Modeling and Simulation Workflow Using Natural Knee Data

Model Benchmarking Specifications

Cleveland Clinic Approach

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Table of Contents

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Synopsis

This document describes planned model re-calibration and benchmarking specifications that are aimed for generating a newly calibrated model of the knee joint based on an initial working and calibrated model[1–4], and an existing joint testing data set from the Natural Knee Data[5], which was acquired on the same specimen and reprocessed for re-calibration process with data descriptions clarified for comprehensibility. Additional data from the same specimen originally available, will be used for benchmarking purposes along with the newly calibrated model. The proposed modeling activities are in response to the *Model Benchmarking* phase[6] of the project *Reproducibility in simulation-based prediction of natural knee mechanics*, a study funded by the National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health (Grant No. R01EB024573)[7]. The outlined choices for modeling and simulation processes represent those of the Cleveland Clinic team. These choices are primarily aimed for pragmatic, yet comprehensive, re-calibration and benchmarking of an anatomically and mechanically detailed and extensible knee joint model incorporating its major tissue structures.

Initial Calibrated Model

Described model re-calibration and benchmarking workflow utilizes partial outputs of an initial calibrated model and derivative modeling and simulation outputs generated through the *Model Calibration* phase[8] of the project *Reproducibility in simulation-based prediction of natural knee mechanics*, a study funded by the National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health (Grant No. R01EB024573)[7]. This model was based on an existing data set from the Natural Knee Data[5], specifically those from specimen DU02. Development of this model was described as part of the model development specifications[1], model calibration specifications[3] and related protocol deviations[2,4]. The model re-calibration workflow will utilize the model calibrated for optimal mesh densities obtained via mesh convergence studies and, material properties in the *Model Calibration* phase[8]. The re-calibration process was necessary as the probed points suggested for registration are different than those used in the *Model Calibration*[8] phase. Additionally, the joint kinetics-kinematics data was provided for model re-calibration and benchmarking is in an extracted form and this extraction process differs from the approach taken in the *Model Calibration* phase[8].

Data Utilized

Described model re-calibration and benchmarking workflow utilizes Natural Knee Data[5], specifically those from specimen DU02. This specific data set was disseminated at the project site of *Reproducibility in simulation-based prediction of natural knee mechanics*, a study funded by the National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health (Grant No. R01EB024573)[7].

Data set was also part of the *Model Calibration* phase[8] of the project in an unprocessed form. The data for re-calibration and benchmarking can be accessed as the package Data for MB – DU02[9]. Donor specifics of specimen DU02 are:

- Right knee
- Age: 44 years
- Gender: Male
- Height: 1.83 m
- Weight: 70.31 kg
- BMI: 21.02

Described model re-calibration and benchmarking specifications utilize following specimen-specific mechanical testing data sets, for calibration, post-calibration simulations and benchmarking:

1. RECALIBRATION-NaturalKneeData_StandardizedData.xlsx – Passive flexion and laxity data (utilized for in situ strain calibration and post calibration simulations). Primarily anterior-posterior and varus-valgus laxity data at lowest flexion angle range for calibration of in situ ligament strains. Primarily passive flexion and laxity data available at four flexion angle ranges for post calibration simulations.
2. BENCHMARKING-NaturalKneeData_StandardizedData_Benchmark_v2.xlsx – Passive flexion and laxity data after anterior cruciate ligament resection. Laxity data available at two flexion angle ranges.

Described model re-calibration specifications also utilize probed points (DU02_raw_probed_points), which were previously disseminated as part of the *Model Development* phase[10]. Details of joint mechanics testing specifics can be found at Natural Knee Data site[5].

Overview of Modeling and Simulation Processes

A previously developed and partially calibrated three-dimensional computational model of the knee[3,4], specifically finite element representation of the tibiofemoral and patellofemoral joints, will be utilized for re-calibration and benchmarking. Calibration completions procedures will include calibration of in situ ligament strains relying on specimen-specific joint kinematics-kinetics data. This model has been partially calibrated for mesh convergence and confirmation of material properties. For re-calibration assessment, two sets of simulations will be performed to understand the influence of model modifications on predicted passive flexion response and to document the correspondence of predicted joint kinematics-kinetics response with specimen-specific passive flexion and joint laxity data. For model benchmarking, a similar but smaller set of simulations will be performed on an ACL resected model and the correspondence of predicted joint kinematics-kinetics response with specimen-specific loading will be obtained to assess the efficacy of the calibration process in development of a general purpose model.

Specimen-specific joint mechanics data will be down-sampled to prepare for in situ ligament strain calibration and for simulation of experimental loading scenarios. Registration will be based on alignment of articular joint surface geometries measured during joint testing by probing[5], and those extracted from raw cartilage geometries[11]. Coherent point drift algorithm[12] will be used to obtain the transformation matrices between probed and image based articular surfaces, which will essentially provide coordinate system transformations between local bone coordinate systems of femur, tibia, and patella during joint testing and image (therefore, model) coordinate system. An initial alignment, using at least three anatomical landmarks from the probed points, and the same anatomical landmarks in the image coordinate system[13], will provide a rough registration as a starting

point for the coherent point drift algorithm[12]. Anatomical landmarks collected during joint testing[5] will be transformed to the model to establish an anatomical joint coordinate system registered to experiments[14]. Joint kinematics-kinetics collected during passive flexion and laxity testing (anterior-posterior translation, internal-external rotation, varus-valgus)[14] will be processed to prepare for modeling and simulation. For passive flexion, data will be down-sampled at every 5°. Anterior-posterior laxity data will be down-sampled at every 5N, internal-external laxity data will be down-sampled at every 50Nmm and varus-valgus laxity data will be down-sampled at 50Nmm. It should be noted that experimental joint kinematics data were assumed to be provided in an absolute fashion including joint coordinate system offsets[14]. Joint kinematics-kinetics of simulations will be relative to the reference state of the model (as build the images), where offsets of the joint coordinate system after its reconstruction can be calculated. Experimental joint kinematics-kinetics will be reported in its native convention[14,15] (in an absolute fashion accommodating experiment offsets) and in a convention amenable to modeling (kinematics described as cylindrical joint movements, kinetics described as loads applied on femur) accommodating both coordinate system offsets of experiment and model reference states.

