



Knee kinematics are primarily determined by implant alignment but knee kinetics are mainly influenced by muscle coordination strategy

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ABSTRACT

Implant malalignment has been reported to be a primary reason for revision total knee arthroplasty (TKA). In addition, altered muscle coordination patterns are commonly observed in TKA patients, which is thought to alter knee contact loads. A comprehensive understanding of the influence of surgical implantation and muscle recruitment strategies on joint contact mechanics is crucial to improve surgical techniques, increase implant longevity, and inform rehabilitation protocols. In this study, a detailed musculoskeletal model with a 12 degrees of freedom knee was developed to represent a TKA subject from the CAMS-Knee datasets. Using motion capture and ground reaction force data, a level walking cycle was simulated and the joint movement and loading patterns were estimated using a novel technique for concurrent optimization of muscle activations and joint kinematics. In addition, over 12'000 Monte Carlo simulations were performed to predict knee contact mechanics during walking, considering numerous combinations of implant alignment and muscle activation scenarios. Validation of our baseline simulation showed good agreement between the model kinematics and loading patterns against the *in vivo* data. Our analyses reveal a considerable impact of implant alignment on the joint kinematics, while variation in muscle activation strategies mainly affects knee contact loading. Moreover, our results indicate that high knee compressive forces do not necessarily originate from extreme kinematics and *vice versa*. This study provides an improved understanding of the complex inter-relationships between loading and movement patterns resulting from different surgical implantation and muscle coordination strategies and presents a validated framework towards population-based modelling in TKA.

1. Introduction

Total knee arthroplasty (TKA) is a safe and effective procedure to restore knee function at end-stage osteoarthritis. However, restoring the function of this complex joint is challenging, and some 11–52 % of patients remain dissatisfied following TKA due to poor clinical outcomes (i. e. knee function not completely restored) or pain (Bourne et al., 2010; Gunaratne et al., 2017; Noble et al., 2005). Amongst other important factors, implant malalignment has been reported to be a primary reason behind inferior functionality of the replaced joint, which, in some cases, necessitates a revision surgery (Schroer et al., 2013). As a result, several

biomechanical investigations have tried to understand the role of implant alignment in post-TKA knee joint mechanics (Almaawi et al., 2017; Blakeney et al., 2019; Courtney and Lee, 2017; Gromov et al., 2014). While generally indicating that implant alignment can alter joint kinematics and knee contact force (KCF) distribution, these studies have been exclusively limited to isolated variation of the implant alignment. However, despite altered muscle activation patterns commonly observed in TKA patients (Trepczynski et al., 2018), little is known about the interrelationship and more specifically the relative impact of muscle recruitment strategies vs implant alignment scenarios on post-TKA joint contact mechanics. Towards avoiding abnormal knee

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kinematics and implant overloading after TKA, the consequences of implant mal-alignment in the presence of different muscle activation scenarios need to be assessed. Such knowledge could lead to improved surgical techniques and increased implant longevity, as well as inform rehabilitation protocols.

Instrumented implant studies have measured peak internal KCFs ranging from 2.2 to 3.0 times bodyweight during normal walking (Kutzner et al., 2010), and it has been possible to reproduce this large range of joint loading *in silico* by varying muscle activation strategies in cruciate ligament and menisci deficient knees (Smith et al., 2019), as well as knees after TKA (Trepczynski et al., 2018). Further *in vitro* (Johnston et al., 2019) and *in silico* (Lerner et al., 2015; Ro et al., 2022; Smith et al., 2016) studies have also found that implant alignment, especially in the coronal plane, is highly correlated with kinematics, but only weak correlations with peak tibio-femoral KCFs have been reported. However, these experimental studies have all been challenged by the limited number of implant alignments that can be investigated, while *in silico* studies require comprehensive and yet subject-specific *in vivo* knee kinematics and kinetics for validation - but such data are rarely available.

In order to address these deficits and provide comprehensive experimental and modelling data, the CAMS-Knee project has collected and published synchronized measurements of KCFs using instrumented implants, knee kinematics using moving fluoroscopy, full body kinematics, ground reaction forces, and muscle activation patterns for six patients performing multiple activities of daily living (Taylor et al., 2017). While these data provide a unique insight into the relationships between musculoskeletal kinematics and kinetics in this limited number of cases, a thorough understanding of the relative influence of implant alignment and muscle activation strategies on TKA mechanics can currently only be obtained through computer simulation using for example stochastically perturbed musculoskeletal models. To achieve this, a realistic representation of the knee that accounts for 6 degrees of freedom (DoFs) joint kinematics within musculoskeletal models necessitates formulation of articular contact mechanics and inclusion of the knee ligaments. However, one key obstacle to such models has been the lack of a global optimization method that is able to solve the muscle redundancy problem while simultaneously accounting for the contribution of ligament forces and joint contact mechanics. Here, the Concurrent Optimization of Muscle Activations and Kinematics (COMAK) algorithm (Smith et al., 2019, 2016) now enables detailed skeletal, soft tissue, and implant models to be incorporated within a full body musculoskeletal model to estimate muscle forces, six degree-of-freedom joint kinematics, ligament forces, and articular contact pressures during functional movements.

