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Impact of extracellular matrix and collagen network properties on the cervical intervertebral disc response to physiological loads: A parametric study

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Abstract

Current intervertebral disc finite element models are hard to validate since they describe multi-physical phenomena and contain a huge number of material properties. This work aims to simplify numerical validation/identification studies by prioritizing the sensitivity of intervertebral disc behavior to mechanical properties. A 3D fiber-reinforced hyperelastic model of a C6-C7 intervertebral disc is used to carry out the parametric study. 10 parameters describing the extracellular matrix and the collagen network behaviors are included in the parametric study. The influence of varying these parameters on the disc response is estimated during physiological movements of the head, including compression, lateral bending, flexion, and axial rotation. The obtained results highlight the high sensitivity of the disc behavior to the stiffness of the annulus fibrosus extracellular matrix for all the studied loads with a relative increase in the disc apparent stiffness by 67% for compression and by 57% for axial rotation when the annulus stiffness increases from 0.4 to 2 MPa. It is also shown that varying collagen network orientation, stiffness, and stiffening in the studied configuration range have a noticeable effect on rotational motions with a relative apparent stiffness difference reaching 6.8%, 10%, and 22%, respectively, in lateral bending. However, the collagen orientation does

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not affect disc response to axial load.

Keywords: Intervertebral disc, FE analysis, Fibrous soft tissue, Porous media, Cervical spine kinematics.

1 **1. Introduction**

2 Tissue engineering, replacement and regeneration techniques are increasingly used in the
3 treatment of intervertebral disc diseases. While synthetic material replacements are still
4 limited by the biocompatibility hurdle, biomaterials designed for annulus fibrosus (AF) and
5 nucleus pulposus (NP) repair and replacement have managed to mimic IVD biology and have
6 shown promising results [1, 2]. However, without focusing on mechanical compatibility, these
7 biomaterials-based solutions have not yet shown a long-term performance [2, 3]. Mechanical
8 compatibility is not less critical than biocompatibility since it permits to restore biomechanical
9 behavior of the motion segment, and thus reduces re-herniation and promotes longevity [2, 4].
10 Therefore, a sophisticated comprehension of the biomechanical behavior of the intervertebral
11 disc is invaluable to enhancing the performance of biomaterial-based techniques.

12 The intervertebral disc (IVD) biomechanical behavior is complex and it can not be ex-
13 plored using only experiments or analytical methods [5]. Spine and disc biomechanics are
14 commonly studied using finite element (FE) analysis. FE models developed for the IVD are
15 increasingly improved. However, they become more difficult to implement and validate.

16 Recent models take into account complex structural phenomena taking part in this soft
17 tissue such as the osmotic role of proteoglycans and the mechanical contribution of collagen
18 fibers including fiber cross-links, fiber/matrix interaction, and interlamellar behavior (e.g.
19 [6, 7, 8, 9]). These models generally managed to provide a good agreement with experimenta-
20 tion. However, the uniqueness of the identified mechanical properties is not guaranteed given
21 their relatively large number and their possible interdependency [10, 11]. Furthermore, the

22 impact of the experimentation-related uncertainties on the identification studies remains sig-
23 nificant and it is reflected in the large scatter of the IVD mechanical properties values. Most
24 of the biomechanical experimental tests used in the parameter identification are performed
25 ex-vivo. Cadaveric tissue, generally used to perform biomechanical ex-vivo experimental tests,
26 undergoes several changes in properties related to the conservation conditions which leads to
27 variability in the experimental data [12]. In addition, the relevance of each parameter de-
28 pends on the load type and the nature of the experimental data used for the identification.
29 For example, the micro-channels configuration of a porous medium may increase the apparent
30 stiffness of the tissue in the case of confined consolidation compared to the unconfined one
31 [13].

32 Computational validation issues could be treated by several approaches. Multi-objective
33 optimization and the use of huge experimental databases could be suggested. However, these
34 solutions tend to complicate the studies and raise their time-memory cost. Different ap-
35 proaches, based upon the exploitation of quantitative MRI for the construction and the val-
36 idation of FE models were introduced [14, 11]. This technique seems efficient but is limited
37 by the MRI resolution and needs to be clinically validated. Recent studies introduced prob-
38 abilistic and deterministic deep learning approaches to reduce the cost of complex behavior
39 tissue models including porous media, hyperelastic anisotropic tissue, and multiscale models.
40 Despite their promising results in model reduction and simulation acceleration, these meth-
41 ods present some limitations related to the handle with irregular mesh and some particular
42 boundary conditions [15, 16, 17]. Therefore, sensitivity studies remain an essential tool to
43 improve and validate IVD FE models [18, 5]. Studying the impact of varying the parameter
44 values permits to better understand the IVD model biomechanics and manage the validation
45 studies. It allows sorting parameters by relevance and fixing the values of those with no
46 significant effect, simplifying the study by focusing on the most important parameters and

47 therefore helping to obtain a more accurate result.

48 Several sensitivity analyses have been conducted on lumbar spine FE models. The impact
49 of structural, mechanical, and morphological properties of vertebrae, IVD, and ligaments in
50 the lumbar spine was studied under different loads [19, 20, 21, 22, 5]. The obtained results
51 have contributed to the understanding of lumbar spine biomechanics and the studying of some
52 FE models accuracy. However, fewer sensitivity studies have been carried out for the cervical
53 spine and they are limited on the sensitivity of the stiffness of the spinal components, assumed
54 to be linear elastic, on spine biomechanics [23, 24]. The current study represents a sensitivity
55 analysis of C6-C7 IVD mechanical properties using a nonlinear poroelastic FE model with
56 fiber reinforcement. The objective is to determine and analyze the sensitivity of the model
57 to both the matrix mechanical properties and the collagen network configuration. For this
58 purpose, physiological loads are used in the simulations. By prioritizing the contribution of
59 the model properties in the IVD biomechanics for different load types, this work aims to
60 create a benchmark for numerical studies.

61

62 **2. Material and methods**

63 *2.1. Constitutive formulation*

64 The definition of quantities of interest permits to perform the mesh sensibility test and
65 to choose the constitutive model of the study [25]. In our case, we were interested in the
66 maximum stress linked to the solid phase, the fluid flow linked to the fluid phase and the
67 apparent stiffness which is a global quantity linked to the entire domain.

68 The choice of the constitutive model has been based on the quantities of interest and on
69 the mechanical aspects studied in the literature. In vivo measurements have shown that
70 the cervical IVD undergoes large strain during physiological motion [26]. It was also shown

71 that the collagen fibers do not contribute only to the tissue response to mechanical loads
72 but also to its swelling behavior [27, 28]. On the other hand, The compressibility of the
73 extracellular matrix (ECM) has been largely investigated and discussed. Although several
74 finite element studies have adopted a nearly-incompressible model for the extracellular matrix,
75 recent experimental studies have highlighted the auxetic compressible behavior of the annulus
76 fibrosus [29, 30]. These results revealed the importance of studying the IVD behavior in
77 large deformation, taking into account the annulus anisotropy, the compressibility of the
78 extracellular matrix (ECM), and the fluid flow in the porous network.

79 The constitutive formulation implemented for this study is based on the biphasic swelling
80 model [31, 32, 33]. The IVD is assimilated to a superposition of two immiscible and isothermal
81 phases: a porous solid skeleton describing the fiber-reinforced extracellular matrix saturated
82 by an intrinsically incompressible fluid. The total Cauchy stress $\boldsymbol{\sigma}$ is the summation of the
83 solid effective stress tensor $\boldsymbol{\sigma}^e$ and the interstitial fluid stress derived from the hydrostatic
84 pressure p and the osmotic pressure $\Delta\pi$:

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}^e - (p + \Delta\pi)\mathbf{1} \quad (1)$$

85 The hydrostatic pressure p is determined by Darcy and mass conservation laws while
86 respecting the intrinsic incompressibility assumption. The permeability k of the medium is
87 taken isotropic and strain-dependent as proposed in [34]. The osmotic pressure $\Delta\pi$ of the
88 IVD is expressed in terms of the fixed charge density of the proteoglycans C_{fc} which is also
89 taken strain-dependent [33].

$$\Delta\pi = RT(\varphi_i\sqrt{C_{fc}^2 + 4C_e^2} - 2\varphi_e C_e) \quad (2)$$

$$C_{fc} = C_{fc0} \frac{\phi_0}{\phi_0 - 1 + J} \quad (3)$$

where ϕ_0 is the initial porosity, J is the deformation gradient determinant, C_{fc} and C_{fc0} are the current and the initial fixed charge densities respectively, C_e the external salt concentration, R the universal gas constant, T the absolute temperature, and φ_i and φ_e respectively the internal and the external osmotic coefficients. The extracellular matrix of the medium is defined by its total strain energy density W . W was composed of a compressible Neo-Hookean isotropic part W_{NH} for the non-fibrillar matrix and an anisotropic part W_{fi} describing the contribution of each family of fibers i :

$$W = W_{NH}(\mathbf{C}) + \sum_i W_{fi}(\mathbf{C}, \vec{e}_i) \quad (4)$$

$$W_{NH} = \frac{\mu}{2} (I_1 - 3) - \mu \ln(J) + \frac{\lambda}{2} (\ln(J))^2 \quad (5)$$

