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Variabilities in μ QCT-based FEA of a tumoral bone mice model

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Keywords: Bone, Finite Element, Uncertainties, Reproducibility, variabilities

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Abstract

A finite element analysis based on Micro-Quantitative Computed Tomography (μ QCT) is a method with high potential to improve fracture risk prediction. However, the segmentation process and model generation are generally not automatized in their entirety. Even with a rigorous protocol, the operator might add uncertainties during the creation of the model. The aim of this study was to evaluate a μ QCT-based model of mice tumoral and sham tibias in terms of the variabilities induced by the operator and sensitivity to operator-dependent variables (such as model orientation or length). Two different operators generated finite element (FE) models from μ CT images of 8 female Balb/c nude mice tibias aged 10 weeks old with bone tumors induced in the right tibia and with sham injection in the left. From these models, predicted failure load was determined for two different boundary conditions: fixed support and spherical joints. The difference between the predicted and experimental failure load of both operators was large (-122% to 93%). The difference in the predicted failure load between operators was less for the spherical joints boundary conditions (9.8%) than for the fixed support (58.3%), $p < 0.001$, whereas varying the orientation of bone tibia caused more variability for the fixed support boundary condition (44.7%) than for the spherical joints (9.1%), $p < 0.002$. Varying tibia length had no significant effect, regardless of boundary conditions (<4%). When using the same mesh and same orientation, the difference between operators is non-significant (<6%) for each model. This study showed that the operator influences the failure load assessed by a μ QCT-based finite element model of the tumoral and sham mice tibias. The results suggest that automation is needed for better reproducibility.

Keywords: Bone, Finite Element, Uncertainties, Reproducibility, Variabilities

Introduction

Finite Element Analysis (FEA) was used as a potential tool to improve the failure prediction of metastatic bones in ex-vivo studies (Delpuech *et al.*, 2020; Benca *et al.*, 2017, 2019; Derikx *et al.*, 2012; Eggermont *et al.*, 2018; Keyak *et al.*, 2005; Tanck *et al.*, 2009; Oliviero *et al.*, 2020). Although FEA-based prediction provides at least as many correct predictions as the currently used clinical prediction methods (Erdemir *et al.*, 2012), it seems that improvements are still necessary for the FEA-based predictions to completely outperform clinical methods (Viceconti *et al.*, 2005, 2018, 2019, 2020).

A Finite Element (FE) Model might be considered a full deterministic approach and shall not display any variability induced by the operator. However, in QCT-based FEA, the complex geometry and structure of the bone might induce uncertainties. The scan parameters and segmentation process has already been addressed as an operator-induced bias (Stock *et al.*, 2020) that influences QCT-based model predictions (Benca *et al.*, 2020). When the bone is set up for a scan, it is rarely precisely oriented, leading to post-scan reorientation. In addition, if the scanned object is finally truncated for experimental purposes, the cropping of the bone might add additional bias. Even though criteria are provided to the operator in order to achieve the highest reproducibility, uncertainties might remain. Even with micro-Quantitative-Computerized-Tomography-based FEA (μ QCT-based FEA), these limitations should be considered.

Therefore, the aim of this study was to evaluate a μ QCT-based model of mice tumoral and sham tibias in terms of variabilities induced by the operator and sensitivity to operator dependent variables (such as model orientation or length).

Materials & Methods

- Samples

Eight BALB/c nude female mice (six weeks old) were injected with 100,000 human B02 (breast cancer) tumor cells in their right limb and with Phosphate-Buffered Saline (PBS) in their left one (sham limb) to quantify the effect of intra-tibial injection (Delpuech *et al.*, 2017). After 30 days, the mice were sacrificed, and their tibias were extracted (soft tissues kept) and stored in PBS-soaked gauze at -20°C. The tested group consisted of 8 sham limbs and 8 tumoral limbs. Each tibia was scanned and mechanically tested using the same method described by Delpuech *et al.* (2020) and Gardegaront *et al.* (2020) in order to extract the experimental stiffness and failure load. This mechanical test consisted of an axial compression of the embedded tibias until failure (*cf.* Supplementary Material).