As the prime drivers underlying the modulation of loading conditions in the knee joint, it is critical to better understand the inter-relationships between muscle activation strategies and surgical implantation. Using the state-of-the-art CAMS-Knee biomechanical data and COMAK modelling techniques, the main goal of this study was therefore to investigate the influence of variations in implant alignment, which represent different possible surgical outcomes, and muscle activation strategies, which represent varying physical conditions that could be achieved through rehabilitation, on tibiofemoral joint mechanics after TKA. To achieve this, a series of Monte Carlo analyses was performed to predict knee contact mechanics during walking using the COMAK algorithm considering numerous combinations of implant alignment and muscle activation scenarios.

2. Methods

A musculoskeletal model was developed of subject K5R from the CAMS-Knee datasets (male, 95.6 kg, 1.74 m, 65 years) possessing an instrumented implant (Heinlein et al., 2007) in his right knee (Taylor et al., 2017). The model was based on a previously developed full body, muscle-driven model with detailed knee structures (Lenhart et al., 2015)

consisting of 52 DoFs and 44 muscles spanning the right leg, scaled to the subject's anthropometry. The knee model included 14 bundles of nonlinear spring elements representing the major ligaments (Smith et al., 2016). The tibiofemoral and patellofemoral joints were defined so that the 6 DoF kinematics of each joint were guided by the articular contact surfaces represented by detailed 3D triangular mesh geometries of the subject-specific implant (Innex FIXUC, Zimmer Biomet). Implant components were placed within the parent bones based on the implantation data obtained from postoperative CT images (7° posterior tibial slope, 1° varus, <https://www.orthoload.com/cams-knee-project-online>). An elastic foundation model (Young's Modulus = 465 MPa for tibiofemoral, and 165 MPa for patellofemoral contact; Poisson's Ratio = 0.45 for all contact elements) was used to formulate the articular contact mechanics (Bei and Fregly, 2004; Smith et al., 2018).

Skin-marker motion capture data from a representative measured gait cycle of the subject were filtered using a 4th order low-pass Butterworth filter with a 6 Hz cut-off frequency. Considering an equal weight for the markers (see Taylor et al. 2017 for a detailed description of the marker set), we then calculated pelvis, hip, knee, and ankle joint coordinates following an inverse kinematics (IK) approach within the OpenSim modelling environment (v4.3) (Delp et al., 2007; Seth et al., 2018). Using the IK results and the measured ground reaction force data of this representative gait trial, the COMAK algorithm was employed to predict tibiofemoral and patellofemoral translations and rotations as well as muscle, ligament, and KCFs throughout. It should be mentioned that the COMAK algorithm differs from traditional inverse dynamics approaches. While the full-body kinematic parameters, including the tibiofemoral flexion angle, were obtained through IK, COMAK enabled prediction of the unknown tibiofemoral and patellofemoral translations and rotations (Smith et al., 2016, 2019). Specifically, the coordinates of the tibiofemoral joint were iteratively perturbed within the algorithm to optimize a cost function (Eq. (1)) that minimized the sum of squared activations (a_i)² weighted according to muscle volume (V_i) while fulfilling mechanical equilibrium.

$$\min \sum_{i=1}^{n_{\text{muscles}}} V_i^* (a_i)^2 \quad (1)$$

A baseline simulation was performed to predict knee kinematics and KCFs of the baseline model (with subject-specific implantation data), using Eq. (1) to solve the muscle redundancy problem (Fig. 1). The results obtained from the baseline simulation were initially verified against the *in vivo* CAMS-Knee data measured in the lab using the instrumented knee implant and moving fluoroscope (List et al., 2017). These measurements included the representative gait cycle used as an input for the COMAK algorithm, as well as other gait cycles captured from the same subject, to account for experimental variability.

A set of Monte Carlo simulations (each one named as Sim-X, where X is representative of what is varied in the group of simulations; M – Muscle activation strategy; A – implant Alignment; MA – both combined) were then performed to assess the sensitivity of tibiofemoral joint mechanics during walking to implant alignment scenarios and muscle activation strategies following TKA. The simulations were carried out as follows:

Sim-M (Muscle activation strategies): The baseline model with subject-specific implant alignment was used to run 1000 simulations with varying muscle activation strategies. To this aim, the COMAK cost function used to solve muscle redundancy was perturbed to explore the solution space of possible muscle activation scenarios (Eq. (2)):

$$\min \sum_{i=1}^{n_{\text{muscles}}} V_i^* (a_i - a_i^*)^2 \quad (2)$$

Each COMAK simulation was performed with a set of modulating activations a_i^* sampled from random values following a uniform distribution ranging from -0.5 to 0.5, which were different for each muscle and were kept constant throughout the entire gait cycle. Note that these

