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Establishing the relationship between loading parameters and bone adaptation

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ABSTRACT

Cyclic and low-magnitude loading is considered effective in arresting the bone loss as it promotes osteogenesis (i.e. new bone formation) at the sites of elevated normal strain magnitude. In silico models assumed normal strain as the stimulus to predict the sites of new bone formation. These models, however, may fail to fit the amount of newly formed bone. Loading parameters such as strain, frequency, and loading cycle decide the amount of new bone formation. The models did not incorporate this information. In fact, there is no unifying relationship to quantify the amount of new bone formation as a function of loading parameters. Therefore, the present work aims to establish an empirical relationship between loading parameters and a new bone formation parameter i.e. mineral apposition rate (MAR). A neural network model is used to serve the purpose. Loading parameters are supplied as input, whereas, MAR served as output. The model is trained and tested with experimental data. The model establishes an empirical relationship to estimate MAR as a function of loading parameters. The model's predictions of MAR align with in vivo experimental results. The model's response is analyzed which indicates that the bone adaptation characteristics are successfully captured in the relationship. The relationship established may be incorporated further to improve qualitative and quantitative prediction capabilities of computer models. These findings can be extended in future to design and develop effective biomechanical strategies such as prophylactic exercise to cure bone loss.
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1. Introduction

Bone loss is a serious health issue which occurs due to metabolic bone disorders such as osteoporosis, and bone or muscle disuse. In vivo studies observed bone loss in postmenopausal women, bedridden patients, physically challenged individuals, and in astronauts under microgravity environment [1]. In fact, astronauts experience trabecular bone loss of 0.4% to 23.4% during 6 months spaceflight [2]. Bone loss reduces weight bearing strength of long bones which also increases the possibility of frequent bone fractures [3]. Several pharmaceutical drugs such as bisphosphonates are developed over recent years to prevent or inhibit bone loss. Long-term use of these drugs is not recommended due to their adverse effects on bone remodeling activities [4]. Exogenous low-magnitude and cyclic loading may be effective in the inhibition or the reversal of bone loss [5], as loading promotes osteogenesis at the sites of elevated normal strain magnitude [6]. In silico studies of bone adaptation assumed normal strain as an osteogenic stimulus in their attempt to establish a relationship between loading-induced mechanical environment and site-specific new bone formation [7–9]. Tiwari and Prasad [10], however, highlighted that these models may have limited success in explaining the osteogenesis near the sites of minimal normal strain magnitude e.g. the neutral axis of bending. In addition, computer models may also fall short in fitting the quantity of newly formed bone. A reason is that in silico studies modeled osteogenesis for specific in vivo experiment. Accordingly, the model was tuned with specific remodeling parameter or constant to fit the amount of in vivo new bone formation. Thus, it is intuitive that the same model may be unsuccessful in fitting the amount of new bone formation for other in vivo experiments. According to Grosland et al. [11], correlation studies between in vivo results and in silico predictions suggest that the remodeling coefficient may vary with each test model. Therefore, it is difficult to establish a generalized principle of bone adaptation. It is observed that mechanical loading parameters such as frequency, loading cycles and time period also influence the remodeling rate and thus the amount of new bone formation. For example, Burr et al. [12] used an invasive loading model

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of rooster ulna and an intrinsic model of jumping to highlight the importance of loading history in bone adaptation. They reported that the new bone response typically saturates after a certain number of loading cycles. Turner et al. [13] noticed that bone formation rate and mineral apposition rate (MAR) proportionally increases with an increase in strain rate. Hseih and Turner [14] also reported that higher remodeling rate may occur at a lower strain magnitude and higher strain rate. This indicates that strain cannot be the only stimulus which regulates bone adaptation. Experimental investigations also suggested that loading parameters affect mechanosensitivity of bone. Turner et al. [15] observed that new bone formation responds in a dose-dependent manner to loading frequency. Along the same line, Warden and Turner [16] loaded tibiae of C57Bl/6 mice at different loading frequency for fixed as well as different number of loading cycles. The results indicated that the maximal new bone response occurs within a range of loading frequency of 5–10 Hz. Additionally, an increase in the amount of new bone formation is noticed with an increase in frequency up to 10 Hz. Robling and co-workers [16,17] used a four-point loading model of rat tibia to demonstrate the effect of rest-inserted cyclic loading on the new bone formation. These experimental studies have shown that rest insertion restores the mechanosensitivity of bone cells and increases bone formation rate (BFR) and mineral apposition rate (MAR). In vitro studies also confirmed that rest insertion increases the biophysical response as Ca^{2+} concentration and number of responsive cells increases with an increase in the rest time [18]. Cullen et al. [19] indicated that the amount of newly formed bone increases with an increase in the number of loading cycles or time-period. These findings clearly indicate that loading regimen significantly affects bone remodeling parameters such as MAR and BFR. In silico models incorporated normal strain or strain energy density as the stimulus in bone adaptation law to predict the sites of new bone formation. These models used an arbitrary remodeling constant to fit the amount of new bone formation. As loading parameters may affect the bone remodeling rate, therefore, the constants must be selected based on these parameters. This may certainly improve the robustness of computational prediction of new bone formation. Cowin et al. [20] used a cubic approximation on in vivo experimental data specifically MAR to estimate the possible values of remodeling rate coefficients. Most of the computer models, however, did not employ the method suggested by Cowin et al. [20] to compute rate coefficients. Thus, there is no unifying principle to relate the bone remodeling parameters with loading parameters.

