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MODELING BONE RESORPTION USING MIXTURE THEORY WITH CHEMICAL REACTIONS

GHOLAMREZA ROUHI, MARCELO EPSTEIN, LESZEK SUDAK AND WALTER HERZOG

The increasing rate of osteoporosis in an aging population calls for a greater understanding of the cellular mechanism of bone resorption. We propose a biphasic mixture model. The solid phase (matrix) is assumed to be elastic and isotropic, and the fluid phase is assumed to be a linear viscous fluid. We give conservation equations for each constituent and for the whole mixture, and write new constitutive equations for the system. The rate of mass supply to constituents, caused by chemical reactions, is taken from an empirical relation of dissolution kinetics. We derive the biochemomechanical affinity in terms of biological, chemical, and mechanical factors. The strain energy density, hydrostatic pressure, and concentration of different ions present in the mixture are shown to affect the rate of bone resorption.

1. Introduction

Resorption of extra-cellular matrices by osteoclasts [Teitelbaum and Ross 2003] is followed by osteoblastic invasion of the cavity, and subsequent secretion of extra-cellular matrix that is then mineralized [Ducy et al. 2000]. These two processes, which together are called bone remodeling, occur continuously and are in balance in healthy bone [Riggs et al. 2002]. Optimal remodeling is responsible for bone health and strength throughout life. An imbalance in bone remodeling may cause diseases such as osteoporosis. Osteoporosis is characterized by extensive bone resorption. This leads to a disturbance in the bone's microarchitecture, which increases the probability of fractures. It is often called a "silent disease" because there are no symptoms until a bone breaks.

An early hypothesis about the dependence of the structure and form of bones, and the mechanical loads they carry, was proposed by Galileo in 1638 [Ascenzi 1993], and was first described in a semiquantitative manner by Wolff [1892]. Today, it is well accepted that bone growth, maintenance, degeneration, and remodeling are biochemically regulated processes influenced by mechanical loading [Carter 1987; 1996]. There are several theories about the mechanisms of bone adaptation, each with its own governing equation for the process of remodeling (i.e., resorption and formation). They are typically based on a single-phase continuum mechanics approach [Cowin and Hegedus 1976; Hegedus and Cowin 1976; Beaupré et al. 1990; Jacobs et al. 1997; Huiskes et al. 2000; Ramtani and Zidi 2001; 2002; Doblaré and García 2001; Garcia et al. 2002; Ruimerman et al. 2005; Rouhi et al. 2006]. In these models, bone resorption and formation are modeled as a single process. Considering the time duration of bone resorption (1 to 3 weeks [Recker 1983]), its high importance in osteoporosis disease [Aguado et al. 1997], and the prevalence of treating osteoporosis with anti-bone-resorption drugs [Arnaud 2001], only the resorption process is modeled here.

Keywords: bone resorption, mixture theory, chemical reactions, osteoporosis.

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We treat bone as a biphasic mixture of matrix and fluid, and model resorption as an exchange of mass between the solid and fluid phases. This exchange is caused by the secretion of H^+ and Cl^- from osteoclasts, which creates an acidic environment in a sealed zone [Blair 1998; Rouselle and Heymann 2002]. In our model, demineralization depends on the rate of surface processes. Mixture theory with chemical reactions will be used to derive conservation laws of mass, linear and angular momentum, energy, and the entropy inequality. In the conservation of mass equations, the rate of mass transferred to different constituents is assumed given by an empirical relation arising from the dissolution kinetics of the solid phase. The governing equations for bone resorption are derived using the conservation laws, as well as entropy inequality and the appropriate constitutive equations. In the constitutive equations, it is assumed that dependent variables (e.g., free energy) are functions of temperature, deformation gradient, rate of deformation gradient, and the extent of chemical reactions.

To develop a general framework for the description of biochemomechanically driven bone resorption, we made the following assumptions:

- (1) Bone is a biphasic mixture of a solid phase (bone matrix) and a fluid phase (bone fluid).
- (2) The transfer of mass, energy and entropy between the solid and the fluid phases are a result of biochemical reactions that occur between the osteoclasts and the matrix.
- (3) The chemical reactions between osteoclasts and bone matrix are at the interface of the solid and fluid phase.
- (4) The characteristic time of chemical reactions is several orders of magnitude greater than the characteristic time associated with a complete perfusion of the blood plasma in bone; hence any excess heat generated by chemical reactions is quickly carried away by circulation, and bone resorption is considered isothermal.
- (5) The bone matrix obeys small deformation theory [Fritton et al. 2000] and is isotropic and linearly elastic.
- (6) The velocity of the bone matrix is zero.
- (7) The fluid phase is nonrotational, and viscous and inertial effects are neglected because of the slow velocities that are at play.
- (8) A nonpolar mixture assumption is made, thus the stress tensor and the inner part of the stress tensor are symmetric [Bowen 1971].
- (9) Both mechanical and chemical factors affect the rate of bone resorption, thus they both appear in the biochemomechanical affinity as driving forces of the chemical reactions.
- (10) The degree of saturation is a function of the biochemomechanical affinity which contains mechanical (strain energy density and hydrostatic pressure), biological (chemical potential generated by the resorbing cells), and chemical (concentration of different ions in the reaction) factors.
- (11) This biphasic system is closed with respect to mass transfer but open with respect to momentum, energy and entropy transfer.
- (12) The mechanical properties of the matrix are determined by the properties of the mineral phase.
- (13) Dissolution of the matrix is the same as resorption of the mineral phase.

2. Field equations

In this section, conservation equations (mass, linear and angular momentum and energy), biochemomechanical affinity and entropy inequality will be derived for a biphasic model of bone resorption. The conservation equations consist of balance for each constituent and a balance for the mixture as a whole.

Axiom of mass balance. Conservation of mass equations for each constituent and for the whole mixture, respectively, can be expressed as follows:

$$\frac{\partial \rho_s}{\partial t} = \widehat{C}_s, \quad (1)$$

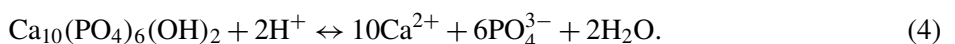
$$\frac{\partial \rho_f}{\partial t} + \text{grad } \rho_f \cdot V_f + \rho_f \text{ div } V_f = \widehat{C}_f, \quad (2)$$

$$\widehat{C}_s = -\widehat{C}_f = \widehat{C}, \quad (3)$$

where ρ_a is the density of the a -th constituent, V_f is the fluid velocity, grad denotes gradient with respect to spatial coordinates, t is the time, and \widehat{C}_a is the rate of mass supplied to the a -th constituent caused by the chemical reactions between the a -th constituent and other constituents of the mixture. The velocity of the matrix is assumed negligible.

Biochemomechanical affinity and dissolution kinetics. Bone matrix consists of 65% mineral and 35% organic matrix. The mineral phase is largely impure hydroxyapatite, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$. The organic matrix is 90% collagen and 10% various noncollagenous proteins [Jee 2001]. It has been shown that the mineral phase is an important determinant of bone elasticity, whereas the organic phase is responsible for the bone post-yield behavior [Reilly and Burstein 1975]. Bone mineral (hydroxyapatite) and organic (collagen I) matrix are degraded independently. Thus a bone resorption model needs two separate expressions, one for each phase. For lack of information about the dissolution of the organic phase, we only consider the mineral phase dissolution and assume that it is equivalent to the dissolution of the bone matrix. Microscopic observations suggest that degradation of collagen closely follows mineral degradation [Chambers et al. 1984], so our assumption may be justified.

Dissolution of minerals occurs at the surface. A major source of uncertainty is the surface reactivity, which depends on chemical composition, atomic structure, and surface topography (including surface curvature). The free energy of surface sites changes as a function of the aforementioned factors. Thus, no universal expression for the dissolution kinetics exists and experimental studies are needed to derive a dissolution kinetics relation for each case. The dissolution kinetics of hydroxyapatite has been the subject of numerous publications [Christoffersen et al. 1996; Dorozhkin 1997a; 1997b; 1997c; Thomann et al. 1989; 1990; 1991; Margolis and Moreno 1992; Hankermeyer et al. 2002; Fulmer et al. 2002; Chow et al. 2003]. Under certain conditions, dissolution is diffusion-limited and occurs with the formation of a calcium-rich boundary at the surface [Thomann et al. 1991]. Because of the small dimensions of the resorption microenvironment (between the osteoclasts and the bone matrix), we assume that dissolution is governed by the reaction kinetics. Bone resorption can then be simplified to (see [Blair 1998; Dorozhkin 1997a; 1997b; 1997c])