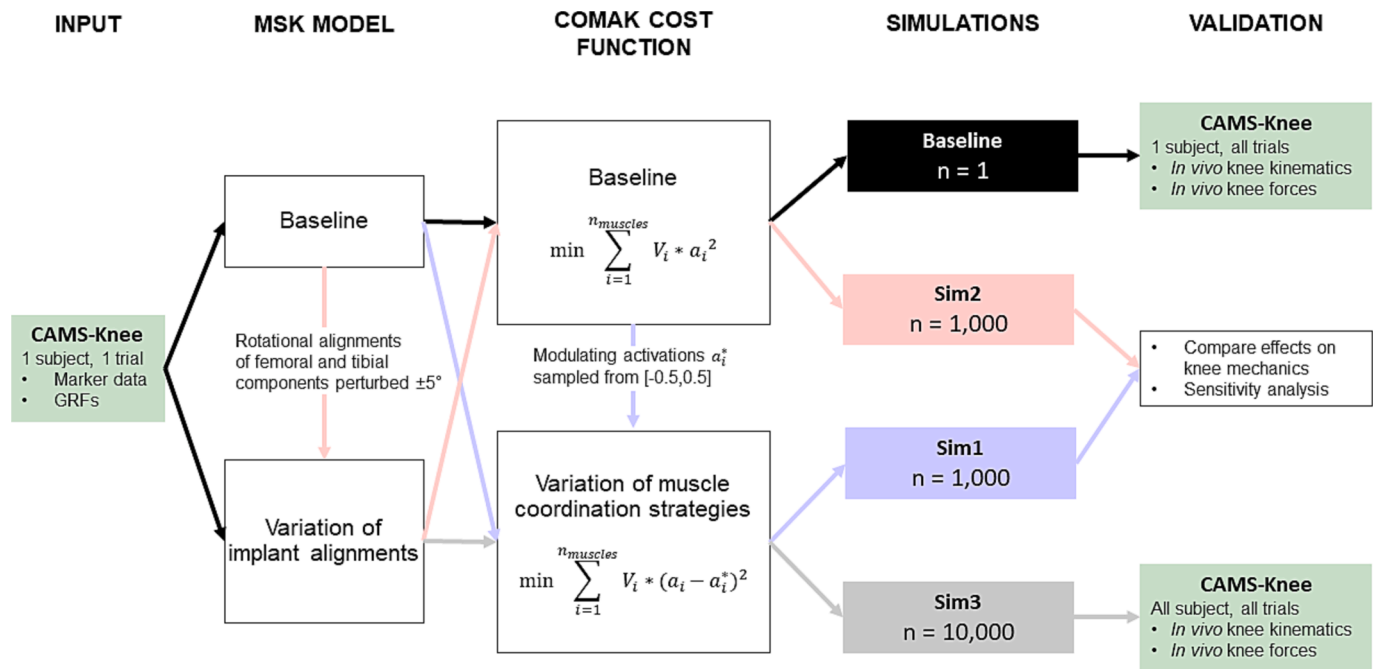


Fig. 1. The musculoskeletal modelling framework included deterministic simulation of level walking using the baseline model as well as Monte Carlo simulations to investigate sensitivity of the knee joint mechanics to implantation and muscle activation scenarios.

modulating activations were not prescribed/imposed, but they were rather used to induce co-contraction and thereby produce different activation strategies. A positive modulating activation encourages muscle activation, while a negative modulating activation penalizes muscle activation.

Sim-A (implant Alignment): Rotational alignments of both the femoral and tibial components were perturbed independently in all three implant planes within $\pm 5^\circ$ around their baseline values (sampled from random values following a uniform distribution ranging from -5 to 5), resulting in 1000 models with random alignment parameters. For each model, a new IK analysis was performed, and the resulting joint coordinates were tracked in the COMAK algorithm using the baseline cost function (Eq. (1)).

Sim-MA (Muscle activation strategies + implant Alignment): To study the combined impact of variations in muscle activation strategy and implant alignment, a set of 100 models with varying implant alignments (sampled as in Sim-A) were used to simulate the level walking cycle considering 100 random muscle activation scenarios (sampled as in Sim-M), resulting in 10,000 simulations. An adequate representation of the impact of the two sources of variability on joint mechanics was confirmed by the matching 5-95th percentile range of the implant kinematics and loading patterns obtained from Monte Carlo simulations with 1000 and 100 perturbations (Figs. S1 and S2). To ensure that our simulation approach for inducing variability in muscle activity and implant alignment produces a realistic representation of the variability in the knee joint mechanics across a TKA population, the simulation outcomes were compared against the corresponding *in vivo* data collected for all walking trials performed by the six subjects measured for the CAMS-Knee project.