- General method

The overall workflow is presented in Figure 1. Two different FE models (Figure 2) were evaluated to determine which one is the most reproducible. The overall process described below (and in supplementary material) has been done by two operators resulting in two different segmentations, orientations, and lengths of the tibia. The scans, loads, materials, and failure load criterion were the same. However, the selection of the elements included for the boundary conditions of the FE model might differ between operators (referred to here as the “boundary conditions location”). The overall reproducibility was evaluated by comparing the results of both operators on each FE model. Then, the uncertainties linked to the orientation and length of the tibia were specifically assessed. The μ QCT acquisition was done using a micro scanner (Bruker Skyscan 1176, Kontiche, Belgium) with a hydroxyapatite calibration phantom for each sample. A segmentation was done using 3DSlicer (4.10.2) to get the geometry of the bones. Then a tetrahedral mesh was created using Ansys (2019 R1), and the elastic properties of the materials were defined with Bonemat (3.2) with an elastic linear bone constitutive law (*cf.* Supplementary materials).

- Finite element model: boundary conditions

The fixed support model (Figure 1) used by Delpuech *et al.* (2020) was created by embedding the inferior diaphyseal face and applying an evenly distributed load on the top 1 mm of the tibia, corresponding to the experimental axial failure load. The orthogonal components of the load were then added to match the model stiffness and the experimental stiffness (Delpuech *et al.*, 2020). The spherical joints model (Figure 1) was created by bounding the inferior diaphyseal face to a spherical joint and applying an evenly distributed load of 15 N (approximately corresponding to the mean of the experimental failure load) to the top 1 mm of the tibia, which is bound to another spherical joint whose axial displacement is free. These boundary conditions were defined to mimic the experimental ones.

- Failure load prediction criterion

Pistoia’s failure load criterion (Pistoia *et al.*, 2002) was adapted to predict the failure load based on the elastic strain obtained with the FEA, and a total failure volume of 2% and a failure strain threshold of 0.01 were considered (Delpuech *et al.*, 2020).

- Overall reproducibility

The results of Operator 1 and Operator 2 were compared to evaluate the reproducibility. Consequently, these results characterized the effect of the variation of each parameter (segmentation + orientation + length of the tibia and variations in the FE model creation) combined. The

reproducibility was quantified as follows: given a sample, two operators execute independently the same fracture prediction protocol for both models. For a certain model, given x_1 and x_2 , the predicted failure load of respectively Operator 1 and Operator 2, and then the relative difference between operators for this sample is $(x_1 - x_2)/\text{mean}(x_1, x_2)$.

- Model sensitivity to orientation

The model sensitivity to orientation was evaluated by defining an initial orientation for each tibia and 4 different rotations (+5° and -5° along coronal axis and +5° and -5° along sagittal axis). The sensitivity of the fixed support and spherical joints models were evaluated. The sensitivity metrics applied were based on the amplitude of variation of the predicted failure load for each sample (*i.e.* the difference between the maximum predicted failure load and the minimum predicted failure load among each rotation for each sample). Given x_i , the predicted failure load for an oriented model of one sample, the relative amplitude of variation for a sample is $(\max(x_i) - \min(x_i))/\text{mean}(x_i)$.

- Tibial length sensitivity

The tibias were scanned before being embedded, thus creating the need to truncate the scanned tibia for the FEM. The truncated part corresponds to the embedded distal diaphysis. The extent of the tibia sensitivity was evaluated for the fixed support model (without stiffness correction to avoid additional uncertainty) and the spherical joints model. The evaluation of the tibial length sensitivity was done by defining an original model for each tibia and another evaluation was performed identical to the initial one, except for the embedding of the diaphysis, which was 1.5 mm thicker (called truncated, cf. Supplementary material). The value of 1.5mm represents the uncertainty of the operator to locate precisely where the tibia is embedded. The used sensitivity metrics are based on the relative value of the differences between the predicted failure load of each model. Given the predicted failure load of the original ($x_{\text{orig.}}$) and truncated ($x_{\text{trunc.}}$) mesh, the relative difference for a sample is $(x_{\text{orig.}} - x_{\text{trunc.}})/\text{mean}(x_{\text{orig.}}, x_{\text{trunc.}})$.

