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Cell viability in intervertebral disc under various nutritional and dynamic loading conditions: 3d Finite element analysis

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ABSTRACT

In this study, a new cell density model was developed and incorporated into the formulation of the mechano-electrochemical mixture theory to investigate the effects of deprivation of nutrition supply at boundary source, degeneration, and dynamic loading on the cell viability of intervertebral disc (IVD) using finite element methods. The deprivation of nutrition supply at boundary source was simulated by reduction in nutrition level at CEP and AF boundaries. Cases with 100%, 75%, 60%, 50% and 30% of normal nutrition level at both CEP and AF boundaries were modeled. Unconfined axial sinusoidal dynamic compressions with different combinations of amplitude ($u=10\%\pm2.5\%$, $\pm5\%$) and frequency ($f=1, 10, 20$ cycle/day) were applied. Degenerated IVD was modeled with altered material properties. Cell density decreased substantially with reduction of nutrition level at boundaries. Cell death was initiated primarily near the NP–AF interface on the mid-plane. Dynamic loading did not result in a change in the cell density in non-degenerated IVD, since glucose levels did not fall below the minimum value for cell survival; in degenerated IVDs, we found that increasing frequency and amplitude both resulted in higher cell density, because dynamic compression facilitates the diffusion of nutrients and thus increases the nutrition level around IVD cells. The novel computational model can be used to quantitatively predict both when and where cells start to die within the IVD under various kinds of nutritional and mechanical conditions.

1. Introduction

The intervertebral disc (IVD) cells play a vital role in maintaining IVD health and function. Not only do cells synthesize the extracellular matrix (ECM), a significant structure helping sustain the mechanical force for the IVD in the spine, but they also synthesize catabolic molecules responsible for matrix breakdown. A disruption in the delicate balance between anabolic and catabolic activities leads to alteration of ECM, which is strongly correlated with structural remodeling, leading to tissue disorganization and, resultantly, IVD dysfunction and degeneration (Adams and Roughley, 2006; Bibby and Urban, 2004).

Degenerative changes to IVD include decreased nutrients levels, reduced cell density, reduced proteoglycan synthesis and alteration in collagen distribution (Maroudas, 1975; Maroudas et al., 1975; Oegema, 1993; Roberts et al., 1989; Urban and Roberts, 2003). Reduction of cell density in degenerated IVD tissue greatly diminishes the ability of the cells to synthesize and maintain the ECM structure, deterioration of which further exacerbates the degeneration of IVD tissues.

Due to the avascular nature of the tissue, essential nutrients (e.g., glucose and oxygen) are transported in and metabolic wastes (e.g., lactic acid) out of the tissue through the dense ECM by diffusion (mainly for small molecules) and convection (mainly for large molecules) from the peripheral and endplate vasculatures. Most of the nucleus pulposus (NP) cells rely on nutrients supplied through the cartilaginous endplate (CEP) route while the cells in the annulus fibrosus (AF) region are mainly nurtured through the annulus peripheral pathway (Bibby and Urban, 2004; Maroudas, 1975; Nachemson et al., 1970; Roberts et al., 1989; Urban and Roberts, 2003; Urban et al., 2000). Adequate nutrient supply has long been regarded as a crucial factor for maintaining normal activities of IVD cells (Bibby et al., 2002; Bibby and Urban, 2004; Horner and Urban, 2001; Nachemson et al., 1970; Oegema, 1993; Urban et al., 2000). It has been shown that the density of IVD cells is mainly dependent on glucose concentration (Bibby et al., 2002; Bibby and Urban, 2004; Horner and Urban, 2001; Jackson et al., 2011a; Shirazi-Adl et al., 2010).

