Mathematical Modelling of Bone Tissue Regulation

Zhigen W Lin
Supervised by Dr Pascal Buenzli
Monash University

Summary

In this paper, we look at a simple model for the bone remodeling process. In particular, we are interested in the two main cells that participate in this process – osteoblasts, the cells that form bone, and osteoclasts, the cells that remove bone, as well as how these cells affect the amount of bone over time. Our model consists of three differential equations and includes biochemical, mechanical and geometric feedback. First, we investigate the properties of the steady states of our equations, before moving on to a stability analysis. Finally, we apply beam theory to the system.

1. Introduction

We construct a mathematical model of bone using three differential equations. The main variables we are concerned with are the populations of two key types of cell and how these affect the volume of bone over time.

Of course, this kind of modelling has been attempted before in an even more complex way than we show here. The more complex models included the effects of proteins, protein receptors and hormones. However, it was difficult to study the stability of the steady states in those models, and it also proved arduous to extend those models to include mechanical effects. We aim to overcome these issues by using a simpler model.

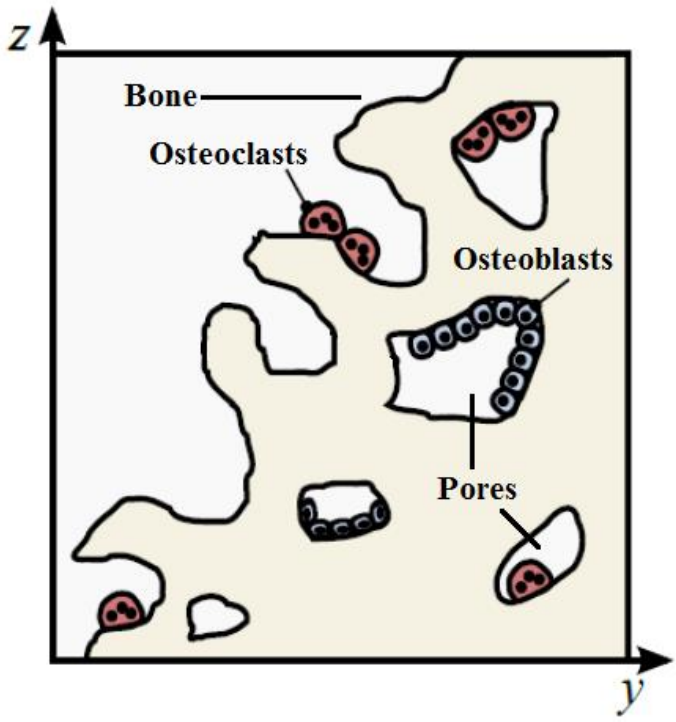


Figure 1: The cells that act in bone (Modified from Buenzli et al. 2013).

The two types of cells we are looking at are osteoblasts, the cells that form new bone, and osteoclasts, the cells that resorb old bone. These cells exist in the *pores* of the bone. The pores are simply the holes in the bone, as depicted in Figure 1. It is clear that the populations of each of these types of cells are dependent on each other, so it is important to cater for this in the model by *coupling* two of the differential equations. Coupling means that the equations are expressed such that the two quantities are not independent of each other. In our case, this means that the differential equation for osteoblasts is dependent on the osteoclast population and the differential equation for osteoclasts is dependent on the osteoblast population.

We want to include three differential factors in our model: biochemical, mechanical and geometric. The biochemical interactions between osteoblasts and osteoclasts are reflected in the first two differential equations. The other factors are introduced in the final differential equation.

The application of our model is to the bone remodeling process. Depending on the success of the initial analysis, the model could be extended to further our understanding of bone disorders such as osteoporosis.

2. Method/Results

Table of terms

The scale of our equations is according to the representative volume element (2-8 mm^3). Many of the variables have been scaled by the representative volume element (V_T).