The chemical driving force for bone resorption (i.e., the chemical reaction shown in Equation (4)) can be expressed by the Gibbs free energy variation per mole

$$\Delta G = \sum_{i=1}^n v_i \mu_i = 10\mu_{\text{Ca}^{2+}} + 6\mu_{\text{PO}_4^{3-}} - 2\mu_{\text{H}^+} - \mu_{\text{Mineral}}, \tag{5}$$

where v_i and μ_i represent the stoichiometric coefficients and chemical potential of the substances involved in the chemical reactions, respectively. The quantity ΔG , can also be expressed as

$$\Delta G = RT \ln \frac{[\text{Ca}^{2+}]^{10} [\text{PO}_4^{3-}]^6 [\text{H}^+]_0^2}{[\text{Ca}^{2+}]_0^{10} [\text{PO}_4^{3-}]_0^6 [\text{H}^+]^2}, \tag{6}$$

where $[X]$ and $[X]_0$ are concentrations of ion X at time t and at equilibrium states, respectively. We hypothesize that *the rate of mass supplied to the a -th constituent caused by chemical reactions with other constituents, \hat{C}_a , can be found using experimental approaches of dissolution kinetics.*

Margolis and Moreno [1992] performed dissolution experiments with hydroxyapatite crystals, in which they measured pH, calcium and phosphate concentrations at a constant temperature. Assuming electroneutrality and congruent dissolution, kinetic data can be derived directly by measuring pH. They proposed the following equation for the rate of dissolution of the mineral phase of the bone matrix:

$$J = k(1 - DS)^m [\text{H}^+]^n, \tag{7}$$

where J is the mineral flux across the real surface of the mineral phase, DS is the degree of saturation, $[\text{H}^+]$ is the concentration of hydrogen ion, and k , m , and n are empirical constants. As stated earlier, it is assumed that J is almost equal to the dissolution rate of the solid phase, i.e. hydroxyapatite + collagen I.

The degree of saturation (DS) is expressed as

$$DS = \left(\frac{[\text{Ca}^{2+}]^5 [\text{PO}_4^{3-}]^3 [\text{OH}^-]}{K_{so}} \right)^{1/9} = \exp \frac{\Delta G}{18RT}, \tag{8}$$

where $[X]$ is the concentration of ion X , K_{so} is the solubility product of hydroxyapatite, R is the universal gas constant, and T is the absolute temperature [Margolis and Moreno 1992].

Since biological, chemical, and mechanical factors have a definite effect on the rate of dissolution, we hypothesize that a biochemomechanical driving force should be considered in the dissolution relation, instead of just a chemical driving force: see Equation (6). We will use a dissipation law to find the biochemomechanical affinity. Dissipation in the system is defined as the difference between the external work rate and the rate of change in free energy. According to the Second Law of Thermodynamics, this quantity should be nonnegative, that is

$$\frac{dD}{dt} = \frac{dW_{\text{ext}}}{dt} - \frac{d\psi}{dt} \geq 0. \tag{9}$$

For a solid-fluid mixture, in a nonequilibrium state, a chemical process will occur on the interface of the solid and fluid phase, resulting in a flow of mass through the boundary and a change in boundary position. In the presence of chemical reactions, the external work rate can be separated into a mechanical

term $W_{\text{ext}}^{\text{mech}}$ and a chemical term $W_{\text{ext}}^{\text{chem}}$:

$$\frac{dW_{\text{ext}}}{dt} = \frac{dW_{\text{ext}}^{\text{mech}}}{dt} + \frac{dW_{\text{ext}}^{\text{chem}}}{dt}. \tag{10}$$

The mechanical work rate can be expressed as

$$\frac{dW_{\text{ext}}^{\text{mech}}}{dt} = \int_{V_s} v^s \cdot b \, dv + \int_{\Gamma} V^s \cdot T \, da, \tag{11}$$

where b is the bulk body force, T is the traction on the surface, V_s is the normal velocity at which the boundary is moving, and v^s is the material velocity of a point at the current boundary position [Silva and Ulm 2002].

Assuming that dissolution occurs only at the solid-fluid interface, then $T = -Pn$ at Γ . Using the equilibrium equation, the divergence theorem, and the definition of strain rate, one can conclude that

$$\frac{dW_{\text{ext}}^{\text{mech}}}{dt} = \int_{V_s} \text{tr}(\sigma D) \, dv - \int_{\Gamma} p v^c \, da, \tag{12}$$

where D is the rate of deformation tensor, tr denotes trace, and v^c is the chemical velocity which is defined by

$$v^c = V^s - v^s \cdot n, \tag{13}$$

where n is the outward unit vector normal to the solid-fluid interface.

The chemical work rate can be expressed as the chemical energy associated with the flow through the surface ($J_\rho = \rho(v^s \cdot n - V^s) = -\rho v^c$), which is proportional to the external chemical potential, μ_{ext} . External chemical potential, μ_{ext} , is the chemical potential generated by the resorbing cells and is also called the biologically generated potential [Silva and Ulm 2002]:

$$\frac{dW_{\text{ext}}^{\text{chem}}}{dt} = - \int_{\Gamma} \frac{\mu_{\text{ext}} J_\rho}{M} \, da = \int_{\Gamma} \mu_{\text{ext}} C_s v^c \, da. \tag{14}$$

C_s is defined as

$$C_s = \frac{\rho}{M}, \tag{15}$$

where ρ and M are the density and the molar mass of the matrix, respectively.