A simplified calibration approach will be implemented to manage the high cost of simulations[2]. The full knee model with converged meshes, confirmed material properties, and experiment coordinate systems will be simulated to replicate a subset of laxity tests performed on the specimen at the lowest available flexion angle range. Given an initial set of in situ strains[1,2], a sequence of simulations will calculate anterior cruciate ligament, posterior cruciate ligament, medial collateral ligament, and lateral collateral ligament in situ strains to minimize differences between predicted and measured anterior laxity, posterior laxity, valgus laxity, and varus laxity responses, respectively. This sequence of simulations and optimizations will be repeated until in situ strains of these ligaments stabilize within a predefined threshold (absolute change of 0.001). Performing simulations only at the lowest flexion range will prevent potentially costly flexion simulations. This analysis assumes that the contribution of certain ligaments dominate laxity characteristics and by doing so, simplifies a multivariate optimization problem to a sequence of scalar optimization problems. Repeated optimizations will likely accommodate for potential contributions from other ligaments.

Multiple customized full knee models will be generated for simulations of passive flexion (test case used in model development[1,2]) and laxity testing. Passive flexion simulations will document the role of model modifications on predictions of knee joint response. Cases will include models with converged meshes, confirmed material properties, and calibrated in situ ligament strains; and with all modifications including experiment coordinate systems. Post calibration and benchmarking simulations will aim for in silico reproduction of experiments. Full knee models with all modifications, driven by registered experiment loading at a given flexion range, will be used. Simulation outputs will be reported along with measured joint kinematics-kinetics data to understand predictive capacity of the model for specimen-specific laxity response. A total of 26 cases will be simulated for post re-calibration: a combination of flexion angles at which laxity tests were performed (four flexion ranges for each laxity), axis of loading (tested degrees of freedom - anterior-posterior translation, internal-external rotation, varus-valgus), direction of loading (positive, negative). For benchmarking another set of passive flexion and laxity simulations will be conducted, this time for fewer load ranges and with the ACL removed from the models. A total of 14 simulations will be conducted for benchmarking.

FEBio[16], along with FEBio PreStrain Plugin[17], will be used to conduct finite element analysis (solid mechanics,

based on implicit static solver). Simulation results will be visualized using PostView[18]. Specimen-specific joint mechanics data and predicted kinematics-kinetics of the joints will be processed to report joint movements in all loading cases. Python[19] and SciPy[20], along with auxiliary Python packages, will be used to automate data analysis, model customization, and post processing. All modeling and simulation outputs, intermediate and final, will be publicly disseminated through an online repository[21].

Detailed Modeling and Simulation Outputs

Model Benchmarking specifications will result in the following intermediate and final outputs. The Workflow section below provides detailed instructions on how to obtain these.

File	Description	File Format
Model Properties	XML based text file which specifies the material properties of all tissues in the model, and the coordinates of the manually chosen anatomical landmarks (used as input for the customization script); including templates for in situ ligament strain calibration, and post-calibration simulations of experiment conditions.	.xml[22]
Customized Models (FEBio Input File)	XML based text file (for finite element analysis with FEBio23) customized to include mesh definitions, tissue interactions, tissue-specific constitutive models, in situ ligament strains, representation of additional stabilizing structures, anatomical knee joint coordinate systems, specialized loading and boundary conditions to represent passive flexion, output requests relevant to knee mechanics; including numerical analysis settings; including customizations for in situ ligament strain calibration, and post-calibration simulations of experiment conditions.	.feb[23]
Raw Simulation Results	Binary (.xplt) and text files (.log) obtained by simulation of passive flexion using calibrated customized model with FEBio23; in addition, results of in situ ligament strain calibration, post-calibration simulations of experiment conditions.	.xplt[23] .log[23]
Processed Simulation Results	CSV based text files storing extracted knee kinematics and kinetics during passive flexion simulations using calibrated model; processed using raw simulation results and supported by graphs as binary image files; in addition, processed results of in situ ligament strain calibration, post-calibration simulations of experiment conditions.	.csv[24] .png[25]
Registration Results	XML based text files which includes coordinate system transformation matrices between joint testing and imaging coordinate systems of bones, experimental anatomical landmarks transformed to model coordinate systems, and registration error estimates.	.xml[22]
Processed Kinematics-Kinetics Data	CSV based text files storing experimental knee kinematics and kinetics downsampled for use in calibrated model, as loading and boundary conditions and to assess predictive capacity; supported by graphs as binary image files, including all experiment conditions.	.csv[24] .png[25]

File	Description	File Format
Model Prediction Errors	CSV based text files storing experimental and model predicted knee kinematics and kinetics and errors describing correspondence between model predictions against experimental data; supported by XML based text file providing prediction errors in summary form. This includes all simulation cases for post-calibration simulations and benchmarking.	.csv[24] .xml[22]
Calibration Results	XML based text files summarizing target parameters and fit error before and after calibration.	.xml[22]

Workflow

Registration for Specimen-Specific Calibration

Target Outcome

Coordinate system transformation matrices between joint testing and imaging coordinate systems of bones and experimental anatomical landmarks transformed to model coordinate system in XML[22] based text files. Full knee model with joint coordinate system defined to align with the experimental coordinate system, in FEBio[16] format (.feb, XML based text file)[23].

Burden

Software requirements:

Python. Python[19] is a high-level multi-platform programming language (free and open source GPL compatible Python Software Foundation license, see https://www.python.org)[19]. Any contemporary version available for the computing platform can be used; 3.8.0 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, version 2.7 may be used.