Term	**Definition**	**Units**	**Restriction**
OB, OC	Osteoblast/osteoclast density (number of cells divided by V_T)	Time	≥0
t	Time	Time	≥0
k_{OB}, k_{OC}	Functions describing biochemical coupling between OB and OC	Time	≥0
A_{OB}, A_{OC}	Apoptosis (death) rates	1/Time	≥0
f_{bm}	Bone volume fraction (fraction of bone in the representative volume element)	None	[0,1]
k_{form}, k_{res}	Constants describing the rate of formation and resorption (technically relating to a single cell)	Volume/Time	≥0

Assumptions of model

$$\frac{\partial OB}{\partial t} \approx 0 \Longrightarrow OB \approx \overline{OB}\left(f_{bm}(t)\right)$$

$$\frac{\partial OC}{\partial t} \approx 0 \Longrightarrow OC \approx \overline{OC}(f_{bm}(t))$$

(Where the bar indicates the steady state.)

This assumption is valid because of the 'separation of the time scale' – cell behavior occurs much faster than the rate at which bone changes.

Other restrictions:

- OB and OC must be non-negative as we cannot have a negative density of cells.
- The functions k_{OB} and k_{OC} are non-negative as otherwise we can have cases where the growth term is negative.
- The constants A_{OB} and A_{OC} are non-negative as otherwise the death/decay term is negative.

Deriving the model

We start with:

$$\frac{\partial OB(\boldsymbol{r}, t)}{\partial t} = C_{OB}\frac{OC}{k_{OB}(f_{bm}) + OC} - A_{OB} \cdot OB$$

Here, r is a spatial vector, t is time and C_{OB} is a constant. The reason we have a non-linear form is discussed in the appendix.

$k_{OB}(f_{bm})$ and OC must be in the same units as they are being added together in the denominator of the first term. This means the following term is dimensionless (as the numerator has the same units as the denominator):

$$\frac{OC}{k_{OB}(\boldsymbol{r}, f_{bm}) + OC}$$

A_{OB} is an apoptosis (death) rate and hence is in the units of 'density/time'. Since OB has units of 'density', $A_{OB} \cdot OB$ has the units '1/time'.

In order to have the subtraction in the middle, C_{OB} is required to have the units '1/time'. Then we simply divide both sides by C_{OB} and set:

$$x = \frac{OB}{C_{OB}}, j = j(\boldsymbol{r}, f_{bm}) = \frac{k_{OB}(\boldsymbol{r}, f_{bm})}{C_{OB}}$$

For our shorthand, we can also write:

$$a = A_{OB}, y = \frac{OC}{C_{OC}}$$

And we have our main equation:

$$\frac{\partial x(\boldsymbol{r}, t)}{\partial t} = \frac{y}{k + y} - ax$$

By making a few more substitutions, we can derive the equation for y/OC using a similar method:

$$b = A_{OC}, k = k(\boldsymbol{r}, f_{bm}) = \frac{k_{OC}(\boldsymbol{r}, f_{bm})}{C_{OC}}$$

These substitutions have been important as they reduce the number of parameters in the model from six to four.

Main equations

For simplicity, let us ignore the dependence of x and y on the spatial vector for the moment, transforming the equations into ordinary differential equations.

$$\frac{dx}{dt} = \frac{y}{j+y} - ax \tag{1}$$

$$\frac{dy}{dt} = \frac{x}{k+x} - by \tag{2}$$

These first two equations are *coupled*, which means that OB depends on OC and OC depends on OB. They are both comprised of two parts – a source/growth term and a sink/decay term.

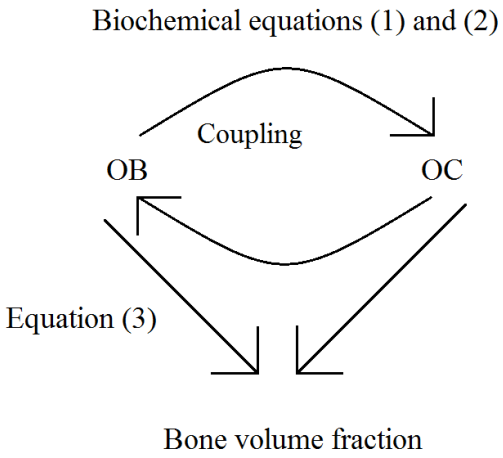
Calculations from these two equations can then be considered in a third equation:

$$\frac{\partial f_{bm}(\boldsymbol{r},t)}{\partial t} = \left(k_{form}OB - k_{res}OC\right)\left(1 - f_{bm}(\boldsymbol{r},t)\right)$$

But without the dependence on r, setting f_{bm} as f and using our simplified notation, this becomes:

$$\frac{df}{dt} = G(f) = \left(k_{form}x - k_{res}y\right)(1-f) \tag{3}$$

We can visualise the model in the following fashion:



Now, we will analyse (1) and (2) initially, before looking at (3) later on.

