Manuscript Number: MEP-D-16-00376R1

Title: Evaluation of predicted knee function for component malrotation in total knee arthroplasty

Article Type: Paper

Section/Category: Regular Issue Paper

Keywords: subject-specific; alignment; soft tissue balancing; kinematic knee rig; in vitro

Corresponding Author: Miss. Valentine Vanheule,

Corresponding Author's Institution: KU Leuven

First Author: Valentine Vanheule

Order of Authors: Valentine Vanheule; Hendrik P Delpoort; Michael S Andersen; Lennart Scheys; Roel Wirix-Speetjens; Ilse Jonkers; Jan Victor; Jos Vander Sloten

Abstract: Soft-tissue balancing for total knee arthroplasty (TKA) remains subjective and highly dependent on surgical expertise. Pre-operative planning may support the clinician in taking decisions by integrating subject-specific computer models that predict functional outcome. However, validation of these models is essential before they can be applied in clinical practice. The aim of this study was to evaluate a knee modelling workflow by comparing experimental cadaveric measures to model-based kinematics and ligament length changes. Subject-specific models for three cadaveric knees were constructed from medical images. The implanted knees were mounted onto a mechanical rig to perform squatting, measuring kinematics and ligament length changes with optical markers and extensometers. Coronal malrotation was introduced using tibial inserts with a built-in slope. The model output agreed well with the experiment in all alignment conditions. Kinematic behaviour showed an average RMSE of less than 2.7 mm and 2.3° for translations and rotations. The average RMSE was below 2.5% for all ligaments. These results show that the presented model can quantitatively predict subject-specific knee behaviour following TKA, allowing evaluation of implant alignment in terms of kinematics and ligament length changes. In future work, the model will be used to evaluate subject-specific implant position based on ligament behaviour.

Journal: MEDICAL ENGINEERING & PHYSICS

Title of Paper: Evaluation of predicted knee function for component malrotation in total knee arthroplasty

Declarations

The following additional information is required for submission. Please note that this form runs over two pages and failure to respond to these questions/statements will mean your submission will be returned to you. **If you have nothing to declare in any of these categories then this should be stated.**

Conflict of interest

All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Please state any sources of funding for your research

This work has financial support by the Baekeland scheme of the agency for Innovation by Science and Technology (IWT) under grant number IWT 110554 to V. Vanheule and the Danish Council for Independent Research (DFF) under grant number DFF-4184-00018 to M. S. Andersen.

Ethical Approval

Work on human beings that is submitted to *Medical Engineering & Physics* should comply with the principles laid down in the Declaration of Helsinki; Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, and the 41st World Medical Assembly, Hong Kong, September 1989. You should include information as to whether the work has been approved by the appropriate ethical committees related to the institution(s) in which it was performed and that subjects gave informed consent to the work.

DOES YOUR STUDY INVOLVE HUMAN SUBJECTS? Please cross out whichever is not applicable.

Yes (cadaver study)

~~**No**~~

If your study involves human subjects you **MUST** have obtained ethical approval.

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

The study protocol was approved by the local Ethics Committee of the University Hospital of Pellenberg (Belgium).

DOES YOUR STUDY INVOLVE ANIMAL SUBJECTS? Please cross out whichever is not applicable.

~~Yes~~

No

If your study involves animals you must declare that the work was carried out in accordance with your institution guidelines and, as appropriate, in accordance with the EU Directive 2010/63/EU. <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32010L0063>

--

This information must also be inserted into your manuscript under the acknowledgements section prior to the References.

If you have no declaration to make please insert the following statements into your manuscript:

Competing interests: None declared

Funding: None

Ethical approval: Not required

Dear Editor

We are pleased to submit the revised version of MEP-D-16-00376 "Evaluation of predicted knee function for component malrotation in total knee arthroplasty". We appreciate the constructive feedback of the reviewers and feel we have addressed each of their concerns as outlined below.

The most substantial revision concerns the inclusion of a figure that shows the tibio-femoral kinematics for each individual motion as this is more consistent with the reported RMSE values in the table. In addition, the figure showing the extensometer length changes was omitted. The figure explaining the set-up of the kinematic rig is also updated. All changes in the manuscript were highlighted in yellow.

Reviewers' comments:

Reviewer 2 has stated the following concerns:

1. Figure 3: You state that a hip joint has 2 DOF, one of them being a vertical translation, and an ankle joint has 4 DOF, one of them being a medial-lateral translation. These are very strange joints. There is in general a mix-up between joints and segments (on line 158 it states that 'the hip segment could slide vertically and flex...'). A segment is a body, and when it is rigid it has maximal 6 DOF. A joint connects segments, i.e. places constraints on the relative motion between the segments. In your case, the only true independent coordinate in the knee is the knee flexion angle, all other coordinates are defined by some complex set of constraint equations. This is reflected in your results, where you present RMS values as a function of the knee angle, and not of the other 5 possible parameters. This in itself is in contradiction with your statement on line 228, that there are six DOF between tibia and femur. Your model is a little more complicated, since you would allow small deformations at the knee, making the segment non-rigid, and thereby in principle increasing the DOF of the entire system. An exact formulation [1] for hip joint issue in fig 3 could be: A frame, attached to the femur segment at the position of the hip joint, has 2 DOF.

We agree that the words 'segment' and 'joint' can cause confusion in this figure. Hence, "hip assembly" and "ankle assembly" were used, consistent with the terminology used by Zavatsky in the paper where they demonstrated the full spatial freedom of the tibio-femoral joint in the Oxford rig¹.

The number of DOFs in the tibio-femoral joint is determined by 4 rigid bodies in this set-up: the hip assembly, the femoral segment, the tibial segment and the ankle assembly. Since each free body has 6 DOFs, the total number of DOFs is 24. The hip assembly is constrained in all rotational DOFs and only vertical translation is allowed. The femoral segment is connected to the hip assembly through a joint that only allows flexion-extension. This leaves in total 2 DOFs in the "hip" region. In addition, the ankle assembly is constrained in all rotational DOFs and only medial-lateral translation is allowed. The tibial segment is connected to the ankle assembly via a joint that permitted rotation in all directions but was constrained in all translational DOFs. This leaves 4 DOFs in the "ankle" region. This results in 6 DOFs at the tibio-femoral joint: $24 - 5 \text{ (hip)} - 5 \text{ (femur)} - 5 \text{ (ankle)} - 3 \text{ (tibia)} = 6 \text{ DOFs}$.

In addition, the amount of DOFs in the patello-femoral joint was adjusted (from 6 DOFs to 5 DOFs). In the model, a constant length of the patellar tendon was assumed, limiting one of the DOFs of the patello-femoral joint.

¹ Zavatsky AB. A kinematic-freedom analysis of a flexed-knee-stance testing rig. J Biomech 1997;30:277–80. doi:10.1016/S0021-9290(96)00142-X.

2. Line 111: What is meant by the joint line, how is it defined.

The tibio-femoral joint line in the native knee can be defined as the tangent of the cartilage contact surface between the medial and lateral tibial plateaus with the femoral condyles. This joint line was defined through palpation and indicated with a skin marker following which amputation was performed at the predefined distances.

3. How is the motion defined (line 274, or translation line 290 and at other locations). In Fig 4 some translations are shown but projected on the tibial horizontal plane. What is this, or could this be the tibial plateau. What is then the proximal-distal displacement, if the movement is in a plane.

The 3D rotations of the tibio-femoral joint were described using the joint coordinate system of Grood and Suntay². The body-fixed tibial mechanical axis and femoral flexion axis were used to express internal-external rotation and flexion-extension and the floating axis was used to express varus-valgus rotation. Translations were expressed with respect to the tibial coordinate system.

Figure 4 shows indeed the kinematics projected onto the tibial horizontal plane. To be more consistent with the reported RMSE values from Table 3, we added a new figure showing the 3D kinematics. The kinematic output is shown for each individual motion in addition of showing the projected 2D view on the tibial horizontal plane. This visualisation is also more consistent with the sensitivity study figure.

4. Why not call EPS simply the strain, because that is what it is (line 133, why duplicate on line 220)

We think that ligament length change or ligament elongation is a more appropriate formulation than strain in this study. The extensometers measure the change in length of the ligament between the two extensometer arms. Hence, the model shows the relative length change of the ligament and not the true strain since the ligament could be slack at the reference length.

5. Equation 3 is not correctly defined, the conditions are not unique.

The second condition is changed to $\varepsilon > 2\varepsilon_l$.

6. Line 204 EPSr probably should be EPSI

EPSr is changed to EPSI.

7. Line 217 segment should be segments

Segment is changed to segments.

8. Line 337: if extensometers are not representative, then why present the results in a separate figure. You could also combine figures 5 and 6, or compare extensometer with kinematic based experiments in a table.

We omitted the figure with extensometer elongations and made a comparison with the kinematic based elongations in one table.

9. Table 3: explain PD, ML etc.

Explanation is added in the table caption.

² Grood ES, Suntay WJ. A Joint Coordinate System for the Clinical Description of Three-Dimensional Motions: Application to the Knee. J Biomech Eng 1983;105:136–44.

10. Figure 1 is not clear at all. For left or right knee, front/back/side view, how is it inserted in the knee, etc. As it is now you could (should) leave it out

We omitted Figure 1.

11. Fig 4: I wonder what additional information this gives. We can see that experiment and model looks similar, but how is this quantified, and how should we interpret this? Are the results clinically relevant?

The quantification of the differences is presented in Table 3. The figure showing the 2D kinematics is mainly needed for the discussion (in particular lines 326-332): this anterior motion of the medial femoral condyle cannot be seen on the figure with the individual 3D motions.

Reviewer 3 has reported the following comments:

1. Line 65: Please revise the second half of the text since it is not understandable.

This sentence is split up to improve readability.

2. Line 68: Change the word "paramount" since it is not fitting.

"Paramount" was changed to "of paramount importance"

3. Line 209: MCL and LCL values were obtained from the study of Blankevoort and Huiskes from 1991? Is not there any fresher data with regard to these stiffness and strain values? Please update these references!

Ligament stiffness and slack length are difficult to measure. We acknowledge that using literature values is a limitation in this study, as we stated in the discussion. Blankevoort was one of the first to propose the force-displacement curve for ligaments used in this paper. Many others have also used their ligament parameter values, others search for subject-specific parameters using an optimisation routine in which experimental kinematics are approximated.

In our study, we used the generalised reference strains of Blankevoort and Huiskes. The best alternative is to do our own optimisation routine to search for subject-specific parameters in order to improve the solution. However, in this stage of our research, the aim was to validate a computational efficient knee model that can predict the relative impact of implant alignment on kinematics and ligament length change patterns.

4. I do not recognize the extra added value of Figure 1. I suggest it is removed.

We omitted Figure 1.

We look forward to hearing from you regarding our submission. We would be glad to respond to any further questions and comments that you may have.