Accordingly, the present study attempts to identify an empirical relationship between loading parameters i.e. normal strain magnitude, frequency and cycle, and a bone remodeling parameter i.e. mineral apposition rate (MAR). Artificial neural network (ANN) is a well-known tool to simulate several biological processes. It has the ability to establish an unforeseen relationship between a set of known independent variables and the outcomes of these variables [21]. This approach is recently introduced in the area of biomechanics to establish nondeterministic relationships. For example, Chanda et al. [22] combined ANN and genetic algorithm to build a relationship between implant geometry and bone–implant interface micromotion. Advancement of the neural network methods allowed orthopedic researchers to understand bone remodeling and modeling activities. Nevertheless, limited investigations are carried out using ANN in establishing or understanding the bone adaptation characteristics [23–29]. There is hardly any study in the literature which establishes mineral apposition rate (i.e. MAR) as a function of loading parameters (i.e. strain, frequency, and cycle). The present study aims to answer this question i.e. *how loading parameters must be related to new bone formation*? A neural network is modeled to answer the question. The neural network model is allowed to capture the characteristics of in vivo experimental data available in the literature on loading-induced osteogenesis. The network training provides an empirical equation to estimate MAR as a function of loading parameters. Furthermore, the model is tested with another set of experimental data. The model closely fits experimental MAR noticed in several in vivo studies. The relationship established between the loading regimen and the bone modeling parameter will allow in silico models to efficiently decide the remodeling rate coefficient. This will improve the prediction capacity of computer models. Furthermore, this relationship may further be extended to optimize loading parameters such as strain, frequency, cycles, and rest time to get the maximal osteogenic response. Based on these findings, one can develop a robust computer model of bone tissue adaptation, which can be further used to predict new bone response to any change in loading environment. An understanding of how mechanical cues must be regulated to produce the desired new bone response can be very useful. This will ultimately help orthopedic researchers and medical practitioners in providing informed recommendations on biomechanical interventions such as prophylactic exercises to prevent or cure bone loss.

2. Methodology

In the present study, a neural network model is employed to relate loading parameters to mineral apposition rate (MAR). Four fundamentals steps are used in the neural network model development: (1) experimental data collection; (2) pre-processing of data; (3) neural network design, and (4) model analysis or the simulation of trained network/relationship, as follows:

2.1. Experimental data collection

In vivo animal loading studies exposed long bones such as tibiae or ulnae of rats or mice to cyclic mechanical loading. Cantilever, three or four-point bending, and axial compression are used to load the bone at different load/strain magnitude, frequency, and cycles. Bone remodeling parameters such as mineral apposition rate (MAR) and bone formation rate (BFR) were noted in response to fixed or variable loading parameters. It is noticed that different loading cases also led to different new bone distributions even when loading imparted similar strain distributions. This evidently indicates that variations in loading parameters such as frequency and cycles with experiments may influence the amount of new bone formation. Loading parameters such as normal strain, frequency and cycles, and the corresponding MAR data are collected from in vivo animal loading studies on cortical bone adaptation (supplementary file 1). A recent in vivo study mentioned that cortical bone surfaces (periosteal and endocortical) may exhibit different bone remodeling response [30]. Thus, datasets are separately prepared for both the surfaces.

2.2. Pre-processing of data

The generalization of a neural network model typically depends on input and output parameter selection, and the datasets distribution. In this work, experimental datasets of loading parameters and, corresponding periosteal and endocortical MAR are prepared from the selected in vivo studies (supplementary file 1). Loading parameters served as the input and corresponding MAR is considered as the output of the model. Overall experimental raw data are normalized within a range of 0 to 1 as follows:

$$x_i = \frac{d_i}{d_{\max}} \quad (1)$$

where x_i is the normalized value of each collected raw datasets (d_i), and $d_{\max}$ is the maximum value of the raw experimental data.

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