A Diffeomorphic-Deep-Learning-Based Approach for Quantifying Multi-Axial IVD Biomechanics, In Vivo

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INTRODUCTION: *In vivo* quantification of intervertebral disc (IVD) composition and mechanics may help to elucidate pathomechanisms related to the development of discogenic low back pain (LBP) and IVD degeneration. However, characterizing IVD function *in vivo* has remained challenging.

To address this, we sought to develop a method which could accurately derive multi-axial (3D) estimations of internal IVD mechanics in response to activities of daily living. To do so, we developed a deep-learning-based deformable image registration method which leverages the inherent properties of diffeomorphisms (a spatial transformation which is smooth, one-to-one, and invertible) during training (via loss function penalization) to derive deformation maps (ϕ) between pre- and post-exercise IVD image volumes. Hence, in the present study, we evaluated the accuracy, validity, and applicability of this technique to the study of 3D IVD deformations induced in response to activities of daily living (i.e., treadmill walking).

METHODS: ***Imaging:*** T2-weighted (n = 32; SPACE) MRIs were obtained using previously disseminated sequence parameters[1]. Additionally, segmentations of the L1-L2–L5-S1 IVDs from MRI volumes were performed for the pre- and post-exercise scans as previously described[1-3]. ***Study Design:*** To induce IVD deformations, subjects walked on a treadmill for 30 minutes at a constant speed[1, 2]. ***Model Design****:* The unsupervised deformable image registration network was derived from the VoxelMorph architecture[4]. The model takes two inputs (moving (m); fixed (f)) and estimates a voxel-wise deformation field (ϕ) mapping m to f, yielding $[m \circ \phi]$. The model utilizes a two-component loss function ($L_{total}=L_{sim}+\lambda L_{smooth}$) to optimize the learned deformation field, ϕ. L_{sim} quantifies the local cross-correlation (similarity) between f and $[m \circ \phi]$, while L_{smooth} penalizes the total magnitude of the spatial gradient of ϕ. ***Model training:*** Model training was conducted using a k-fold (k=32), leave-one-subject-out, protocol (5 IVD levels per subject; 10 IVDs per subject total). Models were trained for 2000 epochs (200 steps/epoch). During each step a m and f volume are sampled randomly (without replacement); m was randomly deformed prior to registration using a grid distortion technique; model validation was performed at the end of each epoch. ***Strain Calculations:*** For each pre-post-exercise IVD pair (**Figure 1**) deformation estimations (ϕ) obtained from model testing were smoothed using a gaussian kernel (σ=3); deformation gradients ($\nabla\phi$=F) were calculated using 2nd order central finite difference approximations. Green-Lagrange strains (***E***) were calculated, whereby $\boldsymbol{E}=1/2(F^T \cdot F-I)$. Principal strains (e.g., $\boldsymbol{E_{min}}$) were then calculated by finding the eigen-decomposition of ***E***. Volumetric strain was estimated by calculating the Jacobian determinant matrices using $\boldsymbol{J}=det(\nabla\phi)$, where $\boldsymbol{J}=1$ signifies no change in volume, while $\boldsymbol{J}$=0.90 indicates a 10% decrease in volume. ***Accuracy:*** The accuracy of this technique was estimated using a zero-strain protocol Prior to exercise, two sets of anatomic SPACE image volumes were acquired in series (n=3 subjects). Then, for each unloaded pair of volumes (n=15) the mean (absolute) and median $\boldsymbol{J_{zs}}$ and $\boldsymbol{E_{zs}}$ associated with each ϕ was estimated across all voxels in the image volumes. ***External Validity:*** To assess external validity we directly compared mean minimum principal strain ($\boldsymbol{E_{min}}$; whole IVD) to manual mean strain estimations (previously reported[1]). ***Application:*** We assessed local changes in IVD volume by quantifying pairwise differences in ***J*** between radially subdivided IVD regions (**Figure 3**), using mixed-effects modeling.