2a. Analysing the two biochemical equations

Steady states of osteoblasts and osteoclasts from equations (1) and (2)

For the steady states, it is clear that upon inspection of (1) and (2), there is a zero steady state as x=0 and y=0 is a solution to the differential equations.

For the non-zero steady state, we set:

$$\frac{dx}{dt} = 0 \; and \frac{dy}{dt} = 0$$

Solving for x and y gives us:

$$\bar{x} = \frac{1 - abjk}{a(bj + 1)} \tag{4}$$

$$\bar{y} = \frac{1 - abjk}{b(ak + 1)} \tag{5}$$

Steady states span the entire space

It is easy to see that we can span all the positive $\bar{x}$ and $\bar{y}$ values. Simply look at the initial form of (1) and (2) when we set the derivatives equal to zero:

$$0 = \frac{y}{j+y} - ax$$

$$0 = \frac{x}{k+x} - by$$

We can express these in terms of a and b:

$$a = \frac{y}{x(j+y)} \tag{6}$$

$$b = \frac{x}{y(k+x)} \tag{7}$$

In this form, there is no risk of the right hand side of the equation becoming negative. Hence, it is easy to see that if we fix j and k, and vary a and b, that we can reach any positive $\bar{x}$ and $\bar{y}$ value.

Restrictions

For $\bar{x}$ to be physical, we require that either:

$$1 > abjk \; and \; a(bj+1) > 0$$

OR

$$1 < abjk \; and \; a(bj+1) < 0$$

But a(bj+1)<0 is not possible as a, b and j are all positive.

Hence, we must have:

$$1 > abjk \; and \; a(bj + 1) > 0$$

The first part of the condition is most important and noting that a, b, j and k are all positive, we have the following key condition:

$$0 < abjk < 1 \tag{8}$$

Stability Analysis

To study the system, we use the stability analysis techniques outlined by Strogatz (1994, pp. 129-137).

Let us define:

$$\frac{dx}{dt} = f(x, y) = \frac{y}{j + y} - ax$$

$$\frac{dy}{dt} = g(x, y) = \frac{x}{k + x} - by$$

First, we linearise the system by defining small disturbances (u=x-x* and v=y-y*), expand du/dt and dv/dt using Taylor Series, and ignore the quadratic terms as they are too small.

The key to studying the stability is the Jacobian matrix:

$$A = \begin{pmatrix} f_x & f_y \\ g_x & g_y \end{pmatrix}_{(\bar{x},\bar{y})}$$

$$= \begin{pmatrix} -a & \frac{j}{(j+y)^2} \\ \frac{k}{(k+x)^2} & -b \end{pmatrix}_{(\bar{x},\bar{y})}$$

The determinant (Δ) and trace (τ) of A then allow us to produce a *phase diagram*. A phase diagram is a graph that shows the type of steady state point that we have.