The rate of free energy variation can be written as

$$\frac{d\psi}{dt} = \frac{d}{dt} \int_{V_s} \psi \, dv = \int_{V_s} \left(\frac{\partial \psi}{\partial t} + \text{div}(\psi v^s) \right) \, dv + \int_{\Gamma} \psi v^c \, da. \tag{16}$$

Using (12), (14), (10), and (16) in (9), one obtains for the dissipation rate

$$\frac{dD}{dt} = \int_{V_s} \left(\text{tr}(\sigma D) - \frac{\partial \psi}{\partial t} x - \text{div}(\psi v^s) \right) \, dv - \int_{\Gamma} (\psi + P - \mu_{\text{ext}} C_s) v^c \, da. \tag{17}$$

Equation (17) allows the identification of the driving force in the dissolution process (A):

$$A = \psi + P - \mu_{\text{ext}} C_s. \tag{18}$$

The free energy (ψ) can be expressed as a sum of the mechanical and the chemical energies:

$$\psi = \psi^{\text{mech}} + \psi^{\text{chem}}. \tag{19}$$

The chemical free energy, ψ^{chem} , can be expressed as

$$\psi^{\text{chem}} = C_s \mu_s, \tag{20}$$

where μ_s is the chemical potential of the solid phase in the unstressed condition.

Thus, the driving force for the dissolution process can be written as

$$A = \psi^{\text{mech}} + P + C_s(\mu_s - \mu_{\text{ext}}). \tag{21}$$

A in Equation (21) is the biochemomechanical driving force.

Thus, the Second Law defines the following dissipation condition at the surface:

$$-Au^C \geq 0 \quad \text{at } \Gamma. \tag{22}$$

It is well accepted that biological, chemical and mechanical factors affect the rate of chemical reactions, generally, and the degree of saturation, specifically. By substituting the biochemomechanical driving force A in (21) into the rate of dissolution of the mineral phase, given by Equation (7), one can derive

$$\begin{aligned} J &= k \left(1 - \exp \frac{-A}{18RTC_s} \right)^m [\text{H}^+]^n \\ &= k \left(1 - \left(\frac{[\text{Ca}^{2+}]}{[\text{Ca}^{2+}]_0} \right)^{10/18} \left(\frac{[\text{PO}_4^{3-}]}{[\text{PO}_4^{3-}]_0} \right)^{1/3} \left(\frac{[\text{H}^+]_0}{[\text{H}^+]} \right)^{1/9} \exp \left(\frac{\psi_{\text{mech}} + P}{-18RTC_s} \right) \right)^m [\text{H}^+]^n. \end{aligned} \tag{23}$$

The rate of mass supplied to the fluid phase, i.e. \widehat{C}_f , which is equal to $-\widehat{C}_s$, can be related to J (Equation (23)) using the relation

$$\widehat{C}_f = -\widehat{C}_s = \widehat{C} = \frac{MS_{\text{act}}}{V_{\text{tot}}} J, \tag{24}$$

where S_{act} is the total active area available for the resorption process, V_{tot} is the total volume of the mixture. Since \widehat{C}_a is expressed per unit volume, V_{tot} is assumed to be one.

Now, one can write the conservation of mass equation for the solid phase:

$$\begin{aligned} \frac{\partial \rho_s}{\partial t} = \widehat{C}_s = -\widehat{C} &= k \left(1 - \exp \frac{-A}{18RTC_s} \right)^m [\text{H}^+]^n \\ &= -kS_{\text{act}}M \left(1 - \left(\frac{[\text{Ca}^{2+}]}{[\text{Ca}^{2+}]_0} \right)^{10/18} \left(\frac{[\text{PO}_4^{3-}]}{[\text{PO}_4^{3-}]_0} \right)^{1/3} \left(\frac{[\text{H}^+]_0}{[\text{H}^+]} \right)^{1/9} \exp \left(\frac{\psi_{\text{mech}} + P}{-18RTC_s} \right) \right)^m [\text{H}^+]^n. \end{aligned} \tag{25}$$

To solve Equation (25), we need the area available for resorption, the ion concentrations in the mixture, and the strain energy density of the solid phase and the hydrostatic pressure exerted by the fluid on the solid phase.

