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A two-dimensional model for stress driven diffusion in bone tissue

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A two-dimensional model for stress driven diffusion in bone tissue

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The growth and resorption of bone are governed by interaction between several cells such as bone-forming osteoblasts, osteocytes, lining cells and bone-resorbing osteoclasts. The cells considered in this study reside in the periosteum. Furthermore, they are believed to be activated by certain substances to initiate bone growth. This study focuses on the role that stress driven diffusion plays in the transport of these substances from the medullary cavity to the periosteum. Calculations of stress driven diffusion are performed under steady state conditions using a finite element method with the concentration of nutrients in the cambium layer of the periosteum obtained for different choices of load frequencies. The results are compared with experimental findings, suggesting that increased bone growth occurs in the neighbourhood of relatively high nutrient concentration.

Keywords: bone growth; diffusion; stress enhanced; finite element method; steady state; periosteal membrane

1. Introduction

The goal of this study is to investigate the role of stress gradients in driving diffusion processes in skeletal bones. The hypothesis is that substances that promote bone growth are transported from the medullar cavity to the outer surface of the long skeletal bone by stress driven diffusion. As a result of physiological activity, mechanical stresses occur in skeletal bones. Moreover, the literature contains many examples showing that mechanical oscillating loads stimulate bone remodelling that is prevalent in the cambium layer of the periosteum. However, the transport processes on the cell level are not yet completely understood. Hence, the aim of this study is to analyse the interactions between mechanical loading and transport of nutrients and signal substances that affect remodelling of skeletal bones. The results have implications on such mechanisms as fracture healing, as well as on the medical treatment of disorders including osteoporosis.

It is well known that physical activity promotes bone formation and that bone architecture adapts to loading. Schwarz et al. (2006) gave an overview of observations of the effect of different physical activities on humans and animals. The strain distribution during locomotion is complex (Coleman et al. 2002). Different animal models where loading can be controlled have been used to study these effects as for example by the isolated avian-bone model, used for roosters and turkeys (Lanyon and Rubin 1984; Rubin and Lanyon 1984), as well as by the rat model (Mosley and Lanyon 1998). When developing numerical models of bone adaptation, the strain energy density (Huiskes et al. 2000) is often regarded as driving the process. The strain energy density is caused by muscle loading (Be’ery-Lipperman and Gefen 2005). In these studies, a cellular communication network with osteocytes as mechanosensors is incorporated.

In this investigation, it is assumed that the primary condition leading to bone growth is a change in the chemical environment caused by transport of matter resulting from stress driven diffusion. The change in the chemical environment may consist of changes in the concentration of different substances stimulating, for example, osteoblast recruitment or suppression of osteoclast activity. Experimental evidence that mechanical loading stimulates lining cells at the periosteum to differentiate into osteoblasts has been reported by Pead et al. (1988) and Boppart et al. (1998). In Cardoso et al. (2013), a review was presented on the porosity and permeability of bone, as well as on the interstitial fluid flow through interconnected canals in the bone (Haversian canals, Volkmann canals or the lacunar–canalicular system). In this study, the bone is treated as a homogeneous material, and the interstitial flow, which on the smaller scale was described as flow in canals, is here described as diffusion. As a result of this diffusion, matter that changes the chemical prerequisites for bone remodelling is transported.

Banks-Sills et al. (2011) presented a 1D model based on the hypothesis that the primary condition leading to bone growth is a change of the chemical environment

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caused by stress driven diffusion. An oscillating bending moment was applied which produced a stress gradient over the cross-section of the bone. The flux $J$ and concentration $c$ of the growth-promoting substances were assumed to be governed by Fickian diffusion generalised to include a stress gradient term. In this study, a 2D finite element (FE) model is established. A steady state solution is sought. Comparisons are made to the 1D analytic results. In addition, the 2D model allows for a more realistic comparison between numerically obtained results and experiments found in the literature.

The analysis focuses on the concentration distribution over the bone cross-section and the seepage of nutrients into the cambium layer of the periosteum for different loading frequencies. Comparison with experiments shows that the maximum bone growth appears in the regions where the highest concentration occurs, rather than high stress.

In Section 2, the mathematical 2D model describing the behaviour of the concentration is presented. As the applied loading is sinusoidal, the expected solution should be a combination of sines and cosines with the same frequency. With this assumption in Section 3, the two components of the solution and boundary conditions are decoupled. It is shown that there is an analogy between these governing equations and boundary conditions and those for a plate on an elastic foundation. In this way, the FE method (ABAQUS 2009) may be utilised to solve for these unknowns. The analogy is developed in Appendix A. In Section 4, results are presented. Comparison is made between bone growth observed by Lanyon and Rubin (1984) and the regions where the concentration of bone growth substances is predicted to be the highest by an FE analysis.

2. Model

In this investigation, the transport of matter in a cross-section of a mammal’s long bone is studied. The bone is assumed to be loaded in bending which produces a strain in the direction perpendicular to the cross-section. In addition to the gradient of a concentration field $c$, the gradient of the hydrostatic stress $\sigma_h$, caused by bending, is assumed to provide a driving force resulting in the transport of matter in the plane of the cross-section. This latter contribution controls the diffusion process. The concentration is assumed to deviate only slightly from a constant concentration $c_0$. For more details regarding the implications of this assumption (see Banks-Sills et al. 2011). The applied load is based on the in vivo experiments of Lanyon and Rubin (1984). Avain ulnas were strained in and exposed to oscillating compression of 1 Hz for 100 cycles a day during 8 weeks. As a result of the curvature of the bone, a bending moment is produced. The neutral axis shown in Figure 1 as $N - N$ is defined to coincide with the $x$-axis. This is the axis for which the strain $e_{xx}$ is zero. The moment only produces bending about this axis.