- Sensitivity of boundary conditions locations

Each operator assigned the boundary conditions location of the models using the same segmentation and orientation. Given x_1 and x_2 , the predicted failure loads of a sample are obtained with the FEM of Operator 1 and Operator 2, respectively, and thus the relative difference caused by the different FEM is $(x_1 - x_2)/\text{mean}(x_1, x_2)$.

- Statistical analysis

Descriptive statistics were applied to the difference between the experimental and predicted values of each operator. A two-way ANOVA showed that the operator had a strong effect on the predicted failure. Therefore, the variability induced by each parameter (described below) was quantified. Differences between paired groups were assessed using non-parametric Wilcoxon's signed rank tests with a significance level of 0.05.

Results

- Descriptive statistics

The results obtained by both operators are shown in Figure 3. Operator 1 has an average difference with the experimental values of -37.1% (SD = 35.9%) and 16.8% (SD = 39.1%) respectively for the fixed support and spherical joints models. Operator 2 has an average difference with the experimental

values of 18.7% (SD = 39.6%) and 23.7% (SD = 36.7%) respectively for the fixed support and spherical joints models. Delpuech *et al.* (2020) obtained an average difference of 11% (SD = 8%) for the fixed support model.

- Overall reproducibility

When the individual results between operators are compared, the fixed support model shows high variability induced by the operator with a mean difference between both operators of 58.3% (min: 11.6%, max: 179.1%), while the spherical joints model reduces these variabilities with a mean difference of 9.8% (min: -7.4%, max: 22.5%) ($p < 0.001$) (Figure 4A).

- Model sensitivity to orientation

On average, the fixed support model has 44.7% (min: 17.2%, max: 79.4%) of variation on a 5° uncertainty for the orientation of the model, while the spherical joints model has 9.1% (min: 0.0%, max: 15.7%) ($p < 0.002$) (Figure 4B).

- Tibial length sensitivity

The fixed support and spherical joints models show a low average sensitivity to the tibial length (respectively 0.0% (min: 0.0%, max 0.0%) and 0.1% (min: -3.7%, max: 3.5%)). There are no significant differences between models (See Supplementary Material).

- Sensitivity of boundary conditions locations

When comparing the simulation done by each operator on the same segmented models, the fixed support model shows an average variation of 0.1% (min: -3.5%, max: 5.1%), and the spherical joints model shows an average variation of 0.4% (min: -0.3%, max: 4.7%). There are no significant differences between models.

Discussion

The objective of this study was to evaluate the reproducibility of a fracture-predicting method using μ QCT-based FEA on tumoral mice tibias. Delpuech *et al.* (2020) obtained fairly good results with the fixed support model in comparison to experiments. However, our study revealed that his method presented low reproducibility. Indeed, from the 16 tested samples used in the current study, an average difference between operators of 58% (maximum 179%) was obtained for the fixed support model. The average difference between the predicted load and experimental load in the current study was respectively -37% (SD 36%) and 16.8% (SD 39%) for Operators 1 and 2. Delpuech *et al.* (2020) obtained an average difference with the experimental load of 11% (SD 8%). The better results of Delpuech *et al.* can be explained by the optimization of the Pistoia's criterion parameters in their study performed using the same dataset. This process introduces a bias, as the same dataset was used to calculate the optimization of the criterion and to validate the results (Hawkins 2004). In the case of long bones, a variability induced by the orientation of the applied load was previously highlighted (Schileo *et al.*, 2007). The fixed support model implies a small variation of the load orientation during the stiffness optimization step. Therefore, a small variation of orientation might be found between operators, thus increasing the overall sensitivity of this model. The spherical joints model was shown to be less sensitive to the orientation of the model. From the 16 tested samples, an average of 11% and a maximum variability between operators of 22% has been obtained for the spherical joints model. The small variations induced by the FE model construction and the tibial length implies that the majority of the variability lies in the segmentation and orientation step of the model. The segmentation

sensitivity of the model would have been difficult to evaluate independently from the other parameters; however, a non-independent insight of the segmentation sensibility is available in the supplementary material.