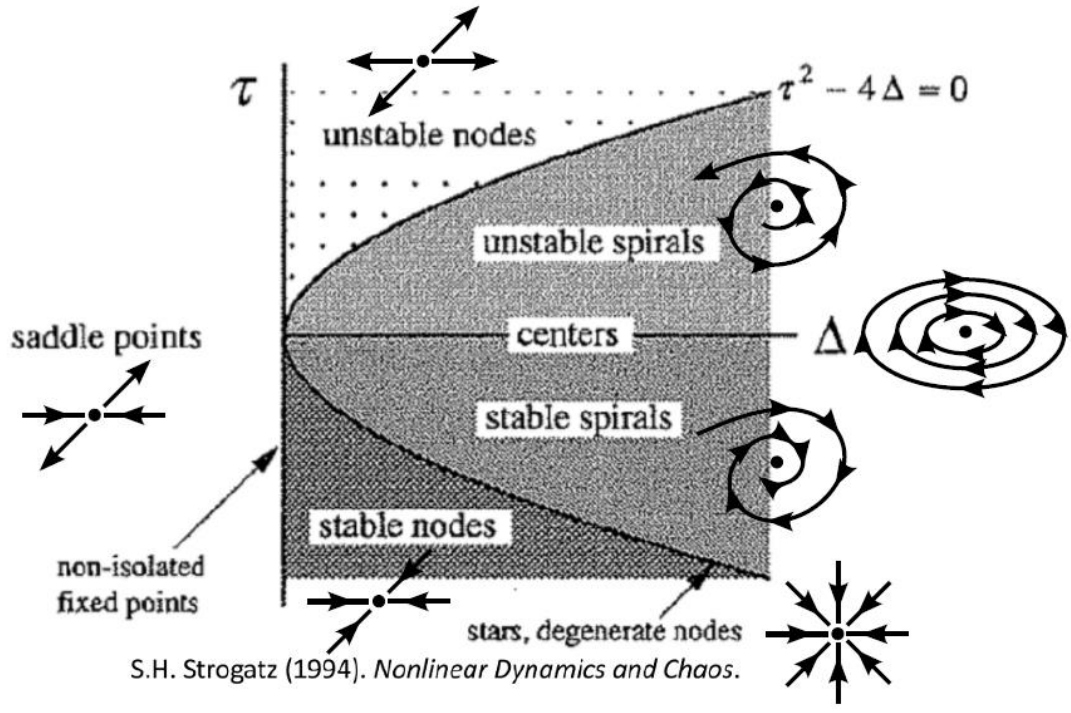


Figure 2: Strogatz's (1994, p. 137) diagram for determining the kind of stable points we get.

Stability analysis: Zero steady state

For the zero steady state, we have:

$$A = \begin{pmatrix} -a & \frac{1}{j} \\ \frac{1}{k} & -b \end{pmatrix}$$

$$\Delta(A) = ab - \frac{1}{jk}$$

But we have abjk<1 from (8), which means that ab<1/(jk). Hence, det(A)<0.

$$\tau(A) = -a - b$$

Inspecting Figure 2 shows that the zero steady state is always an unstable saddle point. The phase diagram for the zero steady state is trivial as the entire region is an unstable saddle point.

We can double check these results by looking at the eigenvectors of A. The eigenvectors show the direction in which we approach the steady state for any initial condition.

Stability analysis: Non-zero steady state

For the non-zero steady state, we have:

$$A = \begin{pmatrix} -a & \frac{j}{(j+\bar{y})^2} \\ \frac{k}{(k+\bar{x})^2} & -b \end{pmatrix}$$

Substituting the steady points in gives:

$$\Delta(A) = ab - \frac{jk}{(j+\bar{y})^2(k+\bar{x})^2}$$
$$= ab - a^2b^2jk$$
$$= ab(1 - abjk)$$

But both ab and (1-abjk) are positive due to (8). So the determinant must be positive.

As before:

$$\tau(A) = -a - b$$

Hence, reading off Figure 2, we have either a stable node or a stable spiral. To determine whether we have a node or a spiral, we need to look at the discriminant of the characteristic equation for A.

$$\tau^2 - 4\Delta$$
$$= a^2(4b^2jk + 1) - 2ab + b^2$$
$$= a^2(4b^2jk + 1) - 2ab + b^2 > (a-b)^2 > 0$$

$$(since\ 4b^2jk + 1 > 1)$$

Hence

$$\tau^2 - 4\Delta > 0$$
$$\Delta < \frac{\tau^2}{4}$$

This means we are in the region underneath the parabolic line in Figure 2. Hence, we have a stable node.

