Modeling and Simulation Workflow Using Natural Knee Data

Model Calibration Protocol Deviations

Cleveland Clinic Approach

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Synopsis

This document describes protocol deviations to the model calibration specifications[1], which were aimed for generating a calibrated model of the knee joint based on an initial working model and an existing, additional joint testing data set from the Natural Knee Data[2], which was acquired for the same specimen. The documentation is in response to *Model Calibration* phase[3] 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)[4]. The decisions for protocol deviations represent those of the Cleveland Clinic team, who launched and has been maintaining the Open Knee(s)[5]. These deviations were in response to unforeseen challenges during the calibration of the model and aim to provide previously missing information. They also facilitated the delivery of a pragmatic, yet comprehensive, calibration of an anatomically and mechanically detailed and extensible knee joint model incorporating its major tissue structures. The document follows the outline of the previously disseminated model calibration specifications[1], augmenting information related to the burden of activities and listing protocol deviations in detail.

Initial Working Model

There is no additional information to report for this section. One can refer to the original model calibration specifications[1] for details.

Data Utilized

There is no additional information to report for this section. One can refer to the original model calibration specifications[1] for details.

Overview of Modeling and Simulation Processes

The broad description of the modeling and simulation processes does not have any major changes. More details can be found in the original model calibration specifications[1]. At a more granular level, the changes to the modeling and simulation workflow should be inferred from the rest of this document.

Detailed Modeling and Simulation Outputs

The outline of modeling and simulation processes did not change in a significant way. More details can be found in the original model calibration specifications[1]. Any specific changes in the type of outputs, file formats, etc. should be inferred from the rest of this document.

Workflow

General Deviations

These deviations are not specific to any particular calibration protocols, however they reflect general changes that were important to note.

By Ariel Schwartz on February 21 2020 –This deviation should have been included in the model development phase protocol deviations[6]. In contacts between rigid and deformable tissues, FEBio[7] requires that the deformable body be defined as the master surface. Our original model specifications listed the opposite relationship – this was a typo. The disseminated models included the correct master/slave definitions.

By Ariel Schwartz on March 5 2020 – Abduction-Adduction axes were labeled backwards in all the model development phase outputs[6,8,9]. This included the labeling of axes in the model files, and any outputs including graphs, csv[10] files, etc. This error has been fixed in all calibration phase outputs.

By Ariel Schwartz on June 30 2020– All models generated in the workflow made use of springs to connect the MCL to the medical meniscus, as a replacement for the ties contact which had been used previously. This decision was made based on experience in the calibration of the model using the Open Knee(s) data[11]. Issues arose in when there was a space between the surfaces where the tie was defined, the software attempted to close the gap, thus shifting the ligaments and bones. Springs with a constant of 1000 N/mm were used to connect all the nodes to in the MCL tied region, to the nearest node in the meniscus tied region. This created an effectively rigid connection between each of the sets of nodes.

Mesh Convergence

Burden

Mesh convergence for du02 was completed by Ariel Schwartz. The activity required 2 weeks of full time effort.

Deviations

Geometry Generation Procedures

By Ariel Schwartz on December 9 2019 – smoothing procedures used in model development phase[12,13] were not reproducible, and caused holes in some meshes. Instead of using the raw stl and performing smoothing, the smoothed meshes from the initial working model were iso parameterized, and re-meshed at the desired mesh densities. Some additional smoothing and manual editing was required after the remeshing step. This means that any loss of volume or detail in the meshes in the initial working model were carried over into the mesh convergence phase.

