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Predicting Bone Modeling Parameters in Response to Mechanical Loading

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ABSTRACT In vivo studies in mechanobiology and mechanotransduction explained the importance of mechanical loading in promoting osteogenesis (new bone formation) and thus, in preventing the bone loss. The literature suggests that the cyclic loading parameters viz. loading cycles, strain and frequency regulate the extent of new bone formation. Nevertheless, the amount of regulation has not been defined. As a result, researchers have been trying a data driven approach to estimate the new bone formation by proposing different empirical models. The models proposed so far have mainly focused on some specific bone modelling parameters such as mineral apposition rate (MAR). The literature, however, suggests that there are equally important bone modelling parameters which are also influenced by the change in cyclic loading parameters. Therefore, the results obtained from earlier computer modelling studies remain incomplete. This paper presents an improved empirical model which attempts to establish a relation between bone modelling parameters mineral apposition rate (MAR) and mineralising surface (MS/BS), and cyclic loading parameters. The results indicate that the proposed model has better accuracy in terms of prediction as compared to the state-of-the-art models involving only one bone modelling parameter i.e., MAR. The model may be useful in designing the optimal loading regimen to induce a desired new bone response. Based on these outcomes, a better bio-mechanical intervention may be developed in future to check bone loss.

INDEX TERMS Bone adaptation, mechanical loading, neural network, frequency, loading cycle.

I. INTRODUCTION

Weakning of bones is a grave health concern often encountered due to aging and metabolic bone diseases, for example, osteoporosis. Other factors e.g., bone or muscle disuse and microgravity environment also promote bone loss. This may sometime lead to frequent fractures in bone [1]. Pharmaceutical drugs prevent or cure weakening of the bones or bone loss, however, it may pose mild to severe side effects [2]. Physical exercise or mechanical stimulation can be a good alternative to cure bone loss. In vivo animal loading studies have reported that cyclic mechanical loading on bone promotes new bone formation [3]. Frost indicated that elevated normal strain above threshold induces osteogenesis [4], [5]. Moreover, it has been observed in past studies that mechanical loading parameters such as strain magnitude, frequency, and loading cycles significantly affect the extent of new bone formation [6]. Several computer modeling techniques attempted to predict the site specific new bone formation as a function of strain magnitude or strain derived strain energy density [7]–[9]. Most of these models assumed a bone modeling rate coefficient based on bone formation parameters such as MAR to predict site-specific new bone thickness around the bone cortex observed during in vivo experiments. Based on correlation analysis between in silico predictions and in vivo experiments, Grosland *et al.* [10] highlighted that remodeling rate coefficient may differ with each mechanobiological test model. It is difficult to ensure that one model will fit the experimental new bone formation reported in the other in vivo study. Thus, there is hardly any unifying mechanism to decide the rate coefficient and hence the site-specific new bone thickness. This poses a significant difficulty in establishing a generalized principle for prediction of new bone formation induced by mechanical loading.

In vivo experimental studies quantified the new bone formation primarily in terms of three bone formation

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parameters which are mineral apposition rate (MAR), mineralising surface (MS/BS) and bone formation rate (BFR/BS) (refer Table 1). The bone formation rate per unit bone surface (BFR/BS) is obtained by multiplying MAR and MS/BS. It has been reported in the literature that the extent of new bone formation is regulated mechanical loading parameters since MAR, MS/BS and BFR/BS are significantly influenced by the change in loading parameters. For example, Burr *et al.* [11] indicated that BFR/BS increases as loading cycles are increased and gets saturated after a certain point. The dependence of new bone response on frequency has also been reported in the literature [12].

The literature indicates that loading-induced normal strain magnitude may not be the only factor which control the amount of new bone formation. This is quite clear from the experimental evidence that loading parameters regulate the amount of new bone formation. Nevertheless, there are very few mathematical models which attempted to predict the amount of new bone formation as a function of loading parameters. Tiwari and Kumar [13] in a preliminary study established an empirical relationship between only one new bone formation parameter i.e., MAR and loading parameters viz. cycles, frequency and strain magnitude. However, there are other important parameters such as BFR/BS and MS/BS which also determine the extent of new bone formation [14]. Therefore, the relationship developed by Tiwari and Kumar [13] is not sufficient to capture the extent of new bone formation and its dependence on loading parameters. Hence, a robust mathematical relationship is indeed required for prediction of amount of new bone formation as a function of loading parameters.

Artificial neural network (ANN) models are widely used to establish unforeseen relationship between mechanical environment and bone remodeling [15]–[18]. This encouraged to proposes an ANN model to establish an unknown relationships between new bone formation parameters such as MAR and MS/BS and loading parameters e.g., strain magnitude, loading cycles and frequency. The model proposed here uses in vivo experimental data for both training and testing. The proposed model predicts MAR and MS/BS in the range of experimental values. Since, BFR/BS can be obtained by the multiplication of other two parameters, it is sufficient to predict MAR and MS/BS only. The outcome of the present study also laid out the suggestions for the improvement of accuracy of neural network implementations for finding the bone adaptation characteristics. Such ANN models can further be enriched with more experimental data and can be modified for the improved prediction of in silico models on site-specific new bone formation in response to a wide range of loading regimens. The model may be very useful in selecting optimal loading regimen to induce a desired range of new bone formation to help orthopedic research and also help in making improved recommendations for osteotherapy. This paper has the following major contributions:

1) Improved data set with input and output loading parameters collected from various in vivo experimental studies [12], [19]–[64].[1]
2) Statistical analysis of the data set.
3) A comparative study of the proposed model with state-of-the-art models.
4) An efficient artificial neural network (ANN) model to predict the amount of new bone formation as a function of cyclic loading parameters.
5) Prediction of optimal values of loading parameters to obtain maximal new bone formation.