Best regards

Valentine Vanheule

Department of Mechanical Engineering

Division BMe

Celestijnenlaan 300C

B-3001 Heverlee, Belgium

valentine.vanheule@kuleuven.be

Phone: +32 16 74 42 71

Fax: +32 16 39 66 00

Highlights:

- Multi-body model quantitatively predicted subject-specific knee behaviour after TKA
- Experimental testing of impact of TKA malrotation on ligament lengths and motion
- Presented model could distinguish effect of TKA malrotation on knee behaviour

1. Title page

Evaluation of predicted knee function for component malrotation in total knee arthroplasty

Valentine Vanheule^{a,b}, Hendrik Pieter Delport^c, Michael Skipper Andersen^d, Lennart Scheys^c,
Roel Wirix-Speetjens^b, Ilse Jonkers^e, Jan Victor^f and Jos Vander Sloten^a

^aBiomechanics section, Katholieke Universiteit Leuven, Celestijnenlaan 300C, 3001 Leuven, Belgium

^bMaterialise N.V., Technologielaan 15, 3001 Leuven, Belgium

^cDepartment of Orthopaedics, University Hospital Pellenberg, Katholieke Universiteit Leuven, Weligerveld 1, 3212 Pellenberg, Belgium

^dDepartment of Mechanical and Manufacturing Engineering, Aalborg University, Fredrik Bajers Vej 5, 9100 Aalborg, Denmark

^eDepartment of Kinesiology, Katholieke Universiteit Leuven, Tervuursevest 101, 3001 Leuven, Belgium

^fDepartment of Physical Medicine and Orthopedic Surgery, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium

Corresponding author

Valentine Vanheule

Department of Mechanical Engineering
Division BMe
Celestijnenlaan 300C
3001 Leuven, Belgium
valentine.vanheule@kuleuven.be

Phone: +32 16 74 42 71

Fax: +32 16 39 66 00

2. Abstract

Soft-tissue balancing for total knee arthroplasty (TKA) remains subjective and highly dependent on surgical expertise. Pre-operative planning may support the clinician in taking decisions by integrating subject-specific computer models that predict functional outcome. However, validation of these models is essential before they can be applied in clinical practice. The aim of this study was to evaluate a knee modelling workflow by comparing experimental cadaveric measures to model-based kinematics and ligament length changes. Subject-specific models for three cadaveric knees were constructed from medical images. The implanted knees were mounted onto a mechanical rig to perform squatting, measuring kinematics and ligament length changes with optical markers and extensometers. Coronal malrotation was introduced using tibial inserts with a built-in slope. The model output agreed well with the experiment in all alignment conditions. Kinematic behaviour showed an average RMSE of less than 2.7 mm and 2.3° for translations and rotations. The average RMSE was below 2.5% for all ligaments. These results show that the presented model can quantitatively predict subject-specific knee behaviour following TKA, allowing evaluation of implant alignment in terms of kinematics and ligament length changes. In future work, the model will be used to evaluate subject-specific implant position based on ligament behaviour.

Keywords: subject-specific, alignment, soft tissue balancing, kinematic knee rig, in vitro

3. Introduction

Creating appropriate soft-tissue balance during total knee replacement surgery is mainly subjective and highly dependent on the surgeon's expertise [1,2]. Pre-operative planning incorporating predictive tools to evaluate functional outcome may support the surgeon by comparing different surgical treatments. Subject-specific musculoskeletal models have a high potential to be used as a predictive tool in clinical practice [3]. In detailed joint models, ligaments strongly influence kinematics since they are highly important structures for guiding and stabilising knee motion [4,5]. However, before applying such models in a clinical setting, validation is of paramount importance. The purpose of this study was to evaluate a computational efficient model that can predict subject-specific knee kinematics and ligament length changes for different implant alignments.

Recently, several studies explored methods that can simultaneously compute motions as well as muscle and contact forces. Hast and Piazza presented a dual-joint workflow in which the knee joint is alternated between a simplified knee joint representation for inverse dynamics and an unconstrained knee with elastic foundation contact [6]. Thelen et al. extended the computed muscle control algorithm (CMC) to co-simulate muscle and contact forces, using an elastic foundation model [7]. Guess et al. presented a two-stage modelling method, an inverse kinematics and a forward dynamics simulation, predicting muscle and contact forces concurrently [8].

Andersen et al. introduced an alternative approach, called force-dependent kinematics (FDK), that extends the fast inverse dynamic simulations with the ability to estimate secondary joint kinematics [9]. This method relies on an assumption of quasi-static force equilibrium in the secondary joint kinematics at each time step during the analysis. In 2014, the FDK method was applied and knee contact forces were validated during walking activities in the winning model of the Grand Challenge competition [10].

Musculoskeletal models have the ability to explore the relationship between implant alignment and functional outcome for different activities of daily living. Others investigated the effects of implant alignment variation during a simulated squat, however, without collecting experimental evidence for the malaligned configurations [11,12]. In our study, we modelled different implant alignment variations and additionally, performed a cadaveric study to validate the predicted knee function for each alignment. FDK was used to simulate knee kinematics and predict ligament length change patterns for three cadaveric knees with TKA performing a squat motion. In addition to the standard implant, malrotation in the coronal plane was introduced by using tibial inserts with a built-in varus or valgus offset [13]. For each specimen, three squats were performed with the knee in neutral, varus or valgus alignment. The model outputs were validated by comparing experimental and model-predicted tibio-femoral motion and ligament length changes. To our knowledge, this is the first study to both simulate and validate the impact of implant alignment on kinematics and ligament length changes as predicted by computer models.

4. Methods

4.1. Experimental data collection

4.1.1. Specimen preparation and imaging

Three cadaveric knee specimens were used for squat simulations in a dynamic knee simulator system. The methodology of the specimen preparation was similar to the workflow described by Victor et al. [14]. The study protocol was approved by the local Ethics Committee.

After thawing the fresh frozen specimens, full leg T1-weighted opposed-phase spoiled gradient echo magnetic resonance imaging (MRI) scans were obtained using a 3T scanner (Ingenia, Philips Healthcare) to visualise soft tissues. The slice thickness was 2 mm and all slices had an in plane resolution of 0.9 mm x 0.9 mm. Subsequently, frames (Medtronic, MN,

110 USA) with reflective spherical markers were rigidly attached to femur, tibia and patella. Each
111 frame carried 4 markers, which were 6 mm in diameter. The femoral frame was inserted
112 within 21 cm from the joint line, the tibial frame within 18 cm from the joint line and the
113 patellar frame was inserted onto the patella. To allow accurate three-dimensional motion
114 tracking, a six-camera motion capture system (Vicon MX40, Oxford, UK) was used. The
115 optical markers could accurately be located on the pre-operative and post-operative computed
116 tomography (CT) scans.

117 Volumetric CT scans of the full lower leg with the attached markers were obtained on a dual-
118 source multidetector CT scanner (SOMATOM Definition Flash, Siemens), equipped with two
119 64-detector row units, using a slice thickness of 0.75 mm and a pitch of 0.8 mm/rev. The
120 images were processed in Mimics v. 17.0 (Materialise, Leuven, Belgium) to construct the
121 bone models of femur, tibia and patella. These bone geometries were used to identify bony
122 landmarks.

123 Next, the hip and foot were removed from the full leg, with a femoral cut 32 cm proximal of
124 the joint line and a tibial cut 28 cm distal from the joint line. The quadriceps muscle was
125 dissected and its preserved tendon was fixed into a clamp. In addition, the semitendinosus
126 together with the semimembranosus muscle, as well as the biceps femoris muscle were
127 dissected and suture wires were attached to the preserved tendons. The proximal femur and
128 distal tibia were then embedded in aluminium containers, preserving the physiologic
129 alignment in the coronal plane and parallel with the container in the sagittal plane.

130 Two extensometers (MTS, Eden Prairie, MN, USA) were sutured to the medial and lateral
131 collateral ligaments by an experienced surgeon. The fixation of the extensometers was centred
132 over the joint line, on an unloaded and fully extended knee [15]. During the measurements,
133 ligament length change relative to the extended knee was calculated using the formula

$\varepsilon = (L - L_r)/L_r$, where L was the instantaneous length of the extensometer arms connected to the ligament and L_r was the reference length at full extension.

4.1.2. Total knee replacement and imaging

An experienced surgeon (HD) performed the total knee arthroplasty on each specimen using a posterior-stabilised total knee arthroplasty (Performance, Biomet Inc., Warsaw, IN, USA). In addition to the tibial implant placed with standard alignment instrumentation, two variations of the tibial insert were designed through additive manufacturing. These variations were able to artificially simulate a TKA coronal malalignment by their built-in varus or valgus design. The inserts were modelled so that the central height was preserved while making one side thicker and the other side thinner than the neutral insert. For each specimen, three squat trials were performed. Specimen 1 underwent squats with neutral insert, 5° varus insert and 5° valgus insert. Specimen 2 and 3 underwent squats with neutral insert, 3° varus insert and 3° valgus insert. The tibial insert thickness for specimen 2 and 3 was smaller, leading to a smaller varus and valgus angle due to design limitations. The valgus insert squat of specimen 3 is not shown in the results since the quadriceps ruptured during the last experiment.

After the trials, post-operative CT scans were made with the optical markers still attached on the same scanner as the pre-operative scans, allowing to accurately document the implant position.

4.1.3. Knee simulator set-up

The specimens were mounted onto a dynamic knee simulator system, based on the Oxford rig [16]. This mechanical system permits six degrees-of-freedom (DOFs) for both the tibio-femoral and the patello-femoral joint. The femoral container was connected to an artificial hip assembly and the tibial container to an artificial ankle assembly. The quadriceps clamp was connected to an actuator that could apply a variable quadriceps load. Both hamstring wires

were connected with constant-force springs of each 50 N (Type KKF 8077, Lesjöfors, Karlstad, Sweden). The hip assembly could slide vertically and flex and extend, the ankle assembly allowed rotation in all three directions and translated medio-laterally. Sensors detected the quadriceps force, ankle force and relative hip height and these real-time data were processed in a closed feedback system (LabVIEW, National Instruments, Texas, USA), allowing the performance of a squat motion by moving the hip assembly and applying a variable quadriceps force to induce a vertical ankle force of 111 N. The quadriceps load increased during knee flexion, starting from a few hundred Newton at the beginning of the experiment and the load could go up to 2000 N at deep knee bend. A full squat motion began around 30-40° knee flexion and went up to 110-120°. The squat did not begin at full extension to prevent hyperextension [14].

Six infrared emitting cameras (MX40, Vicon, Oxford, UK) tracked the reflecting light from the rigidly attached optical markers on femur, tibia and patella at a sampling frequency of 100 Hz. This provided us an accurate measurement of the knee joint motion during squat. Throughout knee flexion, the three-dimensional (3D) coordinates of the passive markers were tracked and the relative position of all the important landmarks on femur and tibia were computed. The distance between the ligament insertion points on femur and tibia or fibula was used as the ligament length at any given position in the flexion arc of the knee joint.

4.2. Computational model definition

4.2.1. Subject-specific knee model set-up

The experimental set-up was implemented into the AnyBody Modeling System 6.0.5 (AnyBody Technology A/S, Denmark). The knee model consisted of the subject-specific bone geometry segmented from CT scans in Mimics 17.0 (Materialise N.V., Leuven, Belgium). The implant position was determined by the post-operative CT scans. The contact between

femoral and tibial implant and between femoral implant and patella was modelled using a rigid-rigid STL-based contact model. The contact forces were computed based on the penetration depth, d_i , of a vertex into the opponent surface. The penetration volume V_i was approximated by the multiplication of the penetration depth and the opponent triangle area A_i , so that for the i th vertex

$$V_i = A_i d_i \quad (1)$$

The direction of the contact force was determined by the normal of the triangle and the contact force magnitude for each contributing element was computed using a linear force law between the penetration volume and the pressure module P

$$F_i = P V_i \quad (2)$$

A pressure module of 4.6 GN/m^3 was used, based on previous tests where the trade-off between the penetration depth and the numerical issues of solving contact between two surfaces with high stiffness was investigated [10].