For each Monte Carlo analysis, non-converged simulations (total 17) were repeated with another set of random inputs. Joint angles and translations obtained from COMAK simulations were transformed to the joint coordinate system axes according to Grood and Suntay (1983). KCFs and moments were normalized to body weight (BW) and body weight times height (BW*H), respectively. Variability of tibiofemoral kinematics, KCFs, and moments were described by the 5-95th percentile range. To investigate the relative contribution of each source of uncertainty towards the overall variation in post-TKA joint mechanics, these

5-95th percentile ranges of kinematic and kinetic parameters of the three Monte Carlo analyses were compared against each other at the instants of greatest variability.

To understand if simulations with extreme loading conditions result in excessive translations and rotations of the joint and *vice-versa*, simulations that exhibited extreme tibiofemoral kinematics were also compared against those with extreme KCFs. Since a visual inspection of our scatter plots indicated either no correlation or monotonic relationships between modelling input and outcome parameters, Spearman's correlation coefficient, r_s , was used to analyse the relationships between peak values of the model outcomes and the corresponding implantation data.

3. Results

3.1. Baseline model validation

In general, there was a good agreement (trends and parameter ranges) between the baseline simulation predictions and the knee kinematics captured by the moving fluoroscope, as well as the knee kinetics measured by the instrumented implant (Fig. 2). During the stance phase, tibiofemoral translation and rotation trends were well followed, except for the mediolateral translation, which showed an offset of up to 1.8 mm compared to the experimental data. Discrepancies in kinematic parameters between the baseline model and *in vivo* data were greatest at mid-swing (4.0 mm for AP translation (38.7 % of the peak), 1.05° for adduction, and 7.0° for axial rotation).

The comparison between forces obtained from the baseline simulation and those measured *in vivo* indicated good agreement for the axial force and moment as well as for the abduction moment (Root Mean Square Error (RMSE) = 0.21 BW for axial force (8.51 % of the peak force), $6.51 \cdot 10^{-4}$ BW*H for axial moment, $3.40 \cdot 10^{-3}$ BW*H for abduction moment (22.5 % of the peak)). However, the *in silico* data for anteroposterior and mediolateral forces did not follow the trends from *in vivo* data, and presented absolute errors of up to 0.26 BW).

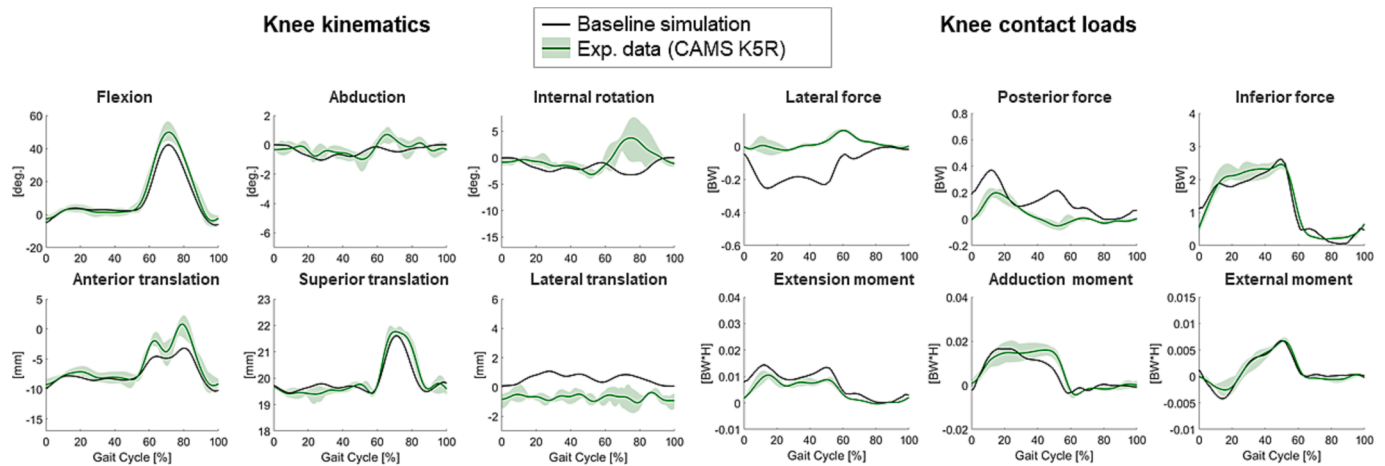


Fig. 2. Knee kinematics and knee kinetics resulting from the baseline simulation compared to multiple experimental measurements from subject K5R from the CAMS-Knee datasets (shading shows 5-95th percentiles of five trials). Movement of the femoral component relative to the tibial component, according to Grood and Suntay.

3.2. Monte Carlo simulations

Simulations for different muscle activation strategies (Sim-M), resulted in considerable variability for all muscle activations (Fig. S3), and for all KCFs and moments. The range of variability was generally consistent throughout the walking cycle, with slightly larger variations at around 50 % gait cycle, when the KCF experiences its second peak. The results indicated that muscle activation strategies could cause considerable variations of up to 1.72, 0.45, and 0.18 BW in the axial, anteroposterior, and mediolateral forces, respectively. On the other hand, perturbations to muscle activations resulted in only small variations in all tibiofemoral translations (up to 2 mm), with changes of up to 5° in the axial knee rotation.