II. METHODOLOGY

The methodology employed to carry out the proposed work is as follows and is described in detail in the following subsections.

- Data collection from in vivo experimental studies
- Data pre-processing
- Designing of ANN models
- Analysis of the neural network performance

A. EXPERIMENTAL DATA COLLECTION

The most important component of any artificial neural network is the input data which is used for both training and testing. The data is gathered from various in vivo animal loading studies on cortical bone adaptation [12], [19]–[64]. These studies are performed on mice or rats where cyclic mechanical loading is applied on long bones such as tibia and ulna. Loading methods such as axial compression and cantilever bending are used in these studies to load the bone at different number of loading cycles, frequency and strain magnitude. The bone exhibited different response of bone formation when subjected to constant strain, variable frequency and loading cycles either independently or in various combinations. This effect can be observed with change in values of MAR and MS/BS. Table 1 briefly describes various cyclic mechanical loading parameters which are collected from in vivo studies for both periosteal (Ps) and endocortical (Ed) surfaces. As discussed in [42], the bone modelling response can vary at both periosteal and endocortical surfaces, hence, separate data sets are recorded with respect to both the surfaces. It is worth mentioning that data from in vivo axial and cantilever loading studies are extracted as these ladings induce bending like strain distribution as can be observed due to habitual bending of bone.

B. PRE-PROCESSING OF DATA

Data are collected from in vivo experiments where the new bone formation has been reported due to mechanical loading only. Experiments done on rodents especially on C57BL/6 mice are considered to maintatin consistency of physiological condition in data collection to some extent. The loading parameters and corresponding new bone parameters

[1]The data set is available at the following web link https://www.dropbox.com/s/d3ysokm7flwmmzi/dataSet.xlsx?dl=0

TABLE 1. Loading parameters and output parameters used in the model.

Parameter (units)	Description	Type
Strain ($\mu\epsilon$)	Peak value of Minimal Normal Strain induced in Loaded Bone	Input
Frequency (Hz)	Number of Cycles per second in a single loading session	Input
Cycles	Number of Loading Cycles used in single loading session	Input
MAR (μm/day)	Distance between two consecutive labels divided by time of measurement	Output
MS/BS (%)	The amount of bone surface active in mineralization	Output

TABLE 2. Attributes in data set not accounted for training.

Parameter	Description
Rest Time	Time between Consecutive Cycles in a single loading bout
Loading Days	No. of days of Loading in specified period
Days(in Period)	Number of days after which loading schedule is repeated
No. of Weeks or Duration (Days)	Specifies the total duration in which the above specified period is repeated
BFR/BS (μm/day)	Volume of mineralised bone

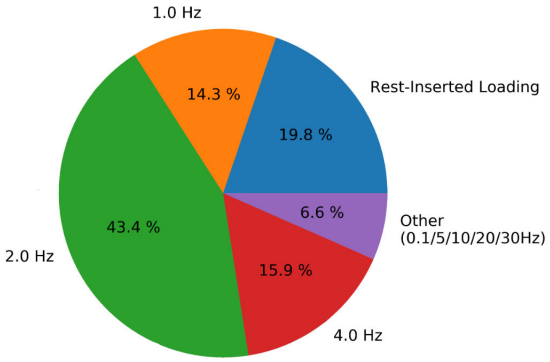

FIGURE 1. Distribution of data based on frequency.

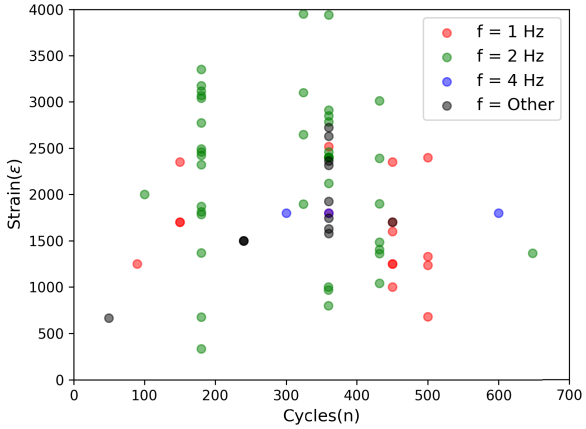

FIGURE 2. Distribution of data on the basis of strain and cycles.

are collected which covers a range of values of loading and bone modeling parameters which are mentioned in Table 1 and 2. For the parameters mentioned in Table 2, sufficient data is not available in the literature at present. Therefore, these parameters are not incorporated in the present study, however, these parameters are also important and have certain roles in the regulation of new bone formation. Fig. 1 shows the distribution of data based on frequency of loading. The figure indicates that 80.2% of the data set is collected from those in vivo studies where continuous cyclic loading is applied and the remaining 19.8% is included from those in vivo studies where rest inserted loading is applied. The amount of available data from rest inserted loading studies is lesser and thus, not sufficient to train the neural network model. Hence, such data has also been excluded for training the model. It is also clear that the in vivo experimental data associated with loading frequencies other than 1 Hz, 2 Hz and 4 Hz is only 6.6%, and such data is also excluded. This analysis has been important to avoid any imbalanced distribution of data which can lead to a model that can not predict the results of minority classes. Once more data on excluded parameters is available in the future, the proposed neural network design can be easily trained on new data and can be used for the prediction as well.