SciPy. SciPy is a Python based open source software platform for mathematics, science and engineering (free and open source BSD-new license, see https://www.scipy.org)[20]. Any contemporary version available for the computing platform can be used; 1.3.1 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, a version compatible with Python 2.7 may be used.

PyCPD. PyCPD is an implementation of coherent point drift algorithm[12] for registration of point clouds including i) scale and rigid registration, ii) affine registration, and iii) Gaussian regularized non-rigid registration (free and open source MIT license, see https://pypi.org/project/pycpd/)[26]. Any contemporary version available for the computing platform can be used; 1.0.5 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, a version compatible with Python 2.7 may be used.

Python Scripts. Python[19] script register_probed_points.py developed and used in the *Model Calibration*[8] phase will be used. The Python script was written to find the transformation from experiment to image coordinate system using the Coherent Point Drift algorithm[12]. The script will be modified to use the landmarks suggested for registration in addition of those used in model calibration[3,4].

Hardware requirements:

Any contemporary computer; desktop, workstation, or laptop. All aforementioned software are supported on multiple platforms including Windows, Mac OS X, and Linux.

Anticipated Man Hours and Expertise Level:

1-2 day of full-time effort from a research engineer with bachelor's degree, mechanical/biomedical background, <3 years of research experience, and familiarity to rigid body dynamics, data processing, and scripting.

Computational Cost:

Minimal compared to required interactions with computer scripts.

Protocols

Input

Experimental probed points on articular cartilage surfaces and anatomical landmarks[1] and raw cartilage geometries from imaging[11]; FEBio[16] model file of the full knee with converged meshes and confirmed material properties.

Registration

Probed points on articular surfaces were provided in the *Model Development* phase[10]. These probed points will be used to find a transformation matrix to transform from each bone coordinate system to the image coordinate system. Coherent point drift algorithm (CPD)[12] will be used to get a rigid transformation to align two point clouds using Python[19]. For each bone, a set of probed points on the articular surfaces are chosen that are similar to a tissue anatomy that was segmented, in this case cartilage. The probed points, and vertices of raw surface geometries will be used as source and target point clouds, respectively, for registration. First, an initial "rough" registration will be done by choosing at least three anatomical landmarks that were probed during experiments, and the same anatomical landmarks in the image coordinate system. These landmarks do not need to perfectly align, they should just be chosen at roughly the same area on the bone. Singular value decomposition will be performed on the point sets to get an initial "rough" transformation matrix (T_i). This rough transformation matrix will be applied to the source point cloud. Next, the CPD[12] algorithm will be applied to the transformed source, and target. This provides a final registration of the point clouds to minimize error while aligning the two point clouds (T_f). The overall transformation from the bone coordinate system to image coordinate system will be calculated as $T = T_f\ T_i$. These will all be performed in an in house Python script, register_probed_points.py, by making appropriate changes to include probed points recommended in the NaturalKneeData_DataDescriptionStandard.docx file provided with the download package[9]. For femur registration, in addition to the probed point taken from articular surface of the femoral cartilage, probed points taken from the border of the articular surface where the cartilage transitions to periosteum and probed points taken from the bony surface of the distal femur will be used.

In following, anatomical landmarks on each bone, which are probed during mechanical testing, will be transformed to image coordinate system to serve as the foundation to redefine model joint coordinate systems and cylindrical joint axes. The coordinate systems of tibia and femur will be updated based on descriptions

provided in the experiment documentation[14]: probed bony landmarks on the tibia (medial and lateral dwell points of the plateau, proximal tip of the medial spine of the tibial eminence, center of the distal intramedullary canal) and femur (posterior of medial and lateral condyles, distal point between condyles, hip ball center, medial and lateral epicondyle) will used to establish the same local coordinate systems for the femur and tibia as in joint mechanical testing. Patella coordinate system will be updated based on the experimental landmarks as well.

Customized Full Knee Model with Experiment Coordinate Systems

After transformation of anatomical landmarks, which were collected and used for coordinate system definitions in experimentation, a full knee model will be created by following the procedures from the model development specifications[1,2]. This time experimental landmarks will be used to define anatomical joint coordinate system in the model. The tibiofemoral floating axis (FTF-axis) will be defined as the cross product between the T_z-axis and the F_x-axis at any given joint position. The patellofemoral floating axis (FPF-axis) will be defined as the cross product between the P_z-axis and the F_x-axis. The in house script FebCustomization_p3.py needs to be run for this purpose. The model will therefore be aligned with the experiment such that the axes as defined in the experiment are the same as the ones defined in the model.

Specimen-Specific Kinematics-Kinetics Data Processing

Target Outcome

Experimental kinematics-kinetics data downsampled presented in a form amenable for simulations with the full knee model, as text files (.csv)[24] and graphs as binary images (.png)[25]. Representation of experimental kinematics-kinetics will be separated for passive flexion and for laxity data (as a function of flexion angle ranges, dominant degree of freedom, loading direction in the dominant degree of freedom).

Burden

Software requirements:

Python. Python is a high-level multi-platform programming language (free and open source GPL compatible Python Software Foundation license, see https://www.python.org)[19]. Any contemporary version available for the computing platform can be used; 3.8.0 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, version 2.7 may be used.

SciPy. SciPy is a Python based open source software platform for mathematics, science and engineering (free and open source BSD-new license, see https://www.scipy.org)[20]. Any contemporary version available for the computing platform can be used; 1.3.1 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, a version compatible with Python 2.7 may be used.

Python scripts. Python script csv_processing_nkd.py developed during the *Model Calibration* phase will be modified to down-sample the processed data provided for re-calibration and benchmarking.

Hardware requirements:

Any contemporary computer; desktop, workstation, or laptop. All aforementioned software are supported on multiple platforms including Windows, Mac OS X, and Linux.

Anticipated Man Hours and Expertise Level:

1 day of full-time effort from a research engineer with bachelor's degree, mechanical/biomedical background, <3 years of research experience, and familiarity to rigid body dynamics, data processing, and scripting.