Simulations for different implant alignments (Sim-A) introduced a high variability in all DoFs of the knee kinematics (Fig. 3). The variability was larger during stance, with the highest impact generally observed at around 50 % of the walking cycle (up to 8 mm for anteroposterior translation, 5° for abduction, and 15° for axial rotation). The sensitivity analysis showed that prosthesis alignment in the sagittal plane had a large influence on knee flexion angle and anteroposterior translation ($0.51 < r_s < 0.70$, Figs. S4 and S7). Similarly, a moderate correlation was observed between peak knee abduction angle and

femoral alignment in the frontal plane ($r_s = 0.57$, Fig. S5). Interestingly, the compressive tibiofemoral contact force was only slightly (approximately 13 %, with the largest sensitivity to the femoral component alignment in the frontal plane, $r_s = 0.61$, Fig. S11) affected by the different implantation scenarios, whereas changes of up to 70 % were estimated for the mediolateral and anteroposterior forces. These findings were also confirmed by the sensitivity plots indicating moderate to strong correlations between peak mediolateral force and implant alignment in the frontal plane ($r_s = 0.81$, Fig. S11 and $r_s = 0.51$, Fig. S14) as well as between the peak anteroposterior force and tibial component alignment in the sagittal plane ($r_s = 0.96$, Fig. S13). Please see the [supplementary information](#) for additional information regarding the sensitivity analyses.

Overall, when the relative influences of the two scenarios (Sim-M vs Sim-A) were compared, it became clear that implant alignment played the greatest role on knee kinematics, while different muscle activation strategies had the greatest influence on knee kinetics (Fig. 3). For example, during the stance phase, variability of knee rotations and translations due to changes in implantation scenarios were 2.5–10° and 1–6 mm larger than those resulting from variations in muscle activation strategy. On the other hand, the range of variability in KCFs obtained from different muscle activation strategies were generally larger than

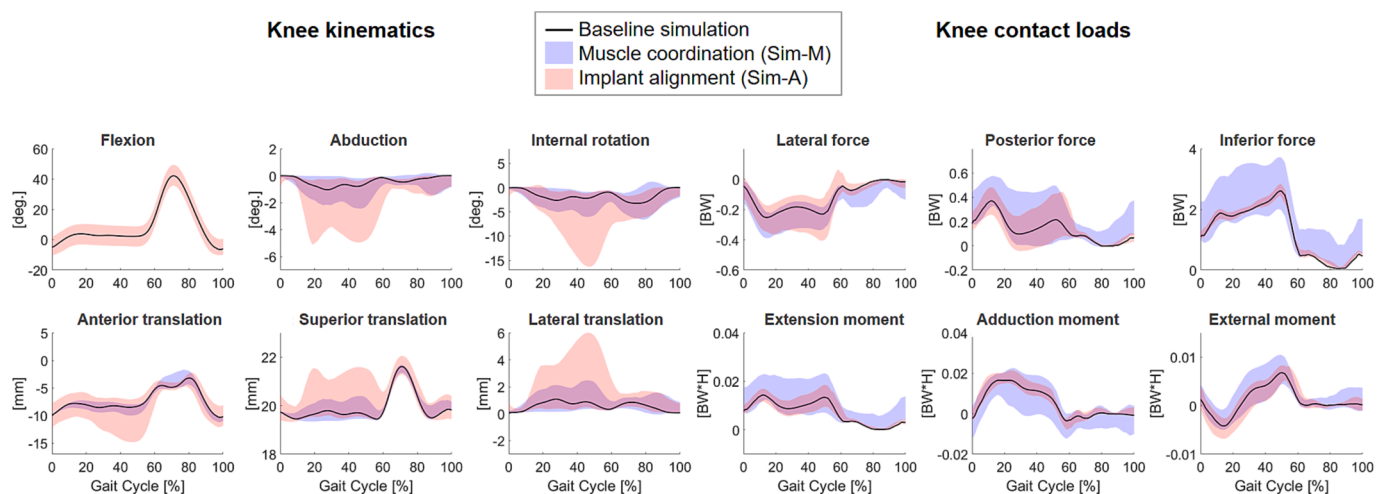


Fig. 3. Knee kinematics and kinetics resulting from two sets of probabilistic simulations: (1) Effects of muscle coordination (Sim-M, 1000 simulations) and (2) Effects of implant alignment (Sim-A, 1000 simulations), with 5-95th percentile values presented as shaded regions. The baseline simulation is included for reference. Movement of the femoral component relative to the tibial component, according to Grood and Suntay.

the corresponding values for varying implantation (e.g. 1.72 BW for axial force compared to 0.44 BW). The only exception to this observation was for the mediolateral force, where the variability due to muscle activation strategy (0.18 BW) was smaller than the corresponding variation obtained from perturbing implant alignment (0.27 BW).