90 where \mathbf{C} is the right Cauchy-Green strain tensor, I_1 is its first invariant and μ and λ are
 91 the parameters of Lamé. The vector \vec{e}_i represents the director vector of the fiber family i
 92 orientation. The anisotropic part was taken null in the NP and the CEP. Two families of
 93 fibers oriented by $\pm\alpha$ were considered in the AF. The fiber strain energy density of the i^{th}
 94 fibers population ($i=1,2$) was defined according to [35].

$$W_{fi} = \frac{a_i}{2b_i} \left(e^{b_i[(1-3K)I_{fi}+KI_1-1]^2} - 1 \right) \quad (6)$$

where a_i (MPa) and b_i (unitless) are the fiber rigidity and non linearity coefficient, K is their dispersion and I_{fi} is a fiber direction invariant written as

$$I_{fi} = \mathbf{C} : (\vec{e}_i \otimes \vec{e}_i) \quad (7)$$

95 The same mechanical parameters were taken for both families of fibers: $a_i = a_{AF}$ and
 96 $b_i = b_{AF}$.

97 *2.2. Finite element model*

98 The unknowns of the equation system were the hydrostatic pressure p and the three-
99 component displacement field. We have used Lagrange quadratic (P2) and linear (P1) poly-
100 nomial functions for the interpolation of the displacement and the pressure, respectively.

101 For this study, we have developed a three-dimensional finite element model of human
102 C6-C7 IVD. We have constructed a parametric geometry based on six experimental studies
103 conducted on the cervical spine morphology [36, 37, 38, 39, 40, 41]. The geometry is composed
104 of a central elliptical *nucleus pulposus* (NP) representing 26% of the total volume, a peripheral
105 *annulus fibrosus* (AF) surrounding the NP and two cartilaginous endplates (CEP) (Fig. 1).
106 The geometry was meshed using the software *Gmsh* [42]. A mesh refinement study was per-
107 formed using 4 20-node hexahedral element meshes with different element number to check
108 the convergence of our quantities of interest against element size. Local refinement was not
109 considered given the absence of geometrical irregularities, high-stress gradient, or common
110 stress concentration areas for the studied loads. The selected mesh has been composed of
111 5940 hexahedral elements (26106 nodes). The model was implemented in the open-source
112 software LMGC90 [43].

113 *2.3. Definition of the fiber orientation*

114 The fiber orientation angle α decreases from the inner to the outer lamella of the AF [44].
115 To respect this property, we have defined the fiber orientation using local spatial distributions
116 progressing continuously from the inner to the outer AF. Two parameters were defined, α_i and
117 α_o , the fiber angle to the transverse plane, at the inner and at the outer lamella, respectively
118 (Fig. 2.B). Given the shape of the IVD geometry, it was necessary to define a local coordinate
119 system centered in the NP center O_{NP} and satisfying two criteria: i) For each element of
120 the AF, fibers are defined in lamellae plane, ii) Elements of the same lamella should have

121 the same fiber orientation. At this stage, the shape of the annular mesh has been useful. To
122 define this coordinate system we started with the resolution of a thermal problem in which
123 we have imposed two different temperatures in the lateral boundary of the AF (T_{AF}) and in
124 the NP (T_{NP}) with $T_{AF} < T_{NP}$ (Fig. 2.A). The heat flux vector in each node defines its local
125 radial vector $\vec{e}_{r_{AF}}$. Then, we defined the axial vector $\vec{e}_{a_{AF}}$ which corresponds to the Z-axis
126 of the global coordinate system. The tangential vector $\vec{e}_{t_{AF}}$ was determined by the cross
127 product ($\vec{e}_{a_{AF}} \wedge \vec{e}_{r_{AF}}$). Finally, the vectors \vec{e}_1 and \vec{e}_2 were defined in each node according to
128 this relation:

$$\vec{e}_1 = \cos(\alpha).\vec{e}_{t_{AF}} + \sin(\alpha).\vec{e}_{a_{AF}} \quad (8)$$

$$\vec{e}_2 = -\cos(\alpha).\vec{e}_{t_{AF}} + \sin(\alpha).\vec{e}_{a_{AF}} \quad (9)$$

129 2.4. Model validation

130 A validation process was conducted to find the reference parameter vectors to perform the
131 sensitivity study. We have compared the behavior of our model in lateral bending, flexion, and
132 axial rotation to experimental previous works by reproducing the applied load described in
133 [45, 46, 47]. These experimental studies provide functions describing the C6-C7 IVD rotation
134 when it is exposed to a 0 to 2Nm pure moment. To compare the behavior of the current
135 model to experimental curves, we have performed 4 tests for each motion by applying 0.5,
136 1, 1.5, and 2Nm moments and determined the IVD orientation angle for each test. Then we
137 have interpolated these points to find the numerical evolution function of each motion (lateral
138 bending, flexion, and axial rotation). The interpolation function used here has been defined
139 in the experimental studies and has the following form: $\theta = \gamma_v + \alpha_v \ln(\beta_v M + 1)$. where θ and
140 M are the rotation angle and the applied moment, respectively, and γ_v , α_v and β_v are the
141 function parameters. In our case, we have taken $\gamma_v = 0$ for all the loads to start from 0° of

142 rotation when a null moment is applied. We have manually varied the model parameters to
143 finally find a parameter vector that permits to closely reproduce the experimental behavior
144 of the C6-C7 IVD (Fig. 3). This parameter vector will constitute the reference vector of the
145 parametric study called for the rest of this paper "the basic model". Here, the basic model is
146 not necessarily the best fit combination with a minimized error compared to the experimental
147 curve. However, we are sure that, with the retained combination, the model reproduces the
148 experimental mechanical response used in this validation step.

149 *2.5. Boundary conditions for the parametric study*

150 The simulations were performed under uniaxial compression and three physiological inde-
151 pendent loads of the cervical spine: lateral bending, axial rotation, and flexion. Each load
152 has been applied in a 3-step sequence (Fig. 4). The first step was a 2-hour preconditioning
153 step. The bottom surface has been constrained in all directions, the remaining boundaries
154 being constraint-free. This step permits to obtain the unloaded IVD equilibrium in which
155 the initial osmotic pressure distribution and the unloaded IVD equilibrium swelling were es-
156 tablished from the fixed charge density and the porosity initial fields (C_{fc0} and ϕ_0 table 2).
157 The second step permits to simulate the head weight. A 100N creep-compressive force was
158 applied on the top surface of the upper CEP in 8 minutes then remains constant until the
159 equilibrium. Finally, starting from the result of the compression-creep step, we have applied
160 a displacement-driven load to simulate the C6-C7 translations and rotations during a phys-
161 iological cervical spine lateral bending, axial rotation, and flexion (Fig. 4). Data for C6-C7
162 kinematics in the cervical segment are obtained from in vivo measurements taken from the
163 literature (table 1). To reproduce the experimental measurements, we have used a y-z-x se-
164 quence (corresponding to flexion/extension-axial rotation-lateral bending) to apply the C6-C7
165 rotations during spine movement. The center of rotation is the center of the most postero-

166 inferior point of the subjacent vertebrae (C7) for lateral bending and axial rotation [48, 49].
167 For the flexion, the rotation center is the center of the subjacent vertebral body [50, 51].

168 2.6. Studied parameter range

169 The parametric study has been carried out by varying 10 parameters (table 2). For the
170 NP and the AF ground substance tissues, the varied parameters were the shear modulus μ
171 defining the ECM stiffness, the first Lamé parameter λ defining its compressibility, and the
172 initial permeability k_0 . Collagen fiber network properties have also been studied by varying
173 their rigidity a , their nonlinearity b , and their directions (α_o and α_i). We have chosen the in-
174 terval of variation of each parameter to be always in the range of values in previous numerical
175 studies found in the literature (table 2). This choice permits testing the sensitivity of the IVD
176 mechanical behavior to model parameters in extended ranges used in previous studies. It is
177 important to mention that even if some cited studies do not use the same constitutive law as
178 the actual work, they were used to define variation range for parameters equivalent to ours
179 in their formulation. For example, we have used the value of a_{AF} in [52] even if this study
180 does not take into consideration the fiber dispersion defined by K_{AF} in our model. We also
181 calculated the equivalent λ_{NP} and μ_{NP} from Young modulus and Poisson's ratio provided in
182 [53] using elastic parameter conversion formulae.