Four ligaments were defined: proximal and distal part of the medial collateral ligament (MCL), lateral collateral ligament (LCL), medial patello-femoral ligament (MPFL) and lateral epicondylar-patellar ligament (LEPL). The insertions were estimated based on an anatomical atlas using the specimen's bony landmarks and two insertion sites of the MCL proximally and distally on the tibia were identified (MCLprox and MCLdist) [14]. Ligaments were represented as non-linear line segments that wrap over analytical surfaces approximating the relevant geometries. One cylinder was placed medially on the tibia to allow the MCLdist to wrap around the medial tibial condyle and another cylinder was fitted to the femoral implant to prevent the quadriceps muscle from penetrating the implant during deep flexion. Two ellipsoids were introduced to wrap the MPFL and LEPL around the femoral condyles (Figure 1).

204 Ligament force was modelled with the following force-displacement relationship [17]

$$f = \begin{cases} 1/4k\varepsilon^2/\varepsilon_l & 0 \leq \varepsilon \leq 2\varepsilon_l \\ k(\varepsilon - \varepsilon_l) & \varepsilon > 2\varepsilon_l \\ 0 & \varepsilon < 0 \end{cases} \quad (3)$$

205 where f is the tensile force, k the ligament stiffness, ε_l the linear strain limit set at 0.03 [18]
 206 and ε the strain calculated with the ligament length L and its zero-load length L_0 using the
 207 equation $\varepsilon = (L - L_0)/L_0$. The zero-load length L_0 was computed using the following
 208 definition:

$$L_0 = L_r/(\varepsilon_r + 1) \quad (4)$$

209 in which L_r is the ligament reference length and ε_r the reference strain. The stiffness and
 210 reference strain of MCL and LCL were based upon values given by Blankevoort and Huiskes
 211 and can be found in Table 1 [17]. The ligament reference lengths were computed with the
 212 intact knee in full extension. Not much information is available regarding the stiffness and
 213 reference strain of the patellar ligaments MPFL and LEPL. The MPFL is the primary restraint
 214 to lateral patellar displacement and lateral soft-tissues contribute less to the overall stability
 215 [19]. Accordingly, MPFL stiffness was chosen in the same range of MCL and LCL and lower
 216 values were attributed to LEPL. Since patellar ligaments are tightest in full extension and
 217 slacken with flexion, positive reference strain values were assigned in the same range of MCL
 218 and LCL [19]. Both MPFL and LEPL were represented by three line segments and their
 219 parameter values are shown in Table 1.

220 To compare the model output to the local extensometer length changes, the reported model
 221 ligament length changes were calculated using the formula $\varepsilon_{model} = (L - L_r)/L_r$. Additional
 222 to the extensometer length changes, kinematic based ligament length changes were measured
 223 by tracking the length changes of the ligament line segment during the experimental motion
 224 compared to the length at full extension.

The simulation mimicked the experimental set-up, such that the same force to the quadriceps tendon was applied and the same vertical motion of the hip assembly was generated. Figure 2 shows how the model was constrained during the simulation. The hip assembly could move up and down and flex and extend. The ankle assembly could rotate in all three directions and could move medio-laterally. Consequently, this configuration provided the tibio-femoral joint with all six DOFs. The patello-femoral joint was modelled with the assumption of a constant length of the patellar tendon, while the three translational DOFs and the spin and tilt (patellar rotation around respectively the anterior-posterior axis and the proximal-distal axis) were solved by the FDK solver. A simple linear torsional spring with spring constant of 100 Nm/rad was included to ensure some stiffness in the patellar tilt direction during deep knee flexion when the patellar ligaments were slack.

4.2.2. Force-dependent kinematics

Knee kinematics were simulated using FDK, an extended inverse dynamics approach, which simultaneously computes ligament forces and secondary joint motions [10]. This methodology relies on an assumption of quasi-static force equilibrium in the secondary joint kinematics at each time step during the analysis, eliminating the need for time integration. This assumption of static equilibrium only applies to the FDK directions and the full dynamics in all other DOFs are taken into account. This modelling approach is implemented into the AnyBody Modeling System (AnyBody Technology, A/S, Aalborg, Denmark).

4.3. Data analysis

4.3.1. Sensitivity study

A sensitivity analysis was performed to investigate the influence of the tibio-femoral model parameters on the output. The insertion points of three ligament line segments (MCLprox, MCLdist and LCL) as well as the patellar tendon were moved from their reference position.

Since the attachment of these structures is known to lay on the bone surface, the attachments were varied in a plane tangent to the bone surface.

From a study investigating the precision in locating landmarks on CT scans, an estimate of the appropriate variability was made [14]. In the study, an intra-variability of around 1 mm and the inter-variability was 3.5 mm or less was reported. Based on these results, a variation of 3.5 mm was first chosen, representing a range of 7 mm.

Consequently, all ligaments insertions were varied from -3.5 mm to +3.5 mm in the anterior-posterior and proximal-distal direction. The insertions of the patellar tendon were varied from -3.5 mm to +3.5 mm in the medial-lateral and anterior-posterior direction. When one of the insertion locations was changed, the reference ligament length was recalculated and updated prior to the simulation.

In addition, the stiffness and reference strain of the three ligament line segments were varied, each from +3.5% to -3.5% of their reference value. A total of 45 configurations were analysed and the overview of these simulations can be found in Table 2.

4.3.1. Metrics

The tibio-femoral rotations were derived using the Grood and Suntay protocol and the translations were reported in the tibial reference frame [20]. Positive values were assigned to medial, anterior and proximal translations and to valgus and external tibial rotations. Each of these trials show the downwards motion of a squat.

The differences between the experimental and simulation results were quantified using the Root-Mean-Square-Error (RMSE) and the Pearson correlation coefficient with ρ categorized as $\rho \leq 0.35$, $0.35 < \rho \leq 0.67$, $0.67 < \rho \leq 0.9$, $0.9 < \rho$ to be weak, moderate, strong or excellent correlations[21,22]

5. Results

The computed tibio-femoral translations (Figure 3) and rotations (Figure 4) showed a good agreement, predicting the proximal-distal, medial-lateral, anterior-posterior, varus-valgus, internal-external motions with an average RMSE of respectively 1.0 mm, 1.2 mm, 2.7 mm, 0.7° and 2.3°. The average Pearson correlation coefficient for the aforementioned motions was 1.00, 0.38, 0.85, 0.93 and 0.95, showing strong or excellent correlations except for the medial-lateral motion. This lower correlation is caused by the low order of magnitude of this motion. An overview of the kinematic RMSE and Pearson correlation coefficient for all trials for each cadaver can be found in Table 3.

Additionally, tibio-femoral motion can be more intuitively analysed when the 3D motion is projected onto a two-dimensional (2D) plane. Figure 5 shows the projected tibio-femoral kinematics during squat. Because of the clinical importance of rotational movement, the projection plane of choice was the tibial horizontal plane. This plane is defined as the plane perpendicular to the tibial mechanical axis and comprises the line connecting the tibial condyle centres. The projections of the centres of the medial and lateral femoral condyles onto the tibial horizontal plane were presented for different flexion angles, namely 40°, 60°, 80° and 100°.

An overview of the ligament length change RMSE and Pearson correlation coefficient for all trials for each specimen can be found in Table 4. The lateral extensometer length change was compared to the model LCL length change and the medial extensometer length change was compared to the model MCLdist length change. The average RMSE was 2.7% for MCLdist and 4.0% for LCL and the average Pearson correlation coefficient was 0.96 and 0.74 for MCLdist and LCL respectively. Figure 6 depicts the predicted subject-specific model length changes compared to the kinematic based experimental length changes for all conditions. The

average RMSE was 0.9% for MCLdist and 2.5% for LCL and the average Pearson correlation coefficient was 0.99 and 0.98 for MCLdist and LCL respectively.

Figure 7 shows the results of the sensitivity study for the three specimens for the neutral insert trial. The translations were the least sensitive to changes in model parameters. The largest changes can be found in internal-external rotation and ligament length changes, presenting changes up to 3.8° in the maximum internal tibial rotation at the end of the simulation, and up to 6.4% in the absolute ligament length change at the end of the simulation. The perturbed simulations of specimen 2 failed to solve if MCL was less strained, hence we removed these failed output resulting in a smaller shaded area for MCL.

6. Discussion

The motivation of this work was to develop a computational efficient subject-specific model that can predict the relative impact of different implant configurations on kinematics and ligament length change patterns. A validation was performed using *in vitro* kinematics and ligament length changes of different component alignments for three different subjects.

The results showed that the kinematics can accurately be predicted, showing an average RMSE of less than 2.7 mm and 2.3° for translations and rotations. The largest RMSE was for anterior-posterior translation. The model consistently underestimated the anterior position of the femur with respect to the tibia during the beginning of the squat, indicating that some anterior-posterior stiffness is missing. In reality, the knee joint is surrounded by the joint capsule membrane, which is lacking in the model. Overall, the kinematics showed an excellent correlation and small RMSE for the three subjects during the three different alignment conditions. The motions are comparable in trend and in magnitude with the results of Baldwin et al., who validated a finite element (FE) knee model with a posterior-stabilised implant for three cadaveric knees inside a mechanical rig [23]. The ligament parameters and

attachment sites were optimised by minimising differences between model-predicted and experimental kinematics. They noted average RMSE of less than 1.8 mm and 2.2° for translations and rotations respectively. Without ligament parameter optimisation, our model achieved similar results. Moreover, the predicted kinematics after component malrotation showed comparable RMSE.

To evaluate the differences caused by malalignment, the different rows for one specimen can be compared in Figure 5. Valgus malalignment resulted in a more externally rotated starting position of the tibia, whereas varus malalignment caused a slightly more internally rotated tibia compared to the neutral alignment. This presents a direct link to ligament behaviour, since the collateral ligaments are known to be important stabilisers. MCL was more strained in valgus and acts as a restraint to tibial internal rotation, LCL experienced more strain in varus, increasing the restraint to tibial external rotation [24].

Next to changes introduced by coronal malalignment, the inter-specimen variability influenced the kinematics as well. Even though the contact geometry was identical for all specimens, different kinematic behaviour between the specimens can be seen, in particular with respect to the amount of anterior-posterior translation. Nevertheless, the model was able to closely match the experimental kinematics for each specimen. All specimens showed posterior femoral rollback laterally, abnormal anterior femoral translation medially was present for Specimen 1. Similar inter-specimen variability of kinematics after TKA was also seen *in vivo* [23]. Abnormal anterior motion was mostly attributed to lack of PCL and unbalanced collateral ligaments [26]. This explanation seems plausible, since anterior translation was mostly present for varus malalignment of Specimen 1, where 5° of malalignment was introduced as opposed to the 3° of malalignment in Specimen 2 and 3. During varus malrotation, MCL was more slack, resulting in more instability.