When both implant alignment and muscle activation strategy were perturbed simultaneously (Sim-MA), the variabilities induced in ab-adduction, axial rotation, compressive force, mediolateral force and contact moments were comparable to the variabilities observed in the experimental data measured across the six subjects of the CAMS-Knee datasets (Fig. 4). For instance, our modelling approach estimated 1.86 BW variability in the axial force, which concurs well with the 1.88 BW calculated for experimental data. However, in specific cases our Monte Carlo simulation overestimated the range of force variability expected for the TKA population (e.g. 0.64 BW vs 0.45 BW for variability in anteroposterior force). On the other hand, when kinematics was considered, the variability predicted by our simulations for the anteroposterior translation and knee flexion angle was smaller than the variation seen in the experimental data (e.g. 2.4 mm and 18.8° over-estimation).

The simulations that exhibited extreme kinematics and loading scenarios at the knee were also explored. Here, a set of 100 simulations with the highest axial rotation from Sim-MA (note, only those within 5-95th percentile range were included) were investigated to explore the role of extreme kinematics on loading conditions (Fig. 5). Similarly, another set of 100 simulations with the highest second peak of the axial KCF was analysed to determine the role of high loading on the joint movement patterns. We found that simulations with the highest axial rotation values generally exhibited the largest translations and rotations in/around the other axes, while presenting mostly low values for the compressive KCFs. Conversely, we found that high compressive KCFs were correlated with translations and rotations, closely matching the baseline simulation results.

4. Discussion

A clear understanding of the relationships between muscle activation strategies and surgical implantation is critical in order to establish the key drivers behind biomechanical deficits in kinematics and kinetics after TKA. In this study, we investigated the effects of different muscle activation strategies and implant alignments on the knee joint mechanics during walking by means of Monte Carlo musculoskeletal simulations. The baseline simulation showed a general agreement between the kinematics and loading patterns obtained from modelling and those

measured *in vivo* (Fig. 2). Our findings reveal that implant alignment largely impacts joint kinematics, while variations in muscle activation strategies mainly affect the knee contact loads (Fig. 3). Moreover, high compressive force values are not necessarily correlated with extreme kinematics (Fig. 5).

Validation of our baseline simulation showed a general agreement between the kinematics and loading patterns obtained from modelling and those measured *in vivo* (Fig. 2). The small mismatch in anteroposterior translation peaks, which was mainly related to the slight overestimation of the knee flexion angles, likely originates from uncertainty in implantation and skin movement artifact (Benoit et al., 2006). The largest differences in knee ab-adduction and axial rotation were found during mid-swing, where the two legs cross each other and make the reconstruction of single-plane fluoroscopy data less reliable. Finally, the highest mismatch in kinematics was found in mediolateral translation, which can be explained by the out-of-plane inaccuracy of single-plane fluoroscopy (Acker et al., 2011). Regarding KCFs and moments, the most distinct errors were observed in anteroposterior and mediolateral force predictions (approx. 0.2 BW). These errors may originate from differences between the ideal CAD model used in the simulations and the actual subject-specific implant geometry. More specifically, potential wear and deformation of the polyethylene inlay (over several years after implantation), may result in a less congruent articular geometry with higher laxities in mediolateral and anteroposterior directions.

Our results show that muscle activation scenarios have a larger influence on KCFs and moments than on knee kinematics (Fig. 3). This seems reasonable since co-contraction contributes to higher KCFs and therefore greater stability at the knee joint (Boeth et al., 2013; Ford et al., 2008; Lewek et al., 2005), so a smaller range of motion could be expected in tibiofemoral kinematics. We found a good agreement in the compressive force variability during stance (second peak range error 1.24 %), when comparing the variability induced in our simulations to that observed experimentally for all CAMS-Knee subjects (Fig. 4). However, our simulations reached axial KCFs up to 1.43 BW during mid-swing, which were far greater than the experimental measurements (maximum 0.35 BW). Such extreme values could likely be avoided by allowing co-contraction only during the stance phase, which might reflect the *in vivo* situation more realistically.