Computational Cost:

Minimal compared to required interactions with computer scripts.

Protocols

Input

Experimental joint kinematics-kinetics data (.xlsx); coordinate system transformation matrices between joint testing and imaging.

Processing of All Passive Flexion Data

The data provided for *Model Calibration* phase[8] was in raw form. The kinematics-kinetics data was re-synchronized after filtering, cropped, sorted and re-sampled for the calibration process.[3,4] For re-calibration and benchmarking, the experimental passive flexion data provided in the RECALIBRATION-NaturalKneeData_StandardizedData.xlsx will be used. These data were provided in an abbreviated fashion with corrected temporal shifts between kinematics and kinetics data. Additionally, the assumed positive direction for tibial extension during calibration[3,4] will be changed to tibial flexion. A Python script, csv_processing_nkd.py, developed during the *Model Calibration* phase[8] will be modified to extract and down-sample (at every 5° for loading in a given direction) data from xlsx[27] files to individual csv[24] files and perform the following,

1. Report bone pose and orientation in an absolute fashion.
2. Transform kinematics data to the convention used in the model, i.e., cylindrical joint translations and rotations, accommodating offsets at model reference state when reconstructing experiment coordinate systems in the model.
3. Transform kinetics data to the convention used in the model, i.e., joint loading applied to femur in model coordinate system, which is registered and aligned to experiment coordinate system.
4. Write kinematics and kinetics to a text based file (.csv) both in experiment and model conventions; plot and store as graphics files (.png).

Processing of All Laxity Data

The data provided for *Model Calibration* phase[8] was in raw form. The kinematics-kinetics data was re-synchronized after filtering, cropped, sorted and re-sampled for the calibration process[3,4]. For re-calibration and benchmarking, the experimental laxity data provided in the RECALIBRATION-NaturalKneeData_StandardizedData.xlsx will be used. These data were provided in an abbreviated fashion with corrected temporal shifts between kinematics and kinetics data. Kinematics-kinetics data for laxity will be extracted and down-sampled based on the flexion angle ranges provided, dominant loading axis (anterior-posterior translation, internal-external rotation, varus-valgus), and direction of loading axis (positive, negative). Additionally, the assumed positive direction for tibial extension during calibration[3,4] will be changed to tibial flexion. A Python script, csv_processing_nkd.py, developed during the *Model Calibration* phase[8] will be

modified to extract and down sample data (anterior-posterior laxity data will be down-sampled at every 5N, internal-external laxity data will be down-sampled at every 50Nmm and varus-valgus laxity data will be down-sampled at 50Nmm for loading in a given direction) from xlsx[27] files to individual csv[24] files. Following the extracting and downsampling the script will also,

1. Report bone pose and orientation in an absolute fashion.
2. Transform kinematics data to the convention used in the model, i.e., cylindrical joint translations and rotations, accommodating offsets at model reference state when reconstructing experiment coordinate systems in the model.
3. Transform kinetics data to the convention used in the model, i.e., joint loading applied to femur in model coordinate system, which is registered and aligned to experiment coordinate system.
4. Write kinematics and kinetics to a text based file (.csv) both in experiment and model conventions; plot and store as graphics files (.png).

Re-Calibration of In Situ Ligament Strains

Target Outcome

Full knee models with converged meshes, confirmed material properties, joint coordinate system defined to align with the experimental coordinate system, and loading and boundary conditions of experiments selected for calibration in FEBio[16] format (.feb, XML[22] based text file)[23]. Simulation results as binary and text output files (.xplt and .log, respectively)[23] and as summary of re-calibration process including target metric, model predictions as a function of in situ ligament strains and fit error (XML[22] based text file). Full knee model with calibrated in situ ligament strains in FEBio[16] format (.feb, XML[22] based text file)[23]. Tissues for which in situ ligament strains will be calibrated include ligaments – anterior/posterior cruciate, medial/lateral collateral.

Burden

Software requirements:

FEBio. FEBio is a nonlinear implicit finite element analysis framework designed specifically for analysis in biomechanics and biophysics (binaries custom open source license; free for academic research use, licensing for commercial use is available, see http://www.febio.org)[16]. FEBio 2.9.1 will be used.

FEBio PreStrain Plugin. PreStrain Plugin provides a general framework for representing prestrain in a finite element model using a prestrain gradient method[17]. Version 1.0 will be used.

Python. Python is a high-level multi-platform programming language (free and open source GPL compatible Python Software Foundation license, see https://www.python.org)[19]. Any contemporary version available for the computing platform can be used; 3.8.0 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, version 2.7 may be used.

SciPy. SciPy is a Python based open source software platform for mathematics, science and engineering (free and open source BSD-new license, see https://www.scipy.org)[20]. Any contemporary version available for the computing platform can be used; 1.3.1 is the latest version at the time of preparation of this document.

Depending on the requirements of legacy Python scripts, a version compatible with Python 2.7 may be used.

Python Scripts. There are existing Python scripts used and/or developed through the *Model Development* phase[10] and *Model Calibration* phase[8]. Scripts for *Customization*, specifically for in situ ligament strains, will be reused (latest editions can be found at the source code repository at https://simtk.org/svn/openknee/app/KneeHub/src/, including revisions used for the *Model Calibration* phase[8]). These scripts will be used for additional customization for compartmental model assembly and reduction, prescription of loading and boundary conditions, extraction of metrics relevant to calibration, and automation of the iterative process to perform calibration. Python scripts *experiment_to_model.py* will be used to to update a full knee model in FEBio[16] to replicate experimental conditions. Experimental kinetics are applied as external femur loads, and experiment flexion angle is prescribed to the extension-flexion joint. Python[19] script *InSituOptimization.py* will be used to update the in situ strain of the target ligament in the FEBio[16] model file, to read simulation results (displacement and load in dominant degree of freedom), to implement a scalar (one dimensional) optimization that will minimize the sum of squared differences between model predicted and experimental loading response in the dominant degree of freedom, and to write optimization results in a text file.