The flux vector $J$ of a selected substance in the bone environment becomes (Li 1984)

$$J(x, y, t) = -D \nabla c(x, y, t) + BV \Lambda c_0 \nabla \sigma_h(x, y, t), \quad (1)$$

where $\nabla = \text{gradient operator in Cartesian coordinates}$ given in two dimensions by

$$\nabla = \left( \frac{\partial}{\partial x}, \frac{\partial}{\partial y} \right). \quad (2)$$

In Equation (1), $D$ is the diffusion coefficient of the substance–bone system, $B$ is the mechanical mobility, $V \Lambda$ is the atomic volume of the bone nutrients and $c_0$ is the initial concentration. As in Banks-Sills et al. (2011), as a first approximation, it has been assumed that $c = c_0$.

Matter is assumed to be conserved and, therefore, the divergence of the flux $J$ is related to the concentration by

$$\nabla \cdot J(x, y, t) = -\dot{c}(x, y, t), \quad (3)$$

where the dot over a quantity indicates its derivative with respect to time and the dot between vectors represents the scalar product. If the flux $J$ is eliminated by combining Equations (1) and (3), the governing equation becomes

$$\dot{c}(x, y, t) = V \Lambda c_0 \nabla \cdot [B \nabla \sigma_h(x, y, t)]. \quad (4)$$

The cross-section of the bone is shown in Figure 1. It is from the right ulna of a turkey and was taken from Figure 4 (a) of Lanyon and Rubin (1984). A coordinate system is introduced with the $z$-axis along the axis of the long bone and the cross-section of the bone within the $x$–$y$ plane. As explained earlier, bending occurs around the $x$-axis which coincides with the neutral axis $N - N$ of the cross-section.
(see Figure 1). The neutral axis was found from the experimental results in Figure 3(a) of Lanyon and Rubin (1984). In addition, two unit vectors are defined on $\Omega_{\text{out}}$ and $\Omega_{\text{in}}$; they are the outward normal vector $\mathbf{n}$ and the tangent vector $\mathbf{m}$ as shown in Figure 1. The material is assumed to be linear elastic with a modulus of elasticity $E$. The stress in the $z$-direction is given by

$$\sigma_z = \kappa Ey,$$

(5)

where $\kappa$ is the curvature due to the bending about the $x$-axis. The concentration $c$ contributes to the bending stress. It was seen in Banks-Sills et al. (2011) that its contribution to the solution is negligible. Hence, it is neglected in this study.

The chemical and mechanical states are assumed to vary insignificantly along the $z$-axis. In addition, apart from $\sigma_z$, all other components of the stress tensor vanish. The stress distribution over the cross-section is in equilibrium with a remote moment. In general, this moment is not parallel to the axis of zero strain, i.e. the neutral axis, denoted by $N - N$ in Figure 1. The component along the $x$-axis is denoted as $M$. This moment is given by

$$M = \kappa EI,$$

(6)

where $I$ is the second moment of area of the cross-section about the $x$-axis. The moment about the $y$-axis does not contribute to the bending stress (Parnes 2001, p. 499).

Using Equations (5) and (6), one obtains the hydrostatic stress as

$$\sigma_n = \frac{1}{3} \sigma_z = \frac{My}{3I}.$$

(7)

The moment is assumed to be oscillating in time with an angular velocity, $\omega$, according to

$$M = M_o \sin \omega t.$$

(8)

It may be noted that a different oscillatory function was assumed in Banks-Sills et al. (2011) where the transient behaviour of the concentration was also sought. The choice here does not affect the steady state solution. Substitution of Equations (7) and (8) into Equation (1) leads to the components of the flux vector $\mathbf{J}$ as

$$J_x(x, y, t) = -D \frac{\partial c(x, y, t)}{\partial x},$$

$$J_y(x, y, t) = -D \frac{\partial c(x, y, t)}{\partial y} + BV_A c_0 \frac{M_o}{3I} \sin \omega t.$$

(9)

In addition, assuming that the diffusion coefficient $D$ and the mechanical mobility $B$ are constants, together with insertion of Equations (7) and (8) into Equation (4), results in the governing differential equation for the concentration as

$$\dot{c}(x, y, t) = D \nabla^2 c(x, y, t).$$

(10)

In this study, a particular geometry was selected. This is a cross-section of a turkey ulna that was examined experimentally in vivo and post-mortem by Lanyon and Rubin (1984). The considered geometry is the bone cross-section shown in Figure 1. The studied substance is continuously supplied to the medullary cavity, i.e. within $\Omega_{\text{in}}$ in Figure 1, so that the concentration within this region is not affected by the amount that diffuses into the bone. At the outer surface of the bone, $\Omega_{\text{out}}$, the outer layer of the periosteal membrane is assumed to be a nearly impermeable layer. Thus, the flux out of the periosteal layer has an insignificant effect on the concentration distribution.

The boundary conditions consist of a constant concentration $c_0$ along the boundary $\Omega_{\text{in}}$ at the medullary cavity and a vanishing flux over the outer boundary $\Omega_{\text{out}}$. These conditions may be written as

$$c(x, y, t) = c_0 \quad \text{for} \quad (x, y) \in \Omega_{\text{in}}$$

and

$$\mathbf{n}(x, y) \cdot \mathbf{J}(x, y, t) = 0 \quad \text{for} \quad (x, y) \in \Omega_{\text{out}}.$$

(11)

(12)