Mesh Generation Procedures

By Ariel Schwartz on December 13 2019 – a Python[14] script was created to transfer tie and contact groups from an existing MED[15] file, to a newly generated mesh of the same tissue, it is:

transfer_med_groups.py – in house script to transfer groups from an existing MED[15] file, to a new mesh of the same tissue geometry. To be used with Python[14] and SALOME[16], source code available at https://simtk.org/svn/openknee/app/KneeHub/src/

Model Generation Procedures

By Ariel Schwartz on December 23 2019 – For all cartilage and menisci compression models, intended prescribed displacements of 2mm were too high, causing unrealistic reaction forces. The following adjustments were made to the prescribed displacements to produce reasonable reaction forces:

-Patella Cartilage model prescribed displacement was reduced to 1.2 mm

-Lateral Tibial Cartilage model prescribed displacement was reduced to 0.6 mm

-Medial and Lateral Meniscus models prescribed displacements were reduced to 1 mm.

-Medial Tibia Cartilage, Femoral cartilage prescribed displacements were reduced to 0.4 mm

By Ariel Schwartz on December 23 2019 –Contact penalty was increased from 0.1 to 1 to reduce penetration in all the compression models.

By Ariel Schwartz on December 23 2019 – In the meniscus compression models, Tibia was included in the model to tie the ends of the meniscus.

Mesh Convergence Procedures

By Ariel Schwartz on December 26 2019 – Femoral cartilage showed some fluctuations in the reaction force results, making it difficult to determine convergence. This may be due to how thin the cartilage is in the areas that were being compressed. Convergence was decided based on results from other cartilage tests. Medial tibial cartilage converged at a sampling rate of 10, and other cartilages at lower mesh densities. It was decided that FMC_IP10 will be the converged mesh density.

Confirmation of Material Properties

Burden

Material properties confirmation for du02 was completed by Ariel Schwartz. The activity required 2 weeks of full time effort.

Deviations

KNOWN LIMITATIONS OF CONSTITUTIVE MODELS

By Ariel Schwartz on September 4 2020- After experiencing difficulties with calibration of in situ strains for this model, more investigation was done which uncovered several limitations of the constitutive models used here.

- Ligaments and meniscus are modeled as uncoupled transversely isotropic Mooney Rivlin materials. Material properties were initially assumed from literature, and ligament models were tested in tension for structural response, and calibrated for the fiber modulus as noted in the calibration specifications[17]. However, the remaining material properties (bulk modulus, ground substance properties) were not changed from what was provided in literature. Under further inspection, we found that the ground substance was generating reaction forces when the ligaments were loaded under compression, as well as contributing significantly to the overall material stiffness. Therefore, adjustment of other material properties is likely necessary in order to ensure accurate structural behavior of the tissues under diverse loading scenarios.
- Further investigation is needed to determine what the appropriate material properties are, and the workflow that should be used to calibrate the material properties, including ground substance properties and bulk modulus for all ligaments and meniscus.

Compartmental Modeling of Structural Tissue Behavior

By Ariel Schwartz on December 21 2019 – a Python[14] script was written to read the model outputs from an FEBio[7] logfile, and fit a line to the final 1/3 of the force displacement curve to determine linear stiffness.

StiffnessFromLog.py – in house script to determine linear stiffness from FEBio[7] model results. To be used with Python[14], source code available at https://simtk.org/svn/openknee/app/KneeHub/src/

Cartilage

By Ariel Schwartz on January 14 2020 - using prescribed force caused instability in the model, and it failed to converge. Instead, a prescribed displacement was used, such that the reaction force was approximately 0.5 N. The stiffness was measured using the force displacement results.

Registration for Specimen-Specific Calibration

Burden

Registration for du02 was completed by Ariel Schwartz. The activity required 1 week of full time effort.

Deviations

By Ariel Schwartz on January 29 2020 – a Python[14] script was written to use coherent point drift algorithm in using the pycpd[18] package to determine the transformation matrix from the experimental bone coordinate system to the image coordinate system. Digitized anatomical landmarks are then transformed to the image coordinate system. It is:

Register_probed_points.py – in house script to transform the digitized anatomical landmarks to the image coordinate system. To be used with Python[14], source code available at https://simtk.org/svn/openknee/app/KneeHub/src/

By Ariel Schwartz on January 29 2020 – instead of using the full raw geometry for the articular cartilage, only the exterior surface of the cartilage was used, to better align with the probed points. Interior elements were manually removed in Meshlab[19].

