A Neural Network Model to Investigate the Effect of Frequency and Time on Loading Induced Osteogenesis

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Abstract

Cyclic and low magnitude mechanical loading is considered beneficial in prevention and the reversal of bone loss. It is believed that loading on bone induces normal strain which inhibits resorption and promotes osteogenesis (i.e., new bone formation) at the sites of elevated normal strain magnitude. Thus, computer models of bone adaptation have assumed normal strain as a stimulus and successfully predicted the locations of osteogenesis; however, these models fall short in fitting the quantity of newly formed bone. Such limitation may be due to non-incorporation of loading parameters such frequency, cycles and time etc. which considerably influence the amount of new bone formation. Nevertheless, a relationship between loading parameters and a remodeling parameter such as mineral apposition rate (MAR) to quantify the amount of newly formed bone, is needed. Accordingly, this study presents a back-propagation neural network model to identify the relationship between loading parameters and MAR. The model establishes an empirical relationship to estimate MAR as a function of loading parameters. The model's predictions closely fits several in-vivo experimental data. The model can be further utilized to define MAR derived remodeling rate coefficients in computer model. These findings may improve the capability of bone adaptation models to predict qualitative and quantitative new bone distribution; and thus will be ultimately useful in design and development of bio-mechanical interventions to prevent or cure bone loss.

1 Introduction

Long bones are usually subjected to various mechanical loads such as gravity, ground reaction force and muscle contraction forces in daily routine. In-vivo studies have reported that these physiological loads are essential to maintain the weight bearing capacity of bone since bone/muscle disuse in case of bedridden patients, physically challenged individuals and microgravity in astronauts result into significant bone loss and thus increases bone fracture risks[1, 2]. Prevention or treatment of such bone loss is a serious concern for clinicians. Recent research efforts have shown

that low-amplitude and cyclic loading on bone may be effective in the recovery from bone loss as it stimulates the osteogenesis (i.e., new bone formation) at the location of elevated normal strain [3, 4, 5]. Computer models of bone adaptation have considered normal strain as a stimulus and successfully predicted the locations of new bone formation for in-vivo experiments [6, 7, 8]. However, these studies have modeled osteogenesis for specific in-vivo experiment and accordingly tuned the model with specific remodeling parameter to fit the amount of new bone formation. Thus, the same model may fail to precisely predict the amount of new bone formation for other experimental studies. It is important to note that loading parameters such as frequency, loading cycle and time significantly influence the amount of new bone formation and remodeling parameters. For example, Hsieh and Turner have shown that an increase in loading frequency may enhance the new bone thickness [9]; whereas, Cullen *et al.* had shown that the amount of newly formed bone increases with increase in number of loading cycles/time [10]. This aspect has been overlooked in most of the computational models. It indicates that models parameter such remodeling rate coefficient must be selected based on loading parameters to improve the efficacy of computational prediction. However, there is no unifying principle to relate bone remodeling parameters such as MAR with loading parameters. In recent years, neural network models have emerged as an efficient tool for establishing an unseen relationship among the given set of parameters [11, 12]. Accordingly, this preliminary study proposes a neural network approach to identify an empirical relationship between loading parameters, e.g., normal strain, frequency and cycles, and MAR. The model opts for a back propagation algorithm. The model captures the characteristics from available experimental data in the literature and provides an equation to estimate MAR as a function of loading parameters. The model has been trained and tested by several in-vivo experimental data. The model's prediction of MAR closely fits several in-vivo experimental results. The results clearly indicate the importance of loading parameters in bone remodeling estimation. These finding may be useful for the development of efficient and universal approaches/models to predict loading induced osteogenesis, which can be further extended to design of bio-mechanical therapies for the prevention and cure of bone loss.

2 Method

2.1 Experimental Data Collection

In the present study, we attempt to model the relationship between loading parameters and a remodeling parameter, i.e., MAR using a neural network modeling approach. There are several in-vivo experimental studies readily available in the literature where rodent longs bones especially tibia or ulna of rat/mice were loaded in cantilever bending [13], axial compression[14], four point [15] and three point bending [16] and MAR were reported in response to loading. However, different loading cases have led to different new bone formation even when the strain distribution were similar. This may be mainly because of differences in other loading parameters such as frequency and cycles etc. Hence, loading parameters such as frequency, cycles, time along with strain and corresponding MAR have been collected from 70

in-vivo studies. 108 experimental data sets have been prepared out of these studies and these data-sets were further used as inputs to the model. We have listed few of these in-vivo studies [17, 18, 19, 20, 21, 22, 10, 9]

