Predicting Cortical Bone Resorption in Disuse Condition Caused by Transient Muscle Paralysis

[1]Himanshu Shekhar, [1]Sanjay Singh, [1]Jitendra Prasad*

[1]Indian Institute of Technology Ropar, Rupnagar, Punjab, 140001

Himanshu Shekhar

Department of Mechanical Engineering,

Indian Institute of Technology Ropar,

Rupnagar, Punjab, India, 140001

Email- himanshu.19mez0001@iitrpr.ac.in

Sanjay Singh

Department of Mechanical Engineering,

Indian Institute of Technology Ropar,

Rupnagar, Punjab, India, 140001

email- 2017mez0012@iitrpr.ac.in

Jitendra Prasad*

Department of Mechanical Engineering,

Indian Institute of Technology Ropar,

Rupnagar, Punjab, India, 140001

email- jprasad@iitrpr.ac.in

***Corresponding author**

Abstract

Load removal from the load-bearing bone, such as in the case of extended space travel and prolonged bed rest, harms bone health and leads to severe bone loss. However, the constitutive idea relating the quantity of bone loss to the absence of physiological loading is poorly understood. This work attempts to develop a mathematical model that predicts cortical bone loss at three sections: ‘distal’, ‘mid-section’, and ‘proximal’ along the length of a mouse tibia. Load-induced interstitial fluid flow-based dissipation energy density has been adopted as a stimulus to trigger mechanotransduction. The developed model takes the loss of stimulus due to the disuse of bone as an input and predicts the quantity of bone loss with spatial accuracy.

In the loaded bone, the fluid velocity is found to be maximum at the endocortical surface and negligible at the periosteal surface due to the permeable and impermeable boundary conditions, respectively, at the two surfaces. In case of disuse of bone, there is no fluid flow, which leads to a more significant loss of fluid flow at the endocortical surface. This loss of fluid flow coincides with the botulinum toxin (Botox)-induced endocortical bone loss data in the literature. Motivated by this fact, we hypothesized that the bone loss site would be the site of maximum stimulus loss due to disuse.

To test the hypothesis, we calculated stimulus loss, i.e., loss of dissipation energy density due to bone disuse, based on the poroelastic analysis of the bone using a finite element method. A novel mathematical model has been then developed that successfully relates this loss of stimulus to the in-vivo bone loss data in the literature. According to the developed model, the site-specific mineral rate is found to be proportional to the square root of the loss of dissipation energy density. To the author’s best knowledge, this model is the first of its kind to compute site-specific bone loss. The developed model can be extended to predict bone loss due to other disuse conditions such as long space travel, prolonged bed rest, etc.

Keywords: Cortical bone loss, disuse of bone, fluid flow, poroelasticity, mathematical modeling, dissipation energy density, botulinum toxin (Botox)

List of Symbols

σ_{ij}	Stress tensor
ε_{ij}	Strain tensor
μ	Viscosity of fluid
p	Pore pressure
ν	Poisson's ratio
$\boldsymbol{v}^{fl}$	Fluid velocity
DED	Dissipation energy density
ϕ	Total dissipation energy density
n_p	Porosity
MRR_{exp}^{i}	Experimental mineral resorption rate at ith point of interest
MRR_{model}^{i}	Model mineral resorption rate at the ith point of interest
q	Fluid flow rate
δ_{ij}	Kronecker delta
Δ	Volumetric strain

1. Introduction

The bone is an example of an optimized structure. The internal architecture of a bone is adapted to the external mechanical load exerted during daily physical activity (Warden et al. 2014) (Huddleston, Rockwell, and Kulund 1980) (Haapasalo et al. 2000) (Charalambous 2014). However, in some cases, these physical activities are disturbed; for example, long space travel (Lang et al. 2004) (Vico et al. 2000), prolonged bed rest (Hargens and Vico 2016) (Rittweger et al. 2009), and paralysis of the lower extremity due to the spinal cord injury(Lee, Shapiro, and Bell 1997). The deficit in mechanical load on the load-bearing bone due to the reason above is undesirable and leads to severe bone loss (Brent, Brüel, and Thomsen 2021). A recent study reveals that the microgravity environment in spaceflight is so harmful that even one year after the mission, the lost bone tissue is not entirely recovered, which may lead to osteoporosis (Gabel et al. 2022). Similarly, the studies involving the Russian Mir and the International Space Station reported that crew member of extended space flight suffers from around 1.2-1.5% bone mass per month from their proximal femur. Likewise, six months of the mission caused a loss of cortical density by 2% from the tibial diaphysis. However, this space-flight-based study is found to be very expensive. Therefore, bedridden, hindlimb unloading, and botulinum toxin (Botox)-induced bone loss have been

made to simulate such a study (Rolvien and Amling 2021). For example, 90 days of bed rest causes 1-2% of the mean cortical loss from the tibial site (Rittweger et al. 2005). Botox-induced endo-cortical bone loss was heterogeneous along the tibial length (Ausk et al. 2012). However, the cellular and molecular mechanism behind how the loss in the mechanical environment is related to bone tissue deterioration needs to be better understood. It has been well recognized that the bone cell osteocyte acts as a mechano-sensor (Qin et al. 2020) (Klein-Nulend et al. 2013) and is densely connected through the lacune canaliculi network (LCN) in the bone matrix. Experimental studies provide insight that the load-induced fluid flow inside the LCN helps in the mass transport necessary to enhance the metabolic function of the bone cells, i.e., osteocytes, which are crucial for maintaining bone health. Moreover, the load-induced fluid flow has gained attention as a prime stimulus for bone's mechanotransduction(Gururaja et al. 2005) (Fritton and Weinbaum 2009) (Verbruggen, Vaughan, and McNamara 2014) (Tiwari and Prasad 2017). Another study illustrates that the load-induced fluid flow through LCN exerts shear stresses on the cell wall (Weinbaum, Cowin, and Zeng 1994), which activates the mechano-sensing cell osteocytes. In addition, the tracer technique also confirms the existence of the fluid flow inside the LCN (Knothe Tate and Knothe 2000) experimentally. However, the in-vivo studies have been so far unable to measure exact fluid velocity, due to the inaccessibility of the LCN. Hence, finite element method have been used to quantify the fluid velocity (Meslier and Shefelbine 2023) to quantify the fluid flow velocity (Steck, Niederer, and Knothe Tate 2003) (Pereira et al. 2015)(Smit 2022) (Kumar, Jasiuk, and Dantzig 2011) (Van Tol et al. 2020) (Teresa et al. 2020). Recently, one study confirmed that Botox-induced muscle paralysis significantly affects the bone's morphology (Gatti et al. 2019), leading to decreased fluid velocity around the osteocyte (Gatti et al. 2021), which motivates us to consider the loss of fluid flow for modelling bone loss.