By Ariel Schwartz on January 29 2020 – to locate the hip ball center, a sphere was fit to the probed points.

By Ariel Schwartz on May 4 2020 – Due to noisy patella articular cartilage data, registration of the patellofemoral joint was not completed. The patella axes from model development phase were used.

By Ariel Schwartz on Aug 3 2020 – After the data processing step, it was noticed that there was a large anterior shift at the start of all experimental trials. This led us to believe there may have been a registration error. Registration of the tibia bone was repeated, this time including probed points from the bone, articular geometry, and plateau perimeter. The bone and cartilage geometry files were merged to use as the target point cloud for registration. The articular geometry of the tibia bone has a mostly planar shape, which has the potential to allow for some loss of accuracy in the registration of the point clouds. The addition of the bone probed points ensures the 3 dimensionality of the point clouds being registered.

Specimen-Specific Kinematics-Kinetics Data Processing

Burden

Data Processing for du02 was completed by Ariel Schwartz. The activity required 2 weeks of full time effort.

Deviations

General Notes

By Ariel Schwartz on February 7 2020 – a Python[14] script was written to process the du02 csv[10] data and provide it in a form amenable for simulations with the full knee model, it is:

csv_processing_nkd.py – in house script to process the csv[10] files provided with Natural Knee[2] experimental data. To be used with Python[14], source code available at https://simtk.org/svn/openknee/app/KneeHub/src/

By Ariel Schwartz on March 3 2020 - The data needed to be filtered in order to calculate the time shift, a built in Scipy Butteworth[20] low pass filter was used, with order N=2, and critical frequency Wn=1/25. These parameters were chosen after playing around with different values and seeing which values maintained the local extrema and reduced noise. Shift was calculated for each data set and kinematics data was shifted by +n data points to match kinetics. (AP: n=18, IE: n=40, VV: n=19, Passive_Flexion: n=23)

By Ariel Schwartz on March 4 2020 - force/torque cutoffs along non-dominant loading axes were not used. Cutting of those axes where forces are above a certain threshold leaves no data, as the forces were significant on those axes throughout the entire experiment. This changes the assumption of pure laxity testing, which in turn may affect the in situ strain calibration, as the assumption was made that we were only activating the ligament along the dominant loading axis when optimizing the in situ strains. Additionally, this indicates that the passive flexion experiment is not "true" passive flexion, as loading exists on other degrees of freedom.

By Ariel Schwartz on July 22 2020 - There was some confusion regarding the directions of the experimental kinematics/kinetics data. DU team provided the positive directions for the kinematics data as: +felx, +val, +ext tibia, +lat tib, +ant tib, +sup tib. The translations were provided as clinical translations. They were converted to cylindrical joint translations for ease of comparison with model joint translations. Experimental kinetics were said to be reported in the Grood and Suntay[21] fixed tibia bone coordinate system. However, upon inspection of the raw kinematics/kinetics data, it appeared to us that the torques did not align with the right handed rotations about the tibia fixed axes for all 3 axes. Using all loading data, to inspect torque vs rotations for each axis we came to the conclusion that the positive directions for the kinetics defined as loads applied to the tibia were +extension, +val, +external, +lat, +ant, +sup.

<u>Laxity Data</u>

By Ariel Schwartz on March 3 2020 - VV data appears to have some data at the beginning of the experiment that was not a part of the test. The first 1260 data points were manually deleted to exclude irrelevant data.

By Ariel Schwartz on March 4 2020 - flexion angles for resampling were chosen based on where there was significant data instead of sampling the data at 15 degree increments. The resampling angles were chosen 15-25 degrees apart, depending on where there was data to work with.