These results can be confirmed numerically using quiver on MATLAB. The following results are produced:

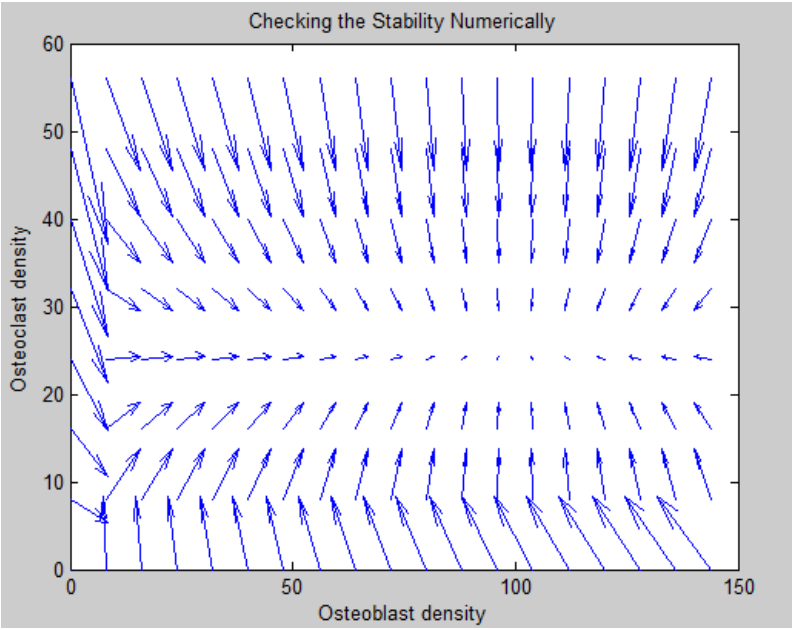


Figure 3: Checking the stability of the non-zero steady state.

For the system in Figure 3, we have set the steady state to be at (100, 30). It is clear to see that any positive initial condition will gravitate towards this point. Again, we can also use eigenvectors to confirm these results.

Note that we are not able to check the stability of the zero steady state in the above diagram because we use the formula for the non-zero steady state.

2b. Bone volume fraction equation

Consider (3) again:

$$\frac{df}{dt} = G(f) = \left(k_{form}x - k_{res}y\right)(1-f)$$

The following simplification can be made:

$$\frac{df}{dt} = G(f) \approx \left(k_{form}\bar{x} - k_{res}\bar{y}\right)(1-f) \tag{9}$$

This is possible because of the assumption earlier that bone evolves much more slowly than cells. Hence, the cells are initially already very close to their steady states. Notice that we have a (1-f) term in these equations. This is to account for the fact that the cells we are concerned with only live within the pores inside the bone. Graphically, this merely flattens the shape of G(f).

The next steps will be to look at what properties we want this equation to have.

Form of G(f)

According to stability theory, if the first time derivative is positive, the system will gravitate towards the right and if it is negative, the system will gravitate towards the left. Hence, we want a graph that looks something like this:

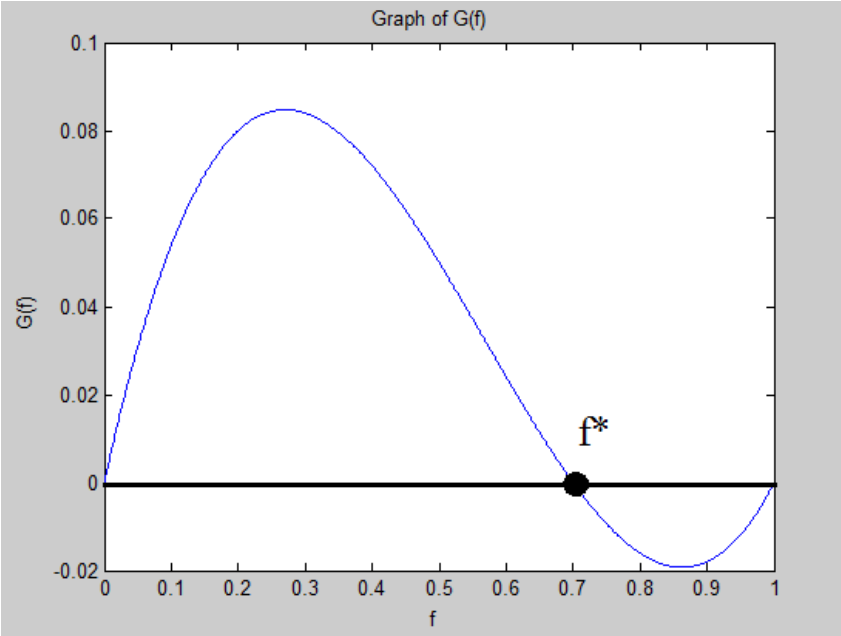


Figure 4: The form of G(f) we want. For any initial value of f, the system always gravitates towards the point f*.