The data is filtered using the above mentioned procedure. Certain outliers (< 1% of the total data points) such as data points extracted from in vivo studies involving 12000/16000 cycles are excluded. Fig. 2 shows the distribution of majority of the data points with respect to values of strain and cycles. The plot clearly shows that majority of experiments are done at values of 180 and 360 number of cycles. Afterwards, there are large number of data points between 400 and 500 number of cycles. Relatively, a very few experiments are conducted using higher number of cycles. The value of strain varies between 1000 and 3500 $\mu\epsilon$ for majority of the data points. This range usually belong to bone deposition to homeostatic bone maintenance to bone deposition, however, loading induced new bone formation has been confirmed at these elevated strain magnitude in most of the bone adaptation studies. For example, Srinivasan *et al.* [26] observed new bone formation at peak strain value of 1330 $\mu\epsilon$. At 180 number of cycles, the most commonly used values of strain are 1600, 2400 an 3200 $\mu\epsilon$. When the number of cycles are 360, strain values are concentrated between 1500 and 3000 $\mu\epsilon$.

The distribution of new bone formation parameters i.e., MAR and MS after filtering are shown in Fig. 3. It can be observed that the values of Ps-MAR lies between 0.2 and 2.0 μm/day which has a mean value of 0.95 μm/day. The values of Ed-MAR extends up to 4.0 μm/day, however, sparse after 2.0 μm/day which has mean at 1.5 μm/day. The values corresponding to MS extend up to 97%. Sparseness is observed after 65%. Values corresponding to Ps-MS and Ed-MS have mean values of 38.96% and 35.31%, respectively. Thus, it can be observed that the majority of data is available in the ranges of 0.5 - 2.0 μm/day for MAR whereas it is 65% for MS.

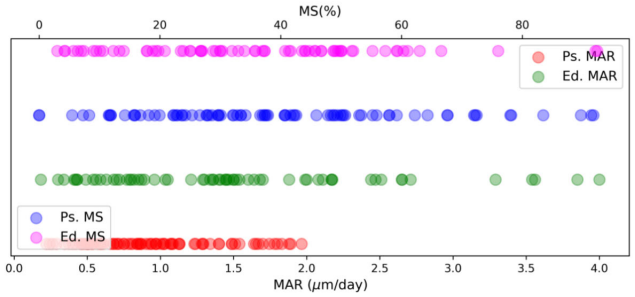

FIGURE 3. Distribution of data over the ranges used to train the networks (Dark color represent high density of data points).

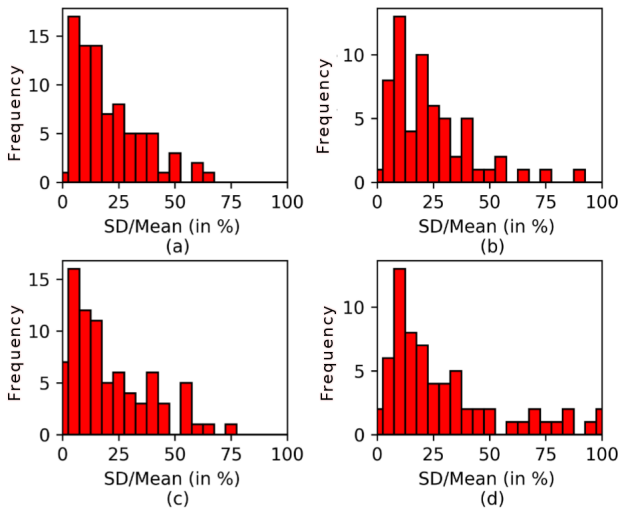

FIGURE 4. SD/Mean in % showing relative standard deviation in individual experimental data points data for (a) Ps-MAR (b) Ed-MAR (c) Ps-MS (d) Ed-MS.

The distribution of bone remodelling parameters extracted from experimental studies are represented in terms of ratio of standard deviations and mean in Fig. 4. This explains the extent of variability of experimental data from the mean values. The coefficient of variations of experimental values are plotted to find out the extent of relative standard deviation in experimental data (Fig. 4). Majority of in vivo experimental data have the coefficient of variation around 25% except few. The filtered data set is normalized by dividing values of individual parameter's values with the maximum value of that parameter using the following relationship:

$$x_i = d_i / d_{max}. \tag{1}$$

C. DESIGNING NEURAL NETWORKS

The complexity of a neural network model depends upon its architecture which can be described in terms of number of hidden layers (referred as depth) and number of neurons in each hidden layer (referred as width). The performance of a neural network varies with the width and depth of the network. To find out the optimal architecture for our data set, six different neural network models are designed as described in Table 3.

TABLE 3. Width and depth of tested neural network architectures.

Network Name	Width of layers		
	H1	H2	H3
NN_4	4	-	-
NN_4_4	4	4	-
NN_8_4	8	4	-
NN_16_4	16	4	-
NN_8_8_4	8	8	4
NN_16_16_4	16	16	4

A bias node is added to each layer in every architecture. A *sigmoid* activation function is used as it closely depicts the bone adaptation characteristics [13]. The function used for updating synaptic weights is Adam Stochastic Optimization Function [65], with three learning rates:

- a learning rate of $3 * 10^{-4}$ decaying at a rate of $5 * 10^{-9}$ at every epoch.
- a learning rate of $7 * 10^{-4}$ decaying at a rate of $5 * 10^{-9}$ at every epoch.
- a learning rate of $1 * 10^{-3}$ decaying at a rate of $5 * 10^{-9}$ at every epoch.