When bone is mechanically strained during the physiological loading, a pressure gradient is generated inside the LCN, forcing fluid to flow in the canalicular channels (Fig 1). Due to the viscous nature of the fluid, it exerts shear stress on the cell membrane, and energy is dissipated. The dissipated energy, which is a function of fluid velocity, is assumed to be a stimulus to the mechano-sensing cell, i.e., osteocyte (Kumar, Jasiuk, and Dantzig 2011). It is evident from the literature that in the case of a loaded bone, the resultant fluid velocity is higher at the endocortical surface while negligible at the periosteal surface (Singh, Singh, and Prasad 2023) due to the permeable and impermeable nature of the respective surfaces (Fan et

al. 2016). Botox-induced calf muscle paralysis pauses the locomotion, resulting in zero strain on bone and, thus, no fluid flow inside the LCN Fig 1(d). Therefore, it is likely to be a more significant loss of fluid velocity at the endocortical surface, which coincides with the in-vivo Botox-induced bone loss pattern at the endocortical surface.

The present work considers the loss of mechanical stimulus, i.e., loss of fluid flow-based dissipation energy density due to the disuse of bone. It develops a mathematical model that can correctly predict cortical bone loss. The developed model was validated using the available Botox-induced bone loss data in the literature (Ausk et al. 2012). Statistical tests were performed, to quantify how accurately the model predicted the in-vivo results. On the availability of relevant experimental data, the developed model can be extended to predict remaining disuse conditions such as long space travels, prolonged bed rest, etc. The rest of the paper has been organized as follow. Section 2 describes the adopted methodology. Section 3 presents the results, which have been discussed in section 4. Conclusions have been drawn in section 5.

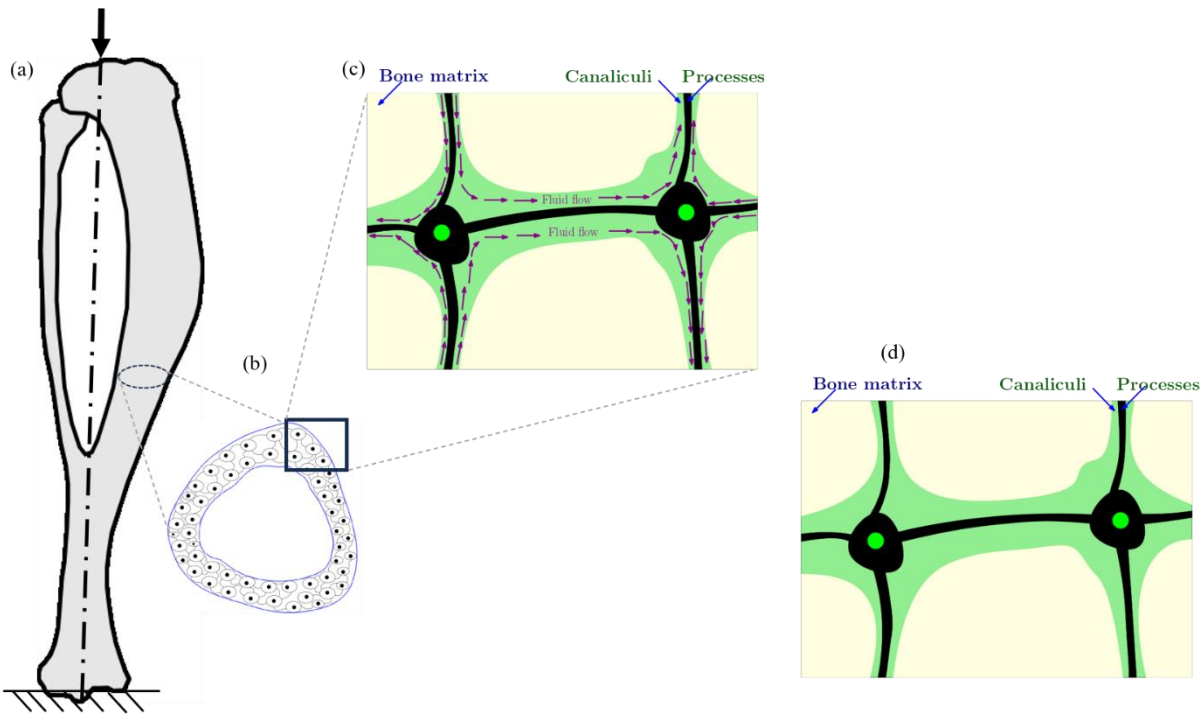

Figure 1: Comparison of fluid flow inside the LCN, physiologically loaded vs disused tibia: (a) axially loaded tibia, (b) schematic of the osteocytes' network at a cross-section of interest, (c) fluid flow inside an LCN (arrows indicate fluid flow) of a physiologically loaded tibia, (d) no fluid flow inside the LCN in case of disuse of the bone.

2. Methods

2.1 Theory of Poroelasticity

Mouse tibia was considered a linear isotropic porous material consisting of solid matrix and fluid-saturated pores (Cowin 1999). The constitutive equations for such material are given as follows (Biot 1941).

$$\sigma_{ij} = 2G\varepsilon_{ij} + \frac{2G\nu}{1-2\nu}\varepsilon_{kk}\,\delta_{ij} - \alpha p\delta_{ij} \tag{1}$$

$$\zeta = \alpha\Delta + \frac{p}{Q} \tag{2}$$

where σ_{ij} and ϵ_{ij} are stress and strain tensors, respectively (i or j represents the Cartesian coordinates, i.e., i or j=1,2,3 respectively corresponds to the x, y, z coordinates). G and ν are the modulus of rigidity, and Poisson's ratio, respectively. p is the interstitial pore pressure, ζ is the increment of the water volume per unit volume of the solid matrix, δ_{ij} is the Kronecker delta (i.e., $\delta_{ij} = 1$ if i=j; $\delta_{ij} = 0$ otherwise), Δ is the dilation that represents the volumetric strain developed in the pore, α and $\frac{1}{Q}$ are the constants.

Equation (3) describes the fluid flow rate through a porous media following the Darcy's law:

$$q_i = -\frac{k}{\mu}\frac{\partial p}{\partial x_i} \tag{3}$$

where, q_i is the fluid mass flow rate, while k and μ represent the isotropic intrinsic permeability and dynamic viscosity of the fluid, respectively.