Equation (25) shows that increasing the concentration of Ca^{2+} with respect to the initial concentration decreases the rate of resorption. This agrees with experimental observations [Lorget et al. 2000]. The same equation demonstrates that increasing the H^+ concentration increases the rate of resorption; we

can increase the H^+ concentration by changing the activity of proton pumps in osteoclasts. Another corollary of Equation (25) addresses a crucial question: Are mechanical factors alone at play in the bone resorption process, or are other factors (e.g., chemical and biological) important as well? As Equation (25) shows, not only the mechanical factors (strain energy density ψ_{mech} and hydrostatic pressure p) but also chemical and biological factors (ion concentration) affect the rate of bone resorption.

If one only considers the effects of chemical factors and ignores the mechanical ones, the conservation of mass equation for the bone matrix will become

$$\frac{\partial \rho_s}{\partial t} = -k S_{\text{act}} M \left(1 - \left(\frac{[Ca^{2+}]}{[Ca^{2+}]_0} \right)^{10/18} \left(\frac{[PO_4^{3-}]}{[PO_4^{3-}]_0} \right)^{1/3} \left(\frac{[H^+]_0}{[H^+]} \right)^{1/9} \right)^m [H^+]^n. \tag{26}$$

On the other hand, if one only considers mechanical factors and discards the chemical ones, the conservation of mass equation for the matrix will become

$$\frac{\partial \rho_s}{\partial t} = -k S_{\text{act}} M \left(1 - \exp\left(\frac{\psi_{\text{mech}} + P}{-18RT C_s}\right) \right)^m. \tag{27}$$

Axiom of linear and angular momentum. Assuming that the body forces and inertia effects are negligible compared to other forces, the solid phase velocity is negligible and it is linearly elastic. Also, the fluid is viscous; the linear momentum equations for the solid, fluid, and the whole mixture are, respectively,

$$\text{div}(2\mu E + \lambda \text{tr } E) + \hat{p}_s = 0, \tag{28}$$

$$\frac{\partial(\rho_f V_f)}{\partial t} + \text{div}(\rho_f V_f \otimes V_f) = \text{div}(-pI + 2\eta D) + \hat{p}_f - \widehat{C} V_f, \tag{29}$$

$$\text{div}(2\mu E + \lambda \text{tr } E + -pI + 2\eta D) = 0, \tag{30}$$

where \hat{p}_a is the momentum supply to the a -th constituent, p is the hydrostatic pressure in the fluid phase, μ , η , and λ are Lamé’s constants, and E and D are strain and rate of deformation tensors, respectively.

Assuming a nonpolar mixture for bone, the axiom of moment of momentum for the a -th constituent can be reduced to

$$T_a = T_a^T. \tag{31}$$

Conservation of angular momentum for the whole mixture can be written as

$$\text{div}(x \times (2\mu E + \lambda \text{tr } E + T_c - pI + 2\eta D)) = 0. \tag{32}$$

Using compatibility requirements for the linear momentum of each constituent and the whole mixture, one obtains

$$\widehat{P}_s + \widehat{P}_f = \widehat{C} V_f, \tag{33}$$

where the parameters in Equation (33) have been introduced earlier.

First and Second Laws of Thermodynamics. Using the First Law of Thermodynamics and assuming that the resorption process is isothermal, the following relations can be derived for the matrix, the fluid,

and the whole mixture, respectively:

$$\rho_s \frac{\partial \varepsilon_s}{\partial t} = \hat{\varepsilon}_s, \tag{34}$$

$$\rho_f \left(\frac{\partial \varepsilon_f}{\partial t} + \text{grad } \varepsilon_f \cdot V_f \right) = \frac{1}{2} \text{tr}(-pD_f + 2\eta D_f^2) + \hat{\varepsilon}_f, \tag{35}$$

$$(\rho_s + \rho_f) \left(\frac{\partial \varepsilon_I}{\partial t} + \text{grad } \varepsilon_I \cdot \frac{\rho_f V_f}{\rho_f + \rho_s} \right) = \text{tr}(2\mu E + \lambda \text{tr } E + T_c - pI + 2\eta D), \tag{36}$$

where ε_a is the internal energy density, $\hat{\varepsilon}_a$ is the energy supplied to the a -th constituent, and ε_I is the inner part of the internal energy density.

The inner part of the internal energy density, assuming that the product of the diffusion velocities is negligible, can be written as

$$\varepsilon_I = \frac{1}{\rho_s + \rho_f} (\rho_s \varepsilon_s + \rho_f \varepsilon_f). \tag{37}$$

In Equations (34)–(36) it is assumed that the external heat supply to the solid and fluid phase is zero and that the products of the diffusion velocities can be neglected.