In Equation (12),

$$\mathbf{n}(x, y) = n_x(x, y)e_x + n_y(x, y)e_y$$

(13)

is the outward unit normal to the boundary $\Omega_{\text{out}}$ and $e_x$ and $e_y$ are unit vectors in the $x$ and $y$ directions, respectively. Substitution of Equations (9) into Equation (12) leads to

$$\mathbf{n} \cdot \nabla c(x, y, t) = n_x \frac{\partial c(x, y, t)}{\partial n} = n_y \frac{BV_A c_0 M_o}{3I} \sin \omega t$$

for $(x, y) \in \Omega_{\text{out}},$

(14)

where $n$ is a coordinate along the direction of $\mathbf{n}$. To simplify the analysis, dimensionless variables are introduced for the flux vector and concentration given by

$$\tilde{\mathbf{J}} = \frac{3I}{BV_A c_0 M_o} \mathbf{J},$$

$$\tilde{c} = \frac{3ID}{BV_A M_o a} c - c_0,$$

(15)

where $a$ is a measure of the width of the bone obtained as the average at four locations (two along the $x$-axis and two along the $y$-axis as in Figure 1); it was found to be 1.8 mm. In addition, the time, space coordinates and the frequency are normalised as

$$\tilde{t} = \frac{D}{a^2} t, \quad \tilde{x} = \frac{x}{a}, \quad \tilde{y} = \frac{y}{a}, \quad \tilde{n} = \frac{n}{a}, \quad \tilde{m} = \frac{m}{a},$$

$$\tilde{\omega} = \frac{\omega}{D a}.$$

(16)
Note that \( n \) and \( m \) represent a local coordinate system normal and tangent to \( \Omega_{\text{out}} \) and \( \Omega_{\text{in}} \) as shown in Figure 1.

Equation (10) may now be written as

\[
\dot{c}(\hat{x}, \hat{y}, \hat{t}) = \hat{\nabla}^2 \hat{c}(\hat{x}, \hat{y}, \hat{t})
\]  

(17)

where the \( \dot{\cdot} \) now represents differentiation with respect to the dimensionless time \( \hat{t} \) and the hat above \( \nabla \) indicates differentiation with respect to the normalised spacial coordinates \( \hat{x} \) and \( \hat{y} \). In addition, the boundary conditions in Equations (11) and (14) may be normalised as

\[
\hat{c}(\hat{x}, \hat{y}, \hat{t}) = 0 \quad \text{for} \quad (\hat{x}, \hat{y}) \in \Omega_{\text{in}}
\]  

(18)

and

\[
\frac{\partial \hat{c}(\hat{x}, \hat{y}, \hat{t})}{\partial \hat{n}} = n_y \sin \omega \hat{t} \quad \text{for} \quad (\hat{x}, \hat{y}) \in \Omega_{\text{out}}.
\]  

(19)

The transient problem is governed by Equations (17)--(19) with the initial condition

\[
\hat{c}(\hat{x}, \hat{y}, 0) = 0.
\]  

(20)

Since in this study, the bone is assumed to be subjected to cyclic loading for an extended period (i.e. \( \hat{t} \gg 1 \)), the steady state solution is sought. The analytical solution for a rectangular bone cross-section found in Banks-Sills et al. (2011) reveals that after a time \( 1.9t_0 \), where \( t_0 = a^2/D \), the concentration decreased by about one-hundredth of its initial value with an exponential decay. Hence, the steady state solution should be valid for \( t \) somewhat greater than about \( 3t_0 \). Limiting the study to steady state reduces the number of variables and eliminates the time dependence as is explained in the next section.

3. Analysis

Because the boundary condition in Equation (19) is sinusoidal, the solution to the partial differential equation in Equation (17) will approach a pure oscillatory state for long time. It may be written in the form

\[
\hat{c}(\hat{x}, \hat{y}, \hat{t}) = \hat{c}_1(\hat{x}, \hat{y}) \sin \omega \hat{t} + \hat{c}_2(\hat{x}, \hat{y}) \cos \omega \hat{t}
\]  

(21)

so that there is a separation of the solution in time and space. Substitution of Equation (21) into Equation (17) leads to

\[
\omega \hat{c}_1(\hat{x}, \hat{y}) = \hat{\nabla}^2 \hat{c}_2(\hat{x}, \hat{y}),
\]  

(22)

\[
\omega \hat{c}_2(\hat{x}, \hat{y}) = -\hat{\nabla}^2 \hat{c}_1(\hat{x}, \hat{y}),
\]  

(23)

where the sine and cosine terms are independent. Equations (22) and (23) may be decoupled as

\[
\hat{\nabla}^4 \hat{c}_i(\hat{x}, \hat{y}) + \omega^2 \hat{c}_i(\hat{x}, \hat{y}) = 0,
\]  

(24)

where \( i = 1, 2 \). In addition, the solution (Equation (21)) may be rewritten as

\[
\hat{c}(\hat{x}, \hat{y}) = \hat{c}(\hat{x}, \hat{y}) \sin (\omega \hat{t} + \varphi),
\]  

(25)

where

\[
\varphi(\hat{x}, \hat{y}) = \tan^{-1}\left[\frac{\hat{c}_2(\hat{x}, \hat{y})}{\hat{c}_1(\hat{x}, \hat{y})}\right].
\]  

(27)

In order to solve Equation (24), four boundary conditions for each function are required.

To this end, by substituting Equation (21) into Equation (18), the boundary condition at the inner boundary of the bone \( \Omega_{\text{in}} \) (see Figure 1) becomes

\[
\hat{c}_1(\hat{x}, \hat{y}) = \hat{c}_2(\hat{x}, \hat{y}) = 0 \quad \text{for} \quad (\hat{x}, \hat{y}) \in \Omega_{\text{in}}.
\]  

(28)

As a result of Equation (28), all gradients of \( \hat{c}_1 \) and \( \hat{c}_2 \) with respect to \( \hat{m} \) along the inner boundary \( \Omega_{\text{in}} \) vanish. Recall that \( \hat{m} \) is the normalised coordinate along the tangent of the boundary. When the direction of \( \hat{m} \) is followed, the body is towards the left. Furthermore, from the boundary condition in Equation (18), it follows that the time derivative of the concentration on the inner boundary vanishes. Thus, from Equation (17), one obtains

\[
\frac{\partial^2 \hat{c}_1(\hat{x}, \hat{y})}{\partial \hat{n}^2} = \frac{\partial^2 \hat{c}_2(\hat{x}, \hat{y})}{\partial \hat{n}^2} = 0 \quad \text{for} \quad (\hat{x}, \hat{y}) \in \Omega_{\text{in}}.
\]  

(29)

Substitution of Equation (21) into Equation (19), at the outer boundary, \( \Omega_{\text{out}} \), leads to

\[
\frac{\partial \hat{c}_1(\hat{x}, \hat{y})}{\partial \hat{n}} = n_y \quad \text{and} \quad \frac{\partial \hat{c}_2(\hat{x}, \hat{y})}{\partial \hat{n}} = 0
\]  

(30)

for \( (\hat{x}, \hat{y}) \in \Omega_{\text{out}} \).