By Ariel Schwartz on March 4 2020 - range of data included at the resampled angles was reduced from +- 1 degree to +- 0.2 degrees, because the data showed that the knee flexion angle was continuously changing during laxity testing so significant noise was introduced when +- 1 degree was used.

By Ariel Schwartz on March 4 2020 - after the above deviations, data was sparse for each flexion angle, so choosing specific loads to average the data would result in empty data sets. Instead, a selection of points was simply extracted from the data set, to create somewhat evenly distributed loading points where possible. This should not have any effect on the optimization procedures, as the experimental conditions will still be applied to the model.

Calibration of In Situ Ligament Strains

Burden

In situ strain calibration for du02 was completed by Ariel Schwartz. The activity required 4 weeks of full time effort.

Deviations

By Ariel Schwartz on February 19 2020 – a Python[14] script was written to update a full knee model in FEBio[7] to replicate experimental conditions. Experimental kinetics are applied as external femur loads, and experiment flexion angle is prescribed to the extension-flexion joint.

experiment_to_model.py – in house script to apply experimental conditions to a full knee model in FEBio[7]. To be used with Python[14], source code available at https://simtk.org/svn/openknee/app/KneeHub/src/

By Ariel Schwartz on February 25 2020 – a Python[14] script was written to update the in situ strain of the target ligament in the FEBio[7] 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.

InSituOptimization.py – in house script to perform in situ strain optimization for the target ligaments. To be used with Python[14], FEBio[7]. Source code available at https://simtk.org/svn/openknee/app/KneeHub/src/

By Ariel Schwartz on June 30 2020– initial attempts as in situ strain calibration failed due to models not converging. It was determined that convergence issues arose when model was attempting to take time steps with very small changes in kinetics/kinematics settings. Control setting were adjusted, so that model attempts to take larger steps when changes are small (during in situ strain application and initial experimental setup).

By Ariel Schwartz on August 4 2020– suspected issue with registration, registration was re-run and calibration re-started (details in Registration protocol deviations)

By Ariel Schwartz on August 4 2020– Initial guess values for ACL, PCL were entered incorrectly into the in situ strain optimization function. This is noted as a protocol deviation, but should not have any influence on the results of the optimization process.

Summary of in final situ strain optimization results:

Test Name	**Anterior Laxity**	**Posterior Laxity**	**Varus Laxity**	**Valgus Laxity**
Ligament of interest	ACL	PCL	LCL	MCL
Experiment kinetics (for generation of models)	Laxity_9deg_AP1_kinetics_in_TibiaCS.csv	Laxity_7deg_AP2_kinetics_in_TibiaCS.csv	Laxity_11deg_VV2_kinetics_in_TibiaCS.csv	Laxity_9deg_VV1_kinetics_in_TibiaCS.csv
Experiment kinematics (for calculation of rms error)	Laxity_9deg_AP1_kinematics_in_JCS.csv	Laxity_7deg_AP2_kinematics_in_JCS.csv	Laxity_11deg_VV2_kinematics_in_JCS.csv	Laxity_9deg_VV1_kinematics_in_JCS.csv
Initial In Situ Stretch guess	0.789	1.024	1.027	1.034
Optimized In Situ Stretch	**0.783**	**0.516**	**1.019**	**1.073**
RMS error on dominant loading axis	**3.915 mm**	**1.027 mm**	**0.137 deg**	**0.557 deg**

By Ariel Schwartz on August 4 2020– results of in situ strain optimization lead ACL and PCL to be in extreme compression (in situ stretch of 0.783,0.516), such that they are were not activated during loading. For the sake of capturing the “Art” of modeling, listed here are the methods used to try and understand and resolve the issue:

- Tried running by minimizing rms error on all axes, not just the loading axis. This reduced PCL compression slightly, but still not enough to activate during loading
- Noticed that IE rotations was very large in the anterior laxity model, but not the experiment. Tried running anterior laxity calibration again, this time fixing IE rotation in addition the previous settings (applied kinetics, fixed FE

rotation). This produced similar results to minimizing rms error on all axes.