183 For each parameter, the reference value was managed to be at the center of the studied
184 range. The higher and the lower values were chosen in a way to be equally distant from the
185 reference value and to form an interval that covers as many previously used values as possible.
186 The first simulation has been performed using the reference parameter values (basic model).
187 Then, for each test, we have varied only one parameter. Only the two fiber orientation angles
188 have been simultaneously varied. To make this simultaneous variation simple we have fixed
189 the mean fiber direction at 35° and defined the parameter $\Delta\alpha$ which represents the difference

190 of the mean angle from inner and outer angles: $\alpha_i = \pm(35 + \Delta\alpha)$ and $\alpha_o = \pm(35 - \Delta\alpha)$.
191 Finally, 37 tests have been performed for each load type. A total of 1320h of computing time
192 was needed in this study (about 220h with parallel computation) using an HPC cluster with
193 28 cores and 128GB of RAM.

194

195 The studied outputs for the creep-compression step were the maximal NP pressure, the
196 maximal normal stress, the axial and radial outflow rates, the final volume change, and the
197 final axial displacement of the upper surface. For the physiological loads, we have studied the
198 maximal normal and shear stress, the axial and radial outflow rates, the final volume change,
199 and the final corresponding moment applied on the upper IVD surface. We have also studied
200 the impact of model parameters on a global output which is the apparent stiffness for the
201 different loads. The apparent stiffness for the rotational loads was calculated about the center
202 of rotation (Appendix).

203 **3. Results**

204 *3.1. Compression step*

205 During the compression step, we can differentiate two stages. The first one is the es-
206 tablishment of the applied force. At this stage, the axial displacement pressurizes the fluid
207 content due to the low permeability of the tissue. The IVD swells following this pressurization
208 until the total establishment of the force. At this instant, the pressure and the radial swelling
209 reach their maximal values. The second stage begins when the applied force is stabilized. In
210 this stage, the water expulsion from the IVD becomes more important, the swelling decreases
211 and the displacement of the loaded CEP continues until the equilibrium. We measured the
212 influence of modifying the model parameters on the NP pressure, the normal stress, and the
213 axial and radial flow rates at the end of the first stage. We studied also two equilibrium

214 results which are the volume loss caused by the water expulsion and the final displacement of
215 the loaded face which will determine the apparent stiffness of the IVD. With the basic model,
216 the relative change in IVD height was 4.8% and the relative change in its volume was 4.3%.
217 Figure 5 shows the effect of modifying the model parameters on the IVD response to com-
218 pression. Results show that the shear modulus of the AF ground substance μ_{AF} is the most
219 influential parameter on IVD response to compressive load. The AF compressibility λ_{AF} ,
220 affects significantly the radial flow rate. This parameter has a lower influence on the axial
221 flow rate, the final displacement, and the volume loss but it contributes clearly to their deter-
222 mination. The NP and the AF permeabilities k_{0NP} and k_{0AF} play also an important role in
223 the pressurization stage. The pore pressure is very sensitive to the NP permeability and the
224 radial flow rate is highly influenced by the AF permeability. However, the permeabilities do
225 not contribute to the equilibrium state. Apart from the fiber rigidity, no noticeable influence
226 was found on fiber parameters. The reference apparent stiffness obtained with the basic model
227 was about $337Nmm^{-1}$. This value depends on model parameters in a nearly linear way with
228 high sensitivity to the AF stiffness μ_{AF} and less noteworthy dependency on fiber rigidity a_{AF}
229 and AF compressibility λ_{AF} . No significant effect on the IVD apparent stiffness was found
230 for the other parameters.

231 *3.2. Lateral bending*

232 Figure 6 illustrates the influence of modifying model parameters on the IVD response to
233 lateral bending. The IVD normal stress, the axial flow rate, and the volume change in lateral
234 bending were dominated by the shear modulus of the AF ground substance μ_{AF} . The radial
235 flow rate is highly sensitive to the AF permeability and depends less on μ_{AF} . A less noticeable
236 dependency of the IVD outputs to the AF ground substance compressibility λ_{AF} was found.
237 Contrary to compression, we have noticed a significant dependency of the IVD behavior on

238 fiber parameters in lateral bending. The fiber non-linearity parameter b_{AF} has a crucial role
239 in the determination of the shear stress, the lateral bending moment, and the volume change.
240 Modifying the fiber rigidity a_{AF} has a noticeable effect on the same outputs. Although fiber
241 direction parameter $\Delta\alpha$ has not the same importance in the IVD response to lateral bending,
242 we have found that varying this parameter may affect the shear stress and the radial outflow
243 rate. On the other hand, apart from μ_{NP} , which slightly affects the radial flow rate, the NP
244 parameters varying in the study range has not a real influence on the IVD response to lateral
245 bending. The apparent stiffness in lateral bending found with the basic model was about
246 $16Nmrad^{-1}$. This value is affected by modifying b_{AF} in the first row then AF stiffness μ_{AF}
247 and fiber rigidity a_{AF} . The dependency of the LB apparent stiffness to these parameters is
248 nonlinear.

249 3.3. Flexion

250 Figure 7 shows the influence of modifying model parameters on the IVD response respec-
251 tively to flexion. The studied outputs depend essentially on the fiber nonlinearity b_{AF} and
252 the AF ground substance shear modulus μ_{AF} . A less significant effect of the fiber rigidity
253 a_{AF} and orientation $\Delta\alpha$ was found. The AF permeability k_{0AF} has a significant effect on
254 the radial flow rate value. The AF ground substance compressibility λ_{AF} contributes to the
255 determination of the normal stress and the volume change. In a similar way to lateral bend-
256 ing, apart from μ_{NP} , varying the NP parameters in the study range does not affect the IVD
257 response to flexion. The apparent stiffness in lateral bending found with the basic model was
258 about $4.4Nmrad^{-1}$. The flexion apparent stiffness depends, in a nonlinear way, on b_{AF} , μ_{AF}
259 and a_{AF} in descending order.

260 3.4. Axial rotation

261 The results of the effect of modifying model parameters on IVD response to axial rotation
262 are shown in figure 8. As for the other types of load, varying μ_{AF} has a high effect on the
263 maximal stress and the flow rates in axial rotation. In addition, the permeability of the AF
264 slightly contributes to the determination of the radial flow rate where the role of NP per-
265 meability remains negligible. The fiber parameters b_{AF} and a_{AF} role remains crucial in the
266 determination of shear stress, the axial rotation moment, and the volume change. We note
267 that fiber orientation contributes more significantly to the IVD response to axial rotation than
268 its contribution to flexion and lateral bending. Similarly to the two latter motion results, the
269 apparent stiffness value is dominated by b_{AF} , μ_{AF} and a_{AF} with a more noticeable effect of
270 the NP shear modulus μ_{NP} . The axial rotation apparent stiffness value found with the basic
271 parameters was $2.83Nmrad^{-1}$.

272 The apparent stiffness values found with the three physiological rotations are significantly
273 smaller than the apparent stiffness computed with $2Nm$ pure moments applied in the valida-
274 tion study with ($25.8Nmrad^{-1}$ in lateral bending, $15.3Nmrad^{-1}$ in flexion, and $24.9Nmrad^{-1}$
275 in axial rotation). This comparison reveals that coupling the different rotations and trans-
276 lations during a physiological movement, together with the specific anisotropic hyperelastic
277 properties of the IVD, help reduce the resulting moment that is necessary to turn the head.

278 4. Discussion

279 This study was aimed to answer a key question that precedes any study treating the IVD
280 mechanical modeling: given the data set and objectives, to which mechanical parameters
281 specific attention should be paid? The answer to this question permits reducing the model
282 numerical cost by considering the appropriate assumptions or by reducing the number of pa-
283 rameters in the identification studies. To prioritize model parameters we have conducted a

284 parametric study using an anisotropic poro-hyperelastic model of the IVD and we have ex-
285 amined the effect of varying 10 parameters, in the literature range, on the model response to
286 physiological day-to-day loads.

287 Our methodology in the definition of parameters range has been oriented to cover the most
288 used values in literature. Therefore, it does not consist of a sensibility study where we try
289 to find the effect of each parameter on a limited interval but of a parametric study where we
290 have examined the parameters contribution to the IVD behavior based on the variety of these
291 parameter values used by previous works. Although this choice imposes a very varied width
292 of parameters range, it allows examining the utility of using very high or very low parameter
293 values compared to the most commonly used order of magnitude. For example, the common
294 value of b_{AF} is under 200 in the most studies [54, 52, 11, 55] but it takes a value of 300 in [56]
295 and 1045 in [8]. The high dependency of our model on the value of b_{AF} can be explained by
296 the use of those two extreme values.