In conclusion, the operator influences the failure load assessed by a μ QCT-based finite element model of the tumoral and sham mice tibias. The results suggest that automation is needed for better reproducibility.

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References

- Benca, E., Amini, M., & Pahr, D. H. (2020). Effect of CT imaging on the accuracy of the finite element modelling in bone. *European Radiology Experimental*, 4(1), 51. <https://doi.org/10.1186/s41747-020-00180-3>
- Benca, E., Reisinger, A., Patsch, J. M., Hirtler, L., Synek, A., Stenicka, S., Windhager, R., Mayr, W., & Pahr, D. H. (2017). Effect of simulated metastatic lesions on the biomechanical behavior of the proximal femur. *Journal of Orthopaedic Research*, 35(11), 2407-2414. <https://doi.org/10.1002/jor.23550>
- Benca, E., Synek, A., Amini, M., Kainberger, F., Hirtler, L., Windhager, R., Mayr, W., & Pahr, D. H. (2019). QCT-based finite element prediction of pathologic fractures in proximal femora with metastatic lesions. *Scientific Reports*, 9(1), 10305. <https://doi.org/10.1038/s41598-019-46739-y>
- Delpuech, B., Confavreux, C., Bouazza, L., Geraci, S., Clezardin, P., Mitton, D., & Follet, H. (2017). Effect of intra-tibial injection on mechanical properties of mouse bone. *Computer Methods in Biomechanics and Biomedical Engineering*, 20(sup1), S57-S58. <https://doi.org/10.1080/10255842.2017.1382859>
- Delpuech, B., Nicolle, S., Confavreux, C. B., Bouazza, L., Clezardin, P., Mitton, D., & Follet, H. (2020). Failure prediction of tumoral bone with osteolytic lesion in mice. *Advanced Structured Materials*.
- Derikx, L. C., van Aken, J. B., Janssen, D., Snyers, A., van der Linden, Y. M., Verdonchot, N., & Tanck, E. (2012). The assessment of the risk of fracture in femora with metastatic lesions. *The Journal of Bone and Joint Surgery. British volume*, 94-B(8), 1135-1142. <https://doi.org/10.1302/0301-620X.94B8.28449>
- Eggermont, F., Derikx, L. C., Verdonchot, N., van der Geest, I. C. M., de Jong, M. A. A., Snyers, A., van der Linden, Y. M., & Tanck, E. (2018). Can patient-specific finite element models better predict fractures in metastatic bone disease than experienced clinicians? *Bone & Joint Research*, 7(6), 430-439. <https://doi.org/10.1302/2046-3758.76.BJR-2017-0325.R2>
- Erdemir, A., Guess, T. M., Halloran, J., Tadepalli, S. C., & Morrison, T. M. (2012). Considerations for Reporting Finite Element Analysis Studies in Biomechanics. *Journal of Biomechanics*, 45(4), 625-633. <https://doi.org/10.1016/j.jbiomech.2011.11.038>
- Gardegaront, M., Plet, G., Delpuech, B., Bouazza, L., Brevet, M., Pialat, J.-B., Clézardin, P., Confavreux, C. B., Mitton, D., & Follet, H. (2020). Influence of human cancer cell lines on mechanical properties of mice tibia. *Computer Methods in Biomechanics and Biomedical Engineering*, 23(sup1), S115-S116. <https://doi.org/10.1080/10255842.2020.1812859>