- At this point, it was suspected that the assumption that only the ACL would carry the load during anterior loading was broken. Thus, the goal became to determine which other tissues were acting during anterior loading.
- We noticed that the ground substance in the ligaments which had been assumed from literature values (c1) was creating a significant (~10N) reaction force when the ligaments were in compression. Since anterior loading will likely put the PCL in compression, this has the potential to influence the calibration results, as the PCL may carry the anterior load under compression, instead of the ACL under tension. The same may apply in reverse during posterior loading.
- Meniscus properties were adjusted so that the meniscus stiffness was significantly reduced. When meniscus stiffness was reduced, the anterior translation under experimental anterior loads was much more similar to the experiment.
- Conclusions: 2 known limitations in the current model exist. 1) material properties assigned to ligaments produce a reaction force under compression. 2) Meniscus stiffness is too high

By Ariel Schwartz on August 28 2020- Due to time constraints, and known limitations of the model, the decision was made to move forward with experimental loading using the initial guess values from model development phase[8] for ACL, PCL in situ strains, and the converged values for MCL,LCL in situ strains above. It appeared from the results of optimization that the MCL,LCL calibrations were not influenced by the issues seen in the anterior and posterior loading models, and the rms error on the loading axes for MCL,LCL were greatly improved during optimization. Further investigation of material properties of ligaments and menisci is needed to solve the issues that were uncovered.

Customized Full Models

Burden

Generation of customized full models was completed by Ariel Schwartz. The activity made use of an existing script, and there for did not add to the burden.

Deviations

By Ariel Schwartz on August 28 2020 -Experimental loading cases were generated using in house script **experiment_to_model.py**, described above.

<u>Customization for Test Simulation Case</u>

By Ariel Schwartz on August 28 2020 –One additional staged model was added to the list. First the mcl-mns tie was swapped for springs, so that an assessment could be made on how that change affects the model kinematics-kinetics.

<u>Customization for Experimental Loading Cases</u>

By Ariel Schwartz on August 28 2020 –Additional experimental loading model was added to the list – F90, to replicate the experimental passive flexion with kinetics. This model was initially excluded due to the assumption that the passive flexion test simulation case was sufficient for comparison to experimental passive flexion. However, as noted in data processing protocol deviations the experimental passive flexion loading cannot be considered true passive flexion due to loading on other axes, thus this model was added to replicate the experimental conditions for passive flexion, including kinetics.

By Ariel Schwartz on August 28 2020 –Control setting were changed to speed up the model run-times. During model calibration phase using Open Knee(s) data[17], more efficient control setting were discovered and these were applied to the Natural Knee models. Some requested must points were removed in the in situ strain and initial loading stages, so the model could take larger steps when the loading increment was small. Min_residual in the control section was increased to 0.01, to assist in convergence when loading increment was small.

Simulations

Burden

Simulations were completed by Ariel Schwartz and Snehal Chokhandre. The activity required 3 days of computational time, plus approximately 1 week full time effort troubleshooting models that failed to converge (exact time is unknown, this issue was revisited several times over the course of 1 month).

Deviations

Experimental Loading Cases

Note: Specifics on which nodes and elements were excluded from each model can be found in the model files included in the calibration phase outputs packages.

By Ariel Schwartz on September 2 2020 – F062_AT, F065_IR, F081_IR, F084_PT, F097_AT, F105_VR, and F106_VL failed to converge with initial settings. Model outputs indicated negative jacobians in elements located in the MCL-FMB tie region, LCL-FMB tie region, and ACL-FMB tie region. The problematic nodes were excluded from the tie regions for all the models in a new Geometry file, and then the models converged fully.

By Ariel Schwartz on September 22 2020 – F084_ER, F090, F091_VR, and F103_IR failed to converge fully. These models converged past the initial loading state, and included 1 or more successful steps of experimental loading. Several attempts to get the models to converge fully were unsuccessful.

