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Optimising bone shape with renewable mechanical memory

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Contents

Abstract

Bone has been observed to adapt to the mechanical loading exerted on it. Previous models describing how bone changes due to stress assume a single mechanical set point that doesn't account for cellular processes involved in mechanical adaptation. The 'osteostat' model is a new theory of bone mechanobiology that has a changing set point which optimises for the amount of strain applied over time. A time-dependent model of bone adaptation has been done in previous work. This model had bone adapt to a stress applied over years. This project extends that model into the spatial setting. The model was had very little change in shape at low values of bone volume. Local averages were introduced to allow for the outward and inward shape change of the bone. The model with the local averaging ran into similar issues due to low bone volume fractions reaching a steady state too quickly to the strain, making it unable to create more bone beside it. In future, accounting for changes in the transduced mechanical signal may create a more accurate depiction of bone growth.

1 Introduction

Bone is a dynamic tissue. It is strong and light so it requires a constant renewal process to maintain its mechanical handling abilities over its lifetime (Hartmann et al. 2011). Wolff's law states that bone adapts to the level of mechanical loading placed on it (Turner 1998). This can be observed in Huiskes (1997) where an implanted hip is at risk of coming loose due to loss of bone volume around the site of the implant (Figure 1). The change in stress caused by the implant's insertion resulted in bone forming and resorping to keep the bone mechanically optimal. As a side effect, bone close to the implant wasn't under as much stress. This lead it to resorping the bone that wasn't necessary for the stress optimisation of the bone.

The mechanostat theory describes a potential mechanism for bone adaption (Frost 1987). It works similarly to a thermostat set at a certain temperature. If the room's temperature deviates from the set point, an

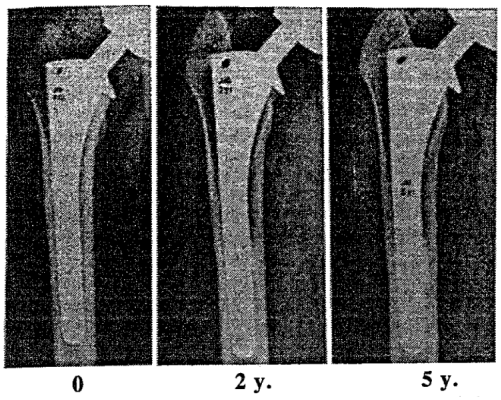

Figure 1: A hip implant changing the surrounding bone due to mechanical loading differences (Huiskes 1997)

appropriate heating/cooling response will bring the room back to the set temperature. For the mechanical loading of bone, there would be a mechanical set point. When there is additional stress than the set point, bone-forming cells – osteoblasts – will form more bone until the stress comes back to the set point. Bone-resorping cells - osteoclasts would resorb bone when the mechanical loading is lower than the set point to remove bone that is mechanically redundant. Biological factors would determine this set point.

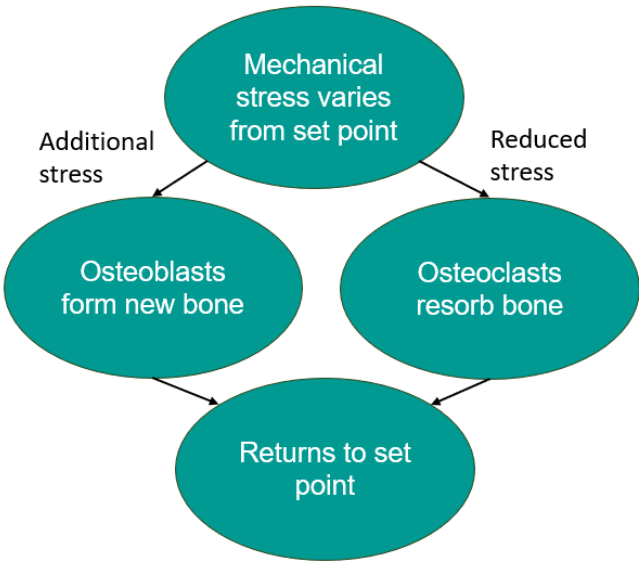

Figure 2: Flow chart depicting the mechanostat model's negative feedback loop

Incorporating biological processes into a theory of bone mechanical adaptation is important to quantify and conceptualise what happens when the stress applied to a bone structure is changed. The osteostat model discussed hereafter will account for biological processes such as the number of osteocytes, the rates of resorption and formation, and the chemical signal relating mechanical stress information to other cells. This project aims to use this model to describe bone adaptation to reduced and increased stress in both a time-dependent and space-dependent framework.

