Longitudinal multiscale finite element modeling for characterizing 4D bone modeling and remodeling in a mouse tibia loading model

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INTRODUCTION: Osteoporosis is known as a silent disease, as it may go undiagnosed in approximately 50% of patients affected by fragility fractures [1]. A potential intervention for improving bone strength and preventing fractures is targeted exercise, or mechanical loading [2]. However, gaps remain in understanding how the bone microstructure adapts to mechanical loading throughout each phase of *in vivo* adaptation in each bone compartment. We previously developed a method for quantifying 4D bone modeling and remodeling dynamics in terms of coupled and uncoupled formation and resorption events using longitudinal µCT imaging [3]. While this method captures trabecular and cortical bone adaptations over 5 weeks of tibial loading, it is essential to have corresponding time-lapse finite element models that accurately predict the local mechanical environment. Here, we establish and validate a multiscale finite element modeling method, based on sub-modeling, that can longitudinally model an *in vivo* tibia segment with physiological boundary conditions.

METHODS: Skeletally mature, 16-week-old C57BL6/J female mice (n=9) underwent unilateral, uniaxial tibial loading to a peak compressive force of 9 N for 5 weeks, five consecutive days per week. To establish this technique as a method for better addressing osteoporosis, which affects females at a higher incidence than males, only female mice were used in this study. Beginning 2 weeks before loading, both proximal tibiae underwent weekly *in vivo* scans (Fig. 1A). Week-to-week bone formation and resorption dynamics can be quantified in a cortical bone volume of interest (VOI) that is 1 mm in length, beginning 2 mm distal from the proximal tibia growth plate, with an isotropic voxel size of 5 µm (Fig. 1A) [3]. Our weekly *in vivo* scans are limited to this tibia segment to minimize radiation exposure and scanning time. As the exact boundary conditions for the cortical VOI are unknown under physiological loading at each timepoint, the whole tibia for all mice were scanned *ex vivo* at 5 weeks to estimate the loading conditions (Fig. 1A). To determine the accuracy of the estimated boundary conditions from the *ex vivo* whole tibia structure on the *in vivo* cortical VOI, mice were randomly divided into three groups (n=3/group) for an *in vivo* whole tibia scan of both tibiae at either week -2, week 0, or week 2 to serve as the ground truth for the strains in the cortical VOI under tibia loading (Fig. 1A). Whole tibia scans were reconstructed at an isotropic voxel size of 20 µm as they were performed in addition to the weekly *in vivo* scans of the proximal tibia. Loaded *in vivo* whole tibiae were aligned by image registration to the corresponding *ex vivo* whole tibia scan at 5 weeks, which were transformed to align their principal axis to the z-axis, corresponding to the direction of loading. A Gaussian filter was used to reduce noise, and a global threshold was applied to segment the bone. Whole tibiae images were converted to finite element models using a standard voxel-to-8-node cubic brick element conversion. Bone was modeled as an isotropic, linear elastic material with a Young's modulus of 15 GPa and a Poisson's ratio of 0.3. A 9 N distributed compressive load was applied to the whole tibiae, following the applied *in vivo* loading. Node-based submodeling was applied to the *in vivo* cortical VOI, using the displacements from the corresponding *ex vivo* whole tibia model (Fig. 1B). Sub-model strains were compared against ground truth strains derived from the *in vivo* whole tibia models. The difference in maximum principal strains (sub-model – ground truth) was computed at each element. Statistical analyses were performed using two-way ANOVA with Tukey's multiple comparisons test. IACUC approved all animal procedures.

RESULTS: Submodeling of the cortical VOI with the *ex vivo* whole tibia captures a strain distribution similar to physiological loading from the *in vivo* whole tibia model, with the posterolateral and anteromedial sites under compression and tension, respectively (Fig. 1B). The strain differences throughout the VOI are relatively small, with larger differences at the boundaries (Fig. 1C). On average, submodeling tends to underestimate the strain with a negative mean strain difference and the cumulative histograms for each group tending to skew left (Fig. 1D). The average magnitude of strain difference and root mean square error (RMSE) at week 2 were 254.43 and 412.71 µε, respectively, and the strain differences were significantly increased in both measures when compared to week –2, but not week 0 (Fig. 1E).

DISCUSSION: With multiscale finite element modeling using submodeling, a segment of interest can be modeled under physiological loading conditions, where the whole tibia bends under uniaxial load. In a subject-specific manner, the whole tibia after 5 weeks of loading can be used to model the *in vivo* cortical VOI through week 2, where bone robustly responds to loading [4], and week 0, where the baseline structure is captured before the onset of mechanical loading. While there is an increase in strain difference when comparing the models at the first baseline scan at week –2, the models can be improved by considering that greater strain differences are observed at the loaded boundaries. While there have been studies using orthogonal x-rays to model the patient-specific whole bone structure [5], an advantage of this technique is that it can be incorporated into our previously used experimental timeline for quantifying bone modeling and remodeling events over 5 weeks of loading, without exposing the animals to additional radiation as the whole tibia structure can be imaged *ex vivo*. Future work will include characterizing this submodeling technique when applied to the models with a finer mesh size, as captured in our weekly *in vivo* µCT scans of the proximal tibia, and to accurately quantify the local mechanical environment of trabecular and cortical bone microstructure as it adapts to mechanical loading.

SIGNIFICANCE: This study develops a method for the physiological modeling of a volume of interest that easily incorporates with time-lapse µCT experimental protocols. Using multiscale finite element modeling, bone microstructure remodeling dynamics can be accurately detailed, which will be essential for developing improved models of bone mechanoadaptation and establishing targeted exercise regimens for reducing fracture risk.

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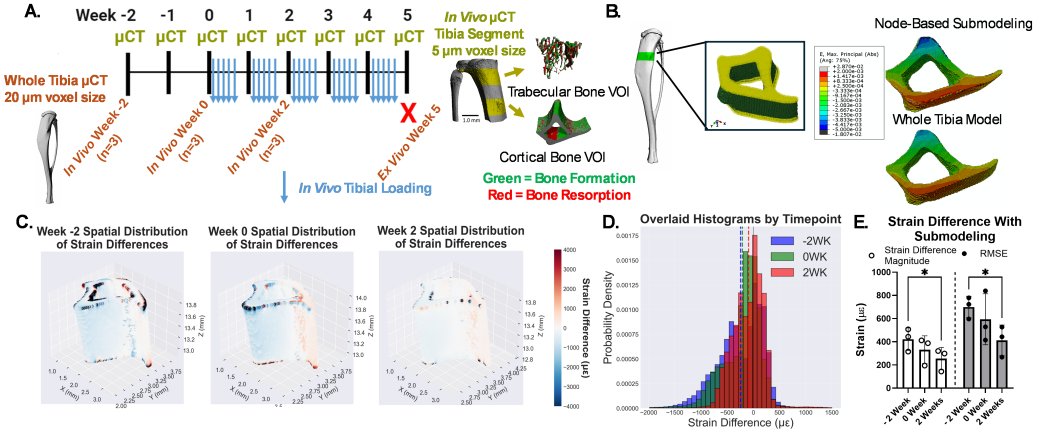

Figure 1. (A) Experiment timeline. **(B)** Node-based submodeling (yellow) was applied to the cortical VOI (green), and representative strain distributions were compared to the whole tibia model. **(C)** Representative spatial distribution of strain differences. **(D)** Cumulative histograms of strain differences for each group. **(E)** Strain difference magnitude and RMSE at each group (n=3/group). *P < 0.05, Vertical bars represent mean ± SD.