SENSITIVITY TO THE POLARITY OF EXTERNAL LOADS IN BONE REMODELING PROCESS

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INTRODUCTION

More than three centuries ago the dependence of the structure and form of bones and the mechanical load they carry was proposed by Galileo in 1638 [1]. It is unanimously believed that Wolff [2] pioneered for proposing that bone adapts to mechanical loading during its growth and development. Although, he hypothesized that these adaptation happens in accordance with mathematical laws, he never tried to formulate a mathematical theory [3]. The common motivating factors for the theoretical and computational modeling efforts were, first, to understand and quantitatively describe the functional adaptation of bone, then, to simulate and predict bone adaptation, and finally to simulate the effects of manipulations to processes, in the hope of testing ideas that may be therapeutically beneficial [4]. Several mechanisms have been proposed to relate changes in mechanical loads to the adaptive responses in bone [5-9]. The first mathematical description of trabecular bone remodeling was introduced by Frost [10-11].

Huiskes et al. [6] developed a semi-mechanistic model for bone remodeling process. This theory includes the latest experimental findings in bone cells physiology, including a separate description of osteoclastic resorption and osteoblastic formation [12]; a biological osteocyte mechanosensory system [13-15]; and role of microdamage [16-18].

By employing a FEA model for different initial bone matrix and loading cases and using their semi-mechanistic model, Huiskes et al. [6] and Ruimerman et al. [7] obtained reasonable results. Recently, Vahdati et al. [19] incorporated cellular accommodation and also effects of microdamage and disuse into Huiskes et al.'s semi-mechanistic model of bone remodeling [6].

Purpose of this research which is based on Vahdati et al.'s recent contribution [19] is to investigate the effect of external load polarity on the bone remodeling process. Knowing that mechanical stimulus for bone remodeling in the former model is rate of strain energy, which is a scalar quantity, one expects to observe an independent behavior of bone remodeling with changing external load direction, of course for the same magnitude of load. Interestingly, our results show a different trend, i.e. bone geometry at the end of remodeling is direction dependent. This odd behavior will be discussed and some interpretation will be raised.

METHODS

Huiskes et al. [6] and Ruimerman et al. [7] assumed that bone tissue contains *n* osteocytes per mm^3 located in the mineralized matrix with a total of *N* in the domain of interest. Also, it is assumed that osteocytes are sensitive to the maximal rate of the strain energy density (SED) in a recent loading history. Each osteocyte *i* measures a mechanical signal, the strain energy density, in its location. The maximal SED rate, $R_i(t)$, in the location of osteocyte *i* is calculated as the derivative of the SED using a loading-time averaging procedure. Then, osteocytes recruit osteoblasts to form new bone. The exponential influence of an osteocyte on its surrounding is assumed to decrease with distancing away from the osteoblasts. The functional representation of the effect of the osteocytes *i* on the osteoblast at location ξ is postulated considering only the spatial variable, i.e.:

$$f_i(\xi) = e^{-\frac{d_i(\xi)}{D}} \tag{1}$$

where $d_i(\xi)$ is the distance between the position of the osteoblast and osteocyte *i*, and D is influential distance of an osteocyte which is a constant. Equation (1) is a mere hypothetic representation of the osteocyte weighted influence, and no experimental data were proposed to support this influence function which could be a place of debate [4]. The total osteoblast recruitment stimulus, $K(\xi,t)$, in location ξ and at time t will be determined by a summation function in which all osteocytes located in a distance less than D will contribute. So, osteoblast recruitment stimulus, K(ξ,t), can be written in terms of mechanosensitivity, μ_i, and maximal strain energy density rate, $R_i(t)$, of osteocyte *i* as follows:

$$K(\xi, t) = \sum_{i=1}^{n} f_i(\xi)\mu_i R_i(t) \quad (2)$$

Rate of change of apparent (or relative) density, $\frac{d\rho}{dt}$, of the trabecular bone is given depending upon the relational comparison of the amount of K(ξ,t) with a constant threshold value, k_{tr}, for bone formation as:

$$\frac{d\rho}{dt} = \tau\left[K(\xi, t) - k_{tr}\right] - r_{oc} \quad \text{for} \quad K(\xi, t) > k_{tr} \quad (3a)$$

$$\frac{d\rho}{dt} = -r_{oc} \quad \text{for} \quad K(\xi, t) \le k_{tr} \quad (3b)$$