1.1 Acknowledgement of Authorship

This work was produced under the supervision of Dr Pascal Buenzli and Dr Vivien Challis. The Osteostat Model is the work of Dr Buenzli and Dr Chloe Lerebours (Lerebours and Buenzli 2016; Pauchard and Buenzli 2024). The time dependent simulations were first done by Dr Buenzli and Dr Yves Pauchard (Pauchard and Buenzli 2024). Dr Buenzli also wrote the initial MATLAB code for this investigation.

2 Osteostat theory

The osteostat theory works similarly to the mechanostat theory, however, it accounts for the behaviour of osteocytes. Osteocytes are the cells seemingly responsible for the detection of the deviation from the set point as well as control of the response (Lerebours and Buenzli 2016).

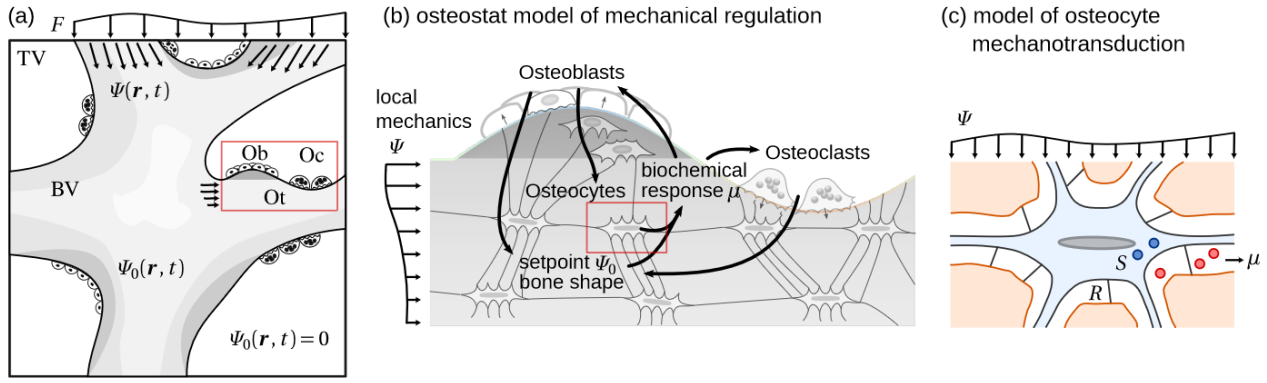

Figure 3: Osteostat theory
(Lerebours and Buenzli 2016; Pauchard and Buenzli 2024)

In Figure 3a a small segment of bone is shown. The Bone Volume (BV) is represented in grey and the Tissue Volume (TV) which represents all tissue i.e. BV, blood vessels and bone marrow. On the surface of the BV, there are bone forming and bone resorping cells – osteoblasts and osteoclasts respectively.

Figure 3b shows how local stress mechanics affects bone response and the set point. When stress is applied (ψ), the osteocytes sense this stress and then determine the biochemical response. If the local stress exceeds the current set point, this will trigger the osteoblasts to form bone and if the stress is less than the set point, this will trigger the osteoclasts to resorb bone. This feedback is then incorporated into the set point through osteoclasts removing the osteocytes with the previous set point and new bone (and the associated osteocytes) formed by the osteoblasts being associated with a new set point. This makes it a moving target problem. The set point is always moving towards the mechanical strain to reach a steady state, while at the same time bone is created/removed so that mechanical strain reaches the set point.

Figure 3c shows the mechanotransduction of the chemical signals, μ. It is a chemical signal produced by osteocytes to communicate the mechanical loading placed on the bone. Osteocytes diffuse this signal out of the

bone through the osteocyte network, where it instructs osteoblasts and osteoclasts to execute their respective functions. (Lerebours and Buenzli 2016)

3 Mathematical Model

The mathematical model used was based on Pauchard and Buenzli (2024). It describes the osteostat model using various ordinary differential equations (ODEs) and dependent equations. These ODEs are solved for using Heun's Method. The dependant equations include the equations for μ, $k_f Ob$ and $k_r Oc$. Equation 1 describes the transduced mechanical signal, μ.

$$\mu \approx \psi - \psi_0 \tag{1}$$

Such that: if $\psi > \psi_0$ then $\mu > 0$ and the bone is overloaded with stress. If $\psi < \psi_0$ then $\mu < 0$ and there is an underload.