297 Our study outlines the out most influence of changing the stiffness of the extracellular ma-
298 trix of AF on the poro-hyperelastic behavior of the cervical disc, by taking into account creep
299 compression, physiological relaxation movements during flexion, bending and axial rotation.
300 It is important to cite that we have faced numerical processing issues when using a low value
301 of μ_{AF} and we suggest using $\mu_{AF} \geq 0.8MPa$ for the same type of model. In the current
302 study, we have found that even the AF compressibility parameters λ_{AF} had a relevant role in
303 the determination of many output results. This influence highlights the necessity of using a
304 compressible extracellular matrix in FE models. These results can explain why many studies
305 using a nearly incompressible model for the IVD are validated with a low bulk modulus which
306 does not satisfy the near incompressibility assumption for the AF (1.45 MPa in [57], 0.8 to 1.4
307 MPa in [11] and 0.67 MPa in [58]). Moreover, very few studies take into account transverse
308 deformation to the traction direction, which are crucial to estimate the compressible behavior

309 of AF [59, 60, 61, 29, 30]. The last two experimental studies have clearly outlined, on bovine
310 and porcine disks respectively, the auxetic behavior of AF, and both report the dependency
311 of the apparent Poisson's ratios to the deformation amplitude, with negative Poisson's ratios
312 in the circumferential radial plane. Therefore, on the compressible behavior of the AF, we
313 conclude that more experimental, numerical, and theoretical studies are needed to understand
314 the complex, non-linear auxetic behavior of the AF. On the other hand, the relevance of the
315 λ_{NP} has not been shown in the current study. We think that the role of this parameter was
316 hidden by its small range of study (0.1 to 0.5MPa). However, the compressible behavior
317 of the human NP has been clearly outlined in several experimental studies [62, 63]. This
318 incites us to suggest using a compressible swelling material for the NP to catch its mechanical
319 behavior except at very high strain rates or under dynamic conditions where a viscoelastic
320 incompressible behavior could be sufficient [64, 65, 66].

321 As we have shown, the permeabilities of the AF and the NP do not contribute to the
322 determination of the equilibrium state. However, the radial flow rates are sensitive to AF
323 permeability and less sensitive to NP permeability. The latter contributes more to the de-
324 termination of the pore pressure. It is known that the water exchange within the IVD is a
325 key factor for nutrient transport and cell activity. Therefore, inaccurate estimation of the
326 permeabilities, especially of the AF, may lead to a loss of sufficiency in the biomechanical
327 models of treating degeneration and growth. The current strain-dependent permeability laws
328 proposed by [34] and [67] are sufficient to investigate the IVD solid-like behavior as reported
329 by many studies. However, given their isotropic formulation, they are not able to describe
330 precisely the water exchange rate in the fiber-reinforced tissues like AF [11]. We anticipate
331 that a more accurate permeability expression that depends on strain but also on collagen fiber
332 network organization will have a higher impact on water flow rates.

333 Another important finding is that collagen fiber properties including rigidity, nonlinearity,

334 and orientation have no significant effect on the response of the IVD to compression. How-
335 ever, they are a determinant factor in the cases of flexion, lateral bending, and axial rotation.
336 As mentioned previously, the high dependency of IVD behavior to the value of b_{AF} may be
337 partially caused by the large difference between its higher and lower tested values. The fiber
338 nonlinearity parameter is not a measurable property which makes it difficult to estimate.
339 Therefore, on b_{AF} value, we suggest performing more oriented AF local identification studies
340 to limit the range of variation of this parameter. Collagen fibers have high stiffness but they
341 do not contribute to the mechanical behavior only when they are in tension. Contrary to
342 compression, in the case of rotational motion, the strain principal directions are near to the
343 fiber orientation angles due to the large torsion deformation, especially in axial rotation. This
344 result comes back to the results of [34, 68] and [69] affirming that isotropic models are able to
345 reproduce the IVD response to compression. However, as underlined by [21], it is essential to
346 consider fiber reinforcement when studying the IVD behavior in axial rotation. Furthermore,
347 collagen network architecture should be neatly described by namely regional orientation dif-
348 ference between inner/outer and posterior/anterior AF.

349 This study also revealed that the collagen network within the AF has a crucial role to
350 optimize the necessary resulting moment to turn the head. In combination with the relative
351 movements of the adjacent vertebrae during axial rotation, lateral bending, and flexion, the
352 mechanical properties of the collagen fiber network appear to be particularly well adapted to
353 reduce the resulting moment by an order of magnitude compared to pure rotations. This key
354 feature has to be taken into account while designing IVD implants.

355 To take back the main aim of this study, we suggest simplifying IVD model validation
356 studies by reducing the number of identified parameters depending on the experimental opti-
357 mization objective and load type. (1) For tests in statics, very slow loading tests, and when
358 the experimental object is not time-dependent such as force-displacement curve, there is no

359 need to identify the permeability value. (2) For fiber-reinforced models, fiber orientation and
360 nonlinearity should not be included in the identified parameter except when studying IVD
361 response to rotational motion. Fiber rigidity is a determinant parameter for all types of load.
362 (3) None of the mechanical parameters of the extracellular matrix of the AF could be ne-
363 glected in the identification process. High attention should be paid to the determination of
364 the stiffness of the AF ground substance.

365 Some sources of uncertainty could be identified from the current results. On a numerical level,
366 the results of this study are provided without focusing on the uncertainty quantification of
367 each parameter in the validation step. However, we can identify some parameters with infi-
368 nite uncertainty such as the two permeabilities for stationary analysis or the fiber orientation
369 for the uniaxial load. In the identification studies, the accuracy of the model needs to be
370 investigated by uncertainty quantification. This will be useful to localize the optimal exper-
371 imental fields to measure, design accurate experiments and therefore minimize model error
372 [72, 73, 74]. On a physiological level, only the IVD prestress related to the osmotic pressure
373 was included. However, a second part, related to the gradient of tissue growth could be taken
374 into account. The IVD prestress was studied for bovine and porcine tissues [75, 76, 77, 29] but
375 no data concerning human disc prestress are yet provided in the literature to our knowledge.
376 In addition, the loading conditions, taken from previous experimental studies, may affect the
377 current results given the non linear anisotropic behavior of the model.

378 Our study, which focused on varying each parameter independently of the others, revealed
379 the complex mechanical behavior in in-vivo solicitations. In future work, the variation of mul-
380 tiple parameters at the same time will be performed. We anticipate this scheme may reveal
381 coupled effects and allow more efficient simplifications of the validation studies.

382 **Nomenclature**

$\boldsymbol{\sigma}$	Total Cauchy stress tensor
$\boldsymbol{\sigma}^e$	Solid phase effective stress tensor
\boldsymbol{C}	Right Cauchy-Green strain
\vec{e}_i	Director vector of the i^{th} fiber family
p	Fluid phase hydrostatic pressure (Pa)
$\Delta\pi$	Osmotic pressure (Pa)
k_0	initial permeability ($m^4 N^{-1} s^{-1}$)
C_{fc}	Fixed charge density ($mol\ m^{-3}$)
C_{fc0}	Initial fixed charge density ($mol\ m^{-3}$)
ϕ_0	Initial porosity (unitless)
J	Deformation gradient determinant
μ	Shear modulus (Pa)
λ	First Lamé parameter (Pa)
a_i	Fiber rigidity (Pa)
b_i	Fiber non linearity coefficient (unitless)
K	Fiber dispersion coefficient (unitless)
I_{fi}	Direction invariant of the i^{th} family fiber
α_i	Inner fiber orientation ($^\circ$)
α_o	Outer fiber orientation ($^\circ$)
$\Delta\alpha$	$(\alpha_i - \alpha_o)/2$ ($^\circ$)

383

384 **Constants**

R universal gaz constant = $8.314 J \text{ mol}^{-1} \cdot K^{-1}$

T Absolute temperature = $310 K$

385 C_e External salt concentration = $150 \text{ mol } m^{-3}$

φ_i Internal osmotic coefficient = 0.9

φ_e External osmotic coefficient = 0.9

386 **Appendix: Apparent stiffness**

The head-weight force in compression and the coupled displacements in the other physiological loads were applied on the upper surface of the disc which is assumed to be rigid. The apparent stiffness is calculated using the applied load or displacement and the resulting displacement or external force, respectively. For compression, the apparent stiffness $A_{pp}S(Nm^{-1})$ is defined as:

$$A_{pp}S = \left| \frac{F_{app}}{w_{res}} \right|$$

where $F_{app}(N)$ is the applied force and $w_{res}(m)$ is the displacement of the upper surface in the z direction (the same direction as the applied force).