By Ariel Schwartz on September 30 2020 – F111_VR, F113_AT, F114_PT failed to converge past the initial loading state of the model. Several attempts to get the models to converge were unsuccessful. The reason for failure is unknown, but likely can be attributed to the high degrees of flexion, possibly causing buckling in a ligament.

Post-Processing

Burden

Post Processing was completed by Ariel Schwartz. The activity made use of a previously existing script, and therefore did not add to the overall burden.

Deviations

By Ariel Schwartz on September 21 2020 –Post processing was performed using scripts **LogPostProcessing.py**, described previously, for extracting joint kinematics and kinetics from the model outputs, and an in house script generated to compare kinematics and kinetics between models and experiment. It is:

model_prediction_errors.py – in house script to calculate rms error between models and experiments kinematics-kinetics. Generates graphs and saves as png[22], and rms error are saved to xml[23]. To be used with Python[14], source code available at https://simtk.org/svn/openknee/app/KneeHub/src/

By Ariel Schwartz on September 22 2020 – Post processing of F084_ER, F090, F091_VR, and F103_IR. These models converged past the initial loading state, and included 1 or more successful steps of experimental loading. Comparison with experimental data was performed, and rms error was calculate for whatever data was available.

By Ariel Schwartz on September 30 2020 – Post processing of F111_VR, F113_AT, F114_PT. Since these model failed to converge past the initial loading state, there was no model data available for comparison with experimental data.

Dissemination

Burden

Dissemination was completed by Ariel Schwartz. The activity took 1 day for file management and uploading.

Deviations

By Ariel Schwartz on November 10 2020 –an internal data management system, MIDAS Platform[24], was used for staging and organization prior to dissemination

Protocol Deviations

Burden

Protocol deviations were completed by Ariel Schwartz. Deviations were reported on an ongoing basis, so exact burden is unknown, however it is estimated that the total amount of time to report deviations was less than 1 day.

Deviations

No deviations.

Overall Burden

Overall burden of the model calibration phase, in regard to data and software, was faithful to the original model calibration specifications[1]. Use of existing, publicly available data, in this case Natural Knee[2] data set, negates the burden for data acquisition. Software packages, which were used for model calibration, were in line with specifications. The activity leveraged SimTK[25] as a collaboration infrastructure within the team, e.g. for version control and public dissemination. Required labor, however, was higher than what was anticipated in the model calibration specifications[1]. Overall, the entire calibration process took approximately 13 weeks of full time effort, including computation time 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 programming to streamline some of the operations, all data processing and modeling activities, record keeping, and dissemination. Now that the scripting to expedite some of the model calibration operations has been completed and the team has a better understanding of the nuances of model convergence, calibration of another working knee model in the Natural Knee[2] data set, with existing experimental data in the same format, will likely be completed in approximately 5 weeks. This estimate includes 3 weeks for mesh convergence and material properties calibration, 1 week for in situ strain optimization computation time, and 1 week for running and troubleshooting models replicating experimental conditions. Mesh convergence and material properties calibration require a significant amount manual intervention from the analyst. The remaining phases require minimal manual intervention, only for troubleshooting when models fail to converge. However, much progress was made during the model calibration phase in understanding how to troubleshoot model convergence issues in a streamlined manner. The overall burden of the model calibration 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.

References

1. Schwartz A, Chokhandre S, Erdemir A. *Modeling and Simulation Workflow Using Natural Knee Data: Model Calibration Specifications - Cleveland Clinic Approach*. Cleveland Clinic; 2019.