Ob is the population of osteoblasts (bone-forming cells) and so $k_f Ob$ describes the rate at which osteoblasts are forming bone. $k_f Ob$ has a baseline value that depends on the transduced mechanical signal, μ, the specific surface which is described as the bone surface divided by the tissue volume (BS/TV). $S_V(f)$ is a fifth-degree polynomial dependent on f based on experimental data.

$$S_V(f) = 14.1 \times f - 10.5 \times f^2 - 17.8 \times f^3 + 43.0 \times f^4 - 28.8 \times f^5 \tag{2}$$

$k_f Ob$ also accounts for the biochemical regulation of osteoblasts α_{Ob} which is 2×10^{-4}mm/day (Pauchard and Buenzli 2024). $S_V(f)\ (1-f)$ relates to the amount of bone surface available and the vascular space.

When $\mu > 0$, additional osteoblasts are generated due to mechanical overload. Therefore, another term is required. The additional terms include γ_{0b} denoting the strength of the mechanical regulation for osteoblasts which is the calculated measurement of 2.08×10^{-5}mm/day also $f\ Ot$ relating to the average density of osteocytes in the bone volume.

$$k_f Ob = \begin{cases} \alpha_{Ob}\ S_V(f)\ (1-f), & \mu \leq 0 \\ \alpha_{Ob}\ S_V(f)\ (1-f) + \gamma_{Ob}\ S_V(f)\ (1-f)\ f\ Ot\ \mu, & \mu > 0 \end{cases} \tag{3}$$

$$\tag{4}$$

$k_f Ob$ and $k_r Oc$ are very similar in structure. The differences include the use of α_{Oc} which is also 2×10^{-4}mm/day, γ_{Oc} being the 7.3×10^{-6}mm/day as well as the value of μ being multiplied by -1.

$$k_r Oc = \begin{cases} \alpha_{Oc}\ S_V(f)\ (1-f), & \mu \geq 0 \\ \alpha_{Oc}\ S_V(f)\ (1-f) + \gamma_{Oc}\ S_V(f)\ (1-f) \times f\ (Ot)\ (-\mu), & \mu < 0 \end{cases} \tag{5}$$

$$\tag{6}$$

The following equations ODEs are used throughout this model. The rate of change in the bone volume fraction balances of bone formation rate $f_f Ob$ and bone resorption rate $k_r Oc$.

$$\frac{df}{dt} = k_f Ob - k_r Oc \tag{7}$$

The rate of change for the change in set point is dependent on the bone volume fraction and the rate of bone formation. It also has the term $\psi - \psi_0$ which controls this set point determination process. When the set point is different from the strain energy density, it will change the set point. However, when they are the same (i.e. the term is equal to zero) then the set point will reach a steady state.

$$\frac{d\psi_0}{dt} = \frac{1}{f} k_f Ob \ (\psi - \psi_0) \tag{8}$$

Below is the rate of change for the osteocyte density, Ot. It is dependent on the bone volume fraction, the rate of bone formation, the rate of cell destruction A, the density of osteocytes, as well as the lacunar density - density of the small spaces containing osteocytes - in newly formed bone.

$$\frac{dOt}{dt} = \frac{1}{f} k_f Ob \ (Ot_f - Ot) - A \times Ot \tag{9}$$

The change in lacunar density over time is related the the bone volume fraction and the lacunar density subtracted from the initial density

$$\frac{dLc}{dt} = \frac{1}{f} k_f Ob (Lc_f - Lc) \tag{10}$$

4 Results and Discussion

4.1 Time dependent simulations

In this simulation, there is both a decrease and increase in stress applied to a bone site. From time 0 to time 30 years, there is a 70% decrease in stress applied to bone compared to the initial stress. From 30 years to 75 years, the stress applied is restored back to its initial value. The time dependent simulations were based on Pauchard and Buenzli (2024).