- Hawkins, D. M. (2004). The Problem of Overfitting. *Journal of Chemical Information and Computer Sciences*, 44(1), 1-12. <https://doi.org/10.1021/ci0342472>
- Keyak, J. H., Kaneko, T. S., Tehranzadeh, J., & Skinner, H. B. (2005). Predicting Proximal Femoral Strength Using Structural Engineering Models. *Clinical Orthopaedics and Related Research*[®], 437, 219–228. <https://doi.org/10.1097/01.blo.0000164400.37905.22>
- Oliviero, S., Owen, R., Reilly, G. C., Bellantuono, I., & Dall'Ara, E. (2020). Optimization of the failure criterion in micro-Finite Element models of the mouse tibia for the non-invasive prediction of its failure load in preclinical applications. *Journal of the Mechanical Behavior of Biomedical Materials*, 104190. <https://doi.org/10.1016/j.jmbbm.2020.104190>
- Pistoia, W., van Rietbergen, B., Lochmüller, E.-M., Lill, C. A., Eckstein, F., & Rügsegger, P. (2002). Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. *Bone*, 30(6), 842-848. [https://doi.org/10.1016/S8756-3282\(02\)00736-6](https://doi.org/10.1016/S8756-3282(02)00736-6)
- Schileo, E., Taddei, F., Malandrino, A., Cristofolini, L., & Viceconti, M. (2007). Subject-specific finite element models can accurately predict strain levels in long bones. *Journal of Biomechanics*, 40(13), 2982-2989. <https://doi.org/10.1016/j.jbiomech.2007.02.010>
- Stock, M. K., Garvin, H. M., Corron, L. K., Hulse, C. N., Cirillo, L. E., Klales, A. R., Colman, K. L., & Stull, K. E. (2020). The importance of processing procedures and threshold values in CT scan segmentation of skeletal elements : An example using the immature os coxa. *Forensic Science International*, 309, 110232. <https://doi.org/10.1016/j.forsciint.2020.110232>
- Tanck, E., van Aken, J. B., van der Linden, Y. M., Schreuder, H. W. B., Binkowski, M., Huizenga, H., & Verdonschot, N. (2009). Pathological fracture prediction in patients with metastatic lesions can be improved with quantitative computed tomography based computer models. *Bone*, 45(4), 777-783. <https://doi.org/10.1016/j.bone.2009.06.009>
- Viceconti, M. (2020). VPH Success Story : CT-based patient-specific model to predict the risk of hip fracture. <https://www.vph-institute.org/news/vph-success-story-ct-based-patient-specific-model-to-predict-the-risk-of-hip-fracture.html>
- Viceconti, Marco, Juárez, M., Curreli, C., Pennisi, M., Russo, G., & Pappalardo, F. (2019). POSITION PAPER : Credibility of In Silico Trial Technologies: A Theoretical Framing.
- Viceconti, Marco, Olsen, S., Nolte, L.-P., & Burton, K. (2005). Extracting clinically relevant data from finite element simulations. *Clinical Biomechanics*, 20(5), 451-454. <https://doi.org/10.1016/j.clinbiomech.2005.01.010>