Adam optimization function is used to maintain adaptive learning rates for each parameter (network weights) separately. The adam update rule can be defined as:

$$\theta_{t+1} = \theta_t - \frac{\eta_t}{\sqrt{\hat{v}_t} + \epsilon} \hat{m}_t \tag{2}$$

where, θ_t is an individual network weight, η_t is the learning rate, and $\hat{m}_t$ and $\hat{v}_t$ are the first and second moment of gradients respectively, which are defined as follows:

$$m_t = \beta_1 m_{t-1} + (1 - \beta_1) g_t \tag{3}$$

$$v_t = \beta_2 v_{t-1} + (1 - \beta_2) g_t^2 \tag{4}$$

where, g_t denotes the gradient of weight θ_t at time-step t and β_1 and β_2 are the exponential decay rates of first and second moment estimates. We use mean of squared errors (MSE) as the loss function. The model tries to minimize MSE for learning the data. The MSE is computed as follows:

$$MSE = \frac{1}{n} \sum_{i=1}^{n} (target_i - output_i)^2 \tag{5}$$

where n is the number of data points used as input to train the neural network. For training and testing, the proposed models are implemented on Keras API [66] using Tensorflow backend which is developed in Python.

D. ANALYSIS OF NEURAL NETWORK PERFORMANCE

The present work attempts different neural network architectures as mentioned in Table 3. During training, 70% of the data set is used whereas, 30% of the data set is kept for testing. The networks are trained several times independently to obtain the global optima. Mean percentage error and correlation are used for analysis of the predicted MAR and MS associated with periosteal and endocortical surfaces. Ultimately, the best of the proposed architectures are compared with the state-of-the-art model ([13]) to describe results.

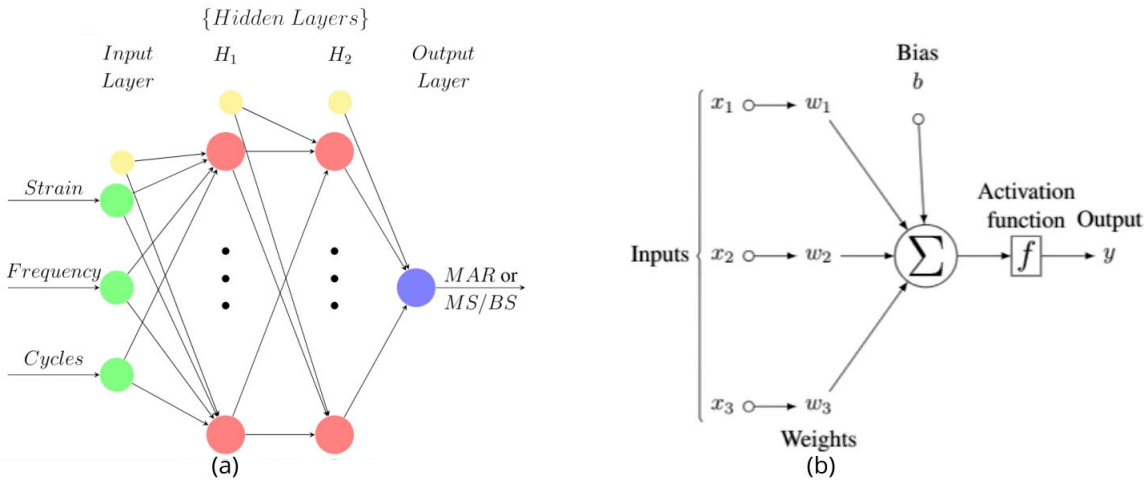

FIGURE 5. Architecture of Neural Network (a) input/output parameters with hidden layers (b) structure of a single neuron.

III. RESULTS AND DISCUSSION

In this section, the results from the neural network models obtained during training and testing of various models are compared. The proposed neural network architectures tested in the present work are mentioned in Table 3. The performance of the best network architecture out of these is compared with state-of-the-art neural network model in [13] and also with linear regression model. A linear regression model predicts output variable as a linear function of input variables which can be represented as follows:

$$Y = AX + B \tag{6}$$

where, Y is the output variable to be predicted (for example, Ps-MAR), X is the vector of input variables (in this study, cycles, strain and frequency), A and B are the coefficients that are determined after training of the linear regression model.

All of the models are trained until the mean squared error converges. The present work uses MSE as a primary performance parameter to compare different models. The model with the smallest value of MSE indicates better performance than the others.

It has been observed that the performance slightly increases with increase in width and depth of neural architecture. The architecture named as NN_8_4 gave the best results in training as well as testing for the bone modeling parameters such as Ps-MAR, Ed-MAR and Ed-MS, however, NN_4_4 has shown improved performance in prediction of the Ps-MS. It is observed that the models does not show any significant improvement in the performance in terms of MSE on further increasing the width and depth. Therefore, the present size of network and the features of the data set are appropriate enough to fit in the neural network model. The following subsection presents detailed discussion on the results obtained from training and testing.