Figure 4 a shows the bone volume fraction over time. At the initial time point, the bone volume fraction sits at 0.85. The reduction in strain correlates with a fall in bone volume down to just above 0.5 reaching a steady state until a larger strain was applied at 30 years. At this time, there is an increase in bone volume up to just above 0.6 before reaching a new steady state. This is consistent with Wolff's law. As the mechanical strain decreases at the initial time, it triggers the osteoclasts that resorb the bone volume. After 30 years, when the initial stress is restored, osteoblasts then add more bone. It is noticeable that the steady state after 30 years never reaches the level it started at. This demonstrates set point adaptation

Variable	***Definition***
f	Bone volume fraction - Bone Volume divided by Tissue Volume (BV/TV). Important for the visualisations of the amount of bone being produced or resorped.
ψ_0	Denotes the mechanical stress set point.
ψ	Denotes the local strain energy density. This is the product of the mechanical stress and mechanical strain.
Ot	The amount of Osteocytes (sensing and controlling cells for the osteostat process).
Lc	Lacunar density. Lc_f refers to the initial density.
$kfOb$	The rate of bone formation.
$krOc$	The rate of bone resorption.
$S_v(f)$	Described by a 5th degree polynomial describing the specific surface (Pauchard and Buenzli 2024).
μ	Transduced mechanical signal

Table 1: Variables used in model (Pauchard and Buenzli 2024)

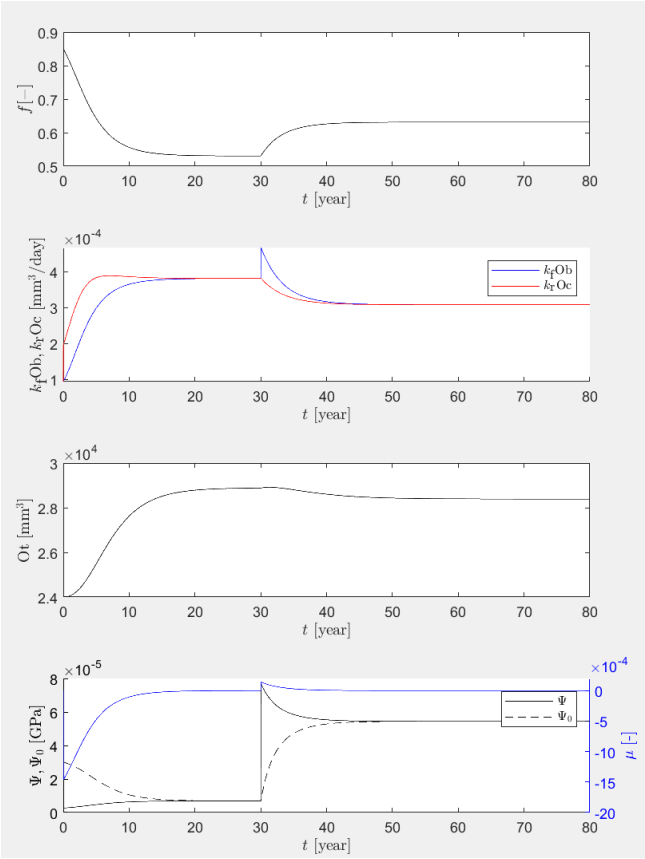

Figure 4: Variable versus time plots depicting osteostat model

Figure 4 b shows the mechanical strain applied, ψ, as well as the mechanical set point , ψ_0, changing over time. After the strain decreased at the initial time, it increases slowly until it reaches the set point. The set point decreases from time zero until it reaches a steady state just under 1e-5 GPa. When the strain was increased at time 30 years, the strain came back down as the set point increases to meet it at a steady state of just under 8e-5 GPa. This is what is expected to happen under the osteostat model.

Figure 4 c shows the biological signal μ which is the difference between the strain and the set point accounting for biological factors. This process creates a bone-forming response when the stress is greater than the set point and a bone-resorping response when the stress is less than the set point as displayed in Equation 1.

4.2 Space dependent simulations

4.2.1 Without averaging

To make this model space-dependent, each of the time-dependant variables in the ODEs became variables dependent on both time and space. Using Figure 5 as a guide, the axis 'x' sits across the long bone cross-section. The bone volume fraction along that line will be analysed.