The fourth set of boundary conditions is obtained by differentiating Equations (22) and (23) with respect to \( \hat{n} \).
and inserting Equation (30) into the result to obtain

\[
\begin{align*}
\frac{\partial}{\partial a} \hat{\nabla}^2 \tilde{c}_1(\hat{x}, \hat{y}) &= \frac{\partial}{\partial a} \left[ -\hat{\omega} \hat{c}_2(\hat{x}, \hat{y}) \right] = 0 \\
\frac{\partial}{\partial a} \left[ \hat{\nabla}^2 \tilde{c}_2(\hat{x}, \hat{y}) \right] &= \frac{\partial}{\partial a} \left[ \hat{\omega} \hat{c}_1(\hat{x}, \hat{y}) \right] = \hat{\omega} n_y
\end{align*}
\] (31)

for \((\hat{x}, \hat{y}) \in \Omega_{\text{out}}\).

In summary, as a result of the complicated geometry of the bone cross-section, a numerical solution is required. Assumption of a time harmonic solution led to a differential equation in space, namely Equation (24). This avoids solution of the time-dependent differential condition in Equation (17) with the time-dependent boundary condition in Equation (19).

The governing equations in Equation (24) together with the boundary conditions in Equations (28)–(31) are solved using an FE formulation. The system is analogous to the differential equation for a plate supported by an elastic foundation with the corresponding boundary conditions (see Appendix A). Hence, the numerical analyses may be conveniently performed using a commercial FE code for structural analysis. In this study, the software (ABAQUS 2009) was used. For more details on the FE formulation of a plate, see, for example, Zienkiewicz (1977).

4. Results

The analogy of a plate on an elastic foundation is used to solve the distribution of the amplitude, \(\tilde{r}\), of the concentration according to Equation (26) in the bone. In Section 4.1, the numerical method is validated by comparison with a 1D analytical solution (Banks-Sills et al. 2011). In Section 4.2, results from the 2D FE analyses are described.

4.1 Validation of the numerical method using a 1D model

To validate the numerical model, a rectangular cross-section of the bone that does not include the medullary cavity (see Figure 2) is considered first, for which an analytical solution is known (Banks-Sills et al. 2011). In that case, a second-order partial differential equation in space and time given in Equation (B1) was solved with the two boundary conditions in Equation (B2) applied at \(y = 0\) and \(y = a\), respectively, and the initial condition given in Equation (B3). The flux across the two remaining sides is assumed to vanish. Thus, the flux across the bone becomes 1D, and the problem depends only on one coordinate, namely \(y\). An exact transient solution for this case was obtained by Banks-Sills et al. (2011). The model is described in detail in Appendix B. Although the problem is 1D, in the analogy, the assumption is made of a plate in the \(xy\)-plane on an elastic foundation. The behaviour in the \(x\)-direction is assumed to be uniform.

In the numerical calculations, a mesh consisting of 19,840 three-noded plate elements was used. There were approximately 200 elements along the \(y\)-axis for the plate in Figure 2. The free mesh was generated with an irregular structure. The solution was obtained by means of a general purpose FE code ABAQUS (2009) using the fully analogous case of an elastic plate on a flexible foundation. The differential equation is given in Equation (B9) and the boundary conditions in Equations (B10) through (B13). The variables \(\tilde{c}_1\) (concentration) should be thought of as the deflection of the plate. The three-noded elements make use of a linear shape function for the displacement.

In carrying out the FE analysis, the elements are required to be sufficiently small in order to capture the details of the solution. An upper limit to the element size above which the analysis fails is related to the wavelength of the solution. The higher the frequency \(\omega\), the smaller the wavelength, so that smaller elements are needed. To understand this, consider the behaviour of Equations (15) through (21) of Banks-Sills et al. (2011) for high frequency, i.e. for large values of \(\eta\). It may be observed in Equations (15)–(21) of Banks-Sills et al. (2011) that for large values of \(\eta\), \(\sinh(\eta y) \approx \exp(\eta y)/2\) and \(\cosh(\eta y) \approx \exp(\eta y)/2\). This implies that the steady state part of \(c(y,t)\) oscillates with a half period of \(\gamma_p = \pi/\eta\). The length \(\gamma_p\) is a characteristic length of the solution for \(c(y,t)\), and therefore, an upper limit of the element size \(\ell\) would be

\[
\ell \ll \gamma_p = \frac{\pi}{\eta} = \pi a \sqrt{\frac{\gamma}{\omega}}
\] (32)

The number of elements along the \(y\)-axis used in the present solution is 200, meaning that an upper limit of the
frequency that will provide an accurate solution is

\[
\ell = \frac{a}{200} \ll \pi a \sqrt{2 \frac{\nu}{\phi}} \Rightarrow \phi \ll 2 \pi^2 200^2 \approx 8 \times 10^5.
\]