From the sensitivity study, it is clear that the ligament length change is sensitive to the model parameters. However, the trend of ligament behaviour as a function of implant alignment can be captured by the model. When comparing the extensometer length changes to the model, an excellent average correlation of 0.96 and RMSE of 2.7% was seen for MCL, while LCL had a strong average correlation of 0.74 and an RMSE of 4.0%. Extensometer length changes are local length changes measured at the mid-region of the ligament, whereas the reported model length changes show average length changes between the insertion points. Hence, additional to the local extensometer length changes, the kinematic based ligament length changes were reported, since experimental ligament length changes are often described using the length between the ligament insertions during the reproduced motion [27]. In our study, these kinematic based length changes showed a strong to excellent correlation and the average RMSE is below 2.5% for all ligament segments. The local extensometer and kinematic based experimental length changes agreed well for MCL, while showing larger deviations for LCL, indicating that the simple ligament model cannot fully represent the variable behaviour of the LCL.

This study investigated the relative behaviour of ligament length changes when varying implant alignment. When introducing the different configurations for the tibial insert, the model and kinematic based experimental strains showed an analogous behaviour. This behaviour is consistent with the results of Delport et al. [28]. They reported that both for the neutral aligned as for the varus or valgus configurations, MCL as well as LCL remained isometric in the beginning of the squat and then started to relax. In addition, the relative relationship between the varus, neutral and valgus alignment corresponds well to our results, resulting in more MCL strain and less LCL strain for valgus malalignment and the other way around for varus malalignment.

The use of mechanical knee simulators in validation studies is a cost-effective and controlled method to mimic real-life conditions. However, this set-up differs from the actual physiologic loading condition, for instance keeping the hip fixed over the ankle and the constant hamstrings load. Despite this artificial representation, the knee motions agree well with *in vivo* motions, supporting the use of such rigs as an intermediate step towards clinical application. Two studies of Victor et al. looked at knee motions, one in a mechanical rig [14] and one in real patients [29]. The *in vitro* study with cadaver knees in a mechanical rig showed mean ranges of motion for tibial rotation and for posterior translation of the medial and lateral femoral condyle of respectively 9.7°, 12.9 mm and 16.3 mm for a PS implant [14]. In the second study, *in vivo* kinematics were measured in TKA patients during deep knee bend with the help of dynamic fluoroscopy [29]. The average range of the aforementioned motions was 10.8°, 14 mm and 23 mm.

The results of the current study need to be seen within the light of the following limitations. The same implant type was used in all three specimens, which meant sacrificing the cruciate ligaments. Cruciate-retaining implants were not tested. Furthermore, the reported extensometer values show only the ligament length changes at the location where the extensometer is sutured. However, ligaments show different length change behaviour at different locations. Ligament model parameters were based on values from literature to demonstrate the generic workflow. However, it is known that ligament zero-load lengths are sensitive parameters in computational models but difficult to measure [30–32]. Other studies often optimize these zero-load lengths until the rotational knee behaviour matches the experimental data [33]. Finally, only coronal implant position variation is modelled here. In future work, we plan to investigate other implant configuration such as joint line variation.

In summary, this work presented a model-based and experimental evaluation of the prediction of knee kinematics and ligament length changes for three different subjects following TKA.

Malalignment was introduced and the associated changes in knee kinematic and ligament length change patterns could be predicted well by the model. Despite the identical implant geometry, inter-specimen differences were both experimentally observed and predicted by the subject-specific model. This validation study is a first, necessary step towards the clinical application of musculoskeletal models. Model credibility to predict component malalignment was assured in this work and the current results support the potential of subject-specific musculoskeletal modelling to aid surgeons in deciding the optimal implant configuration for a patient.

Conflict of interest

The authors declare that they have no conflicts of interest.

7. Acknowledgments

This work has financial support by the Baekeland scheme of the agency for Innovation by Science and Technology (IWT) under grant number IWT 110554 to V. Vanheule and the Danish Council for Independent Research (DFF) under grant number DFF-4184-00018 to M. S. Andersen.

8. References

- [1] Griffin FM, Insall JN, Scuderi GR. Accuracy of soft tissue balancing in total knee arthroplasty. *J Arthroplasty* 2000;15:970–3.
- [2] Abdel MP. Measured resection versus gap balancing for total knee arthroplasty. *Clin Orthop Relat Res* 2014;472:2016–22.
- [3] Fregly BJ, Besier TF, Lloyd DG, Delp SL, Banks SA, Pandy MG, et al. Grand challenge competition to predict in vivo knee loads. *J Orthop Res* 2012;30:503–13.
- [4] Amiri S, Cooke D, Kim IY, Wyss U. Mechanics of the passive knee joint. Part 2: interaction between the ligaments and the articular surfaces in guiding the joint motion. *Proc Inst Mech Eng Part H J Eng Med* 2007;221:821–32.
- [5] Wilson DR, Feikes JD, O'Connor JJ. Ligaments and articular contact guide passive knee flexion. *J Biomech* 1998;31:1127–36.
- [6] Hast MW, Piazza SJ. Dual-joint modeling for estimation of total knee replacement contact forces during locomotion. *J Biomech Eng* 2013;135:021013.
- [7] Thelen DG, Won Choi K, Schmitz AM. Co-Simulation of Neuromuscular Dynamics and Knee Mechanics During Human Walking. *J Biomech Eng* 2014;136:021033.
- [8] Guess TM, Stylianou AP, Kia M. Concurrent prediction of muscle and tibiofemoral contact forces during treadmill gait. *J Biomech Eng* 2014;136:021032.
- [9] Andersen MS, Damsgaard M, Rasmussen J. Force-dependent kinematics: a new analysis method for non-conforming joints. 13th Bienn. Int. Symp. Comput. Simul. Biomech., 2011.

- [10] Marra MA, Vanheule V, Rasmussen J, Verdonschot NJJ, Andersen MS. A Subject-Specific Musculoskeletal Modeling Framework to Predict in Vivo Mechanics of Total Knee Arthroplasty. *J Biomech Eng* 2014;137:020904.
- [11] Thompson JA, Hast MW, Granger JF, Piazza SJ, Siston RA. Biomechanical effects of total knee arthroplasty component malrotation: A computational simulation. *J Orthop Res* 2011;29:969–75.
- [12] Chen Z, Wang L, Liu Y, He J, Lian Q, Li D, et al. Effect of component mal-rotation on knee loading in total knee arthroplasty using multi-body dynamics modeling under a simulated walking gait. *J Orthop Res* 2015;33:1287–96.
- [13] Werner FW, Ayers DC, Maletsky LP, Rullkoetter PJ. The effect of valgus/varus malalignment on load distribution in total knee replacements. *J Biomech* 2005;38:349–55.
- [14] Victor J, Bellemans J. A comparative study on the biomechanics of the native human knee joint and total knee arthroplasty. *Dep Orthop Fac Med* 2009;PhD.
- [15] Delport H, Labey L, De Corte R, Innocenti B, Vander Sloten J, Bellemans J. Collateral ligament strains during knee joint laxity evaluation before and after TKA. *Clin Biomech* 2013;28:777–82.
- [16] Zavatsky AB. A kinematic-freedom analysis of a flexed-knee-stance testing rig. *J Biomech* 1997;30:277–80.
- [17] Blankevoort L, Huiskes R. Ligament-bone interaction in a three-dimensional model of the knee. *J Biomech Eng* 1991;113:263–9.
- [18] Butler DL, Kay MD, Stouffer DC. Comparison of material properties in fascicle-bone units from human patellar tendon and knee ligaments. *J Biomech* 1986;19:425–32.
- [19] Amis AA, Firer P, Mountney J, Senavongse W, Thomas NP. The anatomy and reconstruction of the medial patellofemoral ligament. *Knee* 2003;10:215–20.
- [20] Grood ES, Suntay WJ. A Joint Coordinate System for the Clinical Description of Three-Dimensional Motions: Application to the Knee. *J Biomech Eng* 1983;105:136–44.
- [21] Taylor R. Interpretation of the Correlation Coefficient: A Basic Review. *J Diagnostic Med Sonogr* 1990;6 :35–9.

- 492 [22] Fluit R, Andersen MS, Kolk S, Verdonschot N, Koopman HFJM. Prediction of ground
493 reaction forces and moments during various activities of daily living. *J Biomech*
494 2014;47:2321–9.
495
- 496 [23] Baldwin MA, Clary CW, Fitzpatrick CK, Deacy JS, Maletsky LP, Rullkoetter PJ.
497 Dynamic finite element knee simulation for evaluation of knee replacement mechanics.
498 *J Biomech* 2012;45:474–83.
499
- 500 [24] Athwal KK, Hunt NC, Davies AJ, Deehan DJ, Amis A a. Clinical biomechanics of
501 instability related to total knee arthroplasty. *Clin Biomech* 2014;29:119–28.
502
- 503 [25] Dennis D a, Komistek RD, Colwell CE, Ranawat CS, Scott RD, Thornhill TS, et al. In
504 Vivo Anteroposterior Femorotibial Translation of Total Knee Arthroplasty: A
505 Multicenter Analysis. *Clin Orthop Relat Res* 1998;353:47–57.
506
- 507 [26] Cromie MJ, Siston RA, Giori NJ, Delp SL. Posterior cruciate ligament removal
508 contributes to abnormal knee motion during posterior stabilized total knee arthroplasty.
509 *J Orthop Res* 2008;26:1494–9.
510
- 511 [27] Park SE, DeFrate LE, Suggs JF, Gill TJ, Rubash HE, Li G. Erratum to “The change in
512 length of the medial and lateral collateral ligaments during in vivo knee flexion”. *Knee*
513 2006;13:77–82.
514
- 515 [28] Delport H, Labey L, Innocenti B, De Corte R, Vander Sloten J, Bellemans J.
516 Restoration of constitutional alignment in TKA leads to more physiological strains in
517 the collateral ligaments. *Knee Surgery, Sport Traumatol Arthrosc* 2015;23:2159–69.
518
- 519 [29] Victor J, Mueller JKP, Komistek RD, Sharma A, Nadaud MC, Bellemans J. In Vivo
520 Kinematics after a Cruciate-substituting TKA. *Clin Orthop Relat Res* 2010;468:807–
521 14.
522
- 523 [30] Baldwin MA, Laz PJ, Stowe JQ, Rullkoetter PJ. Efficient probabilistic representation
524 of tibiofemoral soft tissue constraint. *Comput Methods Biomech Biomed Engin*
525 2009;12:651–9.
526
- 527 [31] H. Bloemker K. Computational Knee Ligament Modeling Using Experimentally
528 Determined Zero-Load Lengths. *Open Biomed Eng J* 2012;6:33–41.
529
- 530 [32] Beillas P, Lee SW, Tashman S, Yang KH. Sensitivity of the tibio-femoral response to
531 finite element modeling parameters. *Comput Methods Biomech Biomed Engin*
532 2007;10:209–21.
533

534 [33] Pandy MG, Sasaki K, Kim S. A Three-Dimensional Musculoskeletal Model of the
535 Human Knee Joint. Part 1: Theoretical Construction. Comput Methods Biomech
536 Biomed Engin 1997;1:87–108.
537

538

9. Tables

Table 1: Reference strain (ϵ_r) and stiffness (k) values adapted from Blankevoort and Huiskes [17]. The literature values were slightly adapted since our model has two MCL bundles and one LCL bundle while their model has three bundles for both MCL and LCL. The stiffness was redistributed according to the number of bundles, MCL reference strain could be copied and the LCL reference strain was copied such that the bundle was tensioned in full extension. Both MPFL and LEPL consisted of three bundles and the reported parameter values were assigned to each bundle.