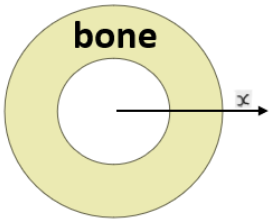

Figure 5: Cross-section at the midshaft of a long bone, with the marrow cavity in the middle

To test the range of bone volume fraction, the bone volume fraction is described initially as a modification of the Gaussian curve with the equation: $f_{initial}(x) = \frac{\exp(-0.5\times(x-10).^2)}{1.02}$ where x is the position along the radial axis. This curve was used as it contained the full breadth of f values (from close to 0 to close to 1). Plotting this over space for 30 years of unloading and 40 years recovery shows Figure 6

Figure 6, shows the initial f in the purple. As the years go on, the amount of bone volume decreases. This is consistent with Wolff's law. For the first 30 years, there was 70% less force applied compared to the initial. This decrease in f points to a decrease in bone volume and an increase in tissue volume. f is generally the lowest when the time is 30 years. After that point in time, the values of f increase because the loading is restored. However, f does not recover to its initial value even though it is under the same amount of stress. The set point changed given the lack of mechanical stress over the significant amount of time. This is assurance that this model is demonstrating the osteostat model.

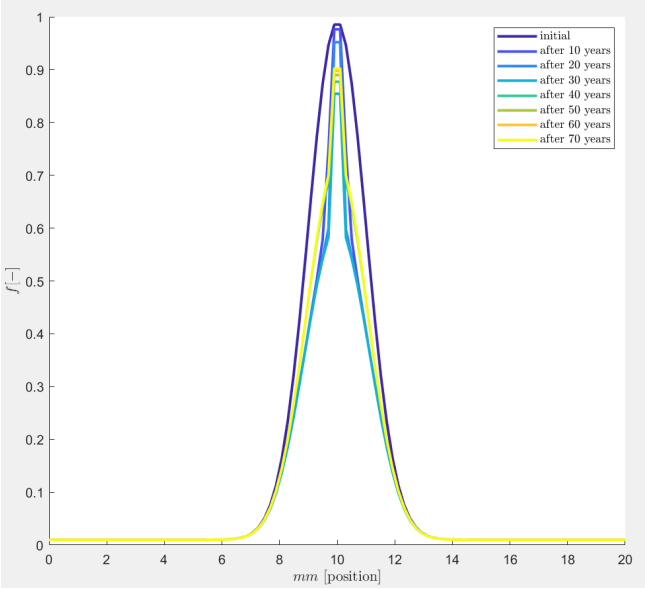

Figure 6: Bone volume fraction versus time over 70 years

4.2.2 With local averaging

It would be expected in a model reflecting bone adaptation that a bone under more force would grow radially. Similar to the implant example, the bone under less stress will resorb in - not just get more porous.

Currently, the model cannot grow outwards or inwards because the bone of the model is dependent on the bone volume fraction. If there is no bone volume fraction, then there cannot be any osteoblasts nor osteoclasts. To improve the model, small averages from the bone around it would allow bone volume to occur grow into places it is not previously. In Figure 7, the yellow represents the bone and the pink is the discretised position next to the bone. In the current model, the bone volume fraction can only change in the yellow area but not the pink. Take the top row of Figure 7. The pink square surrounded by yellow squares would, if stress was applied to that area, fill with bone to strengthen that area. This would cause the pink squares to be considered bone.

In this next model, the averaging as per Figure 8 would be utilised however only in one dimension. When taking an average for a discrete cell and there is bone on both sides of the cell, then the average will contain the values for all three cells. If the discrete cell contains bone and so does one side, then only the two containing cells will be a part of the average. If the discrete cell does not contain bone but the one next to it does then the average is taken of the cell in question and the cell containing bone next to it. 'Not bone' is anything value of $f < 10^{-6}$.

In an area with bone and bone all around it, it will take the average of those cells as well as the cell it's averaging for. When some do contain bone and do not contain bone, only the cells containing bone will be averaged. In one dimension, this only relates to the two discrete sections on either side of it.