2.2 Network Model

A back propagation neural network model with a single hidden layer with four nodes has been used to relate MAR with loading parameters (Fig. 1). Three loading parameters, i.e., normal strain, frequency and loading cycles have been incorporated as inputs to the model whereas corresponding MAR has been considered as an output. Hence, the model has four nodes in hidden layer and one node in output layer. These layers have been connected through synaptic weights. A sigmoid function has been used as an activation function for the hidden and the output layers. MATLAB (Mathworks Inc. Boston) was used to build the neural networks model. The model has been trained with few experimental data sets to capture the characteristics of experimental data. The error (sum of squared errors (SSE)) between model output and the target updates synaptic weights through a feedback algorithm during training. Finally, the model has been tested to check the accuracy of the model. In this study, we have supplied 25%, 50% and 75% of experimental data as training inputs and remaining 75%, 50% and 25% has been tested to check the efficacy of the model. A step-wise learning rate has been used for training the data.

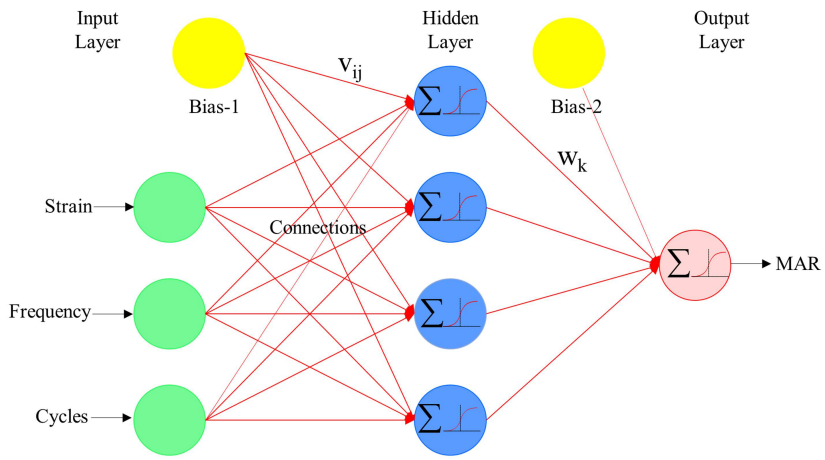

Figure 1: The neural network model to predict MAR

3 Results

3.1 Training Results

The network has been trained in three different batches of 25%, 50% and 75% of experimental data sets. The training performance of the network for these data sets can be noticed from Figs. 2, 3 and 4. The error decreases with an increase in iterations or epochs. The network minimizes the error for all training data sets using multiple learning rates. The training performance was found satisfactory for all batches as the error between the network and the targeted outputs was minimal. These training results establishes an empirical equation to estimate MAR as a function of strain (ϵ), loading frequency(f) and cycles (c), which is as follows:

$$MAR = \frac{1}{1 + e^{-\sum_{j=1}^{4} Z_j w_{jk}}} \tag{1}$$

where

$$Z_j = \frac{1}{1 + e^{-\sum_{i=1}^{3} x_i v_{ij}}} \tag{2}$$

x_i are the inputs, i.e., ϵ, f and c to the model. w_{jk} and v_{ij} are constants obtained from training of experimental data. The constants obtained from training of 50% data sets are given bellow:

$$v_{ij} = \begin{bmatrix} -1.29 & -4.59 & 1.79 \\ 0.82 & 0.85 & 0.36 \\ -2.62 & 5.26 & -10.95 \\ -0.25 & -1.16 & 3.09 \end{bmatrix}$$

and

$$w_{jk} = \begin{bmatrix} -0.48 \\ -8.72 \\ -7.00 \\ 5.89 \end{bmatrix}$$

3.2 Testing Results

The model has been tested to predict MAR for remaining 75%, 50% and 25% of experimental data-sets after training. It can be observed from Fig. 2 that the error between predicted output and experimental data is high (SSE = 0.40) when 75% of experimental data has been tested and only 25% was sent for training. The model's prediction improved when 50% and 75% of data were sent for training and correspondingly 50% and 25% of experimental data have been tested (Figs. 3 and 4). It is interesting to note that the model more closely (SSE = 0.05) predicts MAR for 50% of experimental data which include most of the in-vivo loading cases such as axial loading, cantilever bending and four point bending (Fig. 2). Moreover, the same model closely predicts MAR for a broader range of frequencies (i.e., 1, 2, 5, 10 and 30 Hz) and loading cycles (i.e., 90-1200) which can be noticed from Fig. 2.