In patients with cigarette smoking, malnutrition, or disorders like blood aneurysms, nutrition levels from the boundary vasculatures tends to decrease accordingly, which could lead to cell death and the development of IVD degeneration (Frymoyer et al., 1983; Gyntelbe, 1974; Holm and Nachemson, 1988). Mechanical loading has been shown not only to directly affect the intrinsic cellular activity (Huang et al., 2004; Kasra et al., 2003; Kroeber et al., 2005;

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MacLean et al., 2004; Ohshima et al., 1995; Wang et al., 2007; Wuertz et al., 2009), but also to influence the transport of nutrients through the ECM of the IVD tissue (Huang and Gu, 2007; Huang et al., 2012; Jackson et al., 2011b, in press, 2008; Malandrino et al., 2011; Yao and Gu, 2006, 2007; Yuan et al., 2009). Knowledge of changes in cell viability and metabolism in the IVD under various biological, physical and chemical signals is essential for understanding IVD degeneration.

However, it is difficult to study the complicated cellular environment in IVD in vivo experimentally. Numerical methods therefore have been increasingly used to investigate the transport of nutrients and cell viability within the IVDs (Huang and Gu, 2008; Huang et al., 2012; Jackson et al., 2011a; Sélard et al., 2003; Shirazi-Adl et al., 2010; Soukane et al., 2005, 2007, 2009). Shirazi-Adl et al. (2010) were the first to introduce a theoretical model to describe the coupling of cell viability and nutrition level in IVD. In this model (Shirazi-Adl et al., 2010), it is assumed that cell density varies instantaneously with glucose concentration. This model has also been used in our previous study on cell viability in IVD (Jackson et al., 2011a). One of the disadvantages of this model is that the resurrection of dead cells would occur when the glucose level recovers after falling below certain critical level for cell survival (e.g., 0.5 mM (Bibby and Urban, 2004)). Another problem of this model is that it cannot be used to analyze cell viability in a time-dependent process under dynamic situations. In fact, to date, there is no theoretical model that is capable of adequately describing the effect of nutrition levels on cell viability in a time-dependent manner.

Therefore, the objectives of this study were to develop (1) a novel constitutive model for IVD cell viability and (2) a comprehensive numerical tool to analyze and predict how cell viability was affected by the alteration in the extracellular microenvironment that results from disturbances in nutrition deprivation, degeneration, and dynamic loading in the realistic, human IVDs in a time-dependent manner.

2. Theoretical model

The IVD is assumed as a mixture of intrinsically incompressible elastic solid phase (denoted as 's'), water phase (denoted as 'w'), and charged (Na^+ and Cl^-) and uncharged (glucose, oxygen, lactate) solute (denoted as 'α') phases. The governing equations for the mixture are summarized as follows (Ateshian, 2007; Gu et al., 1998; Lai et al., 1991):

$$\nabla\cdot\boldsymbol{\sigma}=0 \tag{1}$$

$$\nabla\cdot(v^s+J^w)=0 \tag{2}$$

$$\frac{\partial(\phi^w c^\alpha)}{\partial t}+\nabla\cdot(J^\alpha+\phi^w c^\alpha v^s)=Q^\alpha \tag{3}$$

where $\boldsymbol{\sigma}$ is the total stress of the mixture, v^s is the velocity of the solid phase, J^w is the volume flux of water relative to the solid phase, J^α is the molar flux of solute α relative to the solid phase, ϕ^w is the water volume fraction (also known as tissue porosity or water content), c^α is the molar concentration (per unit fluid volume) of solute α, and Q^α is the cellular metabolic rate of solute α per unit tissue volume. The total stress $\boldsymbol{\sigma}$, volume flux of water (J^w), and molar flux of solute α (J^α) can be expressed as

$$\boldsymbol{\sigma}=-p\mathbf{I}+\lambda tr(\mathbf{E})\mathbf{I}+2\mu\mathbf{E} \tag{4}$$

$$J^\alpha=H^\alpha c^\alpha J^w-\frac{D^\alpha\rho^\alpha}{RT}\nabla\tilde{\mu}^\alpha \tag{5}$$

$$J^w=-k\left(\rho_T^w\nabla\mu^w+\sum_\alpha H^\alpha c^\alpha M^\alpha\nabla\tilde{\mu}^\alpha\right) \tag{6}$$