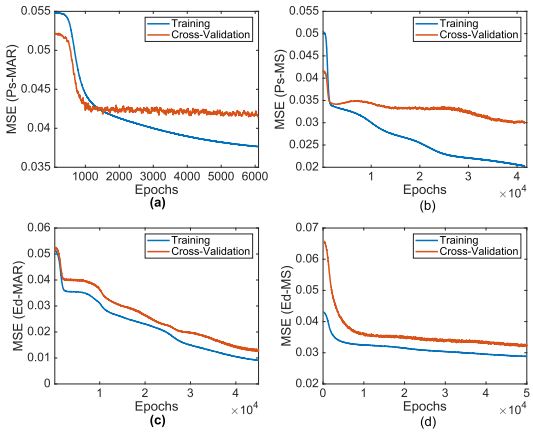

FIGURE 6. Change in values of MSE during training of neural network model.

A. TRAINING RESULTS

Fig. 6 explains that MSE decreases during training and converges after certain iterations. This indicates the successful training of the neural network model. Table 4 summarizes MSE values obtained at the end of the training phase. The proposed neural network model has been able to achieve the reduction in MSE values as compared to that achieved in Linear Regression Model and in Tiwari and Kumar [13]. This explains the new bone formation parameters does not linearly relate to loading parameters as MSE values for linear regression model are higher than the neural network models. Nevertheless, the proposed neural network models in this study and the neural network model proposed in [13] are found close during comparison. The results mentioned in Table 4 also indicates that the proposed model displays a significant reduction in MSE values while training the data set associated with Ps-MS/BS, whereas, only slight improvement is achieved during training for other bone modeling parameters.

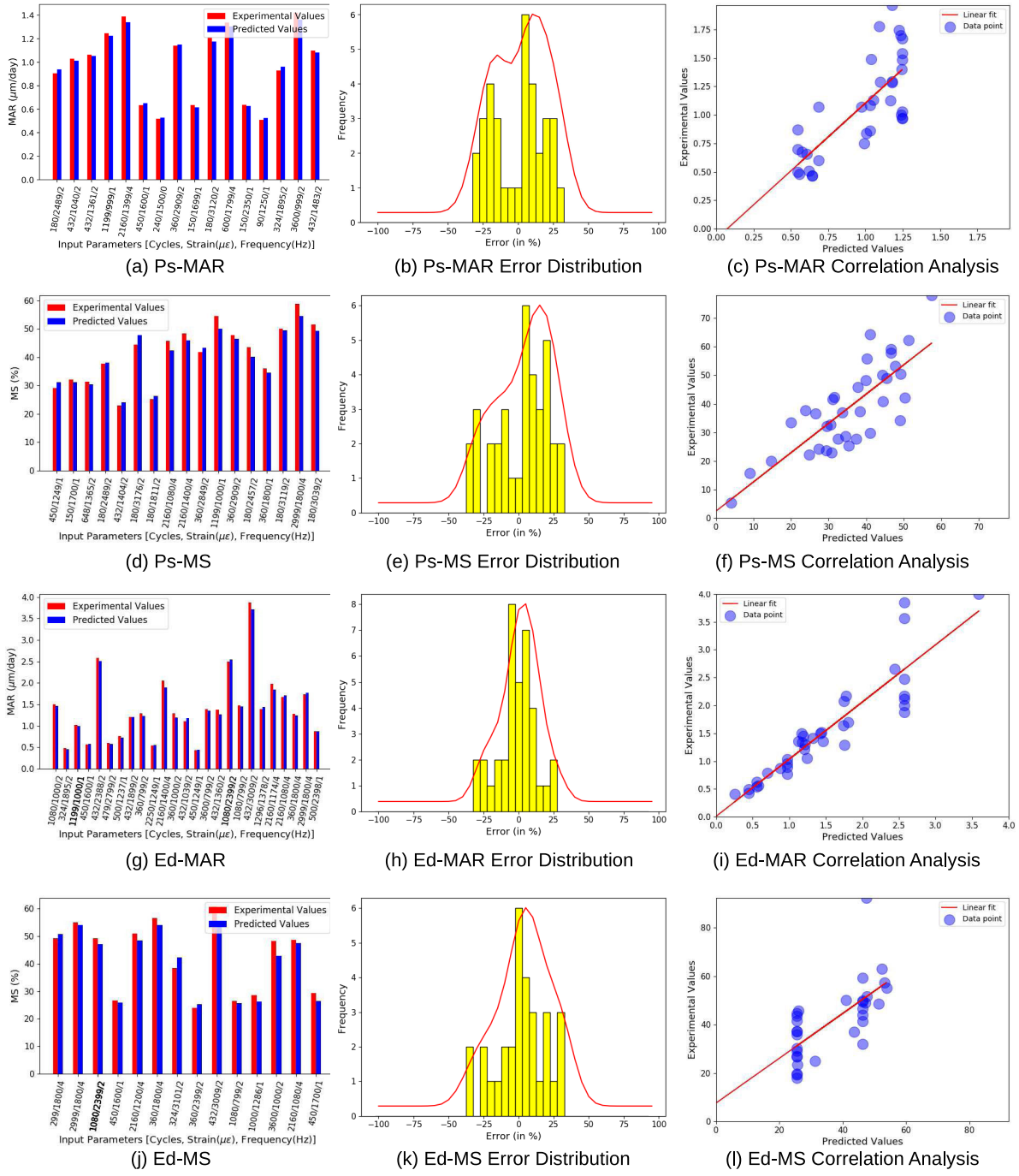

FIGURE 7. Training results of bone formation parameters for (a)-(f) Ps-MAR, Ps-MS (g-l) Ed-MAR, Ed-MS.