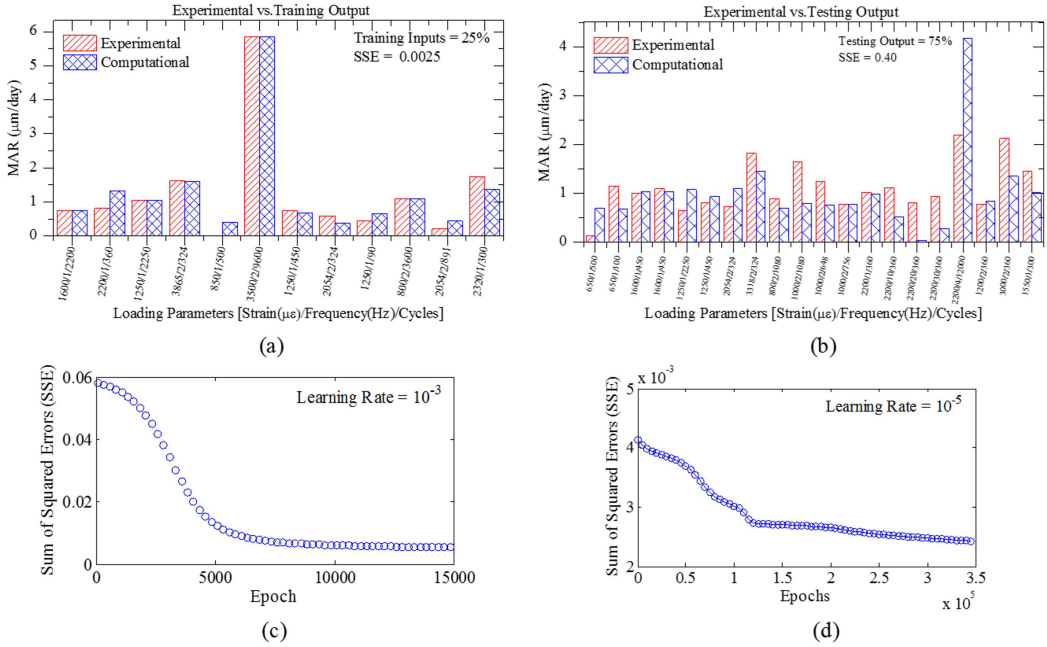

Figure 2: (a) Training and (b) testing outputs vs. experimental data; (c and d) SSE vs. epochs/iterations showing network training performance for 25% data sets.