The FE result \( \tilde{\epsilon}_{\text{FE}} \) is the amplitude of \( \tilde{\epsilon} \) given in Equation (B14). The corresponding analytical result, denoted by \( \tilde{\epsilon}_A \), is the amplitude of the solution and is given in Equation (B15). The solution \( \tilde{\epsilon}_A \) is exact, whereas \( \tilde{\epsilon}_{\text{FE}} \) is a numerical result. The relative per cent error is defined by

\[
\text{err} = \frac{|\tilde{\epsilon}_A - \tilde{\epsilon}_{\text{FE}}|}{\tilde{\epsilon}_A} \times 100\%.
\]

It is now possible to estimate the error for different frequencies. Values of the exact and numerically calculated concentrations \( \tilde{\epsilon}_A \) and \( \tilde{\epsilon}_{\text{FE}} \), respectively, at the upper boundary of the bone, namely \( \tilde{\gamma} = 1 \), are presented in Table 1 for the various values of the normalised frequency \( \phi \) given in Equation (16). The result shows an error that is extremely small, and in some cases zero (to the number of significant figures shown), for small values of the frequency. Recall that the FE analysis is carried out for a plate on an elastic foundation where, in this case, the stiffness of the foundation vanishes (see Equations (B9) and (A7)). It may be noticed in Table 1 that for \( \phi < 0.4 \), the FE and exact solutions are in complete agreement to many significant figures. As \( \phi \to 0 \), the trivial, rigid body, linear solution in Equation (B8) is satisfied by any finite element. Furthermore, the error is within reasonable limits as long as \( \phi \leq 10^4 \); for \( \phi = 10^4 \), the error is less than 2\%. It is interesting to note that according to the restrictions on the element size \( \ell \) in Equation (32), approximately nine elements are equivalent to half the wavelength for this frequency along the \( y \)-axis (there are 200 elements along the \( y \)-axis). One may also observe that the error increases quite dramatically for higher frequencies (see Table 1). In contrast to the 1D model, the 2D model leads to a nonlinear distribution of the concentration at vanishing frequencies \( \phi \) as shown in Section 4.2. The implication is that the error as predicted for the 1D case is likely to underestimate the error occurring in the 2D analyses for low frequencies.

### 4.2 The 2D model

In this section, the 2D model of the bone illustrated in Figure 1 is considered. The solution of the analogous plate on an elastic foundation is found by means of the FE method as explained in Appendix A. Recall that the differential equation for the normalised concentration \( \tilde{c}_i \) is given in Equation (24). The normalised amplitude of the concentration \( \tilde{c}_i \) in Equation (26) is presented in Figure 3 for different normalised frequencies \( \phi \). These results were obtained with a mesh of 3780 three-noded plate elements and 2090 nodal points. There were 15–19 elements across the bone wall.

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<th>( \phi )</th>
<th>( \tilde{\epsilon}_{\text{FE}} )</th>
<th>( \tilde{\epsilon}_A(\phi) )</th>
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<td>5.0000000 \times 10^{-4}</td>
<td>81</td>
</tr>
</tbody>
</table>

The limiting quasi-static case (\( \phi \ll 1 \) and \( \hat{t} \gg 1 \)) is shown in Figure 3(a). This case is obtained by replacing the governing Equation (17) with \( \nabla^2 \tilde{c} = 0 \). Writing \( \tilde{\epsilon} \) as in Equation (21) results in \( \tilde{\epsilon} = \tilde{\epsilon}_1 \sin \phi \hat{t} \). If one considers the boundary conditions in Equations (28) through (31) for \( \tilde{\epsilon}_2 \), noting that \( \phi \ll 1 \), it becomes clear that \( \tilde{\epsilon}_2 \) vanishes everywhere. For low frequencies, the concentration becomes large in both the 1D and 2D models. Unlike the result for the 1D model, where the concentration, \( \tilde{\epsilon}_i \), is proportional to \( \hat{t} \) (consider Equation (B15) for small values of \( \eta \), the result in the 2D model is a non-uniform distribution over the bone cross-section. The difference is essential and influences the concentration at the outer regions of the bone at low frequencies.

The results for moderate frequencies with \( \phi \) being 1 or 2, displayed in Figure 3(b),(c), show that the concentration also becomes large over extended regions of the bone cross-section. Close to the medullary cavity, as well as in two locations (deep blue colour) near the lower part of the cross-section, the concentration vanishes. It follows from Equation (5) that the uniaxial stress that acts on the cross-section is proportional to the \( y \)-coordinate (see Figure 1) and is zero at the neutral axis (\( N-N \)) as may be seen in Figure 4(a). It is noted from Equation (5), that as anticipated, the bending stress is linear in \( y \) as may be seen by the parallel colours in Figure 4(a). Note that the amplitude of the bending stress is plotted. Clearly, the regions close to periosteal surface with high concentration do not fully correlate with those of high stress. For higher frequencies, such as \( \phi = 10 \), the most striking effects are, first, that the concentration amplitude decays and, second, that there is a skin effect in the sense that elevated concentrations only develop close to the periosteal surface (see Figure 3(d)). For the highest frequency used in the calculations \( \phi = 100 \), according to Figure 3(e), the concentration seemingly vanishes everywhere.

It may be noted that a mesh containing 25,312 three-noded plate elements with 12,956 nodal points was used to calculate the deflections of the plate for normalised
Proof

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Figure 3. Normalised concentration amplitude $\tilde{c}$ in Equation (26) distributed over the bone cross-section for different non-dimensional load frequencies $\omega = \omega_0 D$: (a) quasi-static, (b) $\omega = 1$, (c) $\omega = 2$, (d) $\omega = 10$, (e) $\omega = 100$ and (f) concentration scale.

frequencies of $\omega = 2$ and $\omega = 10$. There were between 32 and 52 elements across the bone. A sampling of a few points showed differences between results obtained with the fine mesh and the coarse mesh to be less than 1% for $\omega = 2$ and less than 2% for $\omega = 10$.