Of course, f* need not be exactly where it is in Figure 4.

Geometric factor

We include a geometric or *morphological* factor to (9) by including a function known as the specific surface. Morphological, in this context, refers to the forms and structures that we observe in actual living bone tissue.

This function looks at the amount of surface area that is available on bone, including both the outside of bone and the surface area in the pores of the bone. Note that this function is technically the specific surface of the representative volume element, which means it is an average of the surface areas measured at all possible positions for the representative volume element. The specific surface is determined by calculating the surface area and dividing by the representative volume element.

Using our simplified notation, we can write the specific surface as:

$$s_V(f) = 14.1f - 10.5f^2 - 17.8f^3 + 43.0f^4 - 28.8f^5$$

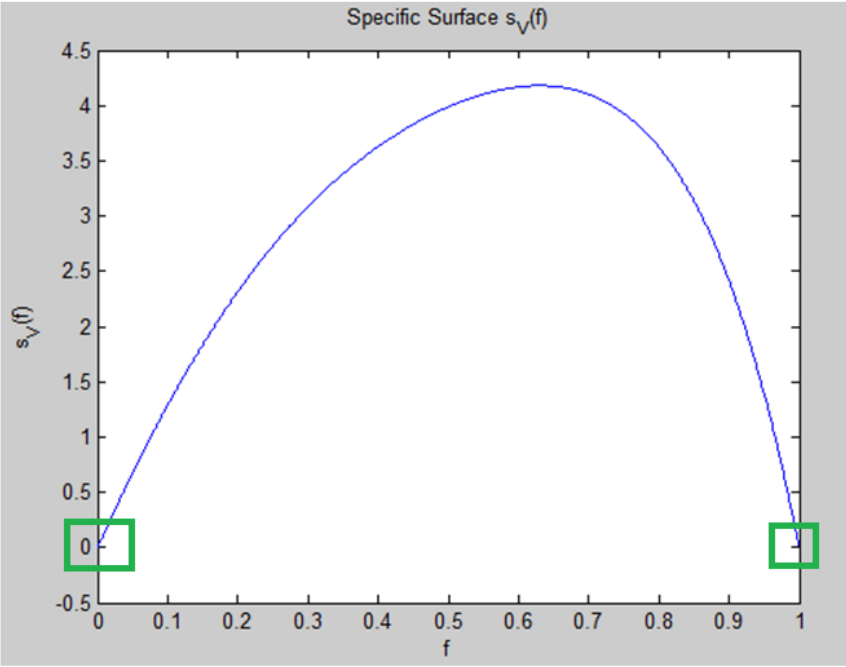


Figure 5: The specific surface function as a geometric factor.

Starting from the centre of a cross section of bone, we can roughly interpret Figure 5 as saying:

- At the centre of the bone, there is no surface area.
- At a point closer to the edge of the bone, we reach a maximum.
- The surface area eventually decreases back to zero once we get to the edge of the bone.

Mechanical factor

Mechanical factors looks at the average amount of weight placed on a bone. To account for the mechanical factor, we simply use the Heaviside step function.

