheme by using two-node elements that represent spherical domains. To the best of our knowledge, no commercial finite element solver allows for the inclusion of all these nonlinearities in biphasic analyses that could ultimately be coupled with mass transport analyses of the infused agent. Knowing the significance of each effect is important for the development of more advanced, three-dimensional computational models that may ultimately aid in devising infusion protocols for the treatment of diseases of brain tissue.

2. Methods

2.1. Governing equations

The biphasic model of constant pressure infusions (García and Smith, 2009) is adapted to constant flow rate infusions. Briefly, considering spherical symmetry and finite deformations, fluid flow and strain are described by the following equations:

$$\frac{1}{r^2}\frac{\partial}{\partial r}[r^2(\sigma_r - p)] - \frac{2}{r}(\sigma_\theta - p) = 0 \tag{1}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}[r^2 v_s] - \frac{1}{r^2}\frac{\partial}{\partial r}\left[\kappa\, r^2 \frac{\partial p}{\partial r}\right] = 0, \tag{2}$$

where σ_r and σ_θ are the effective stresses in radial and tangential direction, respectively, v_s the velocity of the solid phase, p the pore pressure, and κ the hydraulic conductivity. All variables only change with the radial coordinate r, which represents the current position of a material element.

The behavior of the solid phase was represented by the isotropic hyperelastic energy function

$$W = \sum_{k=1}^{N}\frac{\mu_k}{\alpha_k}(\lambda_r^{\alpha_k} + 2\lambda_\theta^{\alpha_k} - 3 - \alpha_k \ln(J)) + \frac{\mu'}{2}(J-1)^2, \tag{3}$$

where λ_r and λ_θ are the radial and circumferential stretch ratios, respectively, μ_k, α_k, and μ' material parameters, and J the determinant of the deformation gradient tensor (Ogden, 1984). The parameters α_k can be adjusted to describe the shape of the stress–strain curve (Miller and Chinzei, 2002; Franceschini et al., 2006) and the parameter μ' depends on the Poisson's ratio. The Young's modulus E and Poisson's ratio v at zero strain are related to the strain energy parameters by the relations

$$E = (1+v)\sum_{k=1}^{N}\alpha_k\mu_k \tag{4}$$

$$v = \frac{\mu'}{2\mu' + \sum_{k=1}^{N}\alpha_k\mu_k}. \tag{5}$$

To be consistent with other analyses of brain tissue (Chen and Sarntinoranont, 2007; García and Smith, 2009; Sobey and Wirth, 2006; Wirth and Sobey, 2006), the variation of hydraulic conductivity with strain was assumed to depend on tissue dilatation as

$$\kappa = \kappa_0 \exp(Me), \tag{6}$$

where κ_0 is the hydraulic conductivity at zero strain, M a nondimensional parameter that controls the variation of hydraulic conductivity, and e the dilatation. This spatial and time varying hydraulic conductivity was used in Darcy's law to calculate the bulk fluid velocity v_f as

$$v_f = -\kappa\frac{\partial p}{\partial r} + \phi_f v_s, \tag{7}$$

where the fraction of the fluid phase ϕ_f (or porosity) was calculated using

$$\phi_f = 1 - (1 - \phi_{f_0})/J, \tag{8}$$

where ϕ_{f_0} is the initial fluid fraction.

2.2. Finite element implementation and verification

The solution of these governing equations was implemented in a custom finite element code written by the authors. The spatial discretization of Eqs. (1) and (2) was accomplished using an updated Lagrangian scheme where linear polynomials were used as the shape and weighting functions. The time derivative of the radial displacement was approximated with the backward difference, and a Newton procedure was implemented to solve the nonlinear set of algebraic equations at each time step (Almeida and Spilker, 1997; Belytschko et al., 2000).

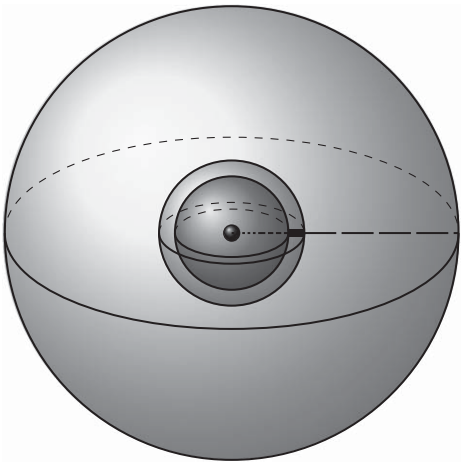

Fig. 1. Schematic of the spherical geometry and finite element mesh used in this study. The innermost sphere represents the infusion cavity, whereas the outermost sphere represents the outer boundary of the computational domain. The horizontal dashed line represents the mesh, which is biased toward the infusion cavity, illustrated by the shorter dashes, in contrast with the longer dashes toward the outer sphere. The thicken portion of the horizontal line corresponds to a single element, and the volume between the concentric spheres at both ends illustrates the spherical domain the element represents.

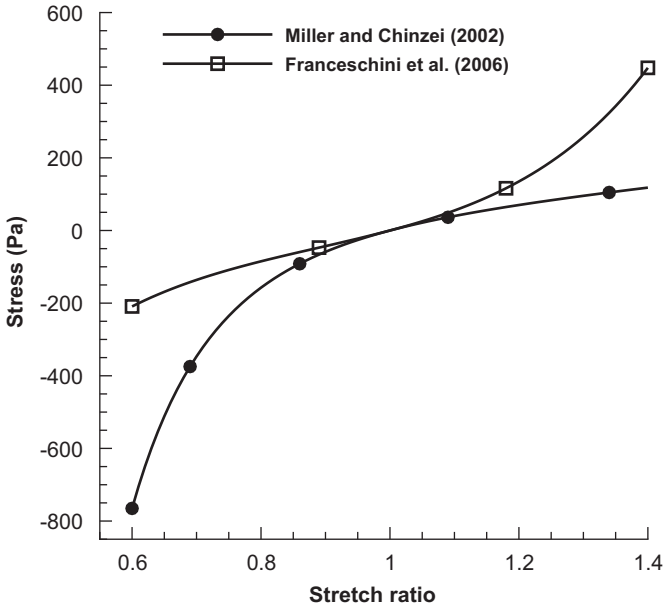

Fig. 2. Uniaxial stress response for the two sets of nonlinear parameters: $\alpha_1 = -4.7$, $\alpha_2 = 0$ from Miller and Chinzei (2002) and $\alpha_1 = 4.31$, $\alpha_2 = 7.74$ from Franceschini et al. (2006). The Young's modulus of 421 Pa is equal to the slope of each curve at zero deformation, i.e., stretch ratio equal to one.