The equations also needed to change so that the averages can be incorporated. Changes to Equation 7 result in Equation 11. The rest of the ODEs will have this averaging incorporated through its inclusion of the bone

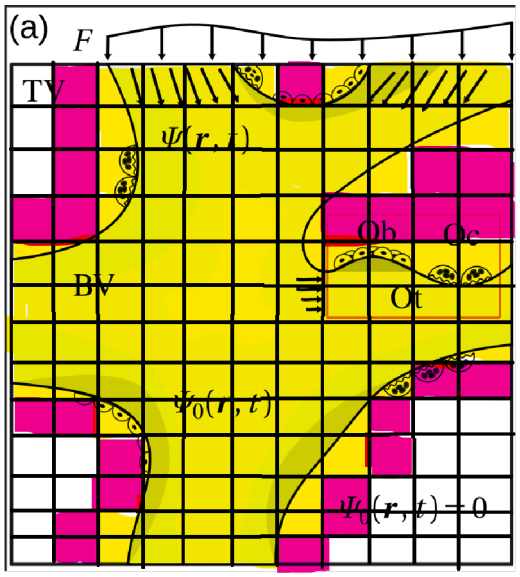

Figure 7: Potential for bone in red (2D)

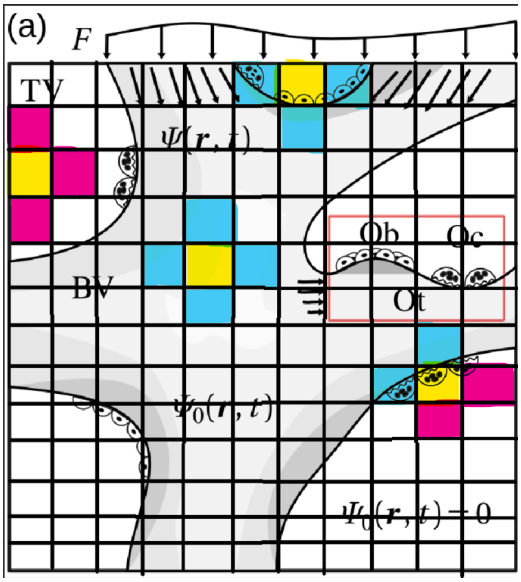

Figure 8: Calculating local averages in 2D

volume fraction in the equation.

$$\frac{df}{dt} = \langle k_f Ob \rangle - \langle k_r Oc \rangle \tag{11}$$

To accomplish this in the model, the method of solving the ODEs was changed from Heun's Method to Forward Euler Method. This was to make the code simpler to follow, however, it sacrificed some of the accuracy.

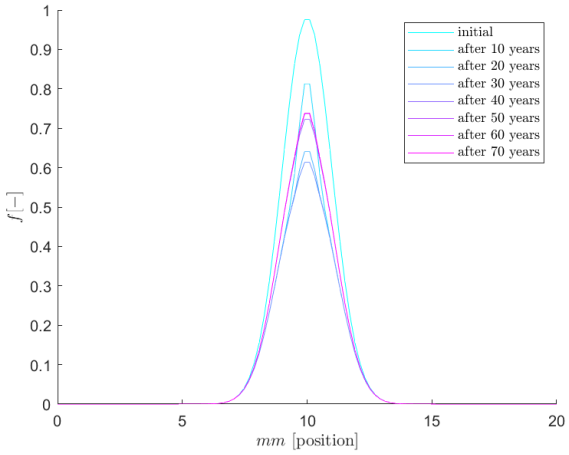

Figure 9: Bone volume fraction versus time over 70 years with averaging

In Figure 9, We see the effect the averaging has when implemented on Figure 6. The local averaging does change the bone response when f is above 0.3. It has a larger decrease in f at the upper limit of f with more significant decreases on either side of that peak in f. Figure 9 generally has a more rounded shape than Figure

6.

It can be noticed, that when f is close to zero, it has little effect on the amount of growth or decrease of bone outward from the centre. Knowing that bone changes shape when stress is applied, it is expected that the bone volume fraction would increase around 5mm and 15mm.