	MCL	LCL	MPFL	LEPL
ϵ_r	0.04	0.08	0.08	0.06
k (N)	4125	6000	2000	1000

Table 2: Summary of the different configurations of the sensitivity study. For each configuration, only one model parameter was perturbed while all other model parameters were kept constant.

Component	Measure	Low value	Initial value	High value
LCL tibia	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
LCL femur	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
MCLprox tibia	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
MCLprox femur	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
MCLdist tibia	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
MCLdist femur	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
Patellar tendon tibia	Med-lat	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
Patellar tendon patella	Med-lat	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
LCL	k	5790 N	6000 N	6210 N
	ϵ_r	0.045%	0.08%	0.115%
MCLprox	k	3980N	4125 N	4270 N
	ϵ_r	0.005%	0.04%	0.075%
MCLdist	k	3980N	4125 N	4270 N
	ϵ_r	0.005%	0.04%	0.075%

Table 3: Comparison of measured and computed kinematics using RMSE and Pearson correlation coefficient ρ . Proximal-distal (PD), medial-lateral (ML), anterior-posterior (AP), varus-valgus (VV) and internal-external (IE) motions are shown.

	RMSE					ρ				
	PD	ML	AP	VV	IE	PD	ML	AP	VV	IE
	(mm)	(mm)	(mm)	(°)	(°)					
Specimen 1										
Neutral	1.34	1.50	2.43	0.67	2.00	1.00	0.40	0.69	0.89	0.94
Varus	1.53	1.16	2.26	0.61	1.97	1.00	0.79	0.66	0.79	0.99
Valgus	0.89	2.19	2.58	0.41	2.91	1.00	-0.08	0.75	0.97	0.94
Specimen 2										
Neutral	0.47	0.89	2.95	0.80	2.65	1.00	0.00	0.91	0.93	0.92
Varus	0.44	0.65	2.18	1.26	3.23	1.00	0.88	0.94	0.99	0.93
Valgus	0.53	0.44	2.41	0.65	2.04	1.00	0.78	0.90	0.86	0.95
Specimen 3										
Neutral	1.38	0.93	3.26	0.45	1.94	0.99	0.43	0.97	1.00	0.97
Varus	1.52	1.82	3.13	0.75	1.58	0.99	-0.16	0.95	1.00	0.97
	1.01	1.20	2.65	0.70	2.29	1.00	0.38	0.85	0.93	0.95
Average	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
	0.45	0.56	0.38	0.25	0.53	0.00	0.39	0.12	0.07	0.02

Table 4: Comparison of experimental and computed ligament length changes using RMSE and Pearson correlation coefficient ρ . Kinematic based length changes (Kin) and extensometer length changes (Ext) are shown.

	RMSE				ρ			
	MCL	MCL	LCL	LCL	MCL	MCL	LCL	LCL
	Ext (%)	Kin (%)	Ext (%)	Kin (%)	Ext	Kin	Ext	Kin
Specimen 1								
Neutral	1.88	0.87	3.45	3.26	0.98	0.99	0.25	0.99
Varus	4.64	1.11	1.99	3.44	0.97	0.99	0.28	0.97
Valgus	2.24	1.09	4.07	1.49	0.96	0.97	0.67	0.95
Specimen 2								
Neutral	2.08	0.44	4.97	1.74	0.99	1.00	0.95	0.97
Varus	2.03	0.76	4.05	2.25	0.94	0.99	0.99	0.98
Valgus	1.87	0.65	3.04	1.39	0.96	0.97	0.98	0.99
Specimen 3								
Neutral	2.83	1.27	5.92	2.73	0.93	0.99	0.87	0.98
Varus	3.95	1.10	4.73	3.82	0.92	0.99	0.92	0.98
Average	2.69	0.91	4.03	2.51	0.96	0.99	0.74	0.98
	± 0.98	± 0.26	± 1.14	± 0.88	± 0.02	± 0.01	± 0.29	± 0.01

1. Title page

Evaluation of predicted knee function for component malrotation in total knee arthroplasty

Valentine Vanheule^{a,b}, Hendrik Pieter Delport^c, Michael Skipper Andersen^d, Lennart Scheys^c,
Roel Wirix-Speetjens^b, Ilse Jonkers^e, Jan Victor^f and Jos Vander Sloten^a

^aBiomechanics section, Katholieke Universiteit Leuven, Celestijnenlaan 300C, 3001 Leuven, Belgium

^bMaterialise N.V., Technologielaan 15, 3001 Leuven, Belgium

^cDepartment of Orthopaedics, University Hospital Pellenberg, Katholieke Universiteit Leuven, Weligerveld 1, 3212 Pellenberg, Belgium

^dDepartment of Mechanical and Manufacturing Engineering, Aalborg University, Fredrik Bajers Vej 5, 9100 Aalborg, Denmark

^eDepartment of Kinesiology, Katholieke Universiteit Leuven, Tervuursevest 101, 3001 Leuven, Belgium

^fDepartment of Physical Medicine and Orthopedic Surgery, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium

Corresponding author

Valentine Vanheule

Department of Mechanical Engineering
Division BMe
Celestijnenlaan 300C
3001 Leuven, Belgium
valentine.vanheule@kuleuven.be

Phone: +32 16 74 42 71

Fax: +32 16 39 66 00

2. Abstract

Soft-tissue balancing for total knee arthroplasty (TKA) remains subjective and highly dependent on surgical expertise. Pre-operative planning may support the clinician in taking decisions by integrating subject-specific computer models that predict functional outcome. However, validation of these models is essential before they can be applied in clinical practice. The aim of this study was to evaluate a knee modelling workflow by comparing experimental cadaveric measures to model-based kinematics and ligament length changes. Subject-specific models for three cadaveric knees were constructed from medical images. The implanted knees were mounted onto a mechanical rig to perform squatting, measuring kinematics and ligament length changes with optical markers and extensometers. Coronal malrotation was introduced using tibial inserts with a built-in slope. The model output agreed well with the experiment in all alignment conditions. Kinematic behaviour showed an average RMSE of less than 2.7 mm and 2.3° for translations and rotations. The average RMSE was below 2.5% for all ligaments. These results show that the presented model can quantitatively predict subject-specific knee behaviour following TKA, allowing evaluation of implant alignment in terms of kinematics and ligament length changes. In future work, the model will be used to evaluate subject-specific implant position based on ligament behaviour.

Keywords: subject-specific, alignment, soft tissue balancing, kinematic knee rig, in vitro

3. Introduction

Creating appropriate soft-tissue balance during total knee replacement surgery is mainly subjective and highly dependent on the surgeon's expertise [1,2]. Pre-operative planning incorporating predictive tools to evaluate functional outcome may support the surgeon by comparing different surgical treatments. Subject-specific musculoskeletal models have a high potential to be used as a predictive tool in clinical practice [3]. In detailed joint models, ligaments strongly influence kinematics since they are highly important structures for guiding and stabilising knee motion [4,5]. However, before applying such models in a clinical setting, validation is of paramount importance. The purpose of this study was to evaluate a computational efficient model that can predict subject-specific knee kinematics and ligament length changes for different implant alignments.

Recently, several studies explored methods that can simultaneously compute motions as well as muscle and contact forces. Hast and Piazza presented a dual-joint workflow in which the knee joint is alternated between a simplified knee joint representation for inverse dynamics and an unconstrained knee with elastic foundation contact [6]. Thelen et al. extended the computed muscle control algorithm (CMC) to co-simulate muscle and contact forces, using an elastic foundation model [7]. Guess et al. presented a two-stage modelling method, an inverse kinematics and a forward dynamics simulation, predicting muscle and contact forces concurrently [8].

Andersen et al. introduced an alternative approach, called force-dependent kinematics (FDK), that extends the fast inverse dynamic simulations with the ability to estimate secondary joint kinematics [9]. This method relies on an assumption of quasi-static force equilibrium in the secondary joint kinematics at each time step during the analysis. In 2014, the FDK method was applied and knee contact forces were validated during walking activities in the winning model of the Grand Challenge competition [10].

Musculoskeletal models have the ability to explore the relationship between implant alignment and functional outcome for different activities of daily living. Others investigated the effects of implant alignment variation during a simulated squat, however, without collecting experimental evidence for the malaligned configurations [11,12]. In our study, we modelled different implant alignment variations and additionally, performed a cadaveric study to validate the predicted knee function for each alignment. FDK was used to simulate knee kinematics and predict ligament length change patterns for three cadaveric knees with TKA performing a squat motion. In addition to the standard implant, malrotation in the coronal plane was introduced by using tibial inserts with a built-in varus or valgus offset [13]. For each specimen, three squats were performed with the knee in neutral, varus or valgus alignment. The model outputs were validated by comparing experimental and model-predicted tibio-femoral motion and ligament length changes. To our knowledge, this is the first study to both simulate and validate the impact of implant alignment on kinematics and ligament length changes as predicted by computer models.

4. Methods

4.1. Experimental data collection

4.1.1. Specimen preparation and imaging

Three cadaveric knee specimens were used for squat simulations in a dynamic knee simulator system. The methodology of the specimen preparation was similar to the workflow described by Victor et al. [14]. The study protocol was approved by the local Ethics Committee.

After thawing the fresh frozen specimens, full leg T1-weighted opposed-phase spoiled gradient echo magnetic resonance imaging (MRI) scans were obtained using a 3T scanner (Ingenia, Philips Healthcare) to visualise soft tissues. The slice thickness was 2 mm and all slices had an in plane resolution of 0.9 mm x 0.9 mm. Subsequently, frames (Medtronic, MN,

110 USA) with reflective spherical markers were rigidly attached to femur, tibia and patella. Each
111 frame carried 4 markers, which were 6 mm in diameter. The femoral frame was inserted
112 within 21 cm from the joint line, the tibial frame within 18 cm from the joint line and the
113 patellar frame was inserted onto the patella. To allow accurate three-dimensional motion
114 tracking, a six-camera motion capture system (Vicon MX40, Oxford, UK) was used. The
115 optical markers could accurately be located on the pre-operative and post-operative computed
116 tomography (CT) scans.

117 Volumetric CT scans of the full lower leg with the attached markers were obtained on a dual-
118 source multidetector CT scanner (SOMATOM Definition Flash, Siemens), equipped with two
119 64-detector row units, using a slice thickness of 0.75 mm and a pitch of 0.8 mm/rev. The
120 images were processed in Mimics v. 17.0 (Materialise, Leuven, Belgium) to construct the
121 bone models of femur, tibia and patella. These bone geometries were used to identify bony
122 landmarks.