For the other physiological loads, the apparent stiffness $A_{pp}S(Nm \text{ rad}^{-1})$ is defined as:

$$A_{pp}S = \left| \frac{\vec{M}_{res} \cdot \vec{e}_p}{\varphi_{app}} \right|$$

where $\vec{M}_{res}(Nm)$ is the global moment of the upper surface points about the center of rotation, $\varphi_{app}(rad)$ is the global cervical segment rotation as described in the table 1 and \vec{e}_p the principal direction of the rotation: \vec{x} for flexion, \vec{y} for lateral bending and \vec{z} for axial rotation. $M_{res}(Nm)$ is obtained according to this equation:

$$\vec{M}_{res} = \iint_{up} \vec{M}_{n,res} dS = \iint_{up} (O\vec{M}_n \wedge \vec{F}_{n,res}) dS$$

387 where $\vec{M}_{n,res}(Nm)$ is the resulting nodal moment, $\vec{F}_{n,res}(N)$ the resulting nodal force, and
388 $O\vec{M}_n(m)$ the final nodal position with regard to the center of rotation.

389 **Conflict of interests**

390 The authors declare that they have no conflict of interests to disclose.

391 **Ethical approval**

392 Not required

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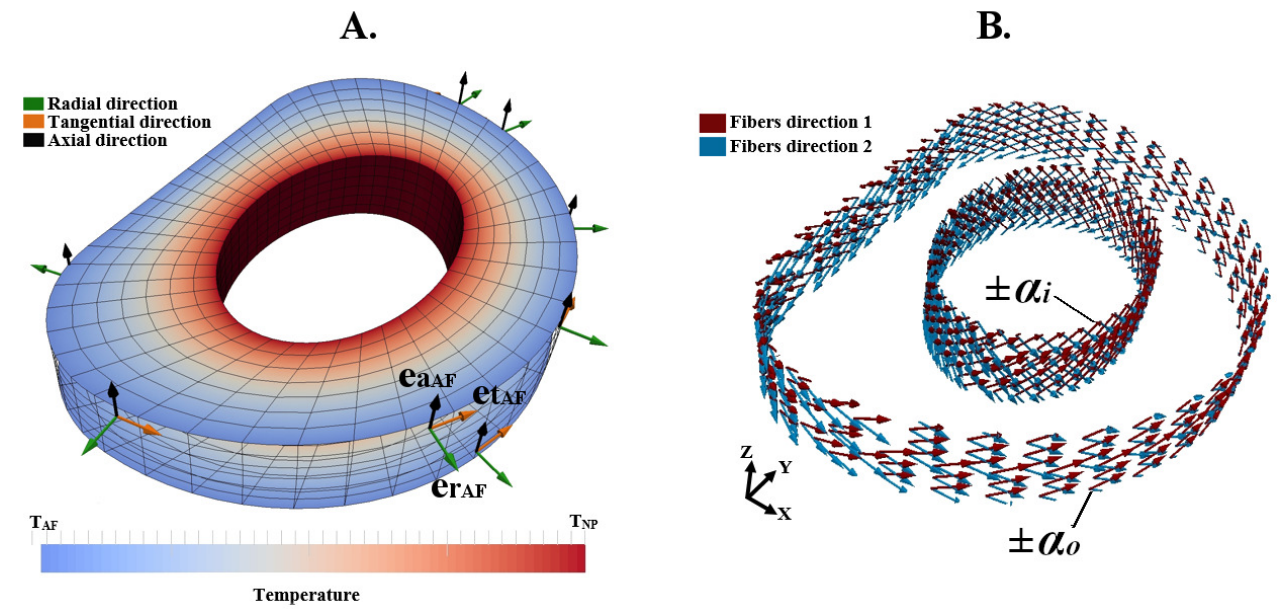
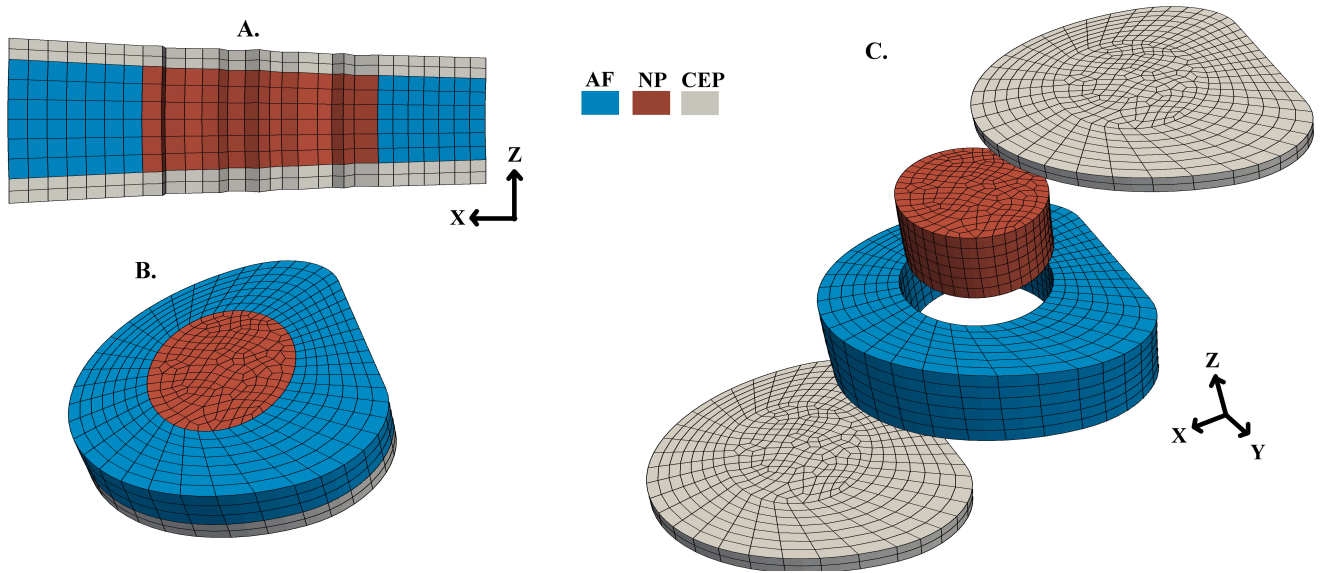


Figure 2: Definition of fiber orientation. A. Thermal solution and definition of the new coordinate system. B. Fibers directions in the inner and the outer lamellae of the AF

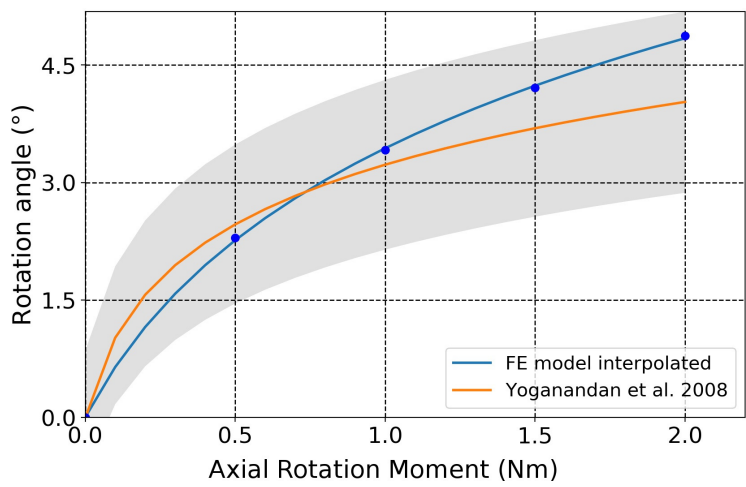
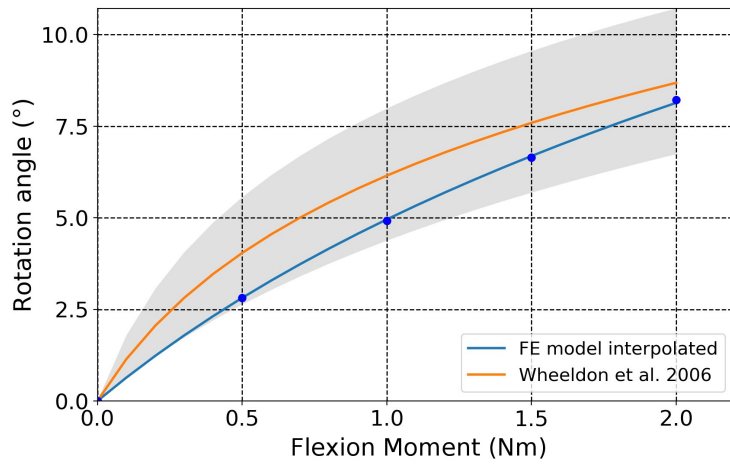
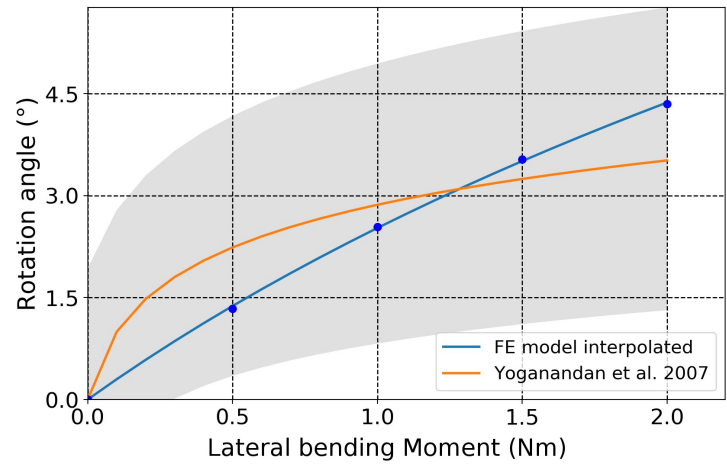


