# Patient Specific Models of Nutrient Availability in Degenerated Intervertebral Discs: Which Patients are Candidates for Stem Cell Therapy?

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# Background

**This is the first study that uses non-invasive MRI techniques to create disc-specific gradient profiles for glucose, oxygen, lactate and pH to select patients for stem cell therapy based on disc nutrient supply.**

*Intervertebral disc degeneration*

**Degeneration of the intervertebral disc (IVD) is a common cause for lower backpain** in 40% adults younger than 30 years and in 90% adults older than 50[1]. A 2006 review estimated total costs attributed to lower backpain in the United States to exceed $100 billion annually[2].

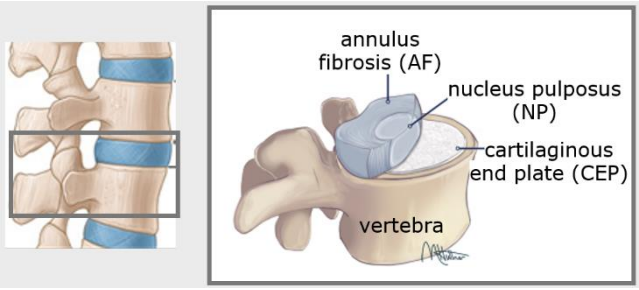


**Figure 1.** Anatomy of the intervertebral disc.

*Current treatments*

Current methods to mitigate lower backpain like pharmacological treatments have been demonstrated to alleviate early and minor symptoms caused by the condition. Invasive surgeries, such as spinal fusion, are necessary for more than 500,000 patients throughout the country yearly[3]. Such **surgeries do not repair the disc** and patients often end up needing more surgeries that increase the risk for further health complications.

*Stem cell therapy*

Studies investigating the use of stem cell therapy to replenish unhealthy disc cells have seen **limited results in humans due to inability of cells to adapt in patient discs**[4,5]. The IVD is known to be avascular and deficient in glucose and oxygen, thus adding stem cells can further intensify nutrient deficiency in the disc. Therefore, **it is important to develop mathematical models that allow the study of nutrient and metabolite diffusion in the disc**.

*Current diffusion models*

Finite element models have been developed to study disc diffusion, but **many of these models were limited in their abilities** to axisymmetric geometries of the disc which fail to accurately represent variations in disc thickness at different locations[6]. These geometric differences affect solute diffusion in and out of the disc. Despite these limitations, the models provide **a practical approach to model cellular metabolism** through coupling reactions of glucose consumption, oxygen consumption and lactate production in the disc[6].

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*Governing equations[6]*

Fick's first law

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{dx^2} - \dot{R}$$

Reaction terms

$$[Oxygen] = \frac{7.28 \cdot [Oxygen] \cdot (pH - 4.95)}{1.46 + [Oxygen] + 4.03 \cdot (pH - 4.95)}$$

$$[Lactate] = e^{-2.74+0.93 \cdot pH+0.16 \cdot [Oxygen]-0.0058 \cdot [Oxygen]^2}$$

$$[Glucose] = -0.5 \cdot [Lactate]$$

$$pH = 8.05 - 0.10 \cdot [Lactate]$$

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# Methods

*MRI images*

- Obtained Sagittal T1-weighted (T1-w), T2-weighted (T2-w) and diffusion weighted imaging (DWI) scans from patients (Figure 2)
- Generated masks for the different parts of the IVD in Materialize Mimics (Figure 2)

