Supplementary Material

Signatures of disease progression in knee osteoarthritis: insights from an integrated multi-scale modeling approach

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# Subject-specific loading and boundary conditions

Figure S1 shows the post-processed patient specific loading and boundary conditions in the 6 degrees of freedom that were used to drive the finite element model. The raw data extracted from the musculoskeletal workflow was filtered using a second order zero-lag Butterworth low-pass filter with a 6Hz cut-off frequency and smoothed.



Figure S1 Patient specific boundary conditions in the 6 degrees of freedom extracted from the musculoskeletal model: Contact force inferior superior direction (N), Valgus-varus Moment (Nm), Anterior-posterior Translation (m), Medial-lateral Translation (m), internal-external rotation (°), flexion angle (°).

# Material properties of the FE model

## Cartilage and menisci

Cartilage was modelled as fibril reinforced poroviscoelastic (FRPVE) material (Wilson *et al.*, 2004; Eskelinen *et al.*, 2019). The 3D collagen network consisted of 17 fibrils. More specifically, 4 primary fibrils that run from the subchondral bone towards the superficial layer of the cartilage and split up following the arcade model of Benninghoff (1925) and 13 randomized secondary fibrils (Wilson *et al.*, 2004). Figure S2 illustrates the collagen fibril orientation in a depth wise manner as well as at the superficial layer of the cartilage tissue.


**Figure S2 Illustration of (A) the superficial collagen fibril orientation of the tibial cartilage according to the split-line patterns and (B) orientation of the collagen fibrils through the depth of the tibial cartilage.**

These fibrils exhibited viscoelastic properties with stress-strain behavior:

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| --- | --- |
| $σ\_{f}=\left\{\begin{matrix}-\frac{η}{2\sqrt{\left(σ\_{f}-E\_{0}ε\_{f}\right)E\_{ε}}}\dot{σ\_{f}}+E\_{0}ε\_{f}+\left(η+\frac{ηE\_{0}}{2\sqrt{\left(σ\_{f}-E\_{0}ε\_{f}\right)E\_{ε}}}\right)\dot{ε\_{f}}, ε\_{f}\geq 0\\0, ε\_{f}<0\end{matrix} \right.$, | (S1) |

where $σ\_{f}$ and $ε\_{f}$ are the fibril stress and logarithmic strain and $\dot{σ\_{f}}$ and $\dot{ε\_{f}}$ are the stress and strain rates, respectively. η is the damping coefficient, E0 is initial modulus and Eɛ is the strain dependent modulus of the fibril network. The stress tensor formulated with respect to the primary and secondary collagen fibrils are the following:

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| --- | --- |
| $\begin{matrix}σ\_{f,p}=Cσ\_{f}\\σ\_{f,s}=σ\_{f}\end{matrix}$, | (S2) |

where $σ\_{f,p}$ and $σ\_{f,s}$ are the stress tensors of the primary and secondary fibrils respectively and C is the ratio between the primary and secondary fibrils.

A compressive neo-Hookean material model was used to model the non-fibrillar matrix reflecting the PG content. The matrix stress is as followed:

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| $σ\_{nf}=\frac{1}{2}K\_{nf}\left(J-\frac{1}{J}\right)I+\frac{G\_{nf}}{J}\left(FF^{T}-J^{\frac{2}{3}}I\right)$, | (S3) |

where **I** is the identity tensor, **F** is the deformation gradient and J is the determinant of **I**. Km and Gm are the bulk and shear moduli which were defined as:

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| --- | --- |
| $$K\_{m}=\frac{E\_{m}}{3\left(1-2ν\_{m}\right)}$$ | (S4) |

|  |  |
| --- | --- |
| $G\_{m}=\frac{E\_{m}}{2\left(1+ν\_{m}\right)} $, | (S5) |

where Em is the Young’s modulus and νm is the Poisson’s ratio of the non-fibrillar matrix. Thus, the total cartilage stress is:

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| --- | --- |
| $σ\_{tot}=σ\_{nf}+ \sum\_{i=1 }^{totalf}σ\_{f}^{i}-pI$, | (S6) |

where p is the fluid pressure and totalf is the total number of fibrils, namely 17 (4 primary and 13 secondary).