Figure 3: Experimental vs numerical response of the C6-C7 IVD to a pure moment load

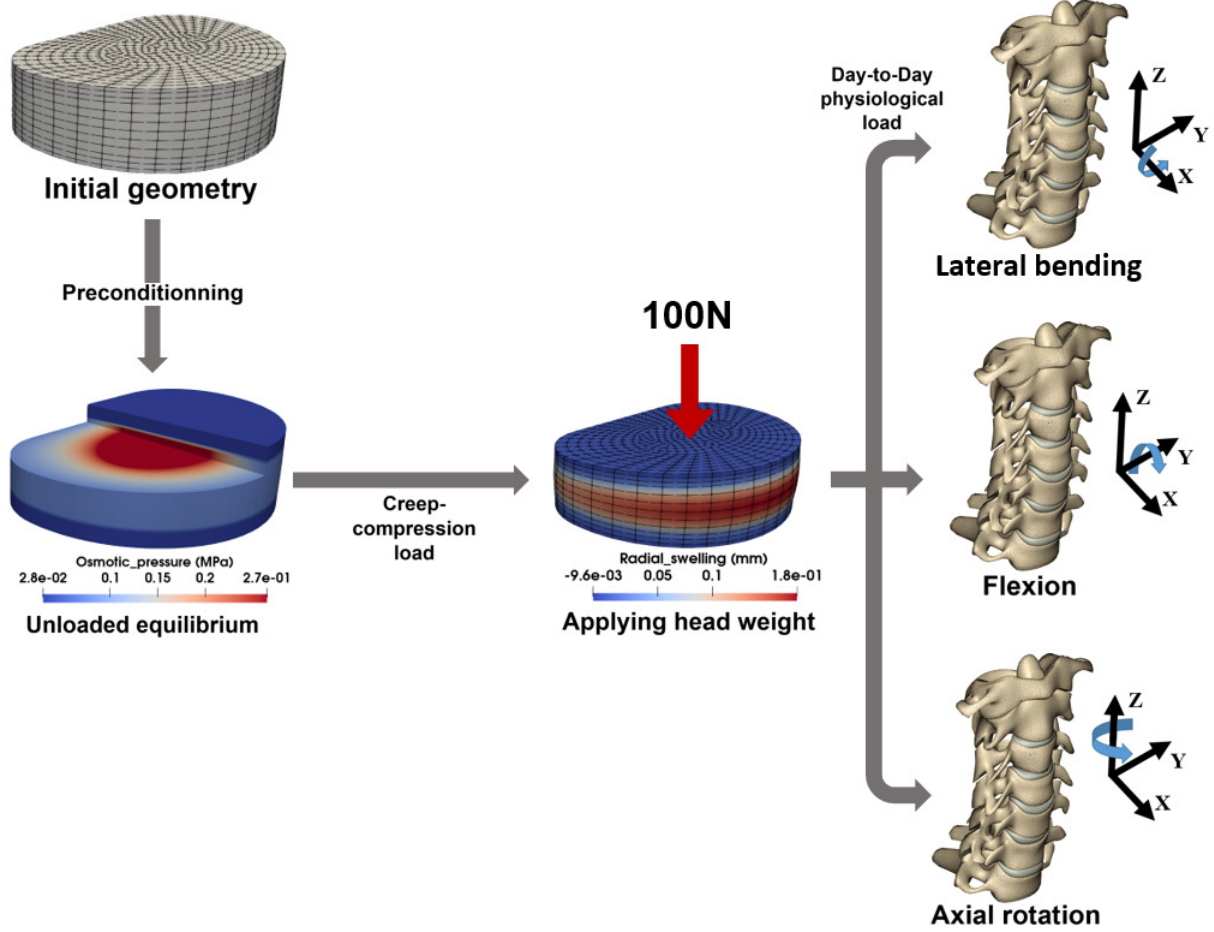


Figure 4: Representation of the IVD model simulation steps

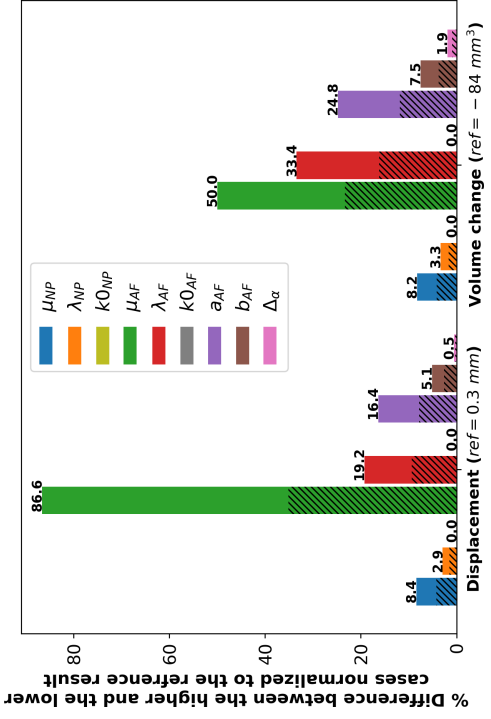
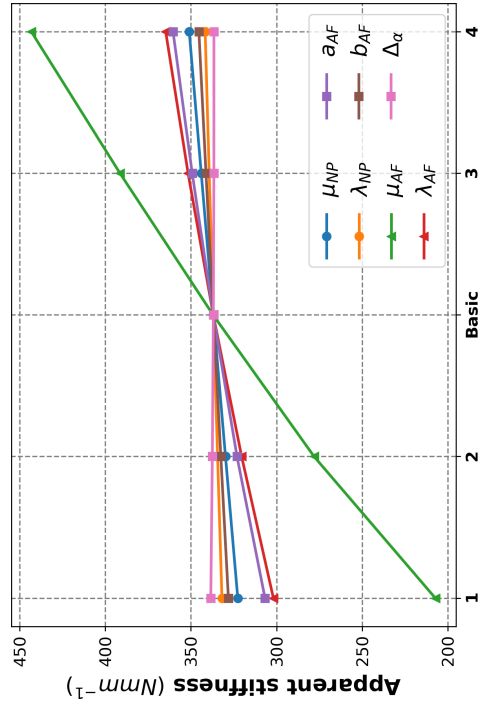
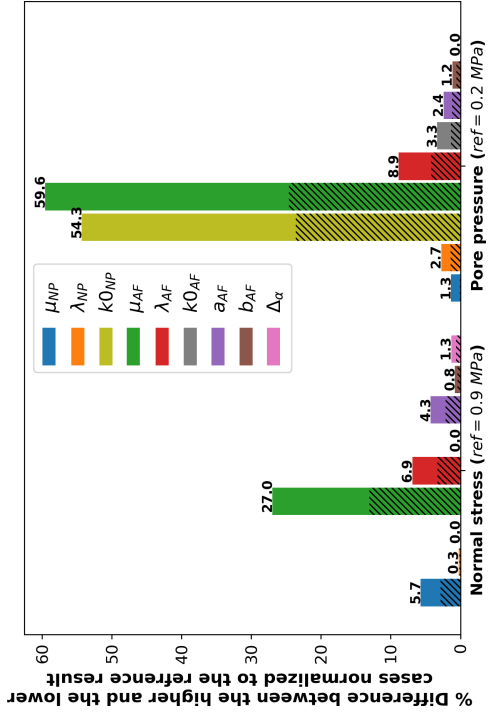
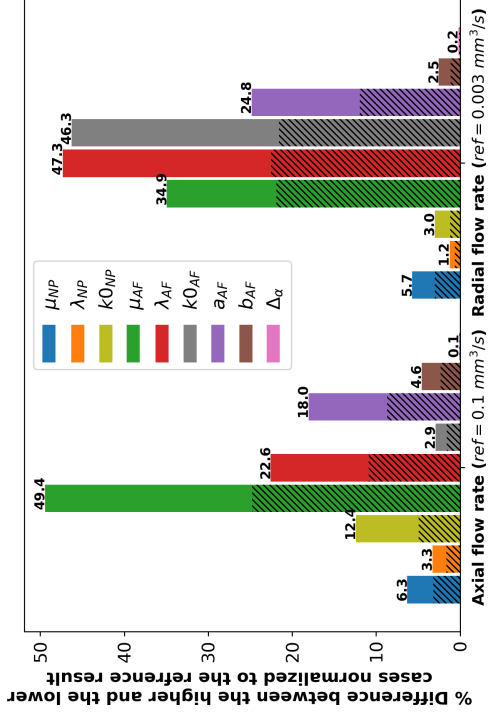


Figure 5: Impact of model parameters on IVD response to compression. The bar charts: difference between the 1 and the 4 cases (the 2 and 3 for the hatched area) normalized to the reference result (ref) obtained with the basic model parameters. The line graph corresponds to the evolution of the apparent stiffness in compression with the different scenarios of 7 parameters.