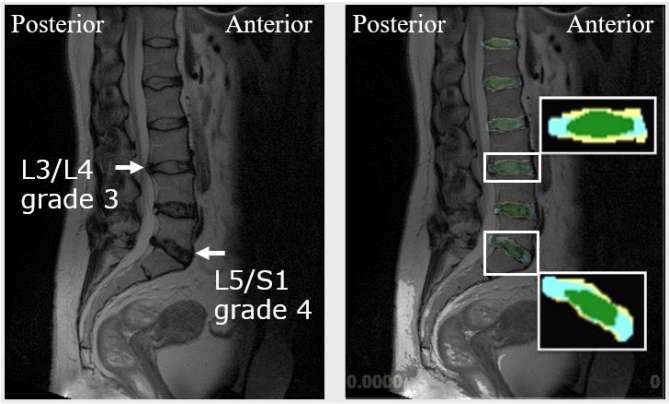


**Figure 2.** T2-w image of lumbar spine in patient 2 (left), and disc masks created in mimics (right).

*Diffusion coefficient maps*

- Converted DWI of the NP to apparent diffusion coefficient (ADC) maps using MATLAB (Figure 3)

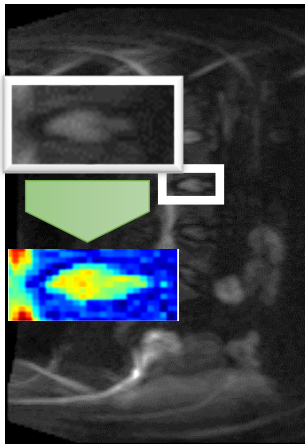

**Figure 3.** DWI scans used to create ADC maps for discs. White areas show enhanced diffusion of water.

*The model*

- Assigned parameters to the different regions of the disc. Parameters include water content, cell density, solute diffusion coefficients, initial conditions and boundary conditions of glucose, oxygen, and lactate
- Generated a 2D steady state diffusion model in COMSOL Multiphysics
- Assumed the disc to be suspended in a well-mixed solution

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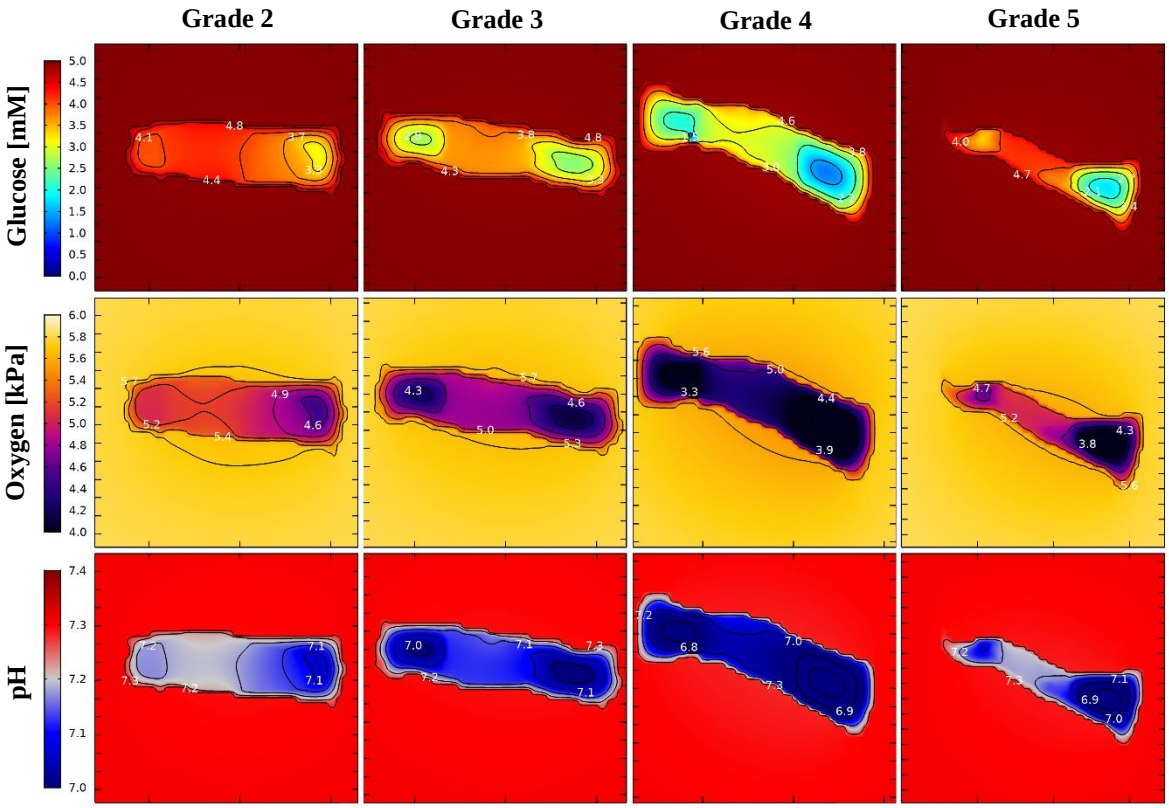
# Results