2. Natural Knee Data | Center for Orthopaedic Biomechanics | University of Denver. Accessed August 14, 2018. https://digitalcommons.du.edu/natural_knee_data/

3. ModelCalibration - kneehub. Accessed August 29, 2019. https://simtk.org/plugins/moinmoin/kneehub/ModelCalibration

4. SimTK: Reproducibility in simulation--based prediction of natural knee mechanics: Project Home. Accessed August 12, 2018. https://simtk.org/projects/kneehub

5. Erdemir A. Open Knee: A Pathway to Community Driven Modeling and Simulation in Joint Biomechanics. *J Med Devices*. 2013;7(4):0409101-0409101. doi:10.1115/1.4025767

6. Schwartz A, Chokhandre S, Erdemir A. *Modeling and Simulation Workflow Using Natural Knee Data: Model Development Protocol Deviations – Cleveland Clinic Approach*. Cleveland Clinic; 2019.

7. FEBio Software Suite. Accessed August 13, 2018. https://febio.org/

8. Schwartz A, Chokhandre S, Erdemir A. *Modeling and Simulation Workflow Using Natural Knee Data: Model Development Specifications – Cleveland Clinic Approach*. Cleveland Clinic; 2018.

9. Schwartz A, Chokhandre S, Erdemir A. *Modeling and Simulation Workflow Using Natural Knee Data: Model Development Outputs Descriptors – Cleveland Clinic Approach*. Cleveland Clinic; 2019.

10. Shafranovich Y. Common Format and MIME Type for Comma-Separated Values (CSV) Files. Published online 2005. Accessed June 10, 2019. https://www.rfc-editor.org/info/rfc4180

11. SimTK: Open Knee(s): Virtual Biomechanical Representations of the Knee Joint: Project Home. Accessed August 12, 2018. https://simtk.org/projects/openknee

12. Schwartz A, Chokhandre S, Erdemir A. *Modeling and Simulation Workflow Using Open Knee(s) Data: Model Development Specifications – Cleveland Clinic Approach*. Cleveland Clinic; 2018.

13. Schwartz A, Chokhandre S, Erdemir A. *Modeling and Simulation Workflow Using Open Knee(s) Data: Model Development Protocol Deviations – Cleveland Clinic Approach*. Cleveland Clinic; 2019.

14. Welcome to Python.org. Python.org. Accessed August 12, 2018. https://www.python.org/

15. Med — SALOME Platform. Accessed August 13, 2018. http://www.salome-platform.org/user-section/about/med

16. Welcome to the www.salome-platform.org — SALOME Platform. Accessed August 12, 2018. https://www.salome-platform.org/

17. Schwartz A, Chokhandre S, Erdemir A. *Modeling and Simulation Workflow Using Open Knee(s) Data: Model Calibration Specifications - Cleveland Clinic Approach*. Cleveland Clinic; 2019.

18. Khallaghi S. *Pycpd: Pure Numpy Implementation of the Coherent Point Drift Algorithm*. Accessed September 23, 2020. https://github.com/siavashk/pycpd

19. Cignoni P, Callieri M, Corsini M, Dellepiane M, Ganovelli F, Ranzuglia G. MeshLab: an Open-Source Mesh Processing Tool. In: *Sixth Eurographics Italian Chapter Conference*. The Eurographics Association; 2008:129-136. doi:10.2312/LocalChapterEvents/ItalChap/ItalianChapConf2008/129-136

20. scipy.signal.butter — SciPy v1.5.2 Reference Guide. Accessed September 23, 2020. https://docs.scipy.org/doc/scipy/reference/generated/scipy.signal.butter.html

21. Grood ES, Suntay WJ. A joint coordinate system for the clinical description of three-dimensional motions: application to the knee. *J Biomech Eng*. 1983;105(2):136-144.

22. Roelofs G. *PNG: The Definitive Guide*. 1 edition. O'Reilly Media; 1999.

23. Extensible Markup Language (XML). Accessed August 13, 2018. https://www.w3.org/XML/

24. Midas Platform - The Multimedia Digital Archiving System. Accessed November 10, 2020. http://www.midasplatform.org/

25. SimTK: Welcome. Accessed August 12, 2018. https://simtk.org/