Hardware requirements:

Any contemporary computer; desktop, workstation, or laptop. All aforementioned software are supported on multiple platforms including Windows, Mac OS X, and Linux.

Anticipated Man Hours and Expertise Level:

1-2 days of full-time effort from a research engineer with bachelor's degree, mechanical/biomedical background, <3 years of research experience, and familiarity to finite element analysis and scripting.

Computational Cost:

A few hours of simulation time (wall clock) for each calibration simulation; a total of 10-30 simulations.

Protocols

Input

Template FEBio[16] model file of the full knee (.feb)[23] and model properties (.xml)[22] files for with converged meshes, confirmed material properties, and experiment coordinate systems; processed specimen-specific kinematics-kinetics data (.csv)[24].

Models

Customization scripts developed for *Model Development* phase, and modified for Model Calibration phase, FebCustomization_p3.py, and, experiment_to_model.py will be used to generate models representative of the loading and boundary conditions of selected laxity tests to calibrate in situ strains. Only joint laxity data at the lowest flexion ranges will be used to modify in situ strains for anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL), and lateral collateral ligament (LCL). The decision to use only these data was made to save on computational cost and time. All other loading scenarios include flexion of the joint prior to performing laxity testing, which can be costly, and often, convergence issues may

arise. This way, the calibration can be performed quickly, and the models are unlikely to have any convergence issues.

Template model (.feb)[23] and model properties (.xml)[22] reflective of converged meshes, confirmed material properties, and experiment coordinate systems will be the basis for customization of models for calibration. Customization script FebCustomization_p3.py was modified to create registered model and experiment_to_model.py was developed to incorporate experimental load cases into the model. Overall, application of loading and boundary conditions and output requests will be similar to those described in the model development specifications with exceptions noted in here. Tibia will be fixed; femur and patella will be free to move and all loads and boundary conditions will be applied in one step. From time 0 to 1, in situ strain will be applied while keeping flexion at 0°. From time 1 to 2, the loads and boundary conditions at the start of experiment will be prescribed, i.e., the flexion angle will be set and the loads in the remaining degrees of freedom will be applied on femur to reflect the loading state of the joint at the start of testing. This step will account for any offsets in bone configuration between imaging and the experiment and it should be done after the prestrain step as we do not want the in situ strain calibration to be dependent on the orientation of the knee in different experiment trials. From time 2 to 3, the loads and boundary conditions of the experiment will be prescribed, i.e., the flexion angle will be constant and the loads in the remaining degrees of freedom will be applied on femur. Load curves for each degrees of freedom (particularly the dominant loading) will be defined based on experiment data points and simulation output will be requested at each experiment point. A total of 4 models will be generated, for laxity loadings at the respective *lowest provided* flexion angle ranges:

Model Name	**Loading from Experiment**	**To Calibrate**
F00_AT_C	Anterior laxity	ACL
F00_PT_C	Posterior laxity	PCL
F00_VL_C	Valgus laxity	MCL
F00_VR_C	Varus laxity	LCL

ACL: anterior cruciate ligament. PCL: posterior cruciate ligament. MCL: medial collateral ligament. LCL: lateral collateral ligament.

Calibration Procedure

An iterative procedure will be used to identify optimal in situ ligament strains in anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL), and lateral collateral ligament (LCL):

1. Use F00_AT_C (with previously modified ACL, PCL, MCL, LCL in situ strains, if any) to find ACL in situ strain by minimizing the difference between model predicted and experimental anterior translation and force.
2. Use F00_PT_C (with previously modified ACL, PCL, MCL, LCL in situ strains, if any) to find PCL in situ strain by minimizing the difference between model predicted and experimental posterior translation and force.
3. Use F00_VL_C (with previously modified ACL, PCL, MCL, LCL in situ strains, if any) to find MCL in

situ strain by minimizing the difference between model predicted and experimental valgus rotation and moment..

4. Use F00_VR_C (with previously modified ACL, PCL, MCL, LCL in situ strains, if any) to find LCL in situ strain by minimizing the difference between model predicted and experimental varus rotation and moment.

5. Repeat steps 1-4 until convergence of in situ strains, i.e., stop when absolute change in calculated in situ strain is less than 0.001.

Customized Full Models for Post-Recalibration Simulations

Target Outcome

Customized full knee models in FEBio[16] format (.feb, XML[22] based text file)[23] prepared for all simulation cases, including passive flexion with joint coordinate system of the *Model Development* phase[10] and all experimental loading conditions. Models will include converged meshes, confirmed material properties and calibrated in situ ligament strains, and for reproduction of experiments, loading and boundary conditions of joint testing registered and transformed to model coordinate system.

Burden

Software requirements:

Python. Python is a high-level multi-platform programming language (free and open source GPL compatible Python Software Foundation license, see https://www.python.org)[19]. Any contemporary version available for the computing platform can be used; 3.8.0 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, version 2.7 may be used.

SciPy. SciPy is a Python based open source software platform for mathematics, science and engineering (free and open source BSD-new license, see https://www.scipy.org)[20]. Any contemporary version available for the computing platform can be used; 1.3.1 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, a version compatible with Python 2.7 may be used.

Python Scripts. There are existing Python scripts developed in *Model Calibration* phase[8]. Latest editions can be found at the source code repository at https://simtk.org/svn/openknee/app/KneeHub/src/. Experimental loading cases will be generated using in house Python script experiment_to_model.py developed in the *Model Calibration* phase[8]. This script allows updating the registered models (obtained using FebCustomization_p3.py) with the appropriate experimental loading. The registered models are customized with converged meshes and confirmed material properties and calibrated in situ ligament strains and experimental joint coordinate system.

Hardware requirements:

Any contemporary computer; desktop, workstation, or laptop. All aforementioned software are supported on multiple platforms including Windows, Mac OS X, and Linux.