*General trends*

- Levels of glucose, oxygen, and pH drop towards the center of the disc (Table 1)
- Average nutrient concentration in the disc decreases as the disc severely degenerates by 15.2% for glucose, and 13.6% for dissolved oxygen (Figure 4)
- Dead zones can be noticed at the interface of the NP and AF where concentrations of glucose and oxygen are the lowest (Table 1)
- Grade 5 discs show better diffusion of solutes due to shorter disc height compared with grade 4 (Figures 4 & 5)

**Table 1.** Nutrient distribution and pH gradient in the disc are strongly correlated to level of disc degeneration.

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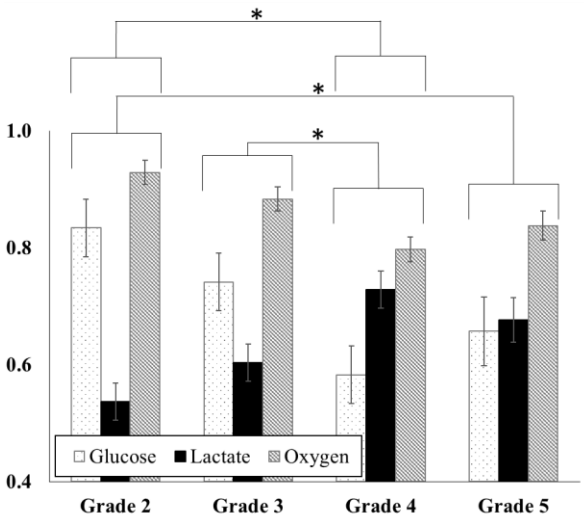


**Figure 4.** Normalized average disc concentration decreases with increasing disc degeneration ($p<0.05$).

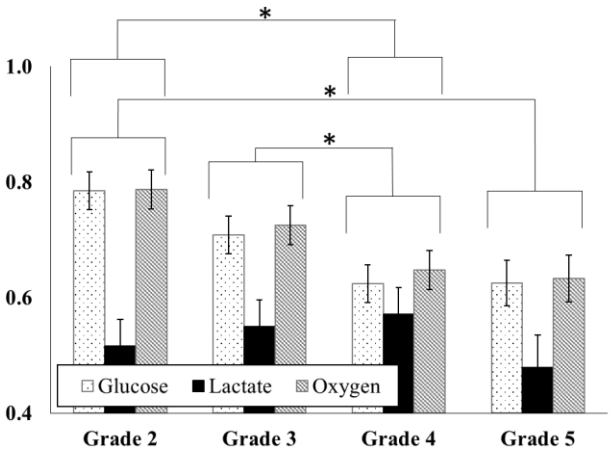


**Figure 5.** Normalized minimum and maximum concentrations are higher in least degenerated discs compared to more degenerated ($p<0.05$).

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## Limitations and future model work

Although the model's predictions of nutrient concentration in the intervertebral disc agree with what is reported in the literature, there are multiple ways in which the model's accuracy and precision can be improved.

1. Including factors that affect solute diffusion like inflammation and mechanical loading which change water content in the NP and AF by 8-10%
2. Incorporating the composition of the disc's extracellular matrix, which affects molecular transport, increases the model's accuracy in predicting nutrient concentration
3. Adding the third dimension in the model allows to better estimate the disc's nutrient holding capacity, and thus improve the model's predictions
4. Validating the model's predictions on human discs will demonstrate the model's applicability in clinical settings to select patients for stem cell therapy

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