The second axiom of thermodynamics for a mixture of N reacting materials without diffusion is the postulate that for every admissible thermodynamical process [Bowen 1968],

$$-\rho(\dot{\psi} + \eta\dot{\theta}) + \text{tr}(TL) - \frac{\text{grad } \theta \cdot q}{\theta} \geq 0. \tag{38}$$

From the consistency requirement for energy balance for the constituents and the whole mixture, we obtain for the biphasic model

$$\widehat{C} = \frac{\hat{\varepsilon}_s + \hat{\varepsilon}_f + V_f \widehat{P}_f}{\varepsilon_f - \varepsilon_s + \frac{1}{2} V_f^2}. \tag{39}$$

Equation (39) shows that in a bone with high value of porosity, the rate of resorption decreases with increasing fluid velocity. In agreement with the aforementioned point, experimental evidence shows that by exerting intermittent forces on bone (i.e., increasing bone fluid velocity and pressure), rate of resorption decreases [Flieger et al. 1998; Rubin et al. 1998; 2001a; 2004].

Using the Second Law of Thermodynamics, one can find the maximum amount of the rate of bone resorption for this biphasic, isothermal process:

$$\widehat{C}_{\text{Max}} = \frac{\rho_s \frac{\partial \eta_s}{\partial t} + \rho_f \left(\frac{\partial \eta_f}{\partial t} + \text{grad } \eta_f \cdot V_f \right)}{\eta_f - \eta_s}. \tag{40}$$

Because of the greater value of $\eta_f - \eta_s$ in cancellous than in cortical bone, Equation (40) predicts that the maximum rate of resorption in cortical bone will be greater than in trabecular bone. This behavior of cortical and trabecular bone, which is well accepted experimentally [Martin and Burr 1989], can be predicted using the conservation of mass equation (27), as well. More research is needed to find the clinical implications of Equation (40) and explore different methods to control it.

3. Damage, pressure, and rate of bone resorption

It is well accepted that physiologic strains produce fatigue damage in bone [Burr and Martin 1993; Mori and Burr 1993; Martin 2003; Taylor et al. 2003]. Damage, in turn, is associated with osteocyte apoptosis and activation of the remodeling process (i.e., resorption and formation) which repairs the damage [Martin 2003]. Experimental studies in which damage is produced by cyclic loading demonstrated that resorption is primarily associated with microcracks [Burr and Martin 1993; Mori and Burr 1993]. It has also been observed that resorption in the vicinity of microcracks occurs more often than expected [Li et al. 2001]. Also, experimental evidence shows that intermittent forces can increase the rate of bone remodeling [Rubin et al. 1998; 2001a; 2001b; 2002; 2004].

Equation (27) can be used to find a theoretical explanation for the experimental observations mentioned. It is well known that there is a stress concentration in the vicinity of cracks and thus an increase in the strain energy density. Using (27), we see that by increasing strain energy density (in the vicinity of cracks), there will be an increase in the biochemomechanical affinity — see (21) — and, as a result, an increase in the rate of resorption. Also, (27) can be used to find a theoretical support for a greater rate of resorption in cortical than trabecular bone [Martin and Burr 1989]. In cortical bone, osteoclasts come into contact with the surface, eroding the bone and producing cavities called cutting cones. In trabecular bone, osteoclasts erode flat surfaces of the bone and produce Howship’s lacunae [Eriksen and Kassem 1992]. The stress and strain energy magnifications in the cutting cones of cortical bone are much greater than in the Howship’s lacunae of trabecular bone. This can lead to a bigger strain energy density for cortical bone and thus — see (27) — a higher rate of resorption than for trabecular bone.

To the best of our knowledge, there is no theoretical model that incorporates hydrostatic pressure of the bone fluid phase with the rate of bone resorption. But there is experimental evidence in favor of the idea that increasing hydrostatic pressure of the bone fluid can enhance rate of bone resorption; see, for example, [Van Der Vis et al. 1998; Skripitz and Aspenberg 2000; Astrand et al. 2003]. If one discards the chemical factors (Equation (27)), effects of both hydrostatic pressure, P , and strain energy density, ψ_{mech} , on the rate of bone resorption can be observed (Figure 1). This figure shows that increasing either P or ψ_{mech} has a direct effect on the rate of bone resorption. The following values have been considered