Anticipated Man Hours and Expertise Level:

2-3 days of full-time effort from a research engineer with bachelor’s degree, mechanical/biomedical

background, <3 years of research experience, and familiarity to finite element analysis and scripting.

Computational Cost:

Minimal compared to required interactions with computer scripts.

Protocols

Input

Template FEBio[16] model file of the full knee (.feb)[23] and model properties (.xml)[22] files for with converged meshes, confirmed material properties, experiment coordinate systems, and calibrated in situ ligament strains; processed specimen-specific kinematics-kinetics data (.csv)[24].

Customization for Test Simulation Case

Customization scripts developed for *Model Development* phase[10], in particular FebCustomization_p3.py, will be used to generate models representative of the test simulation case (passive flexion). Loading and boundary conditions and output requests will be the same, as described in model development specifications and are briefly summarized in here. Tibia will be fixed; femur and patella will be free to move. In one step, in situ strain will be applied from time 0 to 1 while keeping flexion at the lowest flexion range and flexion will be prescribed from time 1 to 2 up to the highest range. Models will be generated to reflect model parameters that are modified in the *Model Calibration* phase[8]:

- with converged meshes, confirmed material properties, and calibrated in situ strains
- with converged meshes, confirmed material properties, calibrated in situ strains, and experiment coordinate systems (to be compared with experimental kinematics-kinetics)

Customization for Experiment Loading Cases

Customization scripts developed for *Model Development* phase[10], and *Model Calibration* phase[8] in particular FebCustomization_p3.py, and experiment_to_model.py will be used to generate models representative of the loading and boundary conditions of experiment laxity tests. Template model (.feb)[23] and model properties (.xml)[22] reflective of converged meshes, confirmed material properties, calibrated in situ strains, and experiment coordinate systems will be the basis. Overall, application of loading and boundary conditions and output requests will be similar to those described in the model development specifications[1,2] with exceptions noted in here. Tibia will be fixed; femur and patella will be free to move and all loads and boundary conditions will be applied in one step. From time 0 to 1, in situ strain will be applied while keeping flexion at 0°. From time 1 to 2, the loads and boundary conditions at the start of experiment will be prescribed, i.e., the flexion angle will be set and the loads in the remaining degrees of freedom will be applied on femur. From time 2 to 3, the loads and boundary conditions of the experimental trial will be applied until the end point of the experiment. Load curves for each degrees of freedom (particularly the dominant loading) will be defined based on experiment data points and simulation output will be requested at each experiment point. The kinematics-kinetics trajectories of experiment will be split to facilitate prescription of loading scenarios in simulations. A total of 24 models will be generated based on the following model naming convention:
F###_$$

where

###: 001, 002, 003, 004, corresponding to *flexion angle ranges from lowest to highest*.

$$: AT, PT, IR, ER, VR, and VL corresponding to anterior laxity, posterior laxity, internal rotation laxity, external rotation laxity, varus laxity, and valgus laxity, respectively.

Customized Models for Model Benchmarking

Target Outcome

Customized full knee models in FEBio[16] format (.feb, XML[22] based text file)[23] prepared for all simulation cases, including passive flexion with joint coordinate system of the *Model Development* phase[10] and, all experimental loading conditions. Models will include converged meshes, confirmed material properties and calibrated in situ ligament strains, and for reproduction of experiments, loading and boundary conditions of joint testing registered and transformed to model coordinate system.

Burden

Software requirements:

Python. Python is a high-level multi-platform programming language (free and open source GPL compatible Python Software Foundation license, see https://www.python.org)[19]. Any contemporary version available for the computing platform can be used; 3.8.0 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, version 2.7 may be used.

SciPy. SciPy is a Python based open source software platform for mathematics, science and engineering (free and open source BSD-new license, see https://www.scipy.org)[20]. Any contemporary version available for the computing platform can be used; 1.3.1 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, a version compatible with Python 2.7 may be used.

Python Scripts. There are existing Python scripts developed in *Model Calibration* phase[8]. Latest editions can be found at the source code repository at https://simtk.org/svn/openknee/app/KneeHub/src/. Experimental loading cases will be generated using in house Python script experiment_to_model.py developed in the *Model Calibration* phase[8]. This script allows updating the registered models (obtained using FebCustomization_p3.py) with the appropriate experimental loading. The registered models are customized with converged meshes and confirmed material properties and calibrated in situ ligament strains and experimental joint coordinate system. An in house Python script ModelReduction_rigids3.py will be used to create models without the ACL.

Hardware requirements:

Any contemporary computer; desktop, workstation, or laptop. All aforementioned software are supported on multiple platforms including Windows, Mac OS X, and Linux.

Anticipated Man Hours and Expertise Level:

1-2 days of full-time effort from a research engineer with bachelor’s degree, mechanical/biomedical background, <3 years of research experience, and familiarity to finite element analysis and scripting.

Computational Cost:

Minimal compared to required interactions with computer scripts.

Protocols

Input

Template FEBio[16] model file of the full knee (.feb)[23] and model properties (.xml)[22] files for with converged meshes, confirmed material properties, experiment coordinate systems, and calibrated in situ ligament strains; processed specimen-specific kinematics-kinetics data (.csv)[24].