where τ is a constant value regulating the rate of the remodeling process and r_{oc} is the constant amount of mineral resorbed by osteoclasts per day. For osteoclast activation per surface site at any given time a probabilistic approach is used in the model, p(ξ,t). This probability was assumed to be regulated either by the presence of microcracks (hypothesis-I) or by disuse (hypothesis- II). In hypothesis-I, the probability of resorption by microcracks was considered spatially random and is assumed as follows:

$$p(\xi, t) = \text{constant} \quad (4)$$

In this study, for the sake of simplicity, only the incidence of the microcracks is considered and the value of p(ξ,t) is set to 10%. Modulus of elasticity of bone, E(ξ,t), is a variable changing with apparent (or relative) density, and is determined using Currey's approach as[20]:

$$E(\xi, t) = E_{max}\,(\rho(\xi, t))^{\gamma} \quad (5)$$

where E_{max} and γ are constants.

Huiskes theory [6] proposes that while osteoblast formation is directly developed by mechanical stimuli from external loads, the osteoclast resorption happens when the microcracks exist with a 10% chance for hypothesis I. The external load is transferred through the mineralized bone matrix where the strain energy density is assessed by the osteocytes [7].

In this study, a 2-D isotropic, square trabecular bone matrix is discretized in micro scale; and the set of equations given above will be solved using finite element approach in a Mat code for the following cases of external load: (1) all compressive; (2) all tensile; (3) shear forces. In doing the simulations, a custom-developed code, with two main parts which is comprised of mechanical and biological calculations, was run for 1000 iteration.

RESULTS

Results of this study are presented in the following figures. The simulation starts with an initial configuration (a), and the resultant adaptation is given in (b) for all figures, respectively. For both compression (Fig. 1) and tension (Fig. 2) loading cases the model eventually resulted in a similar pattern of the bone relative density distribution. In pure shear loading conditions (Figs. 3 and 4) almost exact same final configurations of the relative bone density have been resulted. The variation of the relative density with time for all cases can be seen in Fig. (5). While cases C and D overlap, but a small difference can be noticed between cases A and B. This difference might be attributed to inherent randomness in the model which is probabilistic production of the microcracks (Eq. 4).

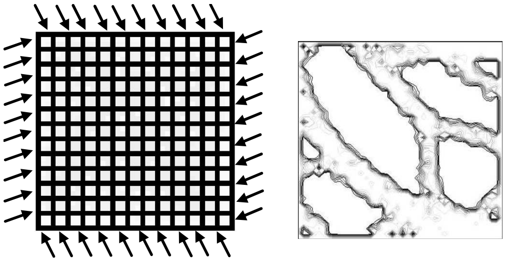

(a) (b)

Fig.1 Bone adaptation in compression loading (Case A) (black= bone, white= bone marrow)

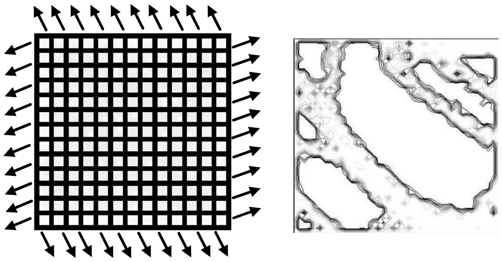
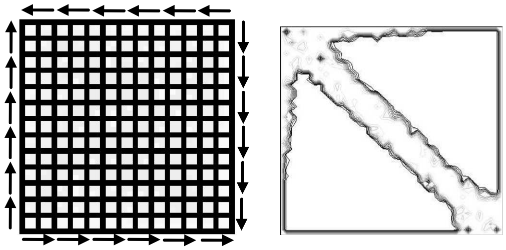
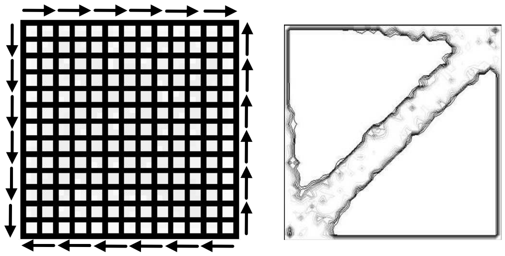

(a) (b)

Fig.2 Bone adaptation in tension loading (Case B) (black= bone, white= bone marrow)