A thin membrane called the periosteal surface, or the peristome, covers the outer bone surface. It consists of two layers: an outer fibrous layer and an inner cambium layer consisting of osteoprogenitor cells, i.e., undifferentiated bone cells capable of differentiating into osteoblasts. The outer layer acts as a connective tissue to its surroundings, such as muscles. Because the osteoprogenitor cells in the cambium layer can differentiate into osteoblasts, they may initiate bone growth when stimulated (Owen 1978).

It is assumed here that the chemical conditions at the bone surface are altered through the stress driven diffusion where transport into the cambium layer is initiated. The effectiveness of the process depends on the permeability of the cambium, as well as the outer layer of the peristome. It is assumed that the cambium layer is permeable and the outer layer of the peristome is impermeable. The thickness of the cambium layer is very small compared with the diameter of the bone so that the concentration at $\Omega_{\text{out}}$ is taken to be the same in the cambium layer. The flux mechanisms are assumed to be similar to those of bone,

Figure 4. Results on the bone cross-section: (a) amplitude of the bending stress and (b) amplitude of the normalised concentration $\tilde{c}$. A denotes newly formed bone and B denotes original bone.
namely the transport is supposed to occur by means of stress driven diffusion. So that it is assumed that in regions of high concentration, bone growth will occur.

The results obtained using the 2D model can be compared with the classical experimental observations made by Lanyon and Rubin (1984) on turkey ulnae. In the present investigation, the cross-section of the right ulna considered in that study was analysed and is illustrated in Figure 1. The birds were exposed to cyclic compression with a frequency of 1 Hz. The average value of the bone width is a = 1.8 mm; the tissue-level diffusion coefficient D was taken from Patel et al. (2005) as 1.57 × 10^{-6} m^2/s. This leads to a value of the normalised frequency of \( \bar{\omega} \approx 13 \), where the natural curvature of the ulnae caused the bone to bend. In Figure 4(a), the bending stress distribution is combined with Figure 4(b) of Lanyon and Rubin (1984) showing the regions of bone growth. It should be noted that the actual ulna underlying the numerical results shown in Figure 4 is the left turkey ulna. There is a slight difference in the original width of the cortical bone with the left bone being somewhat bigger than the right bone. The original bone is marked in the figure with B and the bone growth with A. The differences in grey scale of the bone are distinct with new bone being a deeper shade. The concentration distribution in Figure 3(c) for \( \bar{\omega} = 10 \) is combined with their Figure 4(b). As may be observed, the bone growth is rather diffuse and does not necessarily occur at the parts of the cross-section that are the farthest from the neutral axis where the stress reaches its maximum (see Figure 4(a)). Instead, growth is spread out around the bone not very unlike the distribution of high concentration of Figure 4(b). Furthermore, the absence of bone growth does not necessarily coincide with the neutral axis.

5. Conclusions

Diffusion driven by hydrostatic stress is examined in a cross-section of a long bone. The analysis is 2D and provides an opportunity to study the distribution of growth promoting substances over the cross-section. The analysis is limited to a steady state result with the concentration required not to differ too much from its ambient value. A technique of separating the two phases of the solution into coupled static solutions is used to remove the time dependence of the variables. One part of the solution is in phase with the applied load, whereas the other part is out of phase. These unknown concentrations are found by means of an analogy with the problem of a plate on an elastic foundation. Using this analogy, the FE method is used to solve the plate problem.

It is found that at very low frequencies, the variation of the concentration is in phase with the applied load. It is observed to decay with an increase in frequency. It is assumed that the concentration of the bone nutrients leaks into the cambium layer of the periosteum where osteoblasts are excited to create new bone. Comparison is made with the experimental results for a turkey ulna (Lanyon and Rubin 1984). There is an interesting correlation between the experimental results for bone growth and regions of high concentration. The simulations indicate that there is a thin layer close to the periosteum with high concentration. As compared to the stress distribution (see Figure 4(a)), the concentration is more evenly distributed along the periosteum so that the nutrients are focused on this region. It may be observed in Figure 3(b), (c) that the behaviour is the same also at lower frequencies. The predicted growth seems reasonably correlated apart from a segment on the left side of the cross-section in Figure 4(b) where the growth rate is many times larger than the average. The reason for this is not known. One has to keep in mind that only one experimental observation of a single animal was considered; hence, variations may be expected. Indeed, simulations using the diffusion concept should be compared with other experimental findings. The simulations of the diffusion process could also be combined with a bone adaptation model where the geometry of the bone cross-section is updated while the bone is loaded. In that case, two timescales should be considered: over short time, the loading frequency would drive the diffusion process; for longer times, the changes in the bone cross-section would be observed.

It might be worthwhile in the future to reconsider the more accurate Equation (4) when \( c_0 = c \) to assess the effect of higher concentration values. In addition, more accurate values of the diffusivity constant \( D \) and the mechanical mobility \( B \) would be worth pursuing.

References


Appendix A: Analogy with a plate on an elastic foundation

The analogy between the present problem and a problem for an elastically supported plate is presented in this appendix. The concentration variables \( \hat{c}_1 \) and \( \hat{c}_2 \) are governed by Equation (24), which may be written as

\[
\nabla^2 \hat{c}_1 + \alpha^2 \hat{c}_2 = 0, \quad (A1)
\]

where \( \alpha^2 = 1.2 \). The boundary conditions, Equations (28)–(31), are rewritten as

\[
\begin{align*}
\hat{c}_1(\hat{x}, \hat{y}) &= 0 \quad \text{for} \ (\hat{x}, \hat{y}) \in \Omega_{in}^c \\
\frac{\partial^2 \hat{c}_1(\hat{x}, \hat{y})}{\partial \hat{n}^2} &= 0 \quad \text{for} \ (\hat{x}, \hat{y}) \in \Omega_{in} \\
\frac{\partial \hat{c}_1(\hat{x}, \hat{y})}{\partial \hat{n}} &= f_i \quad \text{for} \ (\hat{x}, \hat{y}) \in \Omega_{out} \\
\frac{\partial}{\partial \hat{n}} \left( \nabla^2 \hat{c}_1(\hat{x}, \hat{y}) \right) &= g_i \quad \text{for} \ (\hat{x}, \hat{y}) \in \Omega_{out},
\end{align*}
\]

(A2)

where \( f_i \) and \( g_i \) are the prescribed values.