The results of our study suggest that implant alignment variation considerably increased the range of motion for all tibiofemoral kinematic (Fig. 3). Similarly, previous studies found that variation in component alignment had a significant effect on the knee kinematics (Johnston et al., 2019), but only weak correlations with KCFs (Smith

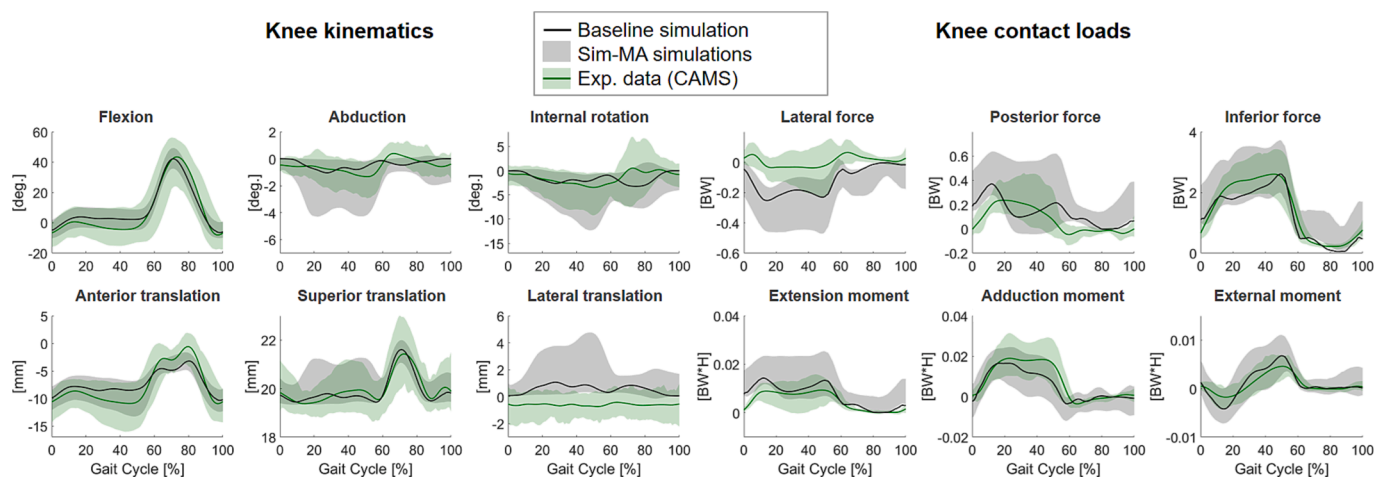


Fig. 4. Knee kinematics and kinetics resulting from 10,000 probabilistic simulations (Sim-MA) compared to experimental data collected from the six CAMS-Knee subjects (45 trials). The baseline simulation patterns as well as average experimental values are included for reference, while shaded areas show 5-95th percentile ranges for the respective values. Movement of the femoral component relative to the tibial component, according to Grood and Suntay.

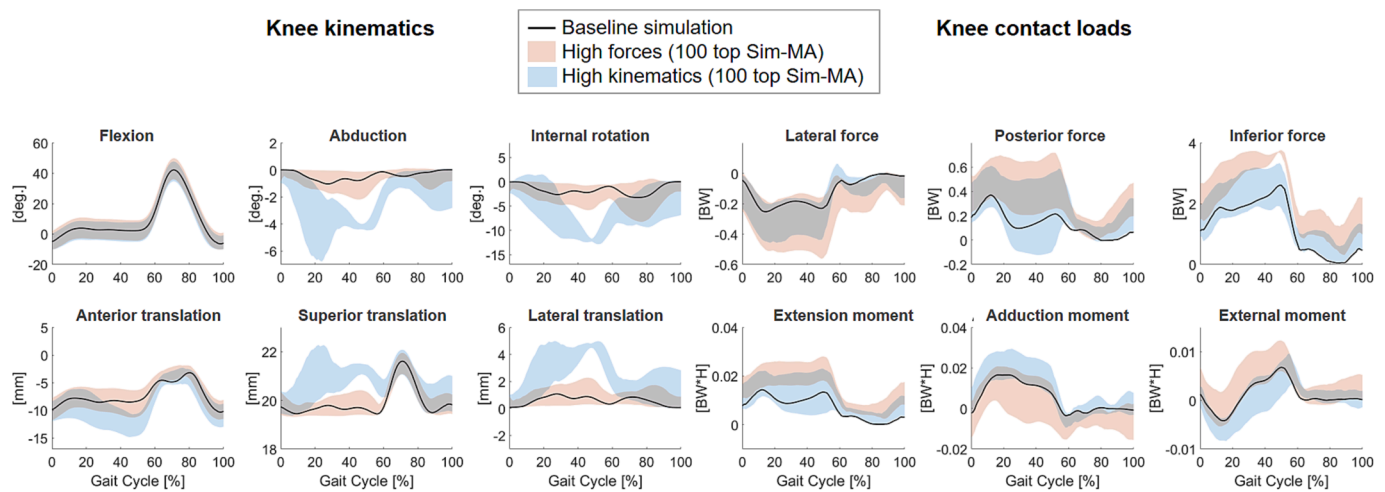


Fig. 5. Knee kinematics and knee kinetics resulting from two sets of probabilistic simulations obtained from Sim-MA: Simulations with extreme forces (100 highest compressive KCFs) and simulations with extreme kinematics (100 with highest IE rotation) are shown, together with their 5-95th percentiles as shaded regions. The baseline simulation is included for reference. Movement of the femoral component relative to the tibial component, according to Grood and Suntay.

et al., 2016; Trepczynski et al., 2018). Clinically, the choice of implantation parameters is often a balance between anatomical and biomechanical factors including limb alignment, joint stability, and range of motion, but our analyses indicate that some extreme implantation scenarios (e.g. if a purely kinematic or purely mechanical alignment is targeted for subjects with severe pre-operative limb alignments) could result in excessive translations and rotations of the joint, even beyond the corrective capacity of adaptation to muscular strategies.