The mass balance equation is as follows:

$$\frac{\partial\zeta}{\partial t} = -\frac{\partial q_1}{\partial x_1} - \frac{\partial q_2}{\partial x_2} - \frac{\partial q_3}{\partial x_3} \tag{4}$$

The above equations finally lead to the following differential equation that needs to be solved:

$$k\nabla^2 p = \alpha\frac{\partial\Delta}{\partial t} + \frac{1}{Q}\frac{\partial p}{\partial t} \tag{5}$$

Additionally, the linear momentum balance can be written as

$$G\nabla^2 u_i + \frac{G}{1-2\nu}\frac{\partial\Delta}{\partial x_i} = \alpha\frac{\partial p}{\partial x_i} \tag{6}$$

Where u_i is the displacement of the solid matrix. The above Eqs. (5) and (6) together have 4 unknowns to be solved for – 3 displacements components (viz. u_1, u_2 and u_3) and the fluid pore pressure p. The problem was solved using a finite element commercial ABAQUS software(Abaqus 2014), as detailed in section 2.6.

2.2 Cage Activity of a Mouse

The mice were monitored in a cage for 24 hrs, and their activities were captured (Hasriadi et al. 2021)—typical activities involved locomotion, rearing, immobilization, and climbing.

- **Locomotion**: The most prominent activity of a mouse in a cage was found to be locomotion. During the locomotion, the tibia is subjected to ground reaction forces, which can be resolved into axial compression and transverse shear forces (Prasad et al. 2010). It was found that the magnitude of shear force is shallow compared to the axial component and hence can be ignored (Mertiya et al. 2022) (Gatti et al. 2021). This leads to only axial force on the mouse tibia. It is seen that axial compression on the tibia is prominent during the locomotion of a mouse.
- **Rearing**: Rearing was the second most cage activity of a mouse. During rearing, a mouse first stands on its hindlimb, which leads to pure axial loading on the murine tibia. After that, the mouse will undergo locomotion.
- **Immobilization**: Immobilization of a mouse exerts static loading on the mouse tibia. Moreover, it has already been established that static loading does not lead to new bone formation (Derbyshire 1985).
- **Climbing**: Climbing leads to no ground reaction forces on the mouse tibia.

The above observation of a caged mouse suggests that the axial loading is typically significant on the tibia of a caged mouse.

2.3 Porosity and permeability of cortical bone

The cortical bone has porosities of different length scales (Cowin 1999), such as vascular porosity and lacune-canalicular porosity, which influence the bone permeability. It is widely accepted in the literature that the loading-induced fluid flow inside the LCN plays an important role in the bone mechanotransduction. Accordingly, only LCN porosity has been considered, viz. $3.79 \times 10^{-21}\ m^2$(Zhou, Novotny, and Wang 2008), as also presented in Table 1.

2.4 Loading and boundary conditions

The physiological loading in the case of a caged mouse is dominated by axial loading (Fig 2(a)). To mimic the physiological condition, a Haversine loading waveform having frequency

1 Hz (Fig 2(c)) was considered in accordance with the literature (Gatti et al. 2021). The axial load associated with physiological loading condition was obtained from the literature (Prasad et al. 2010). In accordance with the literature, the periosteal and endocortical bone surfaces were assumed to be completely impermeable and permeable, respectively, (Singh, Singh, and Prasad 2023) (Gatti et al. 2021) (Fan et al. 2016) implemented through zero-flow and zero-pressure boundary conditions respectively (Fig. 2(b)).

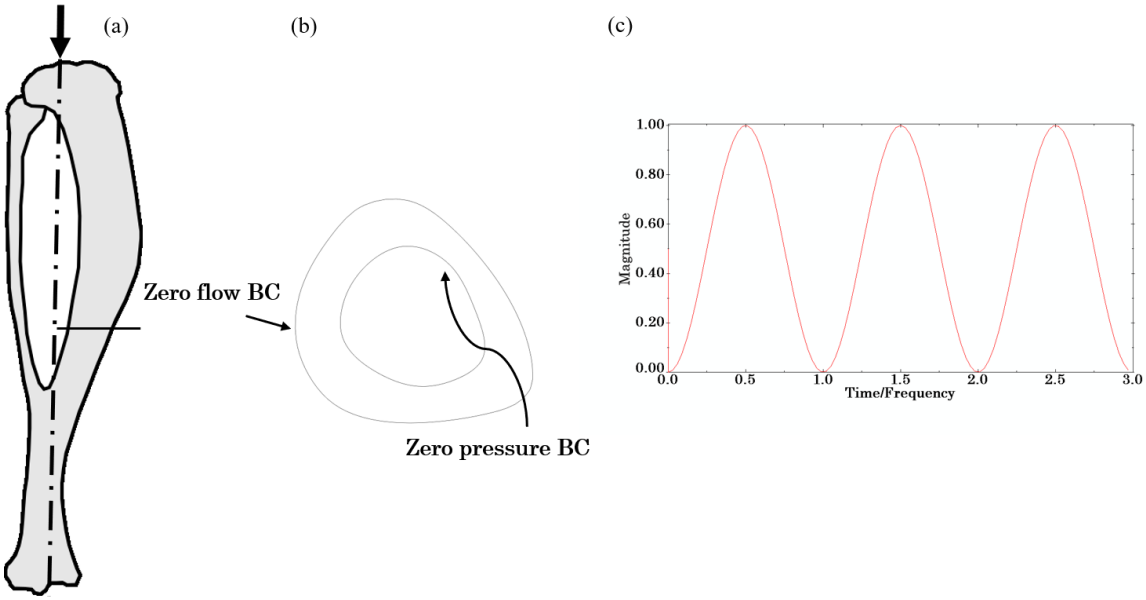

Figure 2: Loading and boundary conditions (a) cage activity is idealized as an axial loading (b) periosteal and endocortical surface of the bone was prescribed zero-fluid-flow and zero-pressure ($p = 0$) conditions, respectively. (c) To mimic the physiological loading, a Haversine loading waveform of 1 Hz frequency was assumed.

2.5 Bone geometry

The whole 3D model of a mouse tibia is computationally expensive, and hence, the tibia was idealized as a prismatic bar having a cross-section similar to that of a C57BL6J, 16-week, young-adult mouse given in the literature. Three prismatic bars (each with length of 10 mm) with cross-sections identical to the distal, mid-shaft, and proximal cross-sections studied by Ausk et al. (Ausk et al. 2012) were created. The prismatic bar of one of the sections, i.e., the distal section, is shown in Fig 3.