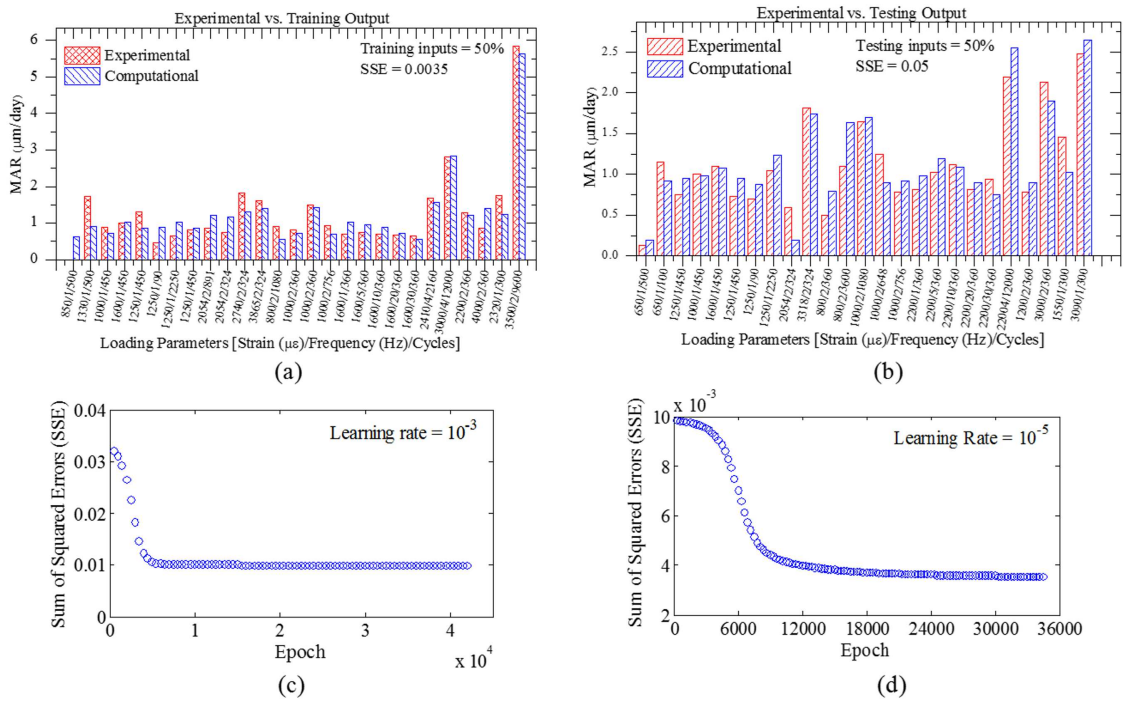

Figure 3: (a) Training and (b) testing outputs vs. experimental data; (c and d) SSE vs. epochs/iterations showing network training performance for 50% data sets.

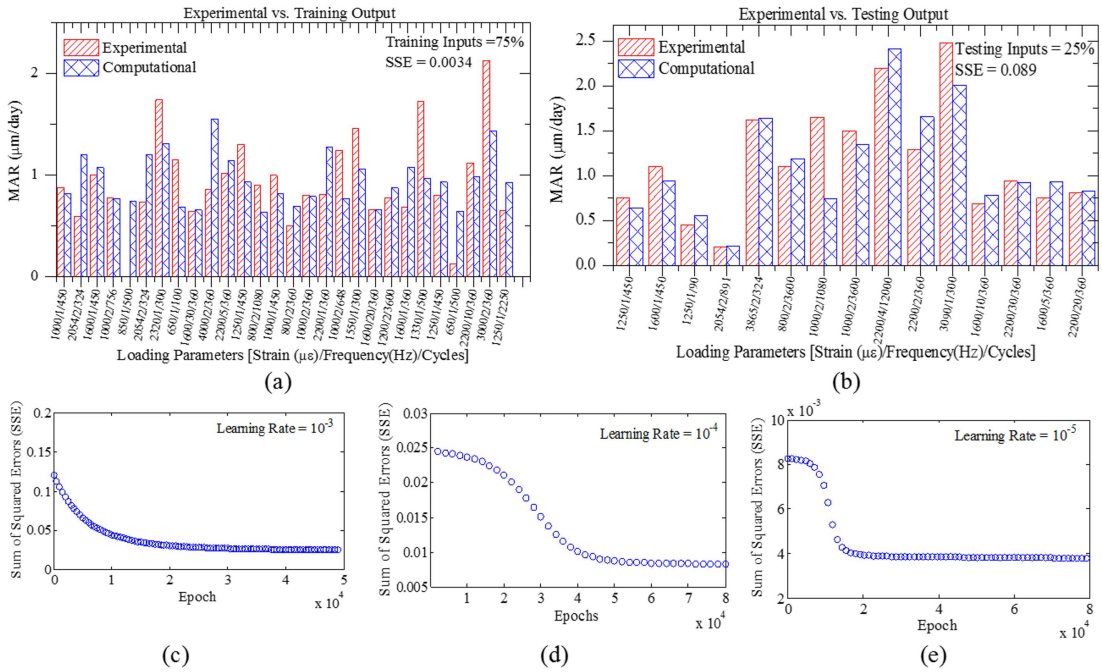

Figure 4: (a) Training and (b) testing outputs vs. experimental data; (c, d and e) SSE vs. epochs/iterations showing network training performance for 75% data sets.

4 Discussion

This study fills the gap between computational prediction and in-vivo experimental results. Available computational models in the literature predict the location of new bone formation, however, failed in predicting the amount of new bone formation as loading parameters change with experiments. Most of the models tuned the remodeling rate parameters to make prediction more close to the in-vivo results. This study may be useful for existing computer models in selection of a suitable remodeling rate constants according to experimental loading condition. The present model in combination with stimulus based models may be useful in the development of a robust computational model to fit all the available experimental data in the literature; thus, the same model can be extended in future to accurately predict the new bone formation for any other in-vivo study. The model can also be useful in understanding the role of frequency and loading cycles. For example, the model captures the characteristic from experimental data that the MAR increase with loading frequency and cycles which can be noticed form the results as well. This is one of the advantage of our model. However, one of the limitations of the model that it captures only a limited number of experimental data. Hence, incorporation of more data will surely improve the accuracy. In addition, the age of the animals and rest insertion time between cycles will be incorporated in future as these parameters also governs the osteogenesis. Collectively, this model provides an insight that a model based on all experimental result can be useful in understanding the loading induced osteogenesis which will surely improve the bio-mechanical intervention to treat or prevent bone loss.

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