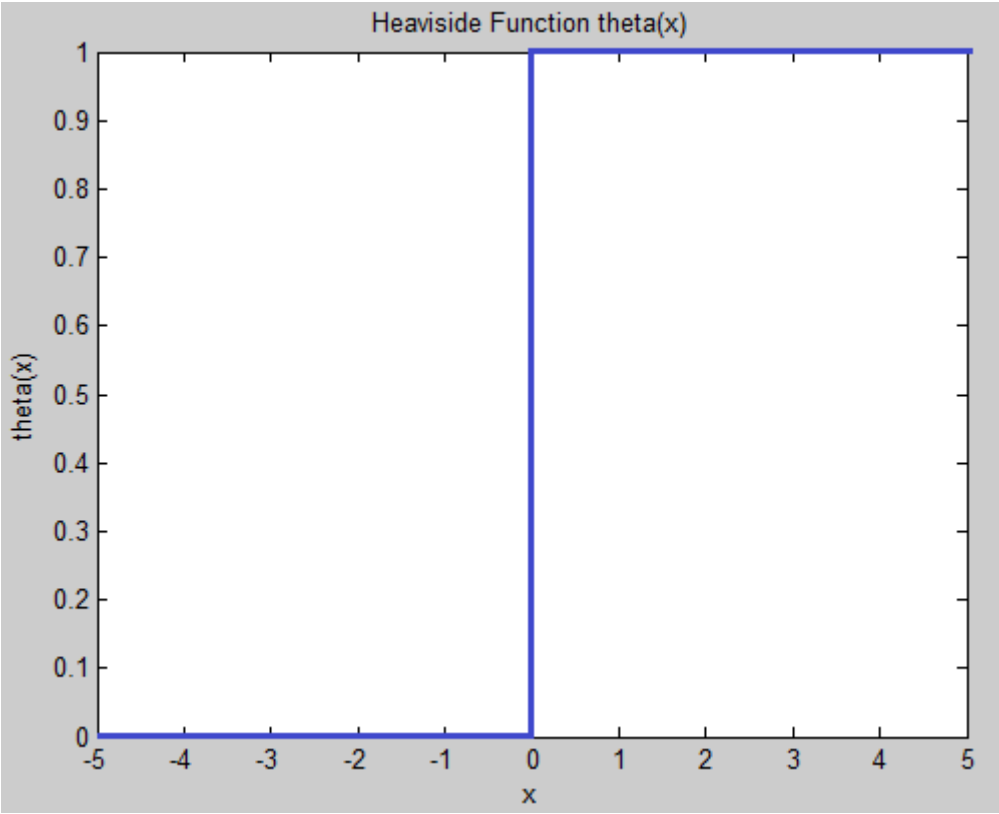


Figure 6: The Heaviside step function as a mechanical factor.

Figure 6 reflects what we actually observe in bone in that:

- If the amount of mechanical load increases, osteoblasts tend to increase in output (form more bone) while osteoclasts stay relatively constant in output.
- If the amount of mechanical load decreases, osteoclasts tend to increase in output (resorb more bone) while osteoblasts stay relatively constant in output.

Inclusion of factors into model

We can include the above factors into (9) in the following way. Recall (9) is:

$$\frac{df}{dt} = G(f) \approx \left(k_{form}\bar{x} - k_{res}\bar{y}\right)(1 - f)$$

Now, we simply set:

$$k_{form}\bar{x} = \alpha s_v(f_{bm})(1 + \beta_{OB}\left(\theta(f^* - f)\right)(f^* - f)) \tag{10}$$

$$k_{res}\bar{y} = \alpha s_v(f_{bm})(1 - \beta_{OC}\left(\theta(f - f^*)\right)(f - f^*)) \tag{11}$$

Recall that we can span the entire space of positive $\bar{x}$ and $\bar{y}$ values (see (6) and (7)), which is why we are allowed to set these to a function that we want.

The dependence on f will eventually go into the parameters j and k from (1) and (2). We could also put the dependence on f into C_{OB} and C_{OC} from the very original equations mentioned in the paper.

Beam Theory

We can apply Euler-Bernoulli beam theory to our bone analysis if we consider the bone system as a very long beam. In particular, this analysis assumes that we are not close to either end of the bone.