Considerable literature has previously addressed the ranges of observed surgical alignment and component variation during TKA (Bell et al., 2014; Cerquiglini et al., 2018; DesJardins et al., 2007; Gromov et al., 2014; Johnston et al., 2019). The values of $\pm 5^\circ$ chosen in our study reflect this variability. However, to decide the appropriate ranges of modulating factors for muscle activations, we found that modifications of -0.5 to 0.5 resulted in a vertical KCF variation of $1.99 - 3.72$ BW, producing KCFs similar to those observed in the CAMS-Knee datasets ($1.64 - 3.42$ BW, see Fig. 4), as well as in the Grand Challenge ($1.80 - 2.80$ BW, (Fregly et al., 2012)) and in the standardised knee loads of Georg Bergmann ($1.80 - 3.40$ BW, (Bergmann et al., 2014)). The results from these simulations therefore represent loading and kinematics of the tibiofemoral joint in a virtual population, resembling the observed inter-subject variability of implant alignment and muscular activity across *in vivo* data from populations with TKA implants.

To ensure longevity of knee prostheses, implant manufacturers usually perform *in vitro* mechanical tests with generic boundary conditions representing knee joint loading and kinematics during a single gait cycle (International Organization for Standardization, 2014, 2009). However, the generic force and displacement patterns recommended by the International Organization for Standardization (ISO) were obtained from simplified musculoskeletal models (Mikosz et al., 1988; Morrison, 1970) and do not account for physiologically realistic joint kinematics that consider variability in implant alignment and muscle activation strategies. As a result, current laboratory tests may not guarantee implant safety for extreme cases of implantation and muscle activation patterns (Zietz et al., 2015) expected across a TKA population (Trepczynski et al., 2018). Our Monte Carlo simulations represent loading and kinematics of the tibiofemoral joint in a virtual population resembling inter-subject variability of implant alignment and muscular activity in subjects with TKA implants. In particular, the high-kinematic and high-load datasets (Fig. 5) can be replicated in laboratory setups to test proper functionality and longevity of the replaced joint under worst-case conditions. Our preliminary investigation proposes boundary conditions that are able to adequately cover the range of variation observed in kinematics and

loading of different types of implants (Kour et al., 2023; Schütz et al., 2019b, 2019a). However, for implants exhibiting very distinct movement patterns (e.g. medial stabilized or mobile bearing implants) the framework presented in the current study provides a state-of-the-art resource for establishing comprehensive datasets for implant-specific preclinical tests.

There are some limitations in this work that should be considered when interpreting the obtained results. First, we performed simulations for only one subject, one type of implant, and one type of activity (walking), using data from a single trial. Regarding the model, although the implant was located and oriented based on CT images, we did not personalize the skeletal geometries or the muscle and ligament properties. Although we did not update the ground reaction forces, the advanced COMAK framework did allow the progressive balancing of joint moments and contact forces, hence resulting in updated kinematics for each different implant alignment, which each differed from the baseline model. Our approach to explore the outcomes of different muscle activation strategies allowed high co-contraction during mid-swing, reaching up to 1.43 BW of axial KCF, but this outcome is unlikely to be realistic. Nevertheless, the framework presented in this work offers a suitable baseline for further investigations that may consider using more personalized models, other types of implants, and simulating other activities.

To conclude, our advanced modelling framework that includes a combination of *in vivo* kinematics and kinetics, as well as state-of-the-art modelling, revealed that implant alignment largely impacts knee kinematics, while muscle activation strategies mainly affect the internal loading conditions within the joint. These results suggest that if the clinical goal for a specific patient is to avoid extreme knee kinematics, i. e., to achieve a more stable knee, then this should be achieved through surgical implantation rather than relying on e.g. muscle coordination retraining. Moreover, we did not find a direct dependency between high compressive forces and extreme kinematics, hence endorsing the requirement for a framework that is able to consider the complete solution space for kinematics and loading scenarios, towards improved pre-clinical implant testing and rehabilitation programs. As a result, we present a validated framework for population-based modelling that allows an improved understanding of the complex interrelationships between loading and movement patterns resulting from different surgical implantation and muscle activation strategies.

CRediT authorship contribution statement

Miriam Febrer-Nafria: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Michael J. Dreyer:** Writing – review & editing, Validation. **Allan Maas:** Writing – review & editing, Funding acquisition. **Colin R. Smith:** Writing – review & editing, Supervision, Software, Conceptualization. **Seyyed H. Hosseini Nasab:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jbiomech.2023.111851>.

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