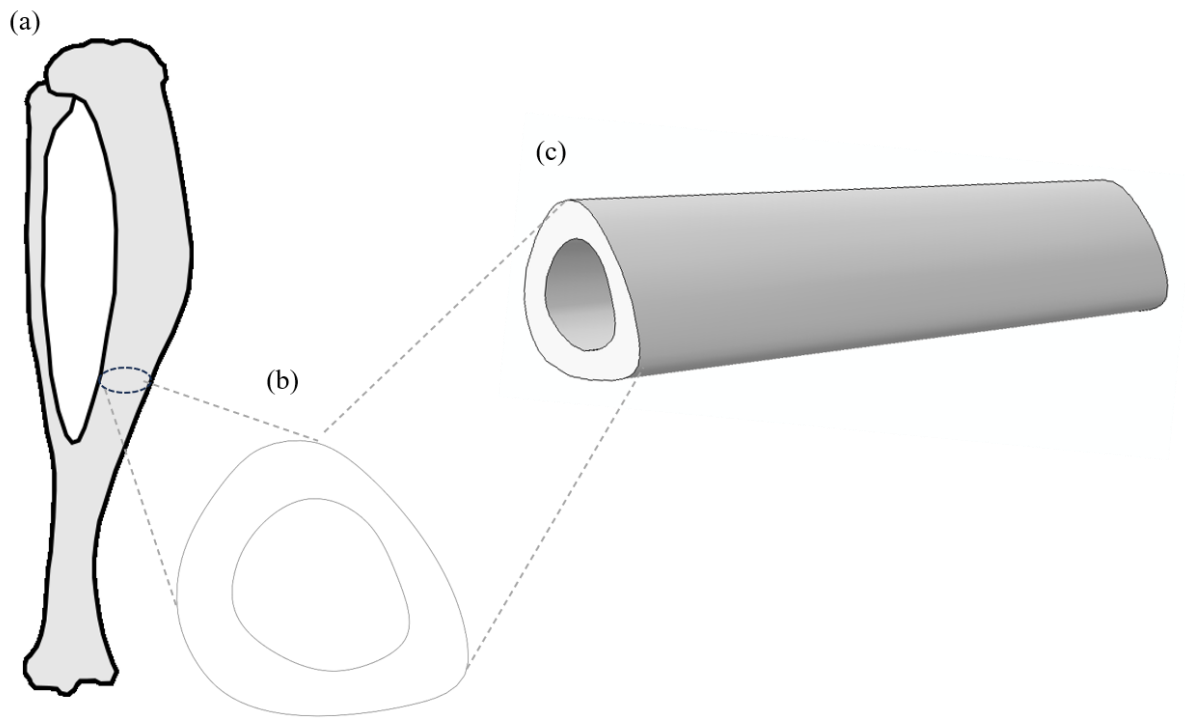

Figure 3: The bone (a) is idealized as a prismatic bar (c) of length 10 mm and having a cross-section similar to that of the "distal section" (b) studied by Ausk et al. (Ausk et al. 2012)

2.6 Finite Element Analysis

The finite element problem was solved using the commercial software ABAQUS (Dassault System). The existing literature assumes that the periosteal and endocortical surfaces of the bone were impermeable and permeable, respectively (Singh, Singh, and Prasad 2023) (Fan et al. 2016). To incorporate such assumptions, a zero-pressure boundary condition was applied at the endocortical surface, whereas the fluid velocity normal to the periosteal surface was prescribed as zero Fig 2(b).

To simulate fully or partially saturated fluid flow through porous media, the soil element (C3D8RP, continuous three-dimensional eight nodded reduced integration pore pressure hexahedral element) type was used, which is available in ABAQUS (Abaqus 2014). These elements had 4 degrees of freedom (3 for the displacement and 1 for pore pressure) per node. The bone material was assumed to be a linear isotropic poroelastic material whose parameters were directly taken from Kumar et al. and have been shown in Table 1. To capture the fluid velocity inside the LCN, a coupled pore fluid diffusion stress analysis was performed in the ABAQUS software. The fluid velocity was computed at the integration point during the applied loading. The physiological-loading-induced strain and corresponding fluid flow velocity at the three sections viz at distal, mid-section, and proximal sections along the tibial

length have been shown in Fig 4. The obtained strain patterns were verified according to the existing literature (Patel, Brodt, and Silva 2014).

Table 1: Poroelastic material properties used in the simulations adapted from (Kumar, Jasiuk, and Dantzig 2011) except the permeability value (Zhou, Novotny, and Wang 2008)

Properties	Magnitude	Unit
Young's modulus of bone	12	GPa
Fluid bulk modulus	2.3	GPa
Solid bulk modulus	17	GPa
Porosity	0.05	
Poisson's Ration	0.3	
Intrinsic permeability (k)	3.79×10^{-21}	m^2

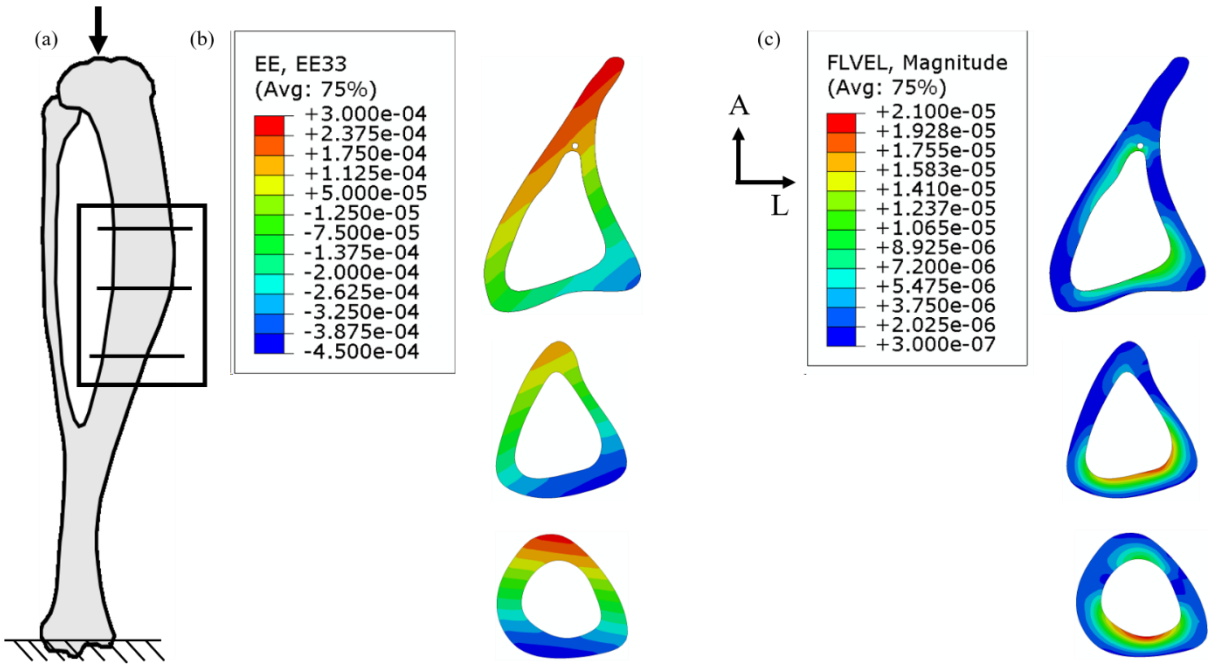

Figure 4: Axial loading environment of a mouse tibia (a) longitudinal strain (EE33) pattern along the tibial length, i.e., at distal, mid-section, and proximal section (b) corresponding fluid velocity (mm/s)

2.7 Botox-induced disuse Activity

Botox-induced calf muscle paralysis incapacitates the muscles to apply force on the tibia, which causes a loss of strain environment. We assume that the application of Botox leads to zero strain on the tibia and, hence, zero fluid velocity (Fig 5).