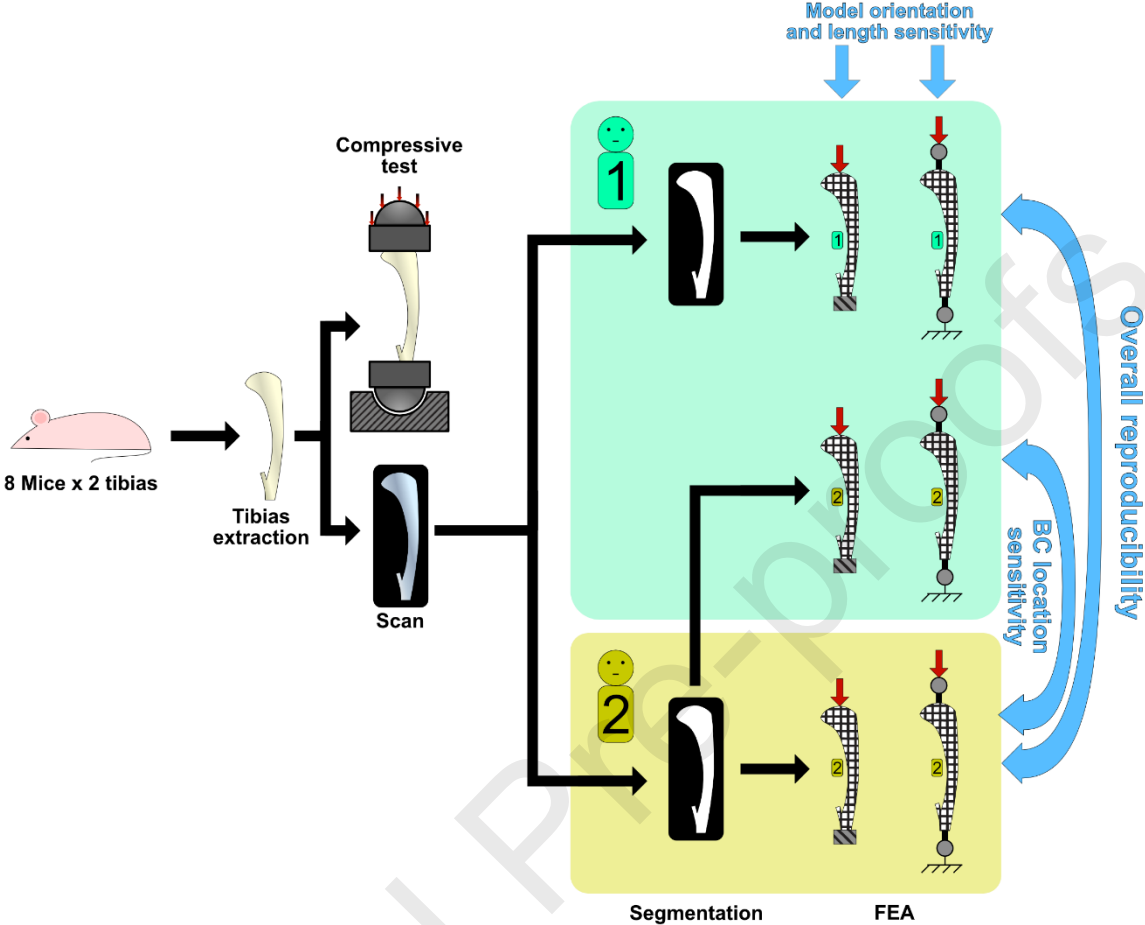
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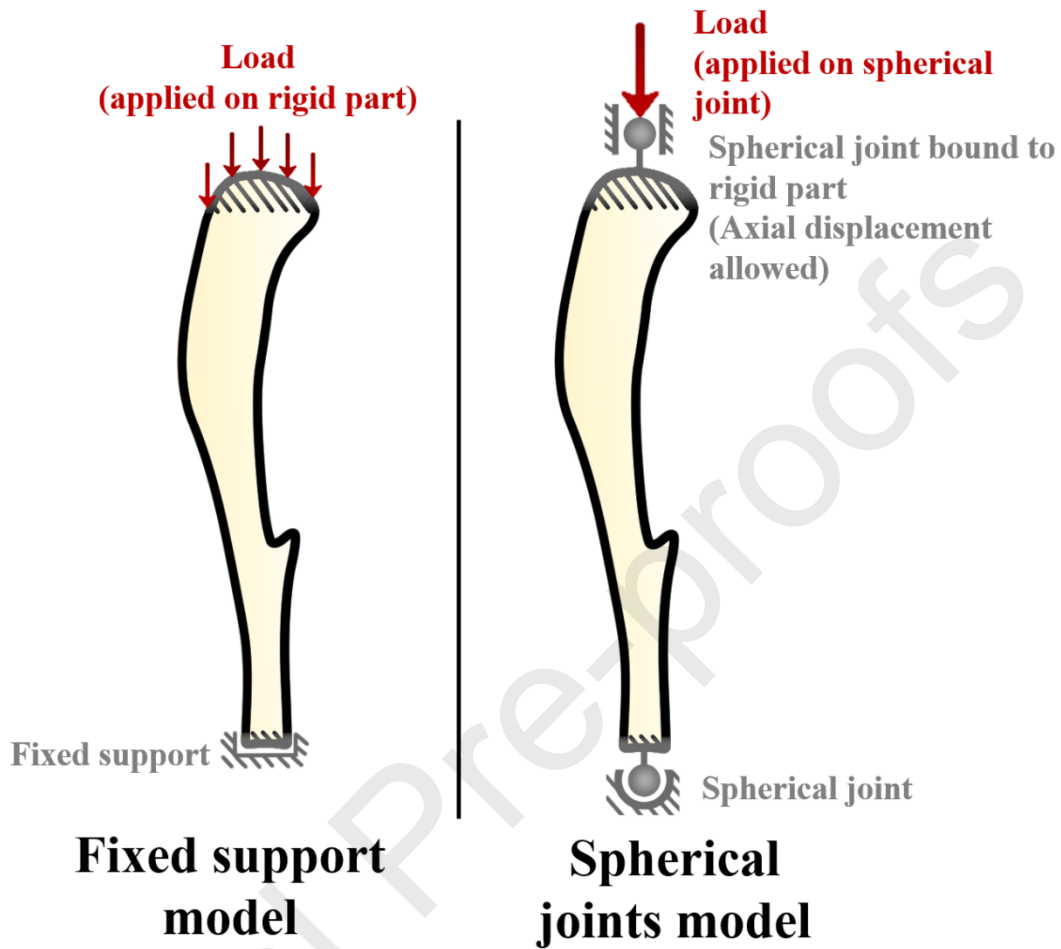
Figure 1: Workflow of the overall method used in this study. The mice tibias were extracted, scanned, and mechanically tested by compression to extract bone stiffness and failure load. The scans were segmented by Operators 1 and 2. Each operator created the finite element models based on their respective segmentations to finally get the predicted failure loads, which were compared to obtain the overall reproducibility. In addition, Operator 1 used the segmentations of Operator 2 to make a second set of finite element models. The predicted failure loads of this set were compared to the initial results of Operator 2 to obtain boundary conditions (BC) location reproducibility. Finally, the orientation and length sensitivity of the models were evaluated using the models of Operator 1.