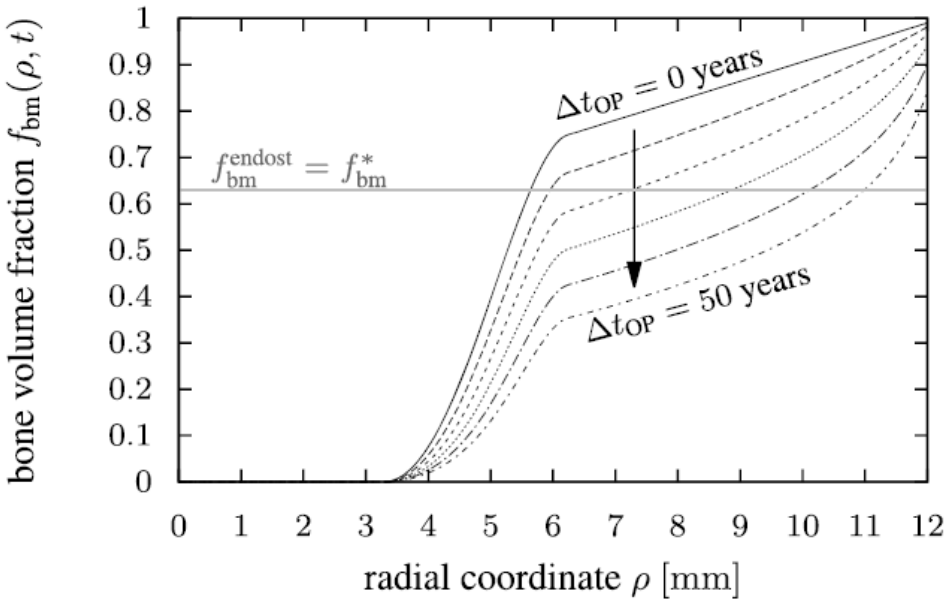


Figure 7: Initial bone volume fraction profile in the form of a smoothed step function (Modified from Buenzli et al. 2013).

Using the Euler-Bernoulli condition, Hooke's Law and Young's Modulus, Buenzli et al. (2013) indicated an initial bone volume fraction profile (f(r,0)) as in Figure 7. From that expression, it is quite easily to determine the strain energy density (SED), as it is of the form:

$$SED(r,t) = \frac{1}{2} E \varepsilon^2 \tag{12}$$

Where

$$E = 15GPa \cdot f(r,t)^3$$

And ε can be determined by solving a set of integral equations suggested in Buenzli et al. (2013).

Assuming that f* also takes the form of the initial bone volume fraction profile provided by Buenzli et al. (2013), we can first invert SED(r,t) into r(SED,t), and then express f*(r) as f*(SED(r,t)). Subsequently, we can used a staggered solution method to solve (9) and the integral equation (12) at the same time.

Note that (12) does not need to be solved at every time step. For example, it could be solved at every fifth time step and then fed back into (9) in order to solve (9).

This is an implementation that we are still attempting to work on at the time this paper was written.

3. Ways to extend analysis

There are several ways to extend the work we have done:

- Considering (1) and (2), it is also possible to set a and b as functions of f, rather than j and k.
- Keep working at simultaneously solving (9) and (12).
- Apply the equations to bone conditions such as osteoporosis.

4. Acknowledgements

I would like to thank:

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5. Appendix – Why not a linear form?

If we instead have:

$$\frac{dOB}{dt} = OC - A_{OB} \cdot OB$$

$$\frac{dOC}{dt} = OB - A_{OC} \cdot OC$$

Here, OB and OC may be scaled as in the previous discussion on this issue.

Setting the two differential equations equal to zero to find the steady states, we obtain the following matrix equation:

$$\begin{pmatrix} -A_{OB} & 1 \\ 1 & -A_{OC} \end{pmatrix} \begin{pmatrix} OB \\ OC \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \tag{A1}$$

For the non-zero steady state, we want the matrix the two-by-two matrix to be non-invertible so that we are not allowed to multiply both sides of the equation by its inverse. Otherwise, we would always get the zero steady state:

$$\begin{pmatrix} OB \\ OC \end{pmatrix} = \begin{pmatrix} -A_{OB} & 1 \\ 1 & -A_{OC} \end{pmatrix}^{-1} \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

$$\begin{pmatrix} OB \\ OC \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

Equivalently, we want the determinant of the two-by-two matrix to be zero. Hence:

$$A_{OB} \cdot A_{OC} - 1 = 0$$
$$A_{OB} \cdot A_{OC} = 1$$

However, even with this expression, matrix system (A1) is not solvable without further information. This means that substituting:

$$A_{OB} = \frac{1}{A_{OC}}$$

Into the first equation gives:

$$OC - \frac{OB}{A_{OC}} = 0$$

But this is exactly the same as the second equation (if we divide both sides by A_{OC}):

$$OB - A_{OC} \cdot OC = 0$$

Hence, we are not closer to solving the equations.

Initial conditions are required in order to solve the matrix system (A1). This is undesirable and hence why we do not use this model. We use a non-linear source term instead. Notice that, in our model, if we let OC increase, the source term grows slower than just the linear source term OC as $k_{OB}(f_{bm})$ is positive.

6. Reference List

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