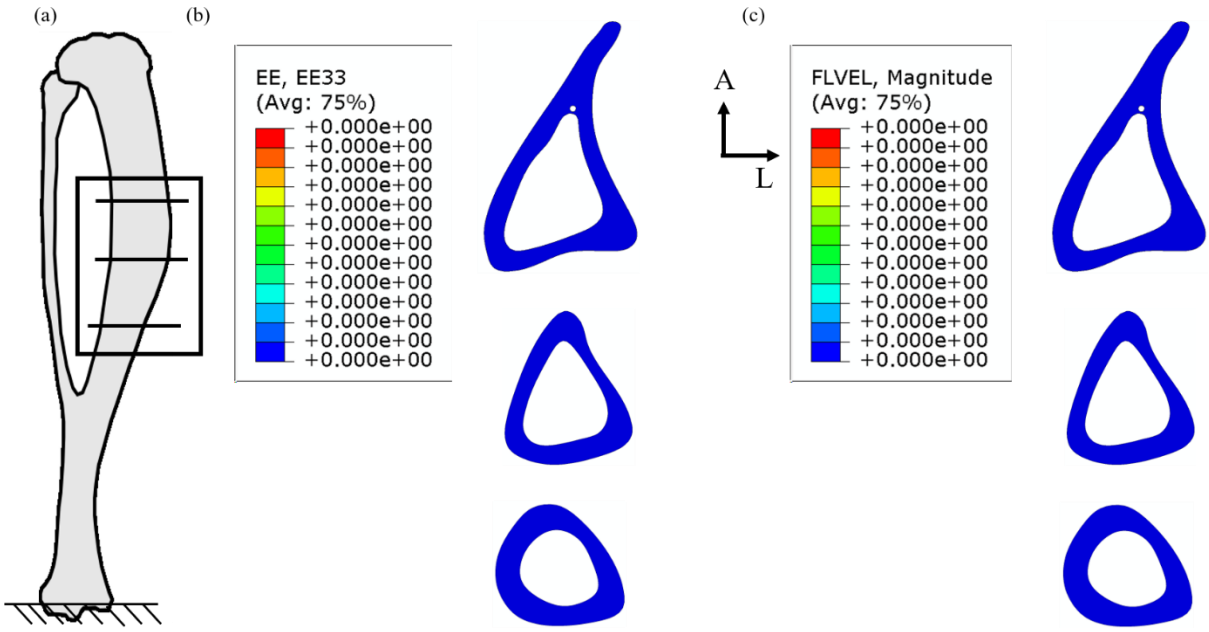

Figure 5: Botox-induced mechanical environment in a mouse tibia (a) a typical mouse tibia (b) strain pattern (zero strain everywhere) (c) fluid flow pattern (zero fluid flow throughout the cross-section)

The Botox-applied calf muscles cause a loss of stimulus that may play a crucial role in cortical bone loss. The stimulus loss can be written as the difference between dissipation energy density due to the cage activity of a mouse and that due to muscle disuse.

2.8 Computation of fluid flow-based dissipation energy density

Load-induced viscous fluid flow inside LCN exerts shear stress on the osteocyte cell membrane, and energy is dissipated. The dissipated energy influences the mechano-sensing cell osteocyte, and further biochemical signaling pathways get activated. According to Kumar et al.,(Kumar, Jasiuk, and Dantzig 2011) the dissipation energy density (DED), which is a function of fluid velocity, can be calculated as:

$$DED = -n_p \boldsymbol{v}^{fl}.\nabla p = \frac{1}{2}\left(n_p \boldsymbol{v}^{fl}\right).\left(\frac{k}{\mu}\right)^{-1}.\left(n_p \boldsymbol{v}^{fl}\right) \tag{7}$$

Where $n_p$is the LCN porosity, $\boldsymbol{v}^{fl}$ is the fluid velocity. To capture the effect of the non-local behavior of osteocytes, a spherical zone of influence (ZOI) was considered (as shown in Fig 6) similar to the earlier study by Singh et al (Singh, Singh, and Prasad 2023). Considering the ZOI, the dissipation energy density was calculated using Eq. (8) at every ith node of interest.

The total dissipation energy density $\phi = DED * N * d$. Where N is the no. of cycles and d is no. of days.

$$DED_i = \frac{\int_V \left(\int_0^T \frac{1}{2} (n_p \boldsymbol{v}^{fl}) . \left(\frac{k}{\mu}\right)^{-1} . (n_p \boldsymbol{v}^{fl}) dt \right) f(|x|) dV}{\int_V f(|x|) dV} \tag{8}$$

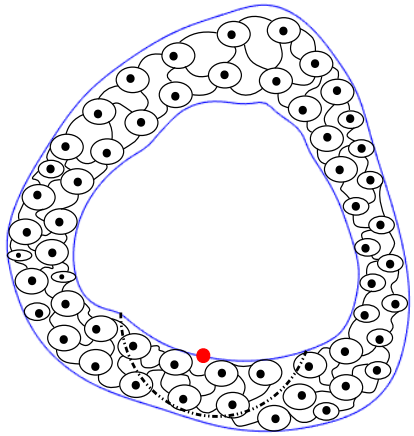

Figure 6: The non-local behavior of the osteocyte is captured through a spherical zone of influence. The red node shows the point of interest.

where $f(|x|) = e^{(-\frac{5|x|}{R})}$ is a weighting function that weights the contribution of osteocytes that fall under the spherical zone of influence. The $|x|$ represents the distance between node of interest and position of osteocytes while R represents the radius of spherical zone.