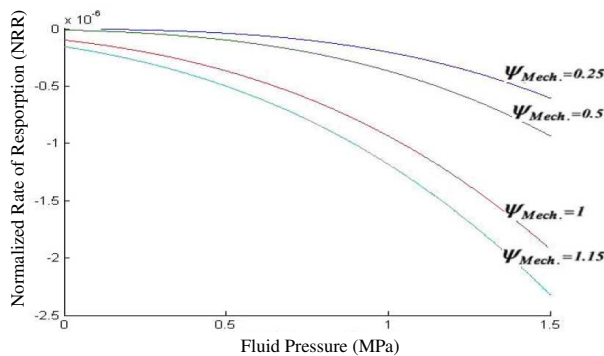


Figure 1. Normalized rate of resorption (NRR) versus fluid pressure for four different values of strain energy density ($kS_{act}M$ is considered a constant). Increasing either fluid pressure P or free energy density of the ψ_{mech} of the solid phase enhances the rate of bone resorption.

for R , T and C_s , respectively: $8.3145 \text{ J mol}^{-1} \text{ K}^{-1}$, 310.15 K and $2988.05 \text{ mol} \cdot \text{m}^{-3}$; the vertical axis, representing $((\partial \rho_s / \partial t)(k S_{\text{act}} M)^{-1})$, has been normalized.

4. Constitutive assumptions and restrictions imposed by the Second Law of Thermodynamics

We assume that the Helmholtz free energy ψ , specific entropy η , stress tensor T , heat flux vector q , and the reaction vector ω are functions of temperature θ , deformation gradient F , and the extent of the chemical reaction vector ζ . Bowen [1968] makes a similar assumption for chemically reacting mixtures. Since the characteristic time for bone resorption (1 to 3 weeks, according to Recker [1983]) is much longer than the frequency of mechanical loading, one can assume that each dependent variable (ψ , η , T , q , and ω) in the constitutive equations is a function of θ , $\text{grad } \theta$, F , \dot{F} , and ζ :

$$\begin{aligned} \psi &= \bar{\psi}(\theta, \theta_{,i}, F, \dot{F}, \zeta); \\ \eta &= \bar{\eta}(\theta, \theta_{,i}, F, \dot{F}, \zeta); \\ T &= \bar{T}(\theta, \theta_{,i}, F, \dot{F}, \zeta); \\ q &= \bar{q}(\theta, \theta_{,i}, F, \dot{F}, \zeta); \\ \omega &= \bar{\omega}(\theta, \theta_{,i}, F, \dot{F}, \zeta). \end{aligned} \tag{41}$$

Taking the material time derivative of (41)₁, we obtain

$$\begin{aligned} \dot{\psi} &= \frac{\partial \bar{\psi}(\theta, \theta_{,i}, F, \dot{F}, \zeta)}{\partial \theta} \dot{\theta} + \psi_{,g}(\theta, \theta_{,i}, F, \dot{F}, \zeta) \cdot \dot{g} \\ &+ \text{tr} \left(\frac{\partial \bar{\psi}(\theta, \theta_{,i}, F, \dot{F}, \zeta)}{\partial F} \dot{F} \right) + \text{tr} \left(\frac{\partial \bar{\psi}(\theta, \theta_{,i}, F, \dot{F}, \zeta)}{\partial \dot{F}} \ddot{F} \right) + \frac{\partial \bar{\psi}(\theta, \theta_{,i}, F, \dot{F}, \zeta)}{\partial \zeta} \dot{\zeta}. \end{aligned} \tag{42}$$

Using Equation (42) in the entropy inequality (38) and making use of standard arguments [Coleman and Gurtin 1967], one can obtain the following relations for the specific Helmholtz free energy, specific entropy, and stress tensor:

$$\psi = \bar{\psi}(\theta, F, \zeta), \tag{43}$$

$$\eta = \bar{\eta}(\theta, F, \dot{F}, \zeta) = - \frac{\partial \bar{\psi}(\theta, F, \zeta)}{\partial \theta}, \tag{44}$$

$$T = \rho \frac{\partial \bar{\psi}(\theta, F, \zeta)}{\partial F} F^T. \tag{45}$$

As a result, entropy inequality reduces to the form

$$- \frac{\text{grad } \theta \cdot q}{\theta} + A(\theta, F, \zeta) \cdot \dot{\zeta} \geq 0, \tag{46}$$

where A is the *chemical affinity* as defined in [Prigogine and Defay 1954]:

$$A = - \frac{\partial \bar{\psi}(\theta, F, \zeta)}{\partial \zeta} \Big|_{V \& \theta = \text{const.}}. \tag{47}$$

If q is independent of $\text{grad } \theta$, then the entropy inequality takes the form

$$A(\theta, F, \zeta) \cdot \dot{\zeta} \geq 0. \quad (48)$$

The affinity A is acting as a driving force for the chemical reactions. When A is zero, there will be a thermodynamic equilibrium state. For bone resorption, an expression for A , as a biochemomechanical driving force was derived (Equation (21)). The role of biological (concentration of H^+ produced by proton pumps in osteoclasts), chemical (chemical potential of the matrix), and mechanical (strain energy density, and hydrostatic pressure) factors is to change the magnitude and polarity of the affinity. When Equation (21) is equal to zero, there will be a resorption equilibrium state analogous with the remodeling equilibrium state in bone remodeling process. Considering Equation (21) as a driving force of resorption process, it seems more reasonable to assume that resorption is controlled by not only mechanical, but also, chemical, and biological factors, simultaneously.