(a) (b)

Fig.3 Bone adaptation in shear loading (Case C) (black= bone, white= bone marrow)



(a) (b)

Fig.4 Bone adaptation in shear (left) loading (Case D) (black= bone, white= bone marrow)

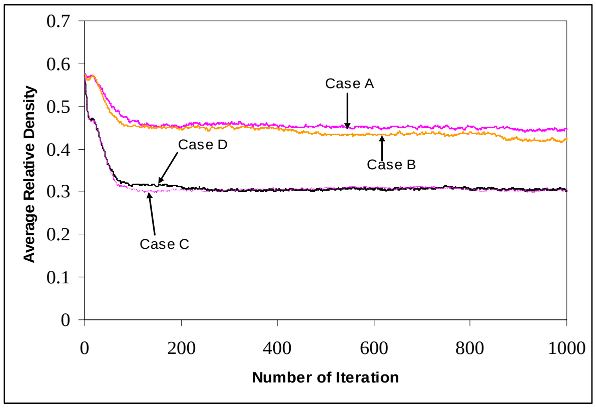


Fig.5 Variation of average relative densities with simulation time

SUMMARY AND CONCLUSIONS

Bone is a dynamic organ, and remodeling process in bone is a continuous resorption followed by apposition of bone, from birth to death. It is well accepted that bone growth, maintenance, degeneration and remodeling are biochemically regulated processes influenced by mechanical loading.

The remodeling process is generally viewed as a material response to functional demands that is governed by an intricate relationship between bone reinforcement and resorption. There is a number of bone remodeling theories, but because of the complexity of the bone remodeling process, none of these models could successfully consider mechanical, chemical and biological factors in a unified way. In Huiskes et al. theory [6], which is a semi-mechanistic model, a scalar quantity (rate of SED) is taken as the mechanical stimulus. Despite its simple form, Huiskes et al.'s theory predicts spongy bone remodeling behavior fairly good. In this study, using this semi-mechanistic model of bone remodeling, the effect of polarity on the remodeling process of a 2-D isotropic, square shape spongy bone matrix has been investigated. The model is initialized with the same configuration of bone matrix for the following different cases of external loadings. The model assuming the scalar SED as stimulus resulted in different final patterns for Case A and B which is expected to be the same, while almost same but asymmetric patterns for Case C and D under the shear loadings in opposite directions.

There are many open questions in the filed of bone remodeling process and theory. One of these crucial open questions is about the exact mechanical stimulus which can initiate bone remodeling process [4]. Different researchers proposed and believe in different stimuli, e.g. strain [5]; stress [2, 21]; effective stress [22-24]; strain energy [25, 26 and 28]; and strain rate [27, 29]. Generally speaking, one can classify the proposed mechanical stimuli for bone remodeling process into two categories as follows: *scalar* and *vector*. No need to say that the first group, i.e. scalar quantity (e.g. strain energy density or its rate) does not have polarity, but a vector quantity (e.g strain, stress, and strain rate) has polarity. In other words, a vector quantity is dependent not only on its magnitude but also on its direction. Choosing strain energy density (a scalar) or strain as causative factors for bone remodeling is as difficult as trying to decide whether stress or strain causes adaptation [30]. Martin and Burr [30] in answer to the question: does adaptation occur in response to stress or strain? say: "The question is intrinsically difficult to answer because stress and strain are proportional to one another."

Despite the fact that strain energy density is a scalar quantity, assuming the same magnitude but different directions for the external loads, various configurations were resulted for different aforementioned modes of loading. It is thought that this odd behavior of the model may be resulted from the stochastic nature of bone resorption in this model. Moreover, knowing that bone is a nonhomogeneous, and an anisotropic material; researchers in this field may require being more realistic and avoiding using very simplistic assumptions such as isotropy and homogeneity for bone. Moreover, because of having different phases in bone, in order to be able to find a more realistic model and to capture different features of the bone remodeling, we may need to move towards multi-phasic continuum mechanics, e.g. mixture theory [31, 32], and do not confine themselves with a single phase approach. Finally, in order to find an answer to the open question of exact mechanical stimulus for bone remodeling, experimental and theoretical research not only at the tissue level, but also at the subcellular and cellular levels (e.g. mechanotransduction of osteocytes) seem to be critically needed.

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