123 Next, the hip and foot were removed from the full leg, with a femoral cut 32 cm proximal of
124 the joint line and a tibial cut 28 cm distal from the joint line. The quadriceps muscle was
125 dissected and its preserved tendon was fixed into a clamp. In addition, the semitendinosus
126 together with the semimembranosus muscle, as well as the biceps femoris muscle were
127 dissected and suture wires were attached to the preserved tendons. The proximal femur and
128 distal tibia were then embedded in aluminium containers, preserving the physiologic
129 alignment in the coronal plane and parallel with the container in the sagittal plane.

130 Two extensometers (MTS, Eden Prairie, MN, USA) were sutured to the medial and lateral
131 collateral ligaments by an experienced surgeon. The fixation of the extensometers was centred
132 over the joint line, on an unloaded and fully extended knee [15]. During the measurements,
133 ligament length change relative to the extended knee was calculated using the formula

$\varepsilon = (L - L_r)/L_r$, where L was the instantaneous length of the extensometer arms connected to the ligament and L_r was the reference length at full extension.

4.1.2. Total knee replacement and imaging

An experienced surgeon (HD) performed the total knee arthroplasty on each specimen using a posterior-stabilised total knee arthroplasty (Performance, Biomet Inc., Warsaw, IN, USA). In addition to the tibial implant placed with standard alignment instrumentation, two variations of the tibial insert were designed through additive manufacturing. These variations were able to artificially simulate a TKA coronal malalignment by their built-in varus or valgus design. The inserts were modelled so that the central height was preserved while making one side thicker and the other side thinner than the neutral insert. For each specimen, three squat trials were performed. Specimen 1 underwent squats with neutral insert, 5° varus insert and 5° valgus insert. Specimen 2 and 3 underwent squats with neutral insert, 3° varus insert and 3° valgus insert. The tibial insert thickness for specimen 2 and 3 was smaller, leading to a smaller varus and valgus angle due to design limitations. The valgus insert squat of specimen 3 is not shown in the results since the quadriceps ruptured during the last experiment.

After the trials, post-operative CT scans were made with the optical markers still attached on the same scanner as the pre-operative scans, allowing to accurately document the implant position.

4.1.3. Knee simulator set-up

The specimens were mounted onto a dynamic knee simulator system, based on the Oxford rig [16]. This mechanical system permits six degrees-of-freedom (DOFs) for both the tibio-femoral and the patello-femoral joint. The femoral container was connected to an artificial hip assembly and the tibial container to an artificial ankle assembly. The quadriceps clamp was connected to an actuator that could apply a variable quadriceps load. Both hamstring wires

were connected with constant-force springs of each 50 N (Type KKF 8077, Lesjöfors, Karlstad, Sweden). The hip assembly could slide vertically and flex and extend, the ankle assembly allowed rotation in all three directions and translated medio-laterally. Sensors detected the quadriceps force, ankle force and relative hip height and these real-time data were processed in a closed feedback system (LabVIEW, National Instruments, Texas, USA), allowing the performance of a squat motion by moving the hip assembly and applying a variable quadriceps force to induce a vertical ankle force of 111 N. The quadriceps load increased during knee flexion, starting from a few hundred Newton at the beginning of the experiment and the load could go up to 2000 N at deep knee bend. A full squat motion began around 30-40° knee flexion and went up to 110-120°. The squat did not begin at full extension to prevent hyperextension [14].

Six infrared emitting cameras (MX40, Vicon, Oxford, UK) tracked the reflecting light from the rigidly attached optical markers on femur, tibia and patella at a sampling frequency of 100 Hz. This provided us an accurate measurement of the knee joint motion during squat. Throughout knee flexion, the three-dimensional (3D) coordinates of the passive markers were tracked and the relative position of all the important landmarks on femur and tibia were computed. The distance between the ligament insertion points on femur and tibia or fibula was used as the ligament length at any given position in the flexion arc of the knee joint.

4.2. Computational model definition

4.2.1. Subject-specific knee model set-up

The experimental set-up was implemented into the AnyBody Modeling System 6.0.5 (AnyBody Technology A/S, Denmark). The knee model consisted of the subject-specific bone geometry segmented from CT scans in Mimics 17.0 (Materialise N.V., Leuven, Belgium). The implant position was determined by the post-operative CT scans. The contact between

femoral and tibial implant and between femoral implant and patella was modelled using a rigid-rigid STL-based contact model. The contact forces were computed based on the penetration depth, d_i , of a vertex into the opponent surface. The penetration volume V_i was approximated by the multiplication of the penetration depth and the opponent triangle area A_i , so that for the i th vertex

$$V_i = A_i d_i \quad (1)$$

The direction of the contact force was determined by the normal of the triangle and the contact force magnitude for each contributing element was computed using a linear force law between the penetration volume and the pressure module P

$$F_i = P V_i \quad (2)$$

A pressure module of 4.6 GN/m^3 was used, based on previous tests where the trade-off between the penetration depth and the numerical issues of solving contact between two surfaces with high stiffness was investigated [10].

Four ligaments were defined: proximal and distal part of the medial collateral ligament (MCL), lateral collateral ligament (LCL), medial patello-femoral ligament (MPFL) and lateral epicondylo-patellar ligament (LEPL). The insertions were estimated based on an anatomical atlas using the specimen's bony landmarks and two insertion sites of the MCL proximally and distally on the tibia were identified (MCLprox and MCLdist) [14]. Ligaments were represented as non-linear line segments that wrap over analytical surfaces approximating the relevant geometries. One cylinder was placed medially on the tibia to allow the MCLdist to wrap around the medial tibial condyle and another cylinder was fitted to the femoral implant to prevent the quadriceps muscle from penetrating the implant during deep flexion. Two ellipsoids were introduced to wrap the MPFL and LEPL around the femoral condyles (Figure 1).

204 Ligament force was modelled with the following force-displacement relationship [17]

$$f = \begin{cases} 1/4k\varepsilon^2/\varepsilon_l & 0 \leq \varepsilon \leq 2\varepsilon_l \\ k(\varepsilon - \varepsilon_l) & \varepsilon > 2\varepsilon_l \\ 0 & \varepsilon < 0 \end{cases} \quad (3)$$

205 where f is the tensile force, k the ligament stiffness, ε_l the linear strain limit set at 0.03 [18]
 206 and ε the strain calculated with the ligament length L and its zero-load length L_0 using the
 207 equation $\varepsilon = (L - L_0)/L_0$. The zero-load length L_0 was computed using the following
 208 definition:

$$L_0 = L_r/(\varepsilon_r + 1) \quad (4)$$

209 in which L_r is the ligament reference length and ε_r the reference strain. The stiffness and
 210 reference strain of MCL and LCL were based upon values given by Blankevoort and Huiskes
 211 and can be found in Table 1 [17]. The ligament reference lengths were computed with the
 212 intact knee in full extension. Not much information is available regarding the stiffness and
 213 reference strain of the patellar ligaments MPFL and LEPL. The MPFL is the primary restraint
 214 to lateral patellar displacement and lateral soft-tissues contribute less to the overall stability
 215 [19]. Accordingly, MPFL stiffness was chosen in the same range of MCL and LCL and lower
 216 values were attributed to LEPL. Since patellar ligaments are tightest in full extension and
 217 slacken with flexion, positive reference strain values were assigned in the same range of MCL
 218 and LCL [19]. Both MPFL and LEPL were represented by three line segments and their
 219 parameter values are shown in Table 1.

220 To compare the model output to the local extensometer length changes, the reported model
 221 ligament length changes were calculated using the formula $\varepsilon_{model} = (L - L_r)/L_r$. Additional
 222 to the extensometer length changes, kinematic based ligament length changes were measured
 223 by tracking the length changes of the ligament line segment during the experimental motion
 224 compared to the length at full extension.

The simulation mimicked the experimental set-up, such that the same force to the quadriceps tendon was applied and the same vertical motion of the hip assembly was generated. Figure 2 shows how the model was constrained during the simulation. The hip assembly could move up and down and flex and extend. The ankle assembly could rotate in all three directions and could move medio-laterally. Consequently, this configuration provided the tibio-femoral joint with all six DOFs. The patello-femoral joint was modelled with the assumption of a constant length of the patellar tendon, while the three translational DOFs and the spin and tilt (patellar rotation around respectively the anterior-posterior axis and the proximal-distal axis) were solved by the FDK solver. A simple linear torsional spring with spring constant of 100 Nm/rad was included to ensure some stiffness in the patellar tilt direction during deep knee flexion when the patellar ligaments were slack.

4.2.2. Force-dependent kinematics

Knee kinematics were simulated using FDK, an extended inverse dynamics approach, which simultaneously computes ligament forces and secondary joint motions [10]. This methodology relies on an assumption of quasi-static force equilibrium in the secondary joint kinematics at each time step during the analysis, eliminating the need for time integration. This assumption of static equilibrium only applies to the FDK directions and the full dynamics in all other DOFs are taken into account. This modelling approach is implemented into the AnyBody Modeling System (AnyBody Technology, A/S, Aalborg, Denmark).

4.3. Data analysis

4.3.1. Sensitivity study

A sensitivity analysis was performed to investigate the influence of the tibio-femoral model parameters on the output. The insertion points of three ligament line segments (MCLprox, MCLdist and LCL) as well as the patellar tendon were moved from their reference position.

Since the attachment of these structures is known to lay on the bone surface, the attachments were varied in a plane tangent to the bone surface.

From a study investigating the precision in locating landmarks on CT scans, an estimate of the appropriate variability was made [14]. In the study, an intra-variability of around 1 mm and the inter-variability was 3.5 mm or less was reported. Based on these results, a variation of 3.5 mm was first chosen, representing a range of 7 mm.

Consequently, all ligaments insertions were varied from -3.5 mm to +3.5 mm in the anterior-posterior and proximal-distal direction. The insertions of the patellar tendon were varied from -3.5 mm to +3.5 mm in the medial-lateral and anterior-posterior direction. When one of the insertion locations was changed, the reference ligament length was recalculated and updated prior to the simulation.

In addition, the stiffness and reference strain of the three ligament line segments were varied, each from +3.5% to -3.5% of their reference value. A total of 45 configurations were analysed and the overview of these simulations can be found in Table 2.

4.3.1. Metrics

The tibio-femoral rotations were derived using the Grood and Suntay protocol and the translations were reported in the tibial reference frame [20]. Positive values were assigned to medial, anterior and proximal translations and to valgus and external tibial rotations. Each of these trials show the downwards motion of a squat.

The differences between the experimental and simulation results were quantified using the Root-Mean-Square-Error (RMSE) and the Pearson correlation coefficient with ρ categorized as $\rho \leq 0.35$, $0.35 < \rho \leq 0.67$, $0.67 < \rho \leq 0.9$, $0.9 < \rho$ to be weak, moderate, strong or excellent correlations[21,22]

5. Results

The computed tibio-femoral translations (Figure 3) and rotations (Figure 4) showed a good agreement, predicting the proximal-distal, medial-lateral, anterior-posterior, varus-valgus, internal-external motions with an average RMSE of respectively 1.0 mm, 1.2 mm, 2.7 mm, 0.7° and 2.3°. The average Pearson correlation coefficient for the aforementioned motions was 1.00, 0.38, 0.85, 0.93 and 0.95, showing strong or excellent correlations except for the medial-lateral motion. This lower correlation is caused by the low order of magnitude of this motion. An overview of the kinematic RMSE and Pearson correlation coefficient for all trials for each cadaver can be found in Table 3.