2.9 Mineral Resorption Rate (MRR)

Exogenous loading-induced fluid flow inside the LCN has been widely accepted in the literature to correlate with bone adaptation. Recently, Sanjay et al. (Singh, Singh, and Prasad 2023) have presented a robust formulation that shows that MAR (mineral apposition rate), i.e., rate of change of new bone thickness, is directly proportional to the square root of total dissipation energy density minus its threshold or reference value. That is,

$$MAR = A\left(\sqrt{\phi_c} - \sqrt{\phi_{phy}}\right), \tag{9}$$

where A is the remodeling rate, ϕ_c is the current dissipation energy density, while ϕ_{phy} represents the dissipation energy density to maintain bone homeostasis (under physiological

loading conditions). In the disuse condition, the fluid velocity is zero, which leads $\sqrt{\phi_c}$ to a zero value. Hence, the expression of MAR is simplified to

$$MAR = -A\left(\sqrt{\phi_{phy}}\right) \tag{10}$$

Here, the negative sign shows bone loss, and hence, mineral resorption rate (MRR) can be written as

$$MRR_{model} = A\left(\sqrt{\phi_{phy}}\right) \tag{11}$$

Thus, MRR_{model} is directly proportional to the square root of the total dissipation energy density. The parameter A is a constant to be determined. The MRR ($\mu m^3/\mu m^2/day$) is defined as the total loss of bone volume per unit of bone surface area per unit time. For the sake of computational convenience, the endocortical bone surface was divided into 360 segments, and then MRR was calculated at every i^{th} point (i.e., a common point of two consecutive segments) as

$$MRR^i_{model} = A\left(\sqrt{\phi_i}\right). \tag{12}$$

As an example, these points are shown in Fig. 7. The constant A was calculated by comparing the experimental bone loss data available in the literature. Experimental endocortical bone loss MRR^i_{exp} for each of the 360 points was computed from Fig 9 using an in-house MATLAB code. The optimization problem was formulated as a minimization of squared error:

$$Min\ f(A) = \sum_{i=1}^{i=360} \left(MRR^i_{exp} - MRR^i_{model}\right)2 \tag{13}$$

The Levenberg Marquardt algorithm (Levenberg 1944) available in MATLAB was used to fit the model in Eq. (12) to the experimental data, i.e. MRR^i_{exp} and find the optimal value of the constant *A*. The parameter A was then used to predict bone loss at the two remaining sections, viz., the mid and proximal sections. A statistical analysis (as detailed in section 2.10) was performed to compare the model prediction to the experimental values.

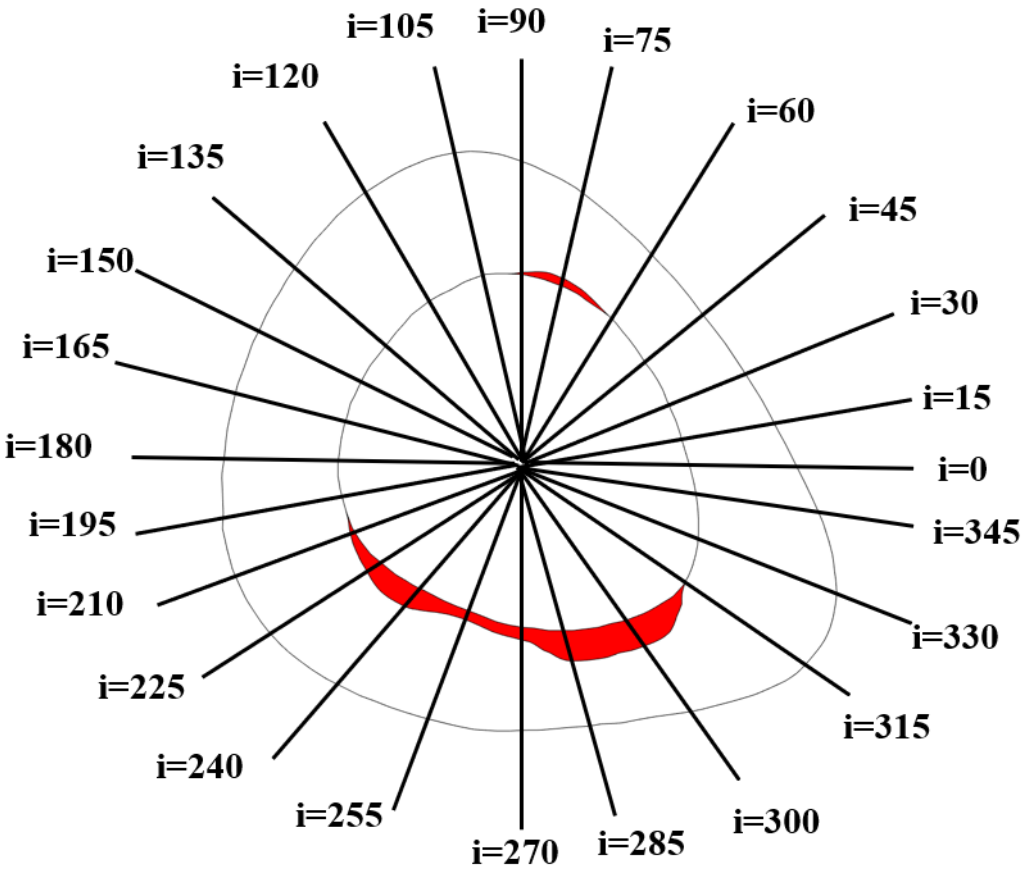

Figure 7: In-vivo cortical bone loss at the distal section of a tibia; endocortical bone surface was divided into 360 points (for clear visibility, the points have been drawn at every 15 degrees).

2.10 Statistical Analysis

A one-sample, two-tailed Student's t-test was used to compare the average bone resorption rate per unit bone surface (BRR/BS) values. A circular goodness-of-fit test, viz, Watson's U^2 test (WATSON 1961), was used to compare the endocortical distribution of bone loss predicted by the model to the in-vivo results.

3. Results

3.1 Distal Section

The developed model was first used to predict cortical bone loss at the distal section. The BRR values have been compared in Fig. 8(a) through a histogram. The obtained site-specific bone loss distribution by the model was shown in Fig. 8(c), whereas the experimental bone loss was shown in Fig. 8(b). The statistical analysis showed that the model BRR/BS, 1.49 $\mu m^3/\mu m^2/day$, was not significantly different from the in-vivo BRR/BS, 1.15±0.67 $\mu m^3/\mu m^2/day$ (p = 0.62, Student's t-test). The predicted bone loss distribution was also

found to be not significantly different from the in-vivo distribution (p = 0.31, Watson's U^2 test).