Customization for Test Simulation Case

Python[19] scripts developed for *Model Development* phase[10], in particular FebCustomization_p3.py, and an in house script ModelReduction_rigids3.py will be used to generate models representative of the test simulation case (passive flexion) with resected ACL (which will be simulated by removing the ACL). Loading and boundary conditions and output requests will be the same, as described in model development specifications and are briefly summarized in here. Tibia will be fixed; femur and patella will be free to move. In one step, in situ strain will be applied from time 0 to 1 while keeping flexion at the lowest flexion range and flexion will be prescribed from time 1 to 2 up to the highest range. Models will be generated to reflect model parameters that are modified in the *Model Calibration*[8] phase:

- with converged meshes, confirmed material properties, and calibrated in situ strains
- with converged meshes, confirmed material properties, calibrated in situ strains, and experiment coordinate systems (to be compared with experimental kinematics-kinetics)

Customization for Experiment Loading Cases

Customization scripts developed for *Model Development* phase[1,2], and *Model Calibration*[8] phase, in particular FebCustomization_p3.py, experiment_to_model.py and ModelReduction_rigids3.py will be used to generate models representative of the loading and boundary conditions of experiment laxity tests with resected ACL (which will be simulated by removing the ACL). Template model (.feb)[23] and model properties (.xml)[22] reflective of converged meshes, confirmed material properties, calibrated in situ strains, and experiment coordinate systems will be the basis. Overall, application of loading and boundary conditions and output requests will be similar to those described in the model development specifications[1] with exceptions noted in here. Tibia will be fixed; femur and patella will be free to move and all loads and boundary conditions will be applied in one step. From time 0 to 1, in situ strain will be applied while keeping flexion at 0°. From time 1 to 2, the loads and boundary conditions at the start of experiment will be prescribed, i.e., the flexion angle will be set and the loads in the remaining degrees of freedom will be applied on femur. From time 2 to 3, the loads and boundary conditions of the experimental trial will be applied until the end point of the experiment. Load curves for each degrees of freedom (particularly the dominant loading) will be defined based on experiment data points and simulation output will be requested at each experiment point. The kinematics-kinetics trajectories of experiment will be split to facilitate prescription of loading scenarios in simulations. A total of 12 models will be generated based on the following model naming convention:

F###_$$

where

###: 001, 002 corresponding to *flexion angle ranges from lowest to highest*.

$$: AT, PT, IR, ER, VR, and VL corresponding to anterior laxity, posterior laxity, internal rotation laxity, external rotation laxity, varus laxity, and valgus laxity, respectively.

Simulations

Target Outcome

Solutions of customized full knee models through finite element analysis using FEBio[16]; generating simulation results as binary and text output files (.xplt and .log, respectively)[23].

Burden

Software requirements:

FEBio. FEBio is a nonlinear implicit finite element analysis framework designed specifically for analysis in biomechanics and biophysics (binaries custom open source license; free for academic research use, licensing for commercial use is available, see http://www.febio.org)[16]. Version 2.9.1 will be used.

FEBio PreStrain Plugin. PreStrain Plugin provides a general framework for representing prestrain in a finite element model using a prestrain gradient method[17]. Version 1.0 will be used.

Hardware requirements:

Any contemporary computer; desktop, workstation, or laptop. All aforementioned software are supported on multiple platforms including Windows, Mac OS X, and Linux. Access to a high performance computing cluster can expedite simulations by running multiple finite element analysis cases in parallel.

Anticipated Man Hours and Expertise Level:

2-3 weeks of full-time effort from a research engineer with bachelor's degree, mechanical/biomedical background, <3 years of research experience, and familiarity to finite element analysis.

Computational Cost:

~2 hours of anticipated simulation time (wall clock) per simulation case; a total of 40 simulation cases.

Protocols

Input

Customized full models in FEBio[16] format (.feb)[23].

Simulation Process

Invoke FEBio[16] with each customized model file as input. If a simulation does not convergence, convergence tolerances and utilization of alternative solution algorithms may need to be employed in a fashion similar to iterations conducted during the *Model Development* phase[10] and *Model Calibration* phase[8].

Post-Processing

Target Outcome

Extraction and summary of knee kinematics and kinetics of all simulation cases as text based files (.csv)[24]; processed using raw simulation results of customized models with FEBio (.log file)[23], supported by graphs as binary image files (.png)[25]; for simulations of experimental conditions, output files (.csv)[24] consolidated with processed joint kinematics-kinetics data and errors indicating correspondence between simulations and joint testing, supported by summary of predictive errors as text files (.xml)[22].

Burden

Software requirements:

Python. Python is a high-level multi-platform programming language (free and open source GPL compatible Python Software Foundation license, see https://www.python.org)[19]. Any contemporary version available for the computing platform can be used; 3.8.0 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, version 2.7 may be used.

SciPy. SciPy is a Python based open source software platform for mathematics, science and engineering (free and open source BSD-new license, see https://www.scipy.org)[20]. Any contemporary version available for the computing platform can be used; 1.3.1 is the latest version at the time of preparation of this document. Depending on the requirements of legacy Python scripts, a version compatible with Python 2.7 may be used.

Python Scripts. Post processing will be performed using scripts LogPostProcessing.py, described previously, for extracting joint kinematics and kinetics from the model outputs, and an in house script generated during *Model Calibration* phase[8] to compare kinematics and kinetics between models and experiment. The script model_prediction_errors.py is developed in house to calculate rms error between models and experiments kinematics-kinetics, generate graphs and save as png[25], and rms error are saved to xml[22]. To be used with Python[19], source code available at https://simtk.org/svn/openknee/app/KneeHub/src/

PostView. PostView is a post-processor to visualize and analyze results from FEBio, finite element analysis package for biomechanics (binaries custom open source license; free for academic research use, licensing for commercial use is available, see https://febio.org/postview/)[18]. The version used for the *Model Calibration* phase[8] will be used.

Hardware requirements:

Any contemporary computer; desktop, workstation, or laptop. All aforementioned software are supported on multiple platforms including Windows, Mac OS X, and Linux.

Anticipated Man Hours and Expertise Level:

1 week of full-time effort from a research engineer with bachelor's degree, mechanical/biomedical background, <3 years of research experience, and familiarity to finite element analysis and scripting.

Computational Cost:

Minimal compared to required interactions with computer scripts.

Protocols

Input

Solutions (simulation results) of customized full models through finite element analysis using FEBio as binary and text output files (.xplt and .log, respectively)[23]; processed experimental knee kinematics and kinetics as text files (.csv)[24].