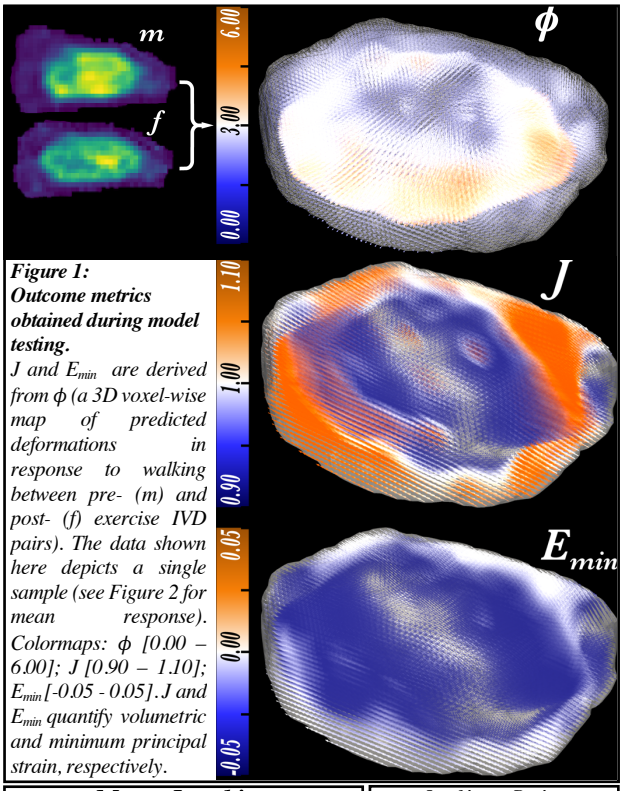

Figure 1: Outcome metrics obtained during model testing. *J and E_{min} are derived from ϕ (a 3D voxel-wise map of predicted deformations in response to walking between pre- (m) and post- (f) exercise IVD pairs). The data shown here depicts a single sample (see Figure 2 for mean response). Colormaps: ϕ [0.00 – 6.00]; J [0.90 – 1.10]; E_{min} [-0.05 - 0.05]. J and E_{min} quantify volumetric and minimum principal strain, respectively.*

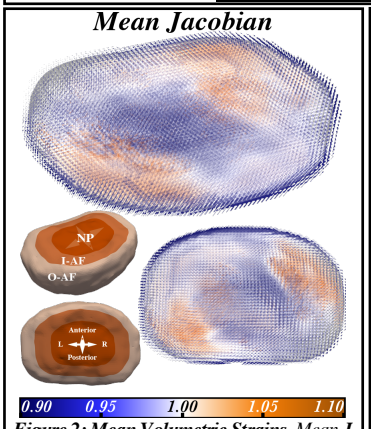

Figure 2: Mean Volumetric Strains. *Mean J across all pairs of IVDs. Here, 1.00> J >1.00 indicates regions of volumetric contraction and expansion, respectively.*

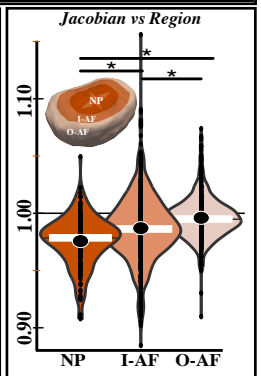

Figure 3: Regional J. *Mean regional Jacobians increased with increasing distance from the centroid of the IVD. *p<0.05.*

RESULTS: Results from our zero-strain study suggest that random errors were small and centered around zero: mean $|\boldsymbol{J_{zs}}|$=1.00 ± 0.01; median $\boldsymbol{J_{zs}}$ =1.00; $|\boldsymbol{E_{zs}}|$=0.39 ± 0.68%; median $\boldsymbol{E_{zs}}$=0.03%. Comparison of $\boldsymbol{E_{min}}$ to manual compressive strain yielded ICC(2,k)=0.62 (moderate reliability). Regional differences in mean ***J*** **(Figure 3)** were significant (multiple p < 0.05).

DISCUSSION: The present study demonstrated that a diffeomorphic-deep-learning-based registration paradigm can be used to accurately estimate 3D (i.e., multi-axial) IVD biomechanics *in vivo*. To this end, we demonstrated that $\boldsymbol{E_{min}}$ agreed with previously validated measures of manual compressive strain [1, 2]. Simultaneously we observed that volumetric strains (***J***) were regionally distinct from one another, increasing from the NP to the O-AF **(Figure 2)**. Closer inspection of this relationship in **Figure 2 (see also: *J* in Figure 1)**, suggests that volumetric fluctuations in the AF are non-homogeneous, having regional concentrations of both expansion and contraction. Notably, this finding echoes our understanding of how fluid convection to surrounding tissues might occur in response to dynamic loading of the IVD[5] (i.e., fluid moving from the aqueous NP to the O-AF as a result of increased hydrostatic pressure due to compressive loading of the IVD). Hence, it may be inferred that deformations estimated using this novel modeling paradigm may reflect both structural and fluid-related tissue deformations induced in response to loading. However, while further testing is needed to determine to what extent these deformations are related to tissue/fluid deformations, these results nevertheless highlight the utility of this novel method for investigating multi-axial (3D) IVD biomechanics, *in vivo*.

SIGNIFICANCE: This novel framework enables the accurate estimation of 3D internal IVD deformations in response to activities of daily living, thereby enhancing our ability to characterize the native function of IVDs.

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REFERENCES: [1] Coppock (2021); [2] Coppock (2022); [3] Coppock (2023a); [4] Balakrishnen (2019); [5] Emanuel (2018)