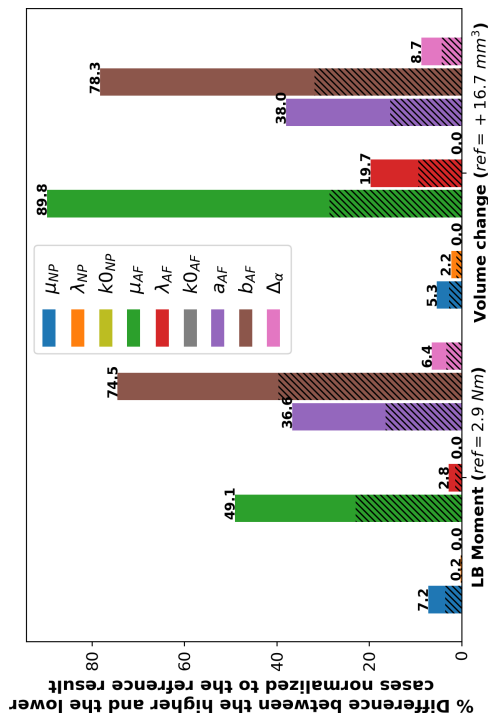
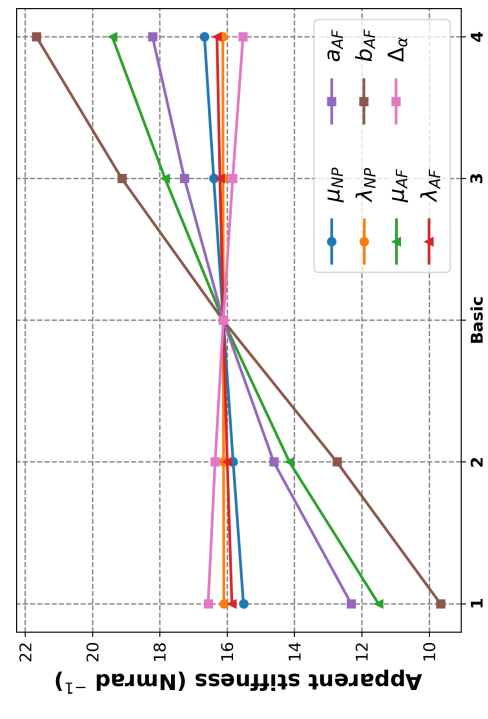
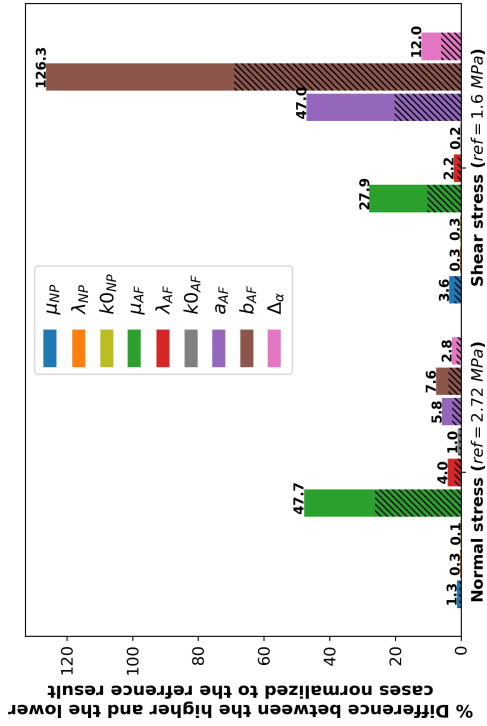
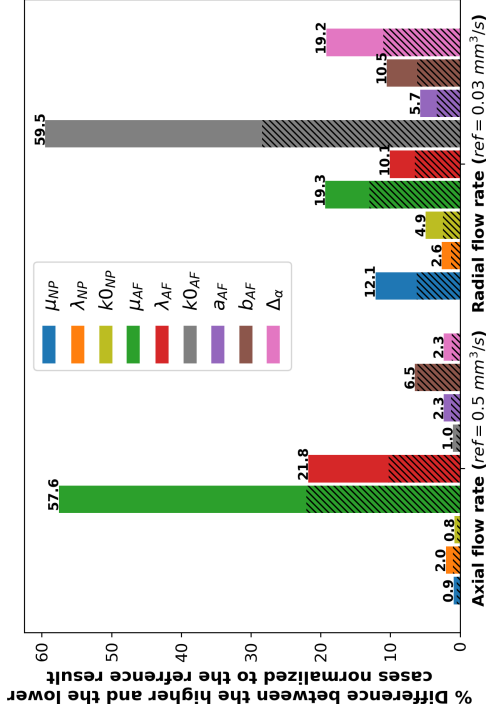


Figure 6: Impact of model parameters on IVD response to lateral bending. The bar charts: difference between the 1 and the 4 cases (the 2 and 3 for the hatched area) normalized to the reference result (ref) obtained with the basic model. The line graph corresponds to the evolution of the apparent stiffness in lateral bending with the different scenarios of 7 parameters.

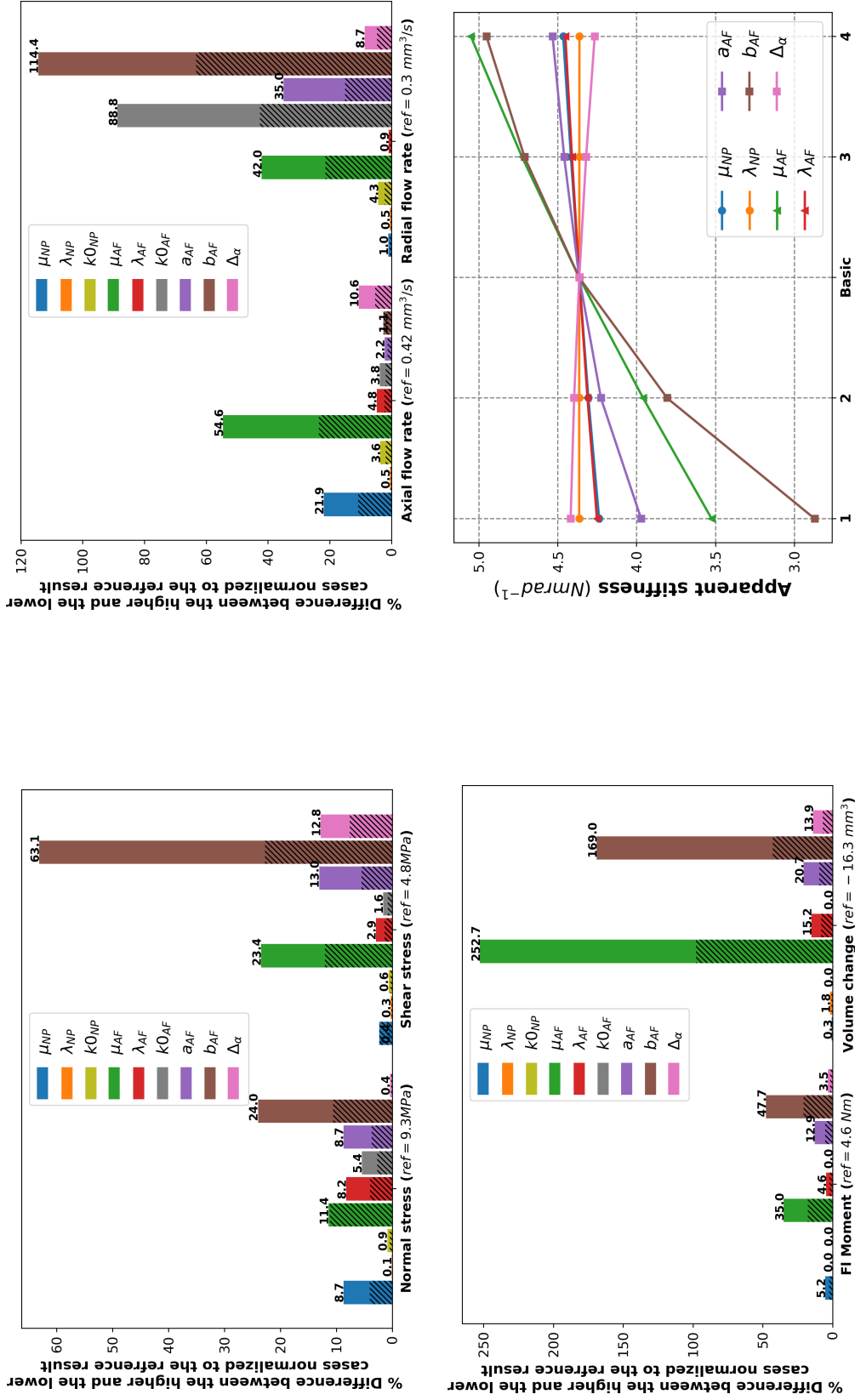


Figure 7: Impact of model parameters on IVD response to flexion. The bar charts: difference between the 1 and the 4 cases (the 2 and 3 for the hatched area) normalized to the reference result (ref) obtained with the basic model. The line graph corresponds to the evolution of the apparent stiffness in flexion with the different scenarios of 7 parameters.