Consider now a plate in its original configuration situated in the \( \hat{x}-\hat{y} \) plane. Kirchhoff’s theory for thin plates provides the differential equation for determining the deflection of the plate when it is subjected to a load \( p(x, y) \) applied in the \( z \)-direction, perpendicular to the plane of the plate. The theory omits effects of shearing on the deflection. The governing differential equation is given by

\[
D \nabla^4 w(x, y) = p(x, y), \quad (A3)
\]

where the plate stiffness is

\[
D = \frac{Eh^3}{12(1 - \nu^2)}. \quad (A4)
\]

Here, \( E \) is the Young’s modulus, \( h \) is the thickness of the plate and \( \nu \) is Poisson’s ratio. If the plate is supported by an elastic foundation, the load \( p \) becomes proportional to the deflection of the plate. This implies that

\[
p(x, y) = -kw(x, y). \quad (A5)
\]

Here, \( k \) is the stiffness of the foundation with dimensions of force \( F \) per unit volume \( L^3 \), i.e. \( F/L^3 \).

Assume that the plate has the shape of a ring as depicted in Figure 1. The plate is assumed to be simply supported at its inner edge, \( \Omega_{in} \), on its outer edge \( \Omega_{out} \), both the slope and shear force in the \( z \)-direction are prescribed. This leads to the following boundary conditions

\[
\begin{align*}
\frac{\partial^2 w(x, y)}{\partial n^2} &= 0 \quad \text{for} \ (x, y) \in \Omega_{in}^c \\
\frac{\partial w(x, y)}{\partial n} &= -\frac{1}{D} \left[ \frac{\partial}{\partial n} (\nabla^2 w(x, y)) \right] \quad \text{for} \ (x, y) \in \Omega_{out},
\end{align*}
\]

(A6)

where \( \partial / \partial n \) is the given rotation around the outer edge of the ring and \( V(x, y) \) is the given line shear load applied at the outer edge in the \( z \)-direction.

With the following replacements

\[
\begin{align*}
x &\rightarrow \hat{x} \quad y \rightarrow \hat{y} \quad n \rightarrow \hat{n} \\
k &\rightarrow \frac{ka^4}{D} \quad \omega_x \rightarrow \hat{\omega}_x
\end{align*}
\]

(A7)

both cases may be treated. For the first case, namely \( \hat{c}_1(\hat{x}, \hat{y}) \)

\[
\begin{align*}
w &\rightarrow \hat{c}_1(\hat{x}, \hat{y}) \quad \theta \rightarrow -D\omega_x(\hat{x}, \hat{y}) \quad V \rightarrow 0;
\end{align*}
\]

(A8)

and for the second case, namely \( \hat{c}_2(\hat{x}, \hat{y}) \)

\[
\begin{align*}
w &\rightarrow \hat{c}_2(\hat{x}, \hat{y}) \quad \theta \rightarrow 0 \quad V \rightarrow -D\omega_x(\hat{x}, \hat{y}).
\end{align*}
\]

(A9)

Thus, the analogy to the governing equations for \( \hat{c}_1 \) and \( \hat{c}_2 \) and their corresponding boundary conditions is established.

It may be interesting to note that the only free variable, the frequency \( \omega_x \) of the load on the bone, appears as the analogous stiffness of the foundation for the elastic plate. Thus, obviously, increasing the stiffness of the foundation leads to a distribution of the displacements of the plate which become increasingly concentrated at the outer edge of the plate, and in the limit of infinite stiffness, all displacements vanish. Thus, also the concentration of the diffusing substance, \( c \), is assumed to concentrate at the edge of the plate as the frequency increases and ought to decrease everywhere with increasing frequency; in the limit of infinite frequency, it should vanish.

Appendix B: 1D problem

The numerical method is validated by comparing it to a 1D problem that was solved analytically (Banks-Sills et al. 2011). The cross-section of the bone is assumed to be rectangular without the medullary cavity; half the cross-section is shown in Figure 2 where \( 2a \) is the height of the cross-section so that
\[-a \leq y \leq a.\] Antisymmetry was assumed so that only half the geometry is analysed here.

The governing partial differential Equation (10) becomes

\[
\dot{c}(y, t) = De^t(y, t),
\]  

(B1)

where the dot (\(\dot{}\)) represents differentiation with respect to \(t\) and the prime denotes differentiation with respect to the \(y\)-coordinate. Two boundary conditions and one initial condition are needed in order to solve Equation (B1). The boundary conditions are given as

\[
c(0, t) = c_0 \quad \text{and} \quad ac'(a, t) = P c_0 (\cos \omega t - 1).
\]  

(B2)

The boundary condition at \(y = 0\) follows from Equation (11). That at \(y = a\) is taken from Equation (12) of Banks-Sills et al. (2011) where \(P\) is a normalised driving force for the transported substance. It may be noted that the boundary condition in Equation (B2) is related to a cosine function, whereas the analogous boundary condition for the 2D problem in Equation (19) is related to a sine function. Because, in this study, the steady state solution is of interest, the phase on the right-hand side of Equation (19) is irrelevant. However, it may be noted that in Section 4.2, the amplitude of the wave is twice that in Banks-Sills et al. (2011). The boundary conditions of the problem are shown in Figure 2. The initial condition from Equation (20) is written here as

\[
c(y, 0) = c_0.
\]  

(B3)