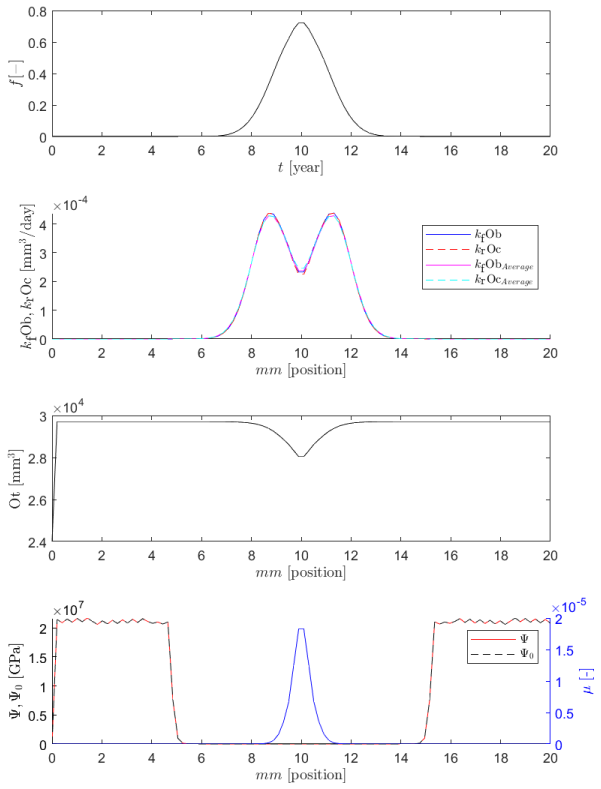

Figure 10: Bone volume fraction (a), k_fOb and k_rOc (b), Osteocyte density (c) as well as μ, set point, and transduced mechanical strain (d) versus position for the local averages (time: 40 years)

Figure 9 shows variables versus position at 40 years. At this point, 30 years of reduced stress has occurred and 10 years of the initial stress has been applied. It can be seen in Pane (b) that the rate of formation and resorption is nearly identical with a slight decrease in k_rOc around position 10. This translates to a slower rate of decreasing bone volume.

Figure 9 also shows how the averaging differs from the actual rate. This will determine how the rest of the model changes with the local averaging. This Figure shows that when local averaging is applied the average $krOc$ increases very slightly over the rate of increases from the rates of the other variables. This implies that there is a larger reduction in bone volume there than previously. However, $kfOc$ is smaller than $kfOb$.

As the previous figures don't show the reduction or addition of size in the position axis for low values of f, testing if it will under larger strain would be beneficial in diagnosing the discrepancy between the model and

the biological expectation. The results of this can be seen in Figure 11.

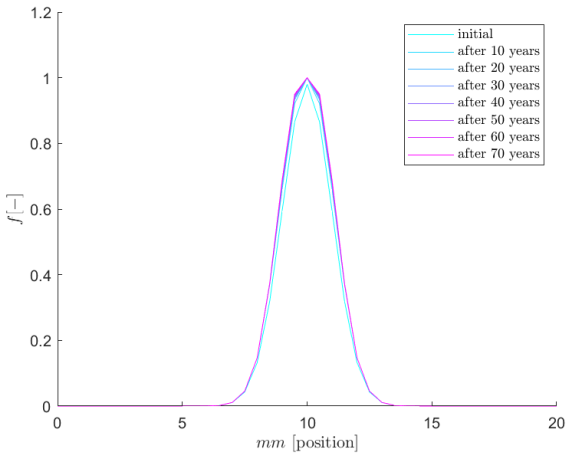

Figure 11: Bone volume fraction versus time over 70 years with averaging and only large loading

It was found during the creation of this model that without a set maximum value for f the value of bone volume fraction exceeded 1. As the proportion of bone volume cannot exceed 1, the maximum value was set to $1 - f_{min}$ so that it was symmetrical to the lower limit. In Figure 11, f does not change in the x-axis for the smaller values of f. This further emphasizes the issue with the model discussed previously.

Figure 12 shows how quickly the bone volume fraction reaches the maximum. Once it reaches this maximum it doesn't dissipate in any way. Further, in Panel (d), the ψ and ψ_0 never meet once this maximum has been achieved. Therefore, it does not reach a steady state and doesn't adapt to and mitigate the strain.

5 Conclusion

Throughout this report, there has been a discussion of the osteostat model, applying that to a mathematical model to a spatial setting, implementing the model, and then adjusting the model.Some parts of the model do not reflect what has been found experimentally in bone biology. Namely, the bone only changed porosity (f) rather than changing wall thickness as expected when stress is applied to bone. This was not fixed by the local averages as the set points adapted very quickly to the stress close to the bone surfaces. Thus, the larger values of f lost porosity as it couldn't spread the strain throughout the bone structure.