Additionally, tibio-femoral motion can be more intuitively analysed when the 3D motion is projected onto a two-dimensional (2D) plane. Figure 5 shows the projected tibio-femoral kinematics during squat. Because of the clinical importance of rotational movement, the projection plane of choice was the tibial horizontal plane. This plane is defined as the plane perpendicular to the tibial mechanical axis and comprises the line connecting the tibial condyle centres. The projections of the centres of the medial and lateral femoral condyles onto the tibial horizontal plane were presented for different flexion angles, namely 40°, 60°, 80° and 100°.

An overview of the ligament length change RMSE and Pearson correlation coefficient for all trials for each specimen can be found in Table 4. The lateral extensometer length change was compared to the model LCL length change and the medial extensometer length change was compared to the model MCLdist length change. The average RMSE was 2.7% for MCLdist and 4.0% for LCL and the average Pearson correlation coefficient was 0.96 and 0.74 for MCLdist and LCL respectively. Figure 6 depicts the predicted subject-specific model length changes compared to the kinematic based experimental length changes for all conditions. The

average RMSE was 0.9% for MCLdist and 2.5% for LCL and the average Pearson correlation coefficient was 0.99 and 0.98 for MCLdist and LCL respectively.

Figure 7 shows the results of the sensitivity study for the three specimens for the neutral insert trial. The translations were the least sensitive to changes in model parameters. The largest changes can be found in internal-external rotation and ligament length changes, presenting changes up to 3.8° in the maximum internal tibial rotation at the end of the simulation, and up to 6.4% in the absolute ligament length change at the end of the simulation. The perturbed simulations of specimen 2 failed to solve if MCL was less strained, hence we removed these failed output resulting in a smaller shaded area for MCL.

6. Discussion

The motivation of this work was to develop a computational efficient subject-specific model that can predict the relative impact of different implant configurations on kinematics and ligament length change patterns. A validation was performed using *in vitro* kinematics and ligament length changes of different component alignments for three different subjects.

The results showed that the kinematics can accurately be predicted, showing an average RMSE of less than 2.7 mm and 2.3° for translations and rotations. The largest RMSE was for anterior-posterior translation. The model consistently underestimated the anterior position of the femur with respect to the tibia during the beginning of the squat, indicating that some anterior-posterior stiffness is missing. In reality, the knee joint is surrounded by the joint capsule membrane, which is lacking in the model. Overall, the kinematics showed an excellent correlation and small RMSE for the three subjects during the three different alignment conditions. The motions are comparable in trend and in magnitude with the results of Baldwin et al., who validated a finite element (FE) knee model with a posterior-stabilised implant for three cadaveric knees inside a mechanical rig [23]. The ligament parameters and

attachment sites were optimised by minimising differences between model-predicted and experimental kinematics. They noted average RMSE of less than 1.8 mm and 2.2° for translations and rotations respectively. Without ligament parameter optimisation, our model achieved similar results. Moreover, the predicted kinematics after component malrotation showed comparable RMSE.

To evaluate the differences caused by malalignment, the different rows for one specimen can be compared in Figure 5. Valgus malalignment resulted in a more externally rotated starting position of the tibia, whereas varus malalignment caused a slightly more internally rotated tibia compared to the neutral alignment. This presents a direct link to ligament behaviour, since the collateral ligaments are known to be important stabilisers. MCL was more strained in valgus and acts as a restraint to tibial internal rotation, LCL experienced more strain in varus, increasing the restraint to tibial external rotation [24].

Next to changes introduced by coronal malalignment, the inter-specimen variability influenced the kinematics as well. Even though the contact geometry was identical for all specimens, different kinematic behaviour between the specimens can be seen, in particular with respect to the amount of anterior-posterior translation. Nevertheless, the model was able to closely match the experimental kinematics for each specimen. All specimens showed posterior femoral rollback laterally, abnormal anterior femoral translation medially was present for Specimen 1. Similar inter-specimen variability of kinematics after TKA was also seen *in vivo* [23]. Abnormal anterior motion was mostly attributed to lack of PCL and unbalanced collateral ligaments [26]. This explanation seems plausible, since anterior translation was mostly present for varus malalignment of Specimen 1, where 5° of malalignment was introduced as opposed to the 3° of malalignment in Specimen 2 and 3. During varus malrotation, MCL was more slack, resulting in more instability.

From the sensitivity study, it is clear that the ligament length change is sensitive to the model parameters. However, the trend of ligament behaviour as a function of implant alignment can be captured by the model. When comparing the extensometer length changes to the model, an excellent average correlation of 0.96 and RMSE of 2.7% was seen for MCL, while LCL had a strong average correlation of 0.74 and an RMSE of 4.0%. Extensometer length changes are local length changes measured at the mid-region of the ligament, whereas the reported model length changes show average length changes between the insertion points. Hence, additional to the local extensometer length changes, the kinematic based ligament length changes were reported, since experimental ligament length changes are often described using the length between the ligament insertions during the reproduced motion [27]. In our study, these kinematic based length changes showed a strong to excellent correlation and the average RMSE is below 2.5% for all ligament segments. The local extensometer and kinematic based experimental length changes agreed well for MCL, while showing larger deviations for LCL, indicating that the simple ligament model cannot fully represent the variable behaviour of the LCL.

This study investigated the relative behaviour of ligament length changes when varying implant alignment. When introducing the different configurations for the tibial insert, the model and kinematic based experimental strains showed an analogous behaviour. This behaviour is consistent with the results of Delport et al. [28]. They reported that both for the neutral aligned as for the varus or valgus configurations, MCL as well as LCL remained isometric in the beginning of the squat and then started to relax. In addition, the relative relationship between the varus, neutral and valgus alignment corresponds well to our results, resulting in more MCL strain and less LCL strain for valgus malalignment and the other way around for varus malalignment.

The use of mechanical knee simulators in validation studies is a cost-effective and controlled method to mimic real-life conditions. However, this set-up differs from the actual physiologic loading condition, for instance keeping the hip fixed over the ankle and the constant hamstrings load. Despite this artificial representation, the knee motions agree well with *in vivo* motions, supporting the use of such rigs as an intermediate step towards clinical application. Two studies of Victor et al. looked at knee motions, one in a mechanical rig [14] and one in real patients [29]. The *in vitro* study with cadaver knees in a mechanical rig showed mean ranges of motion for tibial rotation and for posterior translation of the medial and lateral femoral condyle of respectively 9.7°, 12.9 mm and 16.3 mm for a PS implant [14]. In the second study, *in vivo* kinematics were measured in TKA patients during deep knee bend with the help of dynamic fluoroscopy [29]. The average range of the aforementioned motions was 10.8°, 14 mm and 23 mm.

The results of the current study need to be seen within the light of the following limitations. The same implant type was used in all three specimens, which meant sacrificing the cruciate ligaments. Cruciate-retaining implants were not tested. Furthermore, the reported extensometer values show only the ligament length changes at the location where the extensometer is sutured. However, ligaments show different length change behaviour at different locations. Ligament model parameters were based on values from literature to demonstrate the generic workflow. However, it is known that ligament zero-load lengths are sensitive parameters in computational models but difficult to measure [30–32]. Other studies often optimize these zero-load lengths until the rotational knee behaviour matches the experimental data [33]. Finally, only coronal implant position variation is modelled here. In future work, we plan to investigate other implant configuration such as joint line variation.

In summary, this work presented a model-based and experimental evaluation of the prediction of knee kinematics and ligament length changes for three different subjects following TKA.

Malalignment was introduced and the associated changes in knee kinematic and ligament length change patterns could be predicted well by the model. Despite the identical implant geometry, inter-specimen differences were both experimentally observed and predicted by the subject-specific model. This validation study is a first, necessary step towards the clinical application of musculoskeletal models. Model credibility to predict component malalignment was assured in this work and the current results support the potential of subject-specific musculoskeletal modelling to aid surgeons in deciding the optimal implant configuration for a patient.

Conflict of interest

The authors declare that they have no conflicts of interest.

7. Acknowledgments

This work has financial support by the Baekeland scheme of the agency for Innovation by Science and Technology (IWT) under grant number IWT 110554 to V. Vanheule and the Danish Council for Independent Research (DFF) under grant number DFF-4184-00018 to M. S. Andersen.

8. References

- [1] Griffin FM, Insall JN, Scuderi GR. Accuracy of soft tissue balancing in total knee arthroplasty. *J Arthroplasty* 2000;15:970–3.
- [2] Abdel MP. Measured resection versus gap balancing for total knee arthroplasty. *Clin Orthop Relat Res* 2014;472:2016–22.
- [3] Fregly BJ, Besier TF, Lloyd DG, Delp SL, Banks SA, Pandy MG, et al. Grand challenge competition to predict in vivo knee loads. *J Orthop Res* 2012;30:503–13.
- [4] Amiri S, Cooke D, Kim IY, Wyss U. Mechanics of the passive knee joint. Part 2: interaction between the ligaments and the articular surfaces in guiding the joint motion. *Proc Inst Mech Eng Part H J Eng Med* 2007;221:821–32.
- [5] Wilson DR, Feikes JD, O'Connor JJ. Ligaments and articular contact guide passive knee flexion. *J Biomech* 1998;31:1127–36.
- [6] Hast MW, Piazza SJ. Dual-joint modeling for estimation of total knee replacement contact forces during locomotion. *J Biomech Eng* 2013;135:021013.
- [7] Thelen DG, Won Choi K, Schmitz AM. Co-Simulation of Neuromuscular Dynamics and Knee Mechanics During Human Walking. *J Biomech Eng* 2014;136:021033.
- [8] Guess TM, Stylianou AP, Kia M. Concurrent prediction of muscle and tibiofemoral contact forces during treadmill gait. *J Biomech Eng* 2014;136:021032.
- [9] Andersen MS, Damsgaard M, Rasmussen J. Force-dependent kinematics: a new analysis method for non-conforming joints. 13th Bienn. Int. Symp. Comput. Simul. Biomech., 2011.

- [10] Marra MA, Vanheule V, Rasmussen J, Verdonschot NJJ, Andersen MS. A Subject-Specific Musculoskeletal Modeling Framework to Predict in Vivo Mechanics of Total Knee Arthroplasty. *J Biomech Eng* 2014;137:020904.
- [11] Thompson JA, Hast MW, Granger JF, Piazza SJ, Siston RA. Biomechanical effects of total knee arthroplasty component malrotation: A computational simulation. *J Orthop Res* 2011;29:969–75.
- [12] Chen Z, Wang L, Liu Y, He J, Lian Q, Li D, et al. Effect of component mal-rotation on knee loading in total knee arthroplasty using multi-body dynamics modeling under a simulated walking gait. *J Orthop Res* 2015;33:1287–96.
- [13] Werner FW, Ayers DC, Maletsky LP, Rullkoetter PJ. The effect of valgus/varus malalignment on load distribution in total knee replacements. *J Biomech* 2005;38:349–55.
- [14] Victor J, Bellemans J. A comparative study on the biomechanics of the native human knee joint and total knee arthroplasty. *Dep Orthop Fac Med* 2009;PhD.
- [15] Delport H, Labey L, De Corte R, Innocenti B, Vander Sloten J, Bellemans J. Collateral ligament strains during knee joint laxity evaluation before and after TKA. *Clin Biomech* 2013;28:777–82.
- [16] Zavatsky AB. A kinematic-freedom analysis of a flexed-knee-stance testing rig. *J Biomech* 1997;30:277–80.
- [17] Blankevoort L, Huiskes R. Ligament-bone interaction in a three-dimensional model of the knee. *J Biomech Eng* 1991;113:263–9.
- [18] Butler DL, Kay MD, Stouffer DC. Comparison of material properties in fascicle-bone units from human patellar tendon and knee ligaments. *J Biomech* 1986;19:425–32.
- [19] Amis AA, Firer P, Mountney J, Senavongse W, Thomas NP. The anatomy and reconstruction of the medial patellofemoral ligament. *Knee* 2003;10:215–20.
- [20] Grood ES, Suntay WJ. A Joint Coordinate System for the Clinical Description of Three-Dimensional Motions: Application to the Knee. *J Biomech Eng* 1983;105:136–44.
- [21] Taylor R. Interpretation of the Correlation Coefficient: A Basic Review. *J Diagnostic Med Sonogr* 1990;6 :35–9.