The exact transient solution of this problem is found in Banks-Sills et al. (2011) (Equations (15) through (21)). It is readily observed that one part of the solution decays exponentially with time with a remaining non-decaying part that forms the steady state solution. The latter consists of a time-independent term that is linear in \(y\), and a sinusoidally varying part. In a more compact form, Equations (15) through (21) of Banks-Sills et al. (2011) may be written as

\[
\frac{c(y, t)}{c_0} = \frac{1}{P \left\{ \frac{1}{\eta a} \left[ \frac{\cosh (2\eta y) - \cos (2\eta y)}{2[\cosh (2\eta a) + \cos (2\eta a)]} \cos (\omega t + \varphi_\eta) - \frac{y}{a} \right] \right\}}.
\]  

(B4)

where

\[
\eta = \sqrt{\frac{\omega}{2D}}
\]  

(B5)

and \(\varphi_\eta\) is a phase angle that is a function of \(y\). In Equation (B4), the exponentially decaying term in time has been neglected. The solution may be approximated as being steady state after a long time, related to a characteristic timescale of the problem, such as \(t \gg a^2/D\).

As in Equation (21), the solution is separated into sine and cosine terms, so that

\[
\dot{c}(\hat{y}, \hat{t}) = \hat{c}_1(\hat{y}) \sin \hat{\omega} \hat{t} + \hat{c}_2(\hat{y}) \cos \hat{\omega} \hat{t}.
\]  

(B6)

In Equation (B6), some of the variables have been normalised as in Equation (16); note that in the 1D case, \(a\) represents half the length of the bone (see Figure 2). In addition, \(\hat{c}\) is normalised here as

\[
\hat{c} = \frac{1}{p} \frac{c - c_0}{y} + \frac{y}{a}.
\]  

(B7)

It may be noted that any linear term such as

\[
C_1 y + C_2,
\]  

(B8)

where \(C_1\) and \(C_2\) are constants, represents a trivial solution of Equation (B1) and may be added without reducing the generality of the solution. The term \(y/a\) is added to adjust the boundary condition in Equation (B2) to the purely sinusoidal boundary condition used in this investigation in Equation (19).

As in the 2D case, the functions \(\hat{c}_1(\hat{y})\) and \(\hat{c}_2(\hat{y})\) are independent and may be shown to be solutions of

\[
\hat{c}''_i(\hat{y}) + \omega^2 \hat{c}_i(\hat{y}) = 0,
\]  

(B9)

where \(i = 1, 2\). Equation (B9) is the counterpart to Equation (24) in one dimension. The boundary conditions at the medullar cavity, namely \(\hat{y} = 0\), become

\[
\hat{c}_1(0) = \hat{c}_2(0) = 0
\]  

(B10)

and

\[
\hat{c}''_1(0) = \hat{c}''_2(0) = 0.
\]  

(B11)

Equation (B10) follows from Equation (B2), whereas Equation (B11) may be obtained by writing the 1D versions of Equations (22) and (23). At the outer boundary, namely \(\hat{y} = 1\)

\[
\hat{c}'_1(1) = 0 \quad \text{and} \quad \hat{c}'_2(1) = 1.
\]  

(B12)

Equation (B12) is obtained from the boundary condition in Equation (B2), with the normalisation in Equation (B7) and use of Equation (B6). The fourth boundary condition is

\[
\hat{c}''_1(1) = -\omega \quad \text{and} \quad \hat{c}''_2(1) = 0.
\]  

(B13)

which is obtained by differentiating the 1D form of Equations (22) and (23) by \(\hat{y}\) and making use of Equation (B12).

The fourth-order differential equations given by (B9) are identical to the equation for a beam on an elastic foundation with a spring stiffness \(\omega^2\) per unit length. Here, there is an analogy between the governing equations for the concentration and that of the deflection of a beam. The boundary conditions at \(\hat{y} = 0\) in Equations (B10) and (B11) are those of a simply supported beam. For case 1, i.e., \(\hat{c}_1\), Equation (B12) gives a vanishing rotation and Equation (B13), a prescribed transverse force at \(\hat{y} = 1\). For case 2, Equation (B12) prescribes a rotation and Equation (B13) prescribes a vanishing transverse force.

To avoid confusion, it should be recalled that the bone is modelled in the 2D case as a hollow beam with the \(z\)-direction (see Figure 1) being along the longitudinal axis. The development above is analogous to a beam on an elastic foundation. Here, the longitudinal direction is along the \(y\)-axis (see Figure 2). In order to analyse this latter problem in conjunction with the FE method that was carried out for the original bone cross-section, the beam is assumed to be a plate on an elastic foundation in the \(xy\)-plane as in Figure 2. The behaviour along the \(x\)-axis should be uniform. As a result, the \(yz\)-plane is in a state of plane deformation as opposed
to plane stress which is the usual case for a thin beam. The implication is that the modulus of elasticity \( E \) would be replaced with \( E/(1 - \nu^2) \) in the corresponding solution for a beam. However, since only a relative error is sought here, this substitution does not affect the results.

Finally, in making a comparison between results obtained by means of the FE analysis and the exact solution, the amplitude of each is compared. For the FE result, \( \tilde{c}_{FE} \) is the amplitude of \( \tilde{c} \) which according to Equation (B6) is

\[
\tilde{c}_{FE} = \sqrt{\tilde{c}_1^2 + \tilde{c}_2^2}. \tag{B14}
\]

The corresponding analytical result, denoted by \( \tilde{c}_A \), is the amplitude of the solution in Equation (B4) when scaled according to Equation (B7) and is given by

\[
\tilde{c}_A = \frac{1}{\eta_2} \sqrt{\frac{\cosh(2\eta) - \cos(2\eta)}{2[\cosh(2\eta) + \cos(2\eta)]}} \tag{B15}
\]

The solution \( \tilde{c}_A \) is exact, whereas \( \tilde{c}_{FE} \) is a numerical result.