5. Conclusion and discussion

In this paper, a mixture theory model with chemical reactions for bone resorption process has been presented. A biphasic model, composed of a solid phase (bone matrix), and a fluid phase (bone fluid) is developed. General expression for a driving force of the bone resorption process which contains biological, mechanical and chemical factors is concluded. In the mass conservation equations, rate of mass supplied to the fluid phase by chemical reactions between the matrix and fluid is assumed to be equal to an empirical relation of the dissolution kinetics of the mineral phase of the bone matrix. Degree of saturation is assumed to be a function of the biochemomechanical affinity (Equation (21)), but not only of the Gibbs free energy (Equation (6)). As a result, mechanical, biological and chemical factors appear in the conservation equations, the constitutive assumptions, and the entropy inequality.

Strain energy density has been shown experimentally to be a likely stimulus for bone remodeling [Brown et al. 1990] and was used extensively in many theoretical modeling of bone adaptation; see, for instance, [Jacobs et al. 1997; Huiskes et al. 2000; Doblaré and García 2001; Garcia et al. 2002; Ruimerman et al. 2005]. Here, it is theoretically shown to be an effective mechanical stimulus for the bone resorption. Also, hydrostatic pressure is introduced as another mechanical stimulus for the bone resorption. Using this model, it is also shown that increasing either strain energy density or hydrostatic pressure will enhance rate of bone resorption (Figure 1). The last point can be used as a theoretical justification for many experimental observations [e.g., [Burr et al. 1985; Burr and Martin 1993; Mori and Burr 1993; Schaffler and Jepsen 2000; Li et al. 2001; Martin 2003; Van Der Vis et al. 1998; Skripitz and Aspenberg 2000; Astrand et al. 2003]. This model also shows that an increase in the concentration of H^+ or a decrease in the concentrations of PO_4^{3-} and Ca^{2+} can cause a reduction of the rate of bone resorption. Experimental data can be found in support of this model's predictions of the effect of Ca^{2+} concentration on the rate of bone resorption [Lorget et al. 2000].

Biological tissues are all composed of multiphase constituents, and there are chemical reactions and/or diffusions between different components of them. Cells as live organs in the biological tissues can dictate rate of growth and adaptation, and their activities are affected by different factors (e.g., mechanical, chemical, and biological factors). One purpose of this research was using a mixture theory approach for modeling bone resorption. By this, we hoped to gain new insight about engineering and biological

factors which can change the rate of bone resorption, especially in the osteoporotic cases. Nowadays, the most common method in treating osteoporosis is anti-bone-resorption drugs which inhibit or reduce the bone resorbing cells (i.e. osteoclasts) activity. The reason for using this way of treatment is the lack of information about all the factors affecting osteoclasts' activity. This preliminary theoretical research shows that the activity of osteoclasts and, thus, the rate of bone resorption are not only dictated by biological factors (e.g., hormone levels), but also by engineering factors (hydrostatic pressure, strain energy density, and concentration of different ions present in the resorption process); see Equations (21), (25) and (48). Another goal was to make a novel attempt to combine mixture theory with chemical kinetics. This could be useful not only for modeling growth and adaptation of biological tissues such as bone, cartilage, and muscle, but also for modeling nonbiological processes such as stress corrosion. In order to attain the second goal, more theoretical and experimental research is in progress.

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GHOLAMREZA ROUHI: grouhi@uottawa.ca

Department of Mechanical Engineering, University of Ottawa, 161 Louis Pasteur, Room A017 Ottawa, Ontario, Canada K1N 6N5, Canada

MARCELO EPSTEIN: mepstein@ucalgary.ca

Department of Mechanical and Manufacturing Engineering, University of Calgary, 2500 University Dr. NW, Calgary, Alberta T2N 1N4, Canada

LESZEK SUDAK: lsudak@ucalgary.ca

Department of Mechanical and Manufacturing Engineering, University of Calgary, 2500 University Dr. NW, Calgary, Alberta T2N 1N4, Canada

WALTER HERZOG: walter@kin.ucalgary.ca

Faculty of Kinesiology, University of Calgary, 2500 University Drive NW, Calgary, Alberta T2N 1N4, Canada