Further experimentation of the model and biological theory is required to fully quantify and visualise the changes that mechanical loading has on a bone sample. Local averaging of the transduced mechanical signal may be the solution. If signals from the areas with large values of f such as those in Figure 12 where the set point and strain values never meet, reached the surface of the bone and this would induce the necessary bone formation. Osteocytes operate on a wide network in the bone. The osteocytes that have not fully adapted to the stress may send out chemical signals to the osteocyte network. This would cause the osteocytes in the wider network, which under this model would have already reached a steady state of adaptation, to further

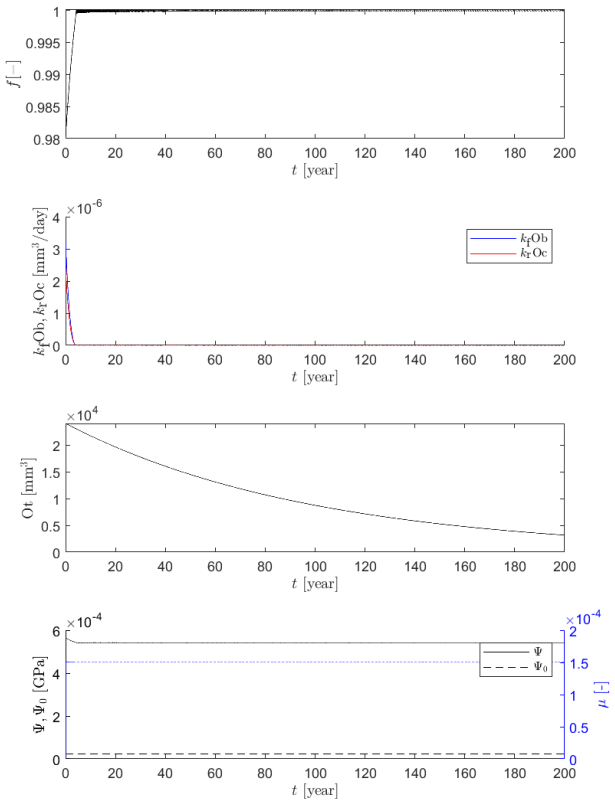

Figure 12: Bone volume fraction (a), k_fOb and k_rOc (b), Osteocyte density (c) as well as μ, set point, and transduced mechanical strain (d) vesrus time for a very large strain (position:10mm)

form/resorb to take that stress off the cells that are becoming too dense.

In conclusion, this projected extended the osteostat model into the spatial setting. The model was unable to reproduce the expected change in the wall thickness of the bone when it was under a changed mechanical loading. Local averages were employed to address the issue, however, the set point of the low values of the bone volume fraction adapted too quickly to allow for the outward and inward growth. In future, accounting for changes in the transduced mechanical signal may allow for the strain to be adapted more evenly and for the model to reproduce the expected result.

References

Frost, H. M. (1987). "Bone "Mass" and the "Mechanostat": A Proposal". In: *The Anatomical record* 219.1, pp. 1–9.

Hartmann, M.A. et al. (Aug. 2011). "Trabecular Bone Remodelling Simulated by a Stochastic Exchange of Discrete Bone Packets from the Surface". In: *Journal of the Mechanical Behavior of Biomedical Materials* 4.6, pp. 879–887. DOI: 10.1016/j.jmbbm.2011.03.005.

Huiskes, Rik (1997). "Validation of Adaptive Bone-Remodeling Simulation Models". In: *BONE RESEARCH IN BIOMECHANICS* 40, pp. 33–48.

Lerebours, Chloé and Pascal R. Buenzli (Sept. 2016). "Towards a Cell-Based Mechanostat Theory of Bone: The Need to Account for Osteocyte Desensitisation and Osteocyte Replacement". In: *Journal of Biomechanics* 49.13, pp. 2600–2606. DOI: 10.1016/j.jbiomech.2016.05.012. (Visited on 11/24/2023).

Pauchard, Yves and Pascal R. Buenzli (2024). "The "Osteostat": A Theory of Bone Mechanosensing and Setpoint Adaptation Based on Osteocytes". In: *Preparation*.

Turner, C. H. (Nov. 1998). "Three Rules for Bone Adaptation to Mechanical Stimuli". In: *Bone* 23.5, pp. 399–407. DOI: 10.1016/S8756-3282(98)00118-5.