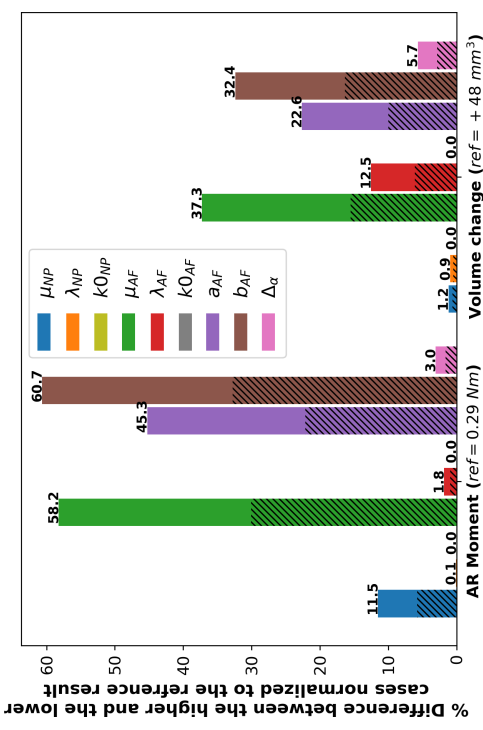
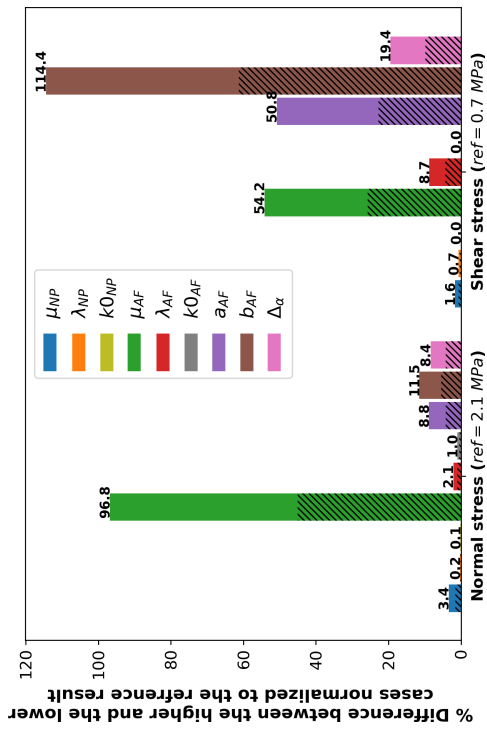
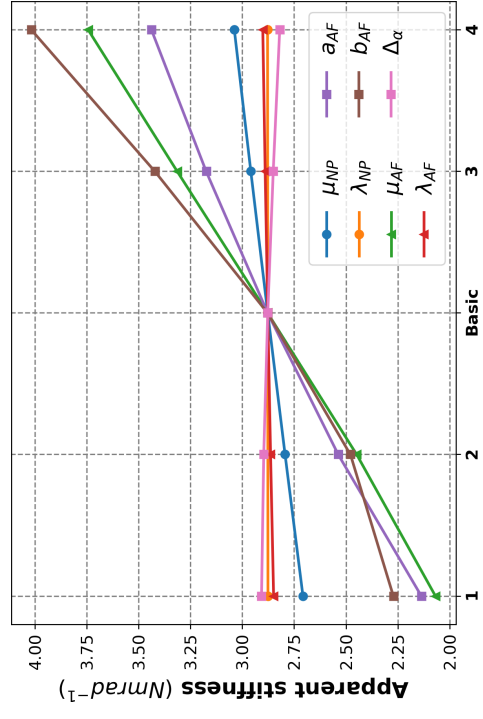
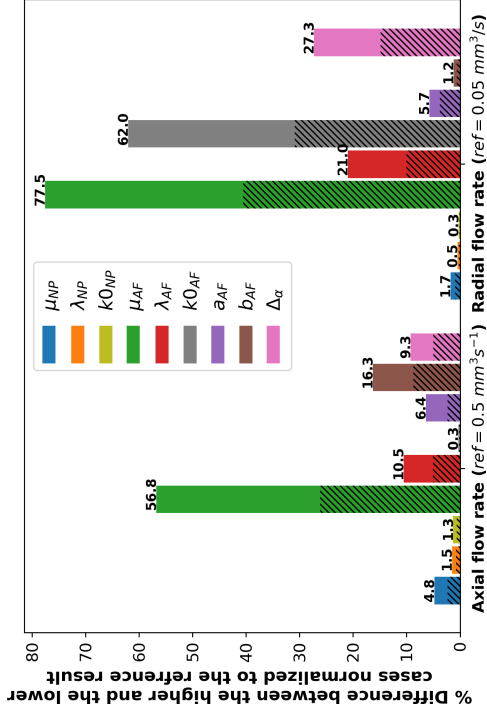


Figure 8: Impact of model parameters on IVD response to axial rotation. The bar charts: difference between the 1 and the 4 cases (the 2 and 3 for the hatched area) normalized to the reference result (ref) obtained with the basic model. The line graph corresponds to the evolution of the apparent stiffness in axial rotation with the different scenarios of 7 parameters.

Table 1: Applied intervertebral range of motion for the relaxation step for each load type. Motion: physiological motion of the whole cervical segment. Intervertebral rotation: C6-C7 rotation with *ILB*:lateral bending, *IFl*: flexion and *IAR*: axial rotation. Intervertebral translation: C6-C7 rotation with *P/A*: posterior(-)/anterior(+), *L/R*: left (-)/Right(+) and *D/U*: down (-)/ up (+). For lateral bending and axial rotation, the intervertebral motion values correspond to 10° and 6°, respectively, of the C3-C7 segment and were taken from the curves in the cited reference. For the flexion, the intervertebral motion values correspond to the half of the studied range of motion (59.5° of the C1-T1 segment) in the cited reference.

Motion	Intervertebral rotation (°)			Intervertebral translation (mm)			Ref
	ILB (X)	IFl (Y)	IAR(Z)	P/A (X)	L/R (Y)	D/U (Z)	
Lateral bending	1.64	-0.15	-0.18	0.0	-0.34	0.08	[49]
Flexion	1.2	7.5	0.8	0.0	0.0	0.0	[51]
Axial rotation	1.1	-0.8	-0.3	0.1	-0.3	0.1	[49]

Table 2: Model parameters values for the basic model and the cases used for the parametric study. Variation of each parameter of this list was separately tested.

	Parameter	Basic	Cases				References used in the definition of the intervals of study
			1	2	3	4	
NP	μ_{NP} (MPa)	0.4	0.1	0.25	0.55	0.7	[58, 53]
	λ_{NP} (MPa)	0.3	0.1	0.2	0.4	0.5	[58, 53]
	$k0_{NP} \times 10^{-4}$ ($mm^4/(Ns)$)	13	3	8	18	23	[52, 57]
	C_{fc0} (mol/m^3)	300	-				[58]
	ϕ_0	0.8	-				[58]
AF ground substance	μ_{AF} (MPa)	1.2	0.4	0.8	1.6	2	[7, 57]
	λ_{AF} (MPa)	1.3	0.2	0.75	1.85	2.4	[70, 4]
	$k0_{AF} \times 10^{-4}$ ($mm^4/(Ns)$)	13	3	8	18	23	[52, 57]
	C_{fc0} (mol/m^3)	150	-				[11]
	ϕ_0	0.7	-				[58]
AF fibrillar network	a_{AF} (MPa)	1.2	0.3	0.75	1.65	2.1	[52, 54]
	b_{AF}	350	50	200	500	650	[11, 8]
	$\Delta\alpha$	5	0	2.5	7.5	10	[52, 71]
	K_{AF}	0.166	-				
CEP	μ_{CEP} (MPa)	7.14	-				[70]
	λ_{CEP} (MPa)	10.44	-				[70]
	$k0_{CEP} \times 10^{-3}$ ($mm^4/(Ns)$)	3.5	-				[70]
	C_{fc0} (mol/m^3)	90	-				[11]
	ϕ_0	0.8	-				