where p is the fluid pressure, $\mathbf{I}$ is the identity tensor, λ and μ are the Lamé constants of the solid matrix, $\mathbf{E}$ is the infinitesimal strain tensor for the solid matrix, k is the hydraulic permeability, ρ^α is the apparent mass density of solute α, ρ_T^w is the true mass density of water, H^α is the convection coefficient (hindrance factor) of solute α, M^α is the molar weight of solute α, D^α is the diffusivity of solute α, R is the universal gas constant and T is the absolute temperature. The metabolic rates of sodium ion (Na^+) and chloride ion (Cl^-) are assumed to be zero (i.e., $Q^{Na^+}=Q^{Cl^-}=0$). The cellular metabolic rates of oxygen, glucose, and lactate (per unit tissue volume) and pH are given as follows (Bibby et al., 2005; Huang and Gu, 2008; Huang et al., 2012):

$$Q^{o_2}=-\frac{V'_{max}(pH-4.95)c^{o_2}}{K'_m(pH-4.59)+c^{o_2}}\rho^{cell} \tag{7}$$

$$Q^{lactate}=\exp(-2.47+0.93pH+0.16c^{o_2}-0.0058c^{o_2^2})\rho^{cell}\frac{c_g}{c_g+k_m^l} \tag{8}$$

$$Q^{glucose}=-0.5Q^{lactate} \tag{9}$$

$$pH=-0.1c^{lactate}+7.5 \tag{10}$$

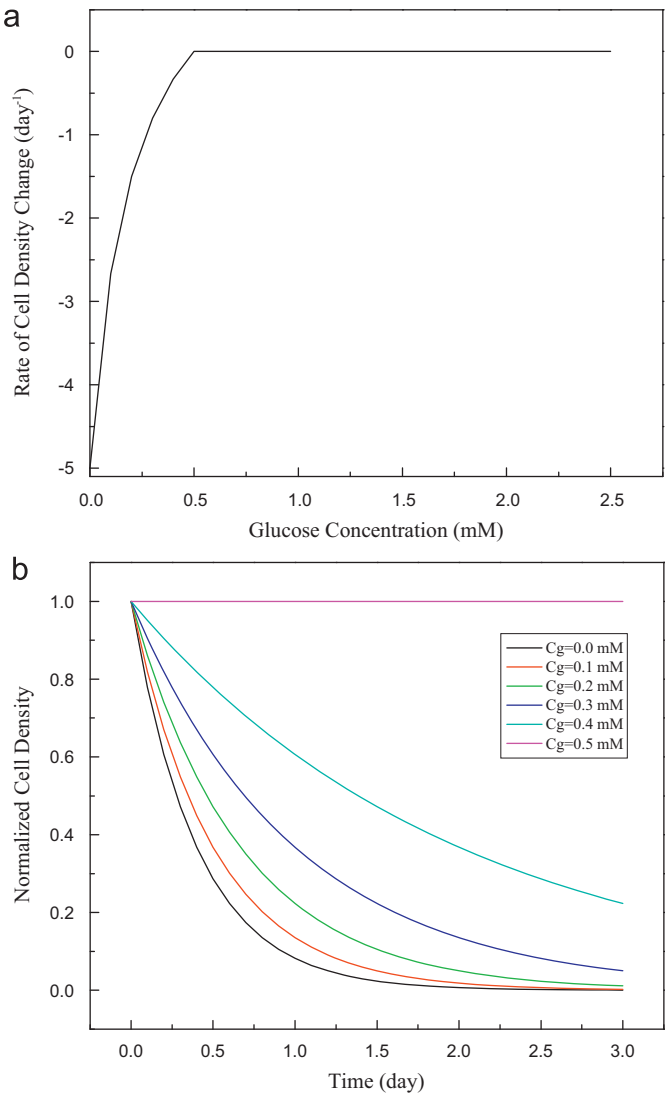

Fig. 1. (a) The rate of cell density (normalized) change as a function of glucose concentration; (b) changes in cell density (normalized) with time at several constant glucose levels. Cells begin to die when glucose levels fall below 0.5 mM, and cell density approaches zero when the glucose concentration is lower than 0.2 mM for a period of 3 days (Bibby and Urban, 2004). No change in cell density occurs when the glucose concentration is above 0.5 mM.