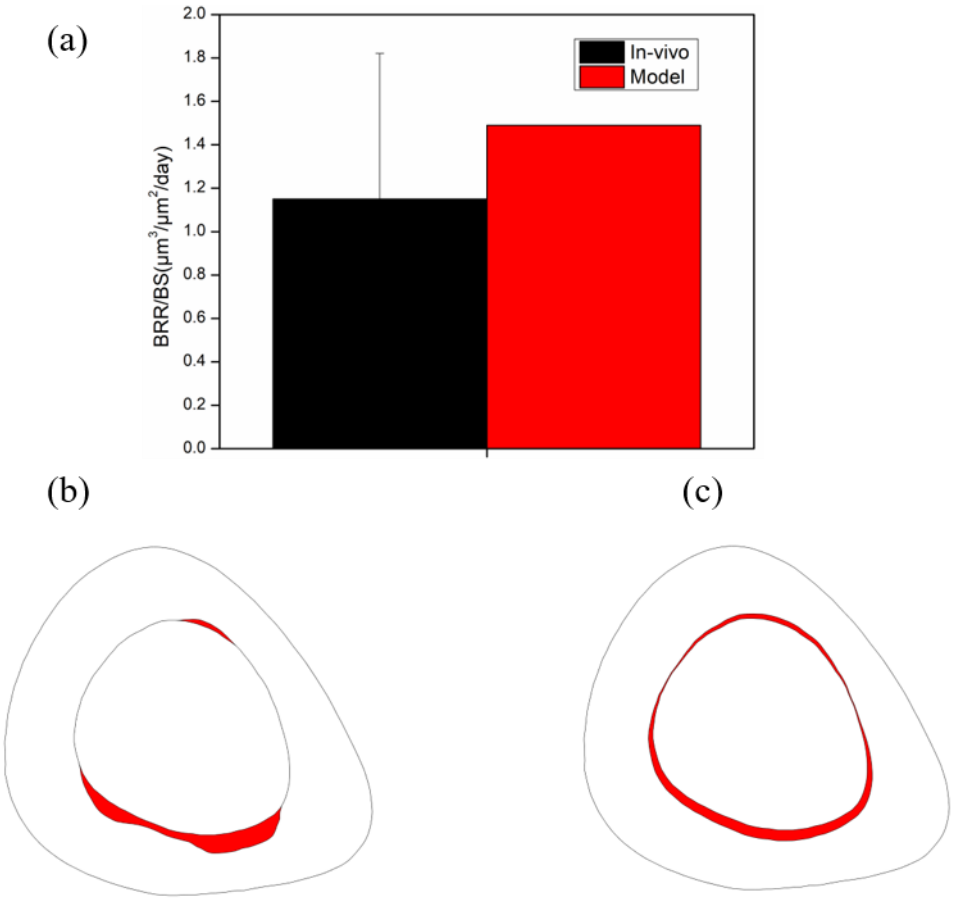

Figure 8: Comparison of model and experimental cortical bone loss at the distal section of a mouse tibia: (a) model BRR/BS is not significantly different from the in-vivo BRR/BS, (b) site-specific in-vivo bone loss (shown in red), (c) predicted bone loss by the model.

3.2 Mid-section

Mid-section cortical bone loss was also predicted using the same resorption rate *A*. The predicted and the in-vivo BRR/BS have been compared in Fig. 9(a). The predicted BRR/BS, (1.41 $\mu m^3/\mu m^2/day$) was found to be not significantly different from the experimental value of 1.43 ± 0.5675 $\mu m^3/\mu m^2/day$ (p = 0.97, Student's t-test). Endocortical bone loss distribution predicted by the model and the in-vivo experiment have also been shown in Fig

9(c) and 9(b), respectively. It was found that the distribution predicted by the model is not significantly different from the in-vivo distribution (p = 0.99 for Watson's U^2 test).

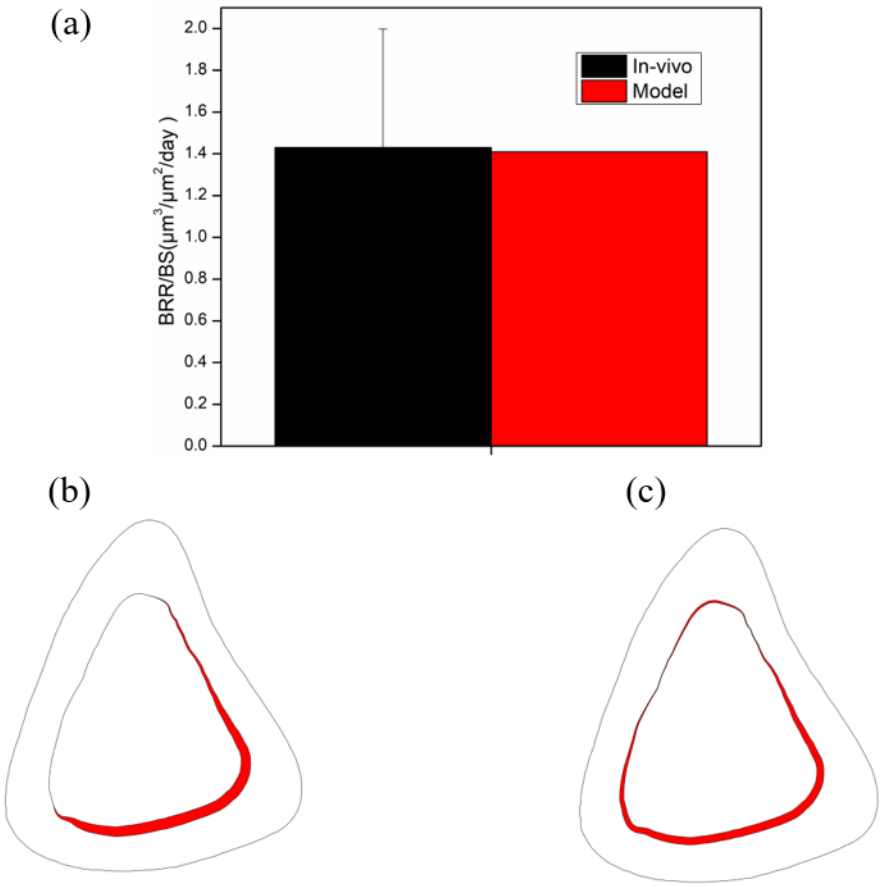

Figure 9: Comparison of the model and the experimental cortical bone loss distribution at the mid-section of a mouse tibia: (a) histogram comparing model BRR/BS to the in-vivo value (error bar represents standard error), (b) in-vivo, site-specific bone loss (shown in red), (c) the bone loss predicted by the model.

3.3 Proximal section

The bone loss at the proximal section of the same tibial bone was predicted using the same resorption coefficient A. The predicted BRR/BS, 1.02 $\mu m^3/\mu m^2/day$, was found to be not significantly different from the experimental BRR/BS 1.23 ± 0.85 (p = 0.80, Student's t-test) Fig 10(a). The site-specific endocortical bone loss distribution has also been compared in Figs. 10(b) and (c). The site-specific cortical bone loss distribution predicted by the model

was significantly different from the experimental bone loss distribution (p = 0.0004 for Watson's U^2 test).