Standalone Processing of Simulation Results

A Python script previously developed in the *Model Development* phase[10] (LogPostProcessing.py) will be used to read the log file and extract, store (as .csv)[24], and plot knee kinematics and kinetics during all simulation cases (as .png)[25] for both tibiofemoral and patellofemoral joints.

Processing of Simulation Results and Experimental Data

A Python script developed in the *Model Calibration* phase[8] will be used to consolidate tibiofemoral joint kinematics and kinetics of experimentation with that of simulation in a text file (.csv)[24]. (model_prediction_errors.py – in house script to calculate rms error between models and experiments kinematics-kinetics. Generates graphs and saves as png[25], and rms error are saved to xml[22]. To be used with Python, source code available at https://simtk.org/svn/openknee/app/KneeHub/src/). Simulation results will be reduced and/or resampled to match experimentation targets, e.g. load levels. Kinematics and kinetics data (3 rotations, 3 translations; 3 forces, 3 torques/moments) will be reported both in a connector based convention (constraint/reaction forces/torques, cylindrical joint movements) and rigid body based convention (forces/moments on femur/tibia, femur/tibia movement). All reporting will use anatomical local coordinate systems of the model, which would already be registered to the experimental local coordinate systems (see Registration for Specimen-Specific Calibration). All kinematics will be reported in a fashion to describe absolute pose and orientation of bones relative to each other, i.e., accounting for offsets of joint coordinate system in reference state of experiment (see Specimen-Specific Kinematics-Kinetics Data Processing) and that of model. Differences between predictions and measurements for each corresponding kinematics and kinetics channel will be reported in the same text file. For each degrees of freedom, root-mean-square error between experimental and model predicted kinematics and kinetics will be calculated and reported in a text file (.xml[22]) to summarize the predictive capacity of the model. Experimental and model predicted kinematics and kinetics will also be plotted (as .png)[25].

Visualization

PostView[18] will be used to take snapshots of the model at different flexion angles, as obtained through simulation of passive flexion. PostView[18] can also be used to inspect tissue stress-strain distributions, export data, images, and animations.

Dissemination

Target Outcome

Modeling and simulation outputs delivered to the public as a download package.

Burden

Infrastructure:

SimTK. SimTK is a free project-hosting platform for the biomedical computation community (see https://simtk.org/). Project sites at SimTK provide source code repositories, wikis to support development; and news, forums, downloads and documents sections to engage with user communities.

Anticipated Man Hours and Expertise Level:

Less than a day of full-time effort (to prepare, organize, and disseminate final package) from a research engineer with bachelor's degree, mechanical/biomedical background, <3 years of research experience, and familiarity to public dissemination.

Protocols

All modeling and simulation outputs of the *Model Benchmarking* phase[6] will be collated as a package and uploaded to the project site of *Reproducibility in simulation-based prediction of natural knee mechanics* located at SimTK[21] (https://simtk.org/projects/kneehub/). This download package will be accessible by the public licensed under Creative Commons Attribution 4.0 International License.

Protocol Deviations

Target Outcome

Protocol deviations to model benchmarking specifications documented and delivered to the public.

Burden

Infrastructure:

SimTK. SimTK is a free project-hosting platform for the biomedical computation community (see https://simtk.org/)[21]. Project sites at SimTK provide source code repositories, wikis to support development; and news, forums, downloads and documents sections to engage with user communities.

Anticipated Man Hours and Expertise Level:

For each protocol deviation, on the order of minutes of full-time effort, and for final report, less than a day of full-time effort, from a research engineer with bachelor's degree, mechanical/biomedical background, <3 years of research experience, and familiarity to finite element analysis.

Protocols

It is anticipated that some deviations to modeling and simulation workflow, described in here as part of *Model Benchmarking* phase[6], will happen. There is also the possibility that some information on model re-calibration and benchmarking specifications may be missing. All these will be documented on an ongoing basis during the execution of the planned workflow. Final document will be submitted to the project site of *Reproducibility in simulation-based prediction of natural knee mechanics* located at SimTK (https://simtk.org/projects/kneehub/) as a publicly accessible document under Creative Commons Attribution 4.0 International License.

Overall Burden

Overall burden of the modeling and simulation workflow described in here is determined by the requirements

for data, labor, software and hardware, and other infrastructure. Use of existing, publicly available data, in this case Natural Knee Data[5], negates the burden for data acquisition. Software and hardware costs are associated with preparation of joint mechanics data and pre-/post-processing of simulations in a coherent manner. It is anticipated that the model re-calibration, post-calibration simulations, benchmarking and analysis of simulation results in light of experimental joint mechanics data can be performed in any contemporary computer, minimizing hardware costs. All software packages used in the modeling and simulation workflow are freely available: Python[19] and SciPy[20] – to utilize Python scripts (existing and some to be developed) for reassembly of meshes, processing of experimental data, model re-calibration, benchmarking and pre- and post-processing of models; FEBio[16] and FEBio PreStrain Plugin[17] – for finite element analysis; and PostView[18] – for visualization of simulation results. The activity will leverage SimTK[21] for public dissemination. SimTK[21] is a freely available project hosting site for biomedical computing. Labor effort will be at a minimum of 4 weeks of full time effort from a research engineer with bachelor's degree, mechanical/biomedical background, less than 3 years of research experience, and familiarity to finite element analysis. This effort level includes all data processing and modeling activities, record keeping, and dissemination. It should be noted that this estimate relies on the assumption that modeling and simulation processes complete as planned, without any significant deviations and iterations. Based on our recent experience in the *Model Calibration* phase[8], convergence problems may require iterative troubleshooting of simulations. High simulation cost (~2 hours for passive flexion) may also be a confounding factor. As a result, this timeline may extend in an agile fashion. The overall burden of the model re-calibration and benchmarking specifications should be evaluated in concert with their desired final outcome – a comprehensive and extensible knee joint model incorporating anatomical and mechanical detail of its major structures, which is capable of reproducing measured specimen-specific response.

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