The detailed training results of the neural network model are shown in Fig. 7. The network training outputs of the model i.e., Ps-MAR, Ps-MS, Ed-MAR and Ed-MS are compared with targeted or experimental values of these parameters noticed in the in vivo experiments. Figs. 7a, 7b, and 7c explains the training results for Ps-MAR. Fig. 7a indicates that training output of Ps-MAR are close to experimental values. Fig.7b presents the distribution of error between training output and target values. The percentage error for most of the training data set lies with in $\pm$ 30% and has a uniform distribution around zero error. Correlation analysis is also performed between the training output and the experimental values. Correlation coefficient $R^2 = 0.89$ indicates that training output is close to experimental values. These results indicates that training has been successful for data set associated with Ps-MAR. Similarly, Figs. 7d, 7e, 7f indicate the training output versus experimental values, error distribution ($\pm$ 25%) and correlation analysis ($R^2 = 0.90$) results

TABLE 4. Comparison of different models on the basis of MSE obtained after training the models.

Output bone modelling Parameters	Linear Regression	Tiwari and Kumar [13]	Proposed Model
Ps-MAR	0.0416	0.0384	0.0376
Ed-MAR	0.0339	0.014	0.0089
Ps-MS/BS	0.0305	0.0246	0.0204
Ed-MS/BS	0.0371	0.0311	0.0288

TABLE 5. Comparison of different models on the basis of MSE obtained after testing the models.

Output bone modelling Parameters	Linear Regression	Tiwari and Kumar [13]	Proposed Model
Ps-MAR	0.0624	0.0491	0.0414
Ed-MAR	0.0422	0.0281	0.012
Ps-MS/BS	0.0418	0.0395	0.0301
Ed-MS/BS	0.0459	0.0401	0.0325

for Ps-MS, respectively. The dataset associated with Ed-MAR has the training output close to experimental values (Fig. 7g). The percentage error is around $\pm$ 30% and the coefficient of regression is also $R^2 = 0.94$ (Figs. 7h and 7i). The model closely achieved the target value during training for the data sets associated with Ed-MS which can be observed from the percentage error ($\pm$ 25%) and correlation coefficient ($R^2 = 0.90$) indicated in Figs. 7j, 7k and 7l. Thus, these results indicate that a healthy training is achieved in the proposed neural network model. The cross validation error is also minimized during the training as shown in Fig. 6. Cross validation error plots explains that the network was prevented from over-fitting. The observations indicates that the network has successfully learned the relationship which exists between the input loading parameters and the output bone remodeling parameters.

B. TESTING RESULTS

Mean squared values obtained while testing the trained model are presented for all the four bone modeling parameters in Table 5. It can be clearly observed that the model has now improved prediction ability as compared to that observed in linear regression model and the model of Tiwari and Kumar [13].

Fig. 8 explains the results obtained from the testing of the model. A comparison between the predicted values and the experimental values are shown in Figs. 8a, 8d, 8g and 8j for the output parameters i.e., Ps-MAR, Ps-MS, Ed-MAR, and Ed-MS, respectively. It can be observed that predicted values are close to experimental results reported in the in vivo studies. This affirms that the model performs well when new values of the loading parameters (not accounted in training) are supplied. The model performance has also been found satisfactory during cross-validation. Figs. 8b, 8e,8h and 8k explains the percentage error distribution. The percentage error for most of the predicted values of the output parameters lies with in $\pm$ 25%. The coefficient of regression between the predicted values of Ps-MAR, Ps-MS, Ed-MAR, and Ed-MS, and experimental values are 0.83, 0.85, 0.88 and 0.84, respectively, which shows a positive and healthy correlation. This much correlation between computational and experimental outputs is reported healthy in a few bone adaptation studies. For example, Gross *et al.* [67] indicated 63% correlation as a strong correlation between new bone distribution and mechanical parameter i.e., strain gradients distribution. This also aligns with testing results presented in the Tiwari and Kumar [13]. This indicates that the model has satisfactorily predicted the value of new bone formation parameter close to the range of experimental values (including standard deviation) observed during in vivo experiment. Therefore, the model developed in the present study has the ability to predict the new bone formation parameters as a function of loading parameters i.e., number of loading cycles, frequency and strain magnitude.

C. MODEL VALIDATION

The above mentioned results indicate that the neural network model with optimal weights is an improvement on the state-of-the-art. The model establishes empirical relationship between cyclic loading parameters and the bone modeling parameters viz. MAR and MS/BS. Therefore, this relationship can be simulated to study the effect of each individual loading parameter on the new bone formation. Fig. 9 explains the response of MAR and MS with change in number of cycles, frequency and strain magnitude. It can be observed that Ps-MAR, Ed-MAR and Ps-MS increases in a nonlinear fashion as number of loading cycles increases and saturates after a certain number of loading cycles (Figs. 9(a)-(c)). Nevertheless, a similar trend has not been observed in case of Ed-MS (Fig. 9(d)). The MAR and MS/BS also increases as values of frequency or strain magnitude increases for any fixed value of loading cycles. This represent a dose-response characteristic which also aligns with the experimental findings of Turner *et al.* [28] and Yang *et al.* [68]. Figs. 9(e)-(g) indicates that MAR and MS/BS both increases as values of strain magnitude increase in dose-response manner. At a fixed value of strain magnitude, both the parameters also increase as values of loading frequency and cycle increase. A similar trend has also been observed when loading frequency is varied for a fixed number of loading cycles and strain magnitude. These trends are in close alignment with in vivo experimental results reported by Hseih and Turner, Turner *et al.* [28] and in a recent study of Yang et al. [68], and simulation results of Kameo *et al.* [69].