The fluid flow in the cartilage tissue was defined based on Darcy’s law:

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| $q=-k∇p$, | (S7) |

where **q** is the vector of the fluid flow flux, $∇p$ pore fluid pressure gradient and k is the permeability. The permeability is deformation dependent and was defined as (van der Voet, 1997):

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| --- | --- |
| $k=k\_{0}\left(\frac{1+e}{1+e\_{0}}\right)^{M}$, | (S8) |

where k0 is the initial permeability, e0 and e are the initial and current void ratio and M is a constant. The depth-dependent fluid fraction was defined as:

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| --- | --- |
| $n\_{f,eq}=0.80-0.15h\_{z}$, | (S9) |

where hz is the normalized depth, defined as 0 at the surface and 1 at the bone interface of the cartilage.

For the menisci a fibril reinforced poroelastic (FRPE) material model was implemented. This model is analogous to the FRPVE model, apart from collagen fibrils where the stress-strain behavior was defined as:

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| $σ\_{f,menisci}=\left\{\begin{matrix}E\_{0}ε\_{f}+\frac{1}{2}E\_{ɛ}ε\_{f}^{2}, ε\_{f}\geq 0\\0, ε\_{f}<0\end{matrix} \right.$, | (S10) |

where $σ\_{f,menisci}$ is the stress in the collagen fibrils of the menisci.

In addition, the fluid fraction ($n\_{f,eq}) $of the menisci is not depth-dependent (0.72). The meniscal horns are modelled as linear springs with ~30 springs per horn. The total spring constant of each meniscal horn is 350 N/mm (Villegas *et al.*, 2007).

Table 1 Material parameters of cartilage and menisci (Wilson *et al.*, 2004; Julkunen *et al.*, 2007; Makris, Hadidi and Athanasiou, 2011; Dabiri and Li, 2013) :

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Geometry | Em (MPa) | E0 (MPa) | Eɛ (MPa) | νm (-) | k0 (mm4/Ns) | M(-) | η(MPa s) | C(-) |
| Femoral cartilage | 0.215 | 0.92 | 150 | 0.15 | 6x10-3 | 5.09 | 1062 | 12.16 |
| Tibial cartilage | 0.106 | 0.18 | 23.6 | 0.15 | 18x10-3 | 15.64 | 1062 | 12.16 |
| Menisci | 0.500 | 28 | - | 0.36 | 1.25x10-3 | 12.16 | - | 12.16 |

## Ligaments

The ligaments were modelled as nonlinear spring bundles, the stiffness was 9840N for the anterior cruciate ligament (ACL), 6000 N for the posterior cruciate ligament (PCL), 2400N for the lateral collateral ligament (LCL) and 8000 N for the medial collateral ligament (MCL) (Lenhart *et al.*, 2015). The force-strain relationship is defined as (Blankevoort and Huiskes, 1991):

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| --- | --- |
| $f=\left\{\begin{array}{c}0, ɛ<0\\\frac{1}{2}K^{ɛ^{2}}/\_{ɛ\_{l}} 0 \leq ɛ\leq 2ɛ\_{l}\\K(ɛ-ɛ\_{l}), ɛ< 2ɛ\_{l}\end{array}\right.$, | (S11) |

where f is the tensile force, K is stiffness of the ligaments and $ɛ\_{l}$ is the end of the toe region (taken as 0.03) and $ɛ$ is the current ligament strain.

## Bone

Part of the tibia bone was modeled for the purpose of facilitating the convergence of the model to a numerical solution. Tibia bone was modeled as linear elastic material with a Young’s modulus of 80GPa which reflects the Young’s modulus of bone apatite (Currey, 2004).

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