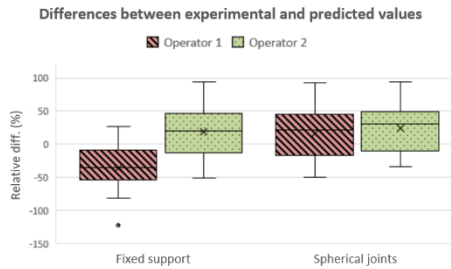
Figure 2: Schematic drawing of the fixed support and spherical joints models. At the bottom, the fixed support has all 6 degrees of freedom blocked, whereas with the spherical joint, only the translations (3 degrees) are blocked. At the top, for the fixed model, a rigid body is applied, allowing 6 degrees (3 translations and 3 rotations), and for the spherical model 3 rotations and only 1 translation are possible.

Figure 3: Differences in the percentage between experimental and predicted values of each operator using the fixed support model (left) and spherical joints model (right).

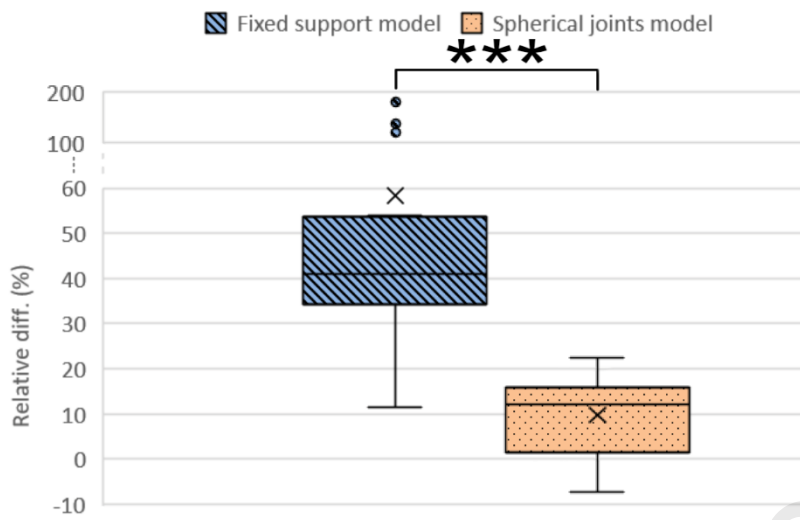
Figure 4: A: Relative differences of the predicted failure load between Operator 1 and Operator 2 for each model. B: Relative amplitude of variation (compared to the mean value) of the predicted failure load among the five rotations of each sample for each model. ** $p < 0.01$, *** $p < 0.001$.







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A Overall reproducibility**B Relative amplitude of variation**