The results presented in the above sub-section affirms that the proposed neural network model adequately captures the dependence of new bone formation on mechanical loading parameters from in vivo experimental data. The proposed model may be useful in estimating the amount new bone formation as a function of loading regimen. This type of relationship is important in the field of orthopedic research. Over the past few years, several mechanobiological models are developed to predict the site-specific new bone formation [70]–[72]. These models involved local mechanics

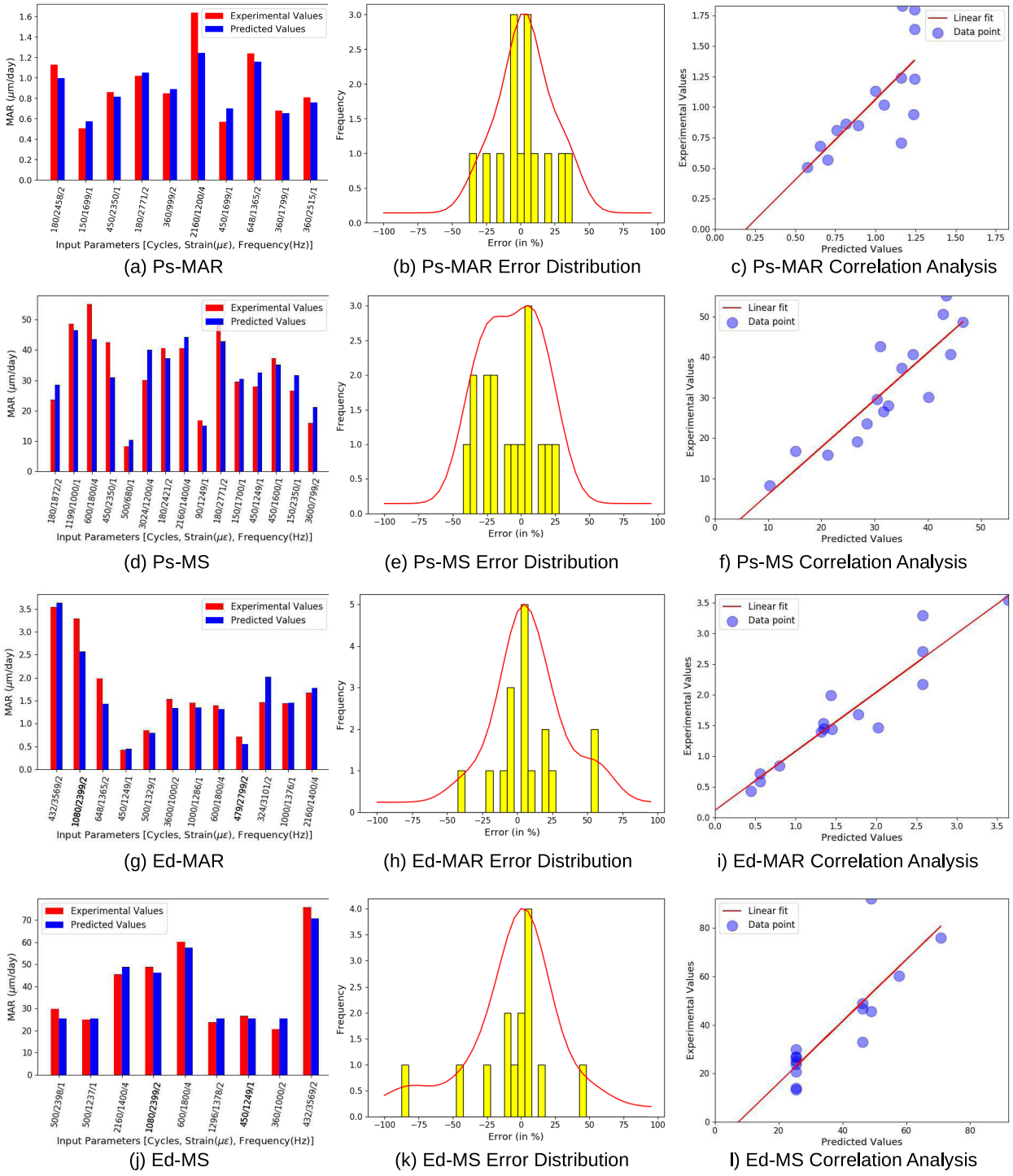

FIGURE 8. Testing results of bone formation parameters for (a)-(f) Ps-MAR, Ps-MS (g-l) Ed-MAR, Ed-MS.

and successfully predicted the site-specificity of new bone formation as a function of normal strain or strain energy density. Nevertheless, the models failed to estimate the amount of new bone formation. A remodelling rate coefficient regulates the amount of newly formed bone in the model. This parameter is usually tuned in such a way that it can fit the experimental new bone formation. Thus, the same model may fail to predict the osteogenesis for other in vivo experiments. A remodeling rate coefficient which is decided on the basis of bone modeling parameters such as MAR and MS, may resolve this problem. This work establishes that bone modeling parameters can be computed as a function of loading