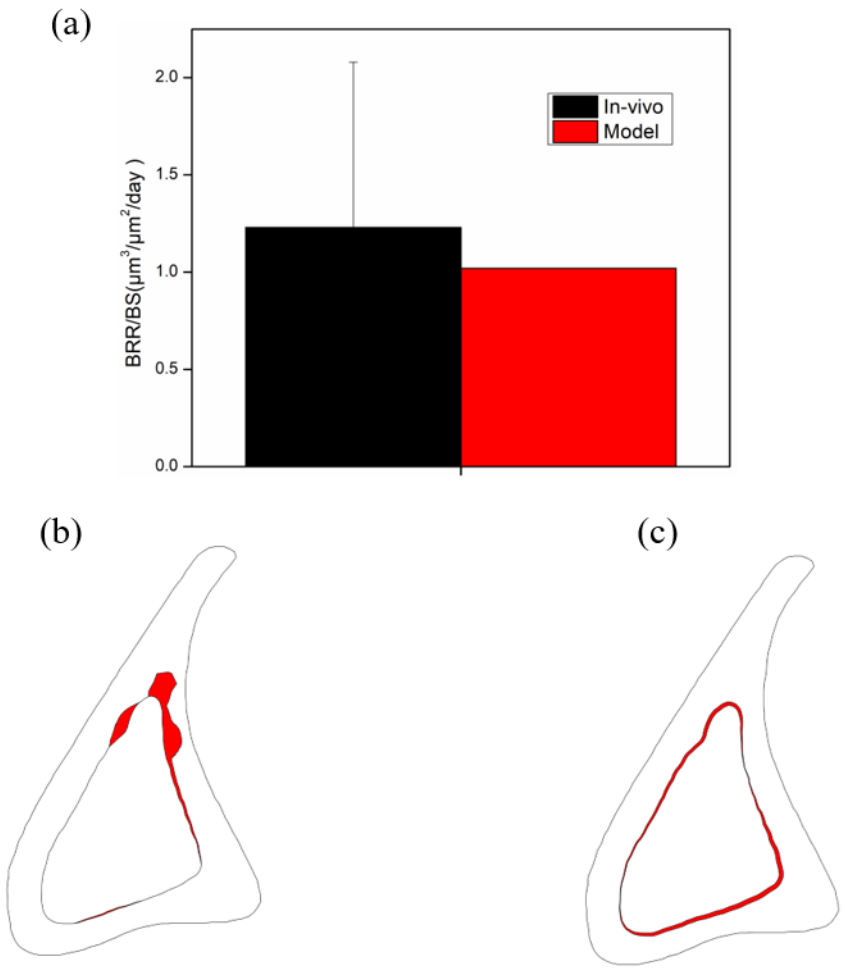

Figure 10: Comparison of model and experimental cortical bone loss at the proximal section of a mouse tibia: (a) model BRR/BS has been compared to the in-vivo BRR/BS using a histogram, (b) in-vivo, site-specific bone loss (shown in red), (c) model, site-specific bone loss distribution (shown in red).

4. Discussions

The present work studies cortical bone tissue loss due to the disuse of bone. It develops a fluid flow-based mathematical model that utilizes the dissipated energy density as a stimulus. To simulate fluid flow inside the LCN, a finite element method was used, considering bone as a poroelastic material. The model was fitted to the existing bone loss data in the literature.

The developed disuse model shows the linear relation between MRR and the $\sqrt{\phi}$ (i.e., the square root of the dissipation energy density), which is in accordance with the earlier work by Sugiyama et al. (Sugiyama et al. 2012). Note that the dissipation energy density is proportional to the square of strain and, hence, MRR is proportional to $\sqrt{\phi}$ is akin to bone formation rate (BFR) being proportional to strain (Prasad 2023). A work by Singh et al. (Singh, Singh, and Prasad 2023) has also shown a similar kind of trend, i.e., the rate of new bone formation is directly proportional to the $\sqrt{\phi}$. There will be a new bone formation when the stimulus exceeds the threshold value.

The present study established that the site of maximum bone resorption coincides with that of the maximum stimulus loss, i.e., the maximum loss of dissipation energy density. The developed model predicted cortical bone loss sites at the distal and mid-section of the mouse tibia. However, it could not predict the bone loss distribution at the proximal section. This may be due to a different anatomical arrangement (viz. muscle attachment) of the proximal section as compared to that at the distal and mid-diaphyseal sites (Charles, Cappellari, Spence, Hutchinson, et al. 2016). It is evident from the anatomical structure of the tibia that the sections under consideration at the distal and mid-section are not attached to any muscle, and, therefore, beam bending alone is sufficient to determine the mechanical environment. The proximal section, on the other hand, is seen to be attached to a calf muscle (Charles, Cappellari, Spence, Wells, et al. 2016), which may alter the mechanical environment. The present work has not incorporated any muscle attachment on the long bone. A more realistic bone model with muscle attachment has been taken as a future work.

A study by Gross and Rubin on the turkey's avian wing bone (viz, radius bone) (Gross and Rubin 1995) reported the bone loss to be uniform along the length as well as along the endocortical perimeter. On the other hand, the work by Ausk et al. (Ausk et al. 2012) presented the bone loss to vary along the length as well as along the endocortical perimeter of the mouse tibia. The reason behind this difference may be the difference in structure (curvature, etc.) and loading condition of the two bones (especially torsion loading (Novitskaya et al. 2017), which may be prominent in avian bones, as discussed by Novitskaya et al.). Further work is needed to model the turkey experimental results. This has also been taken as a future work.

The developed model predicted the bone loss distribution due to Botox-induced muscle paralysis only. Incorporating the other disuse conditions, such as the tail-suspension model,

prolonged bed rest, long space travel, and spinal cord injury, will make the present model robust; however, such experimental data are unavailable in the literature.

Apart from the above, the present work has been developed with several simplifications, as discussed below.

Bone geometry: The present study uses a different prismatic bar for each of the three considered sites (i.e., proximal, mid, and distal). This saves significant computation time; however, analysis of the whole tibia may improve accuracy.

Material properties: The bone is considered a linear isotropic poroelastic material. However, in reality, the bone is highly anisotropic. The cortical bone also consists of different porosities at different length scales (Cowin 1999). In the present study, only LCN porosities have been considered. Incorporating all the porosities may enhance the accuracy of the results.

Biological cues: The present model has considered neither bone loss due to natural aging nor the change in the bone's internal architecture due to aging (Sfeir et al. 2022) (Birkhold et al. 2014). Incorporating the aging effect has also been taken as a future work.

5. Conclusions

This work presented a mathematical model for cortical bone loss in disuse conditions. To the author's best knowledge, there has not been such a model in the literature; hence, the developed model is the first of its kind. It takes the loss of stimulus due to the disuse of bone as an input and predicts the cortical bone loss at the site of interest. The theory of poroelasticity was used to compute the fluid flow pattern in the LCN, and the corresponding finite element problem was solved using the ABAQUS software. The developed mathematical model predicted the in-vivo bone loss for two murine tibial sites (distal and mid-sections), for which data are available in the literature. However, the model could not predict the bone loss distribution at the proximal section. A detailed analysis for this section, incorporating muscle attachments on the tibia, may be needed and has been taken as a future work. The current model can be improved further by incorporating/predicting other disuse conditions such as extended bed rest, long space travel, and spinal cord injury. However, relevant experimental data will be required for these, which are unavailable in the literature.

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