492 [22] Fluit R, Andersen MS, Kolk S, Verdonschot N, Koopman HFJM. Prediction of ground
493 reaction forces and moments during various activities of daily living. *J Biomech*
494 2014;47:2321–9.
495

496 [23] Baldwin MA, Clary CW, Fitzpatrick CK, Deacy JS, Maletsky LP, Rullkoetter PJ.
497 Dynamic finite element knee simulation for evaluation of knee replacement mechanics.
498 *J Biomech* 2012;45:474–83.
499

500 [24] Athwal KK, Hunt NC, Davies AJ, Deehan DJ, Amis A a. Clinical biomechanics of
501 instability related to total knee arthroplasty. *Clin Biomech* 2014;29:119–28.
502

503 [25] Dennis D a, Komistek RD, Colwell CE, Ranawat CS, Scott RD, Thornhill TS, et al. In
504 Vivo Anteroposterior Femorotibial Translation of Total Knee Arthroplasty: A
505 Multicenter Analysis. *Clin Orthop Relat Res* 1998;353:47–57.
506

507 [26] Cromie MJ, Siston RA, Giori NJ, Delp SL. Posterior cruciate ligament removal
508 contributes to abnormal knee motion during posterior stabilized total knee arthroplasty.
509 *J Orthop Res* 2008;26:1494–9.
510

511 [27] Park SE, DeFrate LE, Suggs JF, Gill TJ, Rubash HE, Li G. Erratum to “The change in
512 length of the medial and lateral collateral ligaments during in vivo knee flexion”. *Knee*
513 2006;13:77–82.
514

515 [28] Delport H, Labey L, Innocenti B, De Corte R, Vander Sloten J, Bellemans J.
516 Restoration of constitutional alignment in TKA leads to more physiological strains in
517 the collateral ligaments. *Knee Surgery, Sport Traumatol Arthrosc* 2015;23:2159–69.
518

519 [29] Victor J, Mueller JKP, Komistek RD, Sharma A, Nadaud MC, Bellemans J. In Vivo
520 Kinematics after a Cruciate-substituting TKA. *Clin Orthop Relat Res* 2010;468:807–
521 14.
522

523 [30] Baldwin MA, Laz PJ, Stowe JQ, Rullkoetter PJ. Efficient probabilistic representation
524 of tibiofemoral soft tissue constraint. *Comput Methods Biomech Biomed Engin*
525 2009;12:651–9.
526

527 [31] H. Bloemker K. Computational Knee Ligament Modeling Using Experimentally
528 Determined Zero-Load Lengths. *Open Biomed Eng J* 2012;6:33–41.
529

530 [32] Beillas P, Lee SW, Tashman S, Yang KH. Sensitivity of the tibio-femoral response to
531 finite element modeling parameters. *Comput Methods Biomech Biomed Engin*
532 2007;10:209–21.
533

534 [33] Pandy MG, Sasaki K, Kim S. A Three-Dimensional Musculoskeletal Model of the
535 Human Knee Joint. Part 1: Theoretical Construction. Comput Methods Biomech
536 Biomed Engin 1997;1:87–108.
537

538

9. Tables

Table 1: Reference strain (ϵ_r) and stiffness (k) values adapted from Blankevoort and Huiskes [17]. The literature values were slightly adapted since our model has two MCL bundles and one LCL bundle while their model has three bundles for both MCL and LCL. The stiffness was redistributed according to the number of bundles, MCL reference strain could be copied and the LCL reference strain was copied such that the bundle was tensioned in full extension. Both MPFL and LEPL consisted of three bundles and the reported parameter values were assigned to each bundle.

	MCL	LCL	MPFL	LEPL
ϵ_r	0.04	0.08	0.08	0.06
k (N)	4125	6000	2000	1000

Table 2: Summary of the different configurations of the sensitivity study. For each configuration, only one model parameter was perturbed while all other model parameters were kept constant.

Component	Measure	Low value	Initial value	High value
LCL tibia	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
LCL femur	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
MCLprox tibia	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
MCLprox femur	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
MCLdist tibia	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
MCLdist femur	Ant-pos	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
Patellar tendon tibia	Med-lat	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
Patellar tendon patella	Med-lat	-3.5 mm	reference	+3.5 mm
	Prox-dis	-3.5 mm	reference	+3.5 mm
LCL	k	5790 N	6000 N	6210 N
	ϵ_r	0.045%	0.08%	0.115%
MCLprox	k	3980N	4125 N	4270 N
	ϵ_r	0.005%	0.04%	0.075%
MCLdist	k	3980N	4125 N	4270 N
	ϵ_r	0.005%	0.04%	0.075%

Table 3: Comparison of measured and computed kinematics using RMSE and Pearson correlation coefficient ρ . Proximal-distal (PD), medial-lateral (ML), anterior-posterior (AP), varus-valgus (VV) and internal-external (IE) motions are shown.

	RMSE					ρ				
	PD	ML	AP	VV	IE	PD	ML	AP	VV	IE
	(mm)	(mm)	(mm)	(°)	(°)					
Specimen 1										
Neutral	1.34	1.50	2.43	0.67	2.00	1.00	0.40	0.69	0.89	0.94
Varus	1.53	1.16	2.26	0.61	1.97	1.00	0.79	0.66	0.79	0.99
Valgus	0.89	2.19	2.58	0.41	2.91	1.00	-0.08	0.75	0.97	0.94
Specimen 2										
Neutral	0.47	0.89	2.95	0.80	2.65	1.00	0.00	0.91	0.93	0.92
Varus	0.44	0.65	2.18	1.26	3.23	1.00	0.88	0.94	0.99	0.93
Valgus	0.53	0.44	2.41	0.65	2.04	1.00	0.78	0.90	0.86	0.95
Specimen 3										
Neutral	1.38	0.93	3.26	0.45	1.94	0.99	0.43	0.97	1.00	0.97
Varus	1.52	1.82	3.13	0.75	1.58	0.99	-0.16	0.95	1.00	0.97
	1.01	1.20	2.65	0.70	2.29	1.00	0.38	0.85	0.93	0.95
Average	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
	0.45	0.56	0.38	0.25	0.53	0.00	0.39	0.12	0.07	0.02

Table 4: Comparison of experimental and computed ligament length changes using RMSE and Pearson correlation coefficient ρ . Kinematic based length changes (Kin) and extensometer length changes (Ext) are shown.

	RMSE				ρ			
	MCL	MCL	LCL	LCL	MCL	MCL	LCL	LCL
	Ext (%)	Kin (%)	Ext (%)	Kin (%)	Ext	Kin	Ext	Kin
Specimen 1								
Neutral	1.88	0.87	3.45	3.26	0.98	0.99	0.25	0.99
Varus	4.64	1.11	1.99	3.44	0.97	0.99	0.28	0.97
Valgus	2.24	1.09	4.07	1.49	0.96	0.97	0.67	0.95
Specimen 2								
Neutral	2.08	0.44	4.97	1.74	0.99	1.00	0.95	0.97
Varus	2.03	0.76	4.05	2.25	0.94	0.99	0.99	0.98
Valgus	1.87	0.65	3.04	1.39	0.96	0.97	0.98	0.99
Specimen 3								
Neutral	2.83	1.27	5.92	2.73	0.93	0.99	0.87	0.98
Varus	3.95	1.10	4.73	3.82	0.92	0.99	0.92	0.98
Average	2.69	0.91	4.03	2.51	0.96	0.99	0.74	0.98
	± 0.98	± 0.26	± 1.14	± 0.88	± 0.02	± 0.01	± 0.29	± 0.01

Figure legends

Figure 1: Illustration of the analytical surfaces that were fitted to the bone and implant geometries as wrapping surfaces. One cylinder was placed medially, allowing the MCLdist to wrap around the medial tibial condyle. Another cylinder was fitted to the femoral implant to prevent the quadriceps muscle from penetrating the implant in deep flexion. Two ellipsoids were introduced to wrap the MPFL and LEPL around the femoral condyles.

Figure 2: Illustration of the simulation of the mechanical rig inside AnyBody. The hip joint has 2 DOFs: vertical translation and flexion-extension. The ankle joint has 4 DOFs: all three rotations and medio-lateral translation. This configuration provides the tibio-femoral joint with all six DOFs. The patello-femoral joint was modelled with the assumption of a constant length for the patellar tendon and the other 5 DOF were solved using FDK.

Figure 3: Comparison of experimental and model **tibio-femoral translations** of the three specimens. **Experimental (marker) and computed (line) proximal-distal (black/circles), medial-lateral (red/crosses) and anterior-posterior (blue/squares) translations are shown.** The rows show the results for the different specimens, the columns show the results for the different configurations (varus insert, neutral insert and valgus insert).

Figure 4: **Comparison of experimental and model tibio-femoral rotations of the three specimens. Experimental (marker) and computed (line) varus-valgus (black/circles) and internal-external (red/crosses) rotations are shown.** The rows show the results for the different specimens, the columns show the results for the different configurations (varus insert, neutral insert and valgus insert).

Figure 5: **2D view of experimental (dotted lined) and model kinematics (full line) of the three specimens. The centres of the medial and lateral femoral condyles are projected onto the tibial horizontal plane for different flexion angles (40°, 60°, 80° and 100°).** The rows show the

results for the different specimens, the columns show the results for the different configurations (varus insert, neutral insert and valgus insert). The top view of each specimen's left knee is depicted, with the anterior side pointing upwards.

Figure 6: Comparison of kinematic based experimental and model ligament length changes of the three specimens. Experimental (marker) and computed (line) MCLdist (black/circles) and LCL (red/crosses) strains are shown. The rows show the results for the different specimens, the columns show the results for the different configurations (varus insert, neutral insert and valgus insert).

Figure 7: The different output curves of the sensitivity analysis are shown as a shaded area on the figures. The first column shows translations, the second column rotations and the third and fourth column ligament length changes for the neutral configuration of each specimen (rows). The experimental measured data is shown in dotted line and the simulation with reference values in full line. For the translations, proximal-distal (red), medial-lateral (blue) and anterior-posterior (green) is shown. For the rotations, varus-valgus (red) and internal-external (blue) is depicted.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5
[Click here to download high resolution image](#)

Figure 6

Figure 7