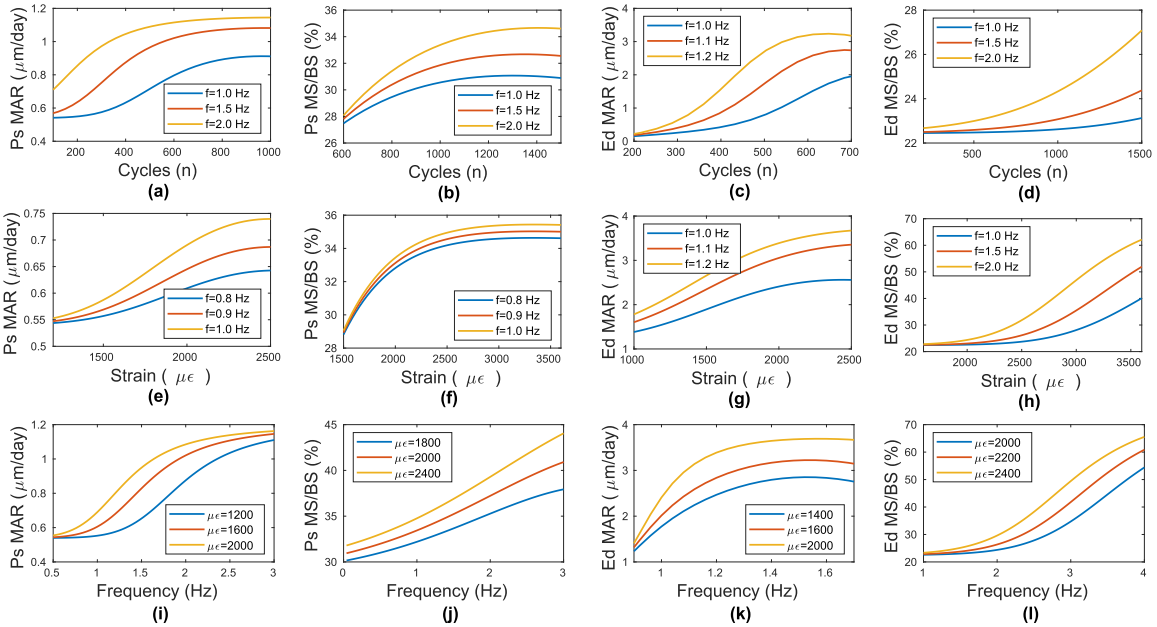

FIGURE 9. Variation of MAR, MS by varying (a)-(d) cycles (e)-(h) strain (i)-(l) frequency, at different values of frequency (for a-h) and strain (for i-l).

parameters, therefore, a suitable remodeling rate coefficient can be introduced in the in silico models to precisely predict the location and the amount of new bone formation. Cowin *et al.* [73] presented a way to calculate the rate coefficients based on MAR and starin magnitude reported in five in vivo studies. However, more experimental data on bone modeling is accommodated in the present work in which nearly all the prime loading parameters influencing the bone modeling are taken into account. Ultimately, the proposed work attempts to decrease this inconsisteny between in silico models and in vivo experimental results. It is worth mentioning that the computational biology models may also fall down due to pathological and physiological changes experienced with in vivo experiments. Our work does not include parameters to covers this aspect and applicable to those experiments where new bone formation is purely due to mechanical loading. Hence, our work will only improve the independency and prediction capacity of existing mechanobiological models. Mechanobiological models qualitatively predict location of osteogenic activity as a function of local mechanics and biological environment, whereas, our model attempts only predicts the quantity of new bone formation only as a function of loading parameters. Thus, the objective of mechanobiological models and our model is different.

The experimental data incorporated in the model is limited due to unavailability of data in the literature. Several other parameters e.g., age, strain, rest-time also affect osteogenesis, however, these parameters are not included in the model. This is the limitation of the proposed model and may be taken as a future work. These consideration may result into a more robust model to predict new bone formation induced by mechanical loading. Most of the data considered in the present study belongs to those experiments where lamellar new bone formation was observed, however, it is observed that a higher loading cycles and strain magnitude woven bone formation may occur. The model presented here does not predict the type of new bone formation (either lamellar or woven) as a function of loading parameter. This may be interesting to develop a model which can also predict the type of bone formation. In future, the data from those in vivo studies can also be included where osteogenesis is studied in response to a combination of pharmaceutical drugs and mechanical loading. This will allow to predict the optimal pharmaceutical and bio-mechanical interventions to obtain a desire new bone response.

IV. CONCLUSION

The present work introduces a new and improved approach to predict the major bone modeling parameters such as MAR and MS/BS based on loading parameters such as cycles, frequency and strain. A neural network model is proposed and an empirical relationship is developed between bone modeling parameters especially MAR and MS and cyclic loading parameters. Testing results of the proposed model shows a considerable improvement over the state-of-the-art models in predicting values of bone formation parameters MAR and MS/BS. Also, a statistical analysis of the data set comprising of loading parameters and bone modelling parameters is described in detail. The proposed model may provide support to in silico model of bone adaptation in precision prediction of loading induced osteogenesis. Based on the outcome of this and other similar studies, better

bio-mechanical strategies may be developed for the prevention of bone loss. This study contributes in the area of orthopedic research focused on bone health improvement.

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