Artificial neural networks in hard tissue engineering: another look at age-dependence of trabecular bone properties in osteoarthritis

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***Abstract*— Artificial Neural Network (ANN) model has been developed to correlate age of severely osteoarthritic male and female specimens with key mechanical and structural characteristics of their trabecular bone. The complex interdependency between age, gender, compressive strength, porosity, morphology and level of interconnectivity was analysed in multi-dimensional space using a two-layer feed-forward ANN. Trained by Levenberg-Marquardt back propagation algorithm, the ANN achieved regression factor of R = 96.3% between the predicted and target age when optimised for the experimental dataset. Results indicate a strong correlation of the 5-dimensional vector of physical properties of the bone with the age of the specimens. The inverse problem of estimating compressive strength as the key bone fracture risk was also investigated. The outcomes yield correlation between predicted and target compressive strength with the regression factor of R = 97.4%. Within the limitations of the input data set, the ANNs provide robust predictive models for hard tissue engineering decision support.**

I. Introduction

Degradation of structural properties and mechanical strength in trabecular tissue has been commonly associated with aging for a normal bone [1-3]. For osteoarthritic specimens, however, the effect of age on the trabecular bone parameters has not yet been sufficiently understood [4-6]. Study by Perill et al. [7] did not reveal statistically significant correlation between the age of osteoarthritis affected patients and structural and mechanical properties of the trabecular bone, when using bivariate linear regression analysis. Although efficient and relatively simple, such statistical approach does not account for a complex interdependency that may exist between the mechanobiological parameters in multi-dimensional space. This necessitates use of more flexible, 'fuzzy' computational methods that can cope with non-linearity, high dimensionality, incomplete datasets and lack of mechanistic equations. Data-driven models offered by machine learning can overcome these challenges with a potential for highly scalable and robust decision-support systems in hard tissue engineering [8]. Of modern machine learning algorithms including decision trees, Bayesian networks, association rule learning and various clustering mechanisms, artificial neural networks (ANN) are particularly effective for regression problems where no initial assumptions can be made about the probabilistic relationships between the inputs and outputs. Moreover, ANNs have been able to perform on smaller datasets in bioengineering domain, where large-scale experiments on living tissue remain infeasible [8-10].

II. Methodology

The dataset used in this study comprises of trabecular bone samples from the femoral heads of 35 patients who undergone total hip arthroplasty due to severe osteoarthritis [7]. For each trabecular bone sample a series of experiments involving micro-CT scanning at the isentropic pixel resolution of 19.5μm with a complete rotation over 185°, deformation testing with extensometer attached to the sample and ashing at 650°C for 24 hours with subsequent mass measurements were conducted [7]. The following mechanical and structural characteristics were determined for the selected 35 trabecular bone samples: a) compressive strength (in MPa) measured in deformation testing, b) porosity (%) characterised by the bone volume fraction BV/TV which was derived from the cross sectional micro-CT images, c) level of interconnectivity indicated by the trabecular thickness factor Tb.Th (dimensionless) which was measured in micro-CT scanning using spherical estimation, and d) morphology characterised by the Structure Model Index (SMI, dimensionless) which was also determined from micro-CT images by approximating the topology of the bone in terms of rods and plates [7, 11].

The extracted data was composed into 1) 5-dimensional matrix of one gender indicator coupled with the four mechanical parameters listed above as the input, and 2) the vector of specimens' age as the corresponding output. The samples were divided into training (60%), validation (20%) and test (20%) sets at random.

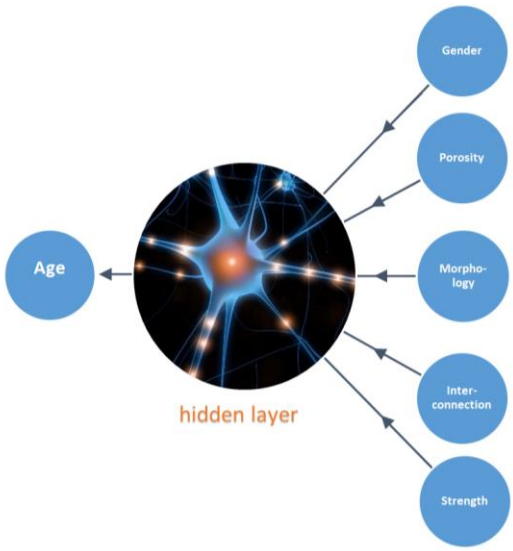

Figure 1. ANN model topology and input/output configuration

A simple two-layer feedforward neural network (Fig. 1) was designed to produce maximum generalisation based on the relatively small dataset of 35 samples. The number of neurons in the hidden layer was chosen to provide at least 5 samples of input-target vector pairs per each perceptron according to a recommended practice [8]. The expected non-linearity in the data was accounted for by using the sigmoid activation transfer functions in the hidden layer neurons, while the output activation transfer function was linear. In order to maximise the learning efficiency of the ANN, a powerful Levenberg-Marquardt backpropagation algorithm [12, 13] was applied to the training set. Cross-validation was used throughout the training process to prevent over-fitting. Performance was measured by the mean squared error (MSE) and the linear regression factor (R) between the specified targets and the outputs predicted by the ANN.

Following the performance assessment on test samples, the trained ANN was simulated with incomplete input matrices in order to determine the relative importance of the mechanobiological parameters. Specifically, each input parameter under investigation was iteratively substituted by its mean value across all samples. This altered input was fed into the ANN and the corresponding decrease in predictive power was measured. Unlike conventional non-linear principal component analysis, the proposed input parameter sensitivity analysis (IPSA) utilises the same ANN in order to establish key inputs, thus allowing for a more intuitive perspective on otherwise a 'black-box' process [14, 15].

Furthermore, by selecting the most effective split and order of the training and validation samples among more than 2000 random combinations, it was possible to optimise the ANN model to the available dataset. Such optimisation assumes that the 35 experimental samples are fully representative of the entire population of the osteoarthritic specimens for which the model could be used.

Similar ANN design and optimisation methodology was undertaken in relation to the inverse problem – the system in which age is one of the model inputs and compressive strength is the output.

III. Results and Analysis

The generalising ANN correlated the actual and predicted age with R = 87.0% for test samples and R = 85.9% for all samples (Table I).

TABLE I. Summary of key performance measures for the ANN models

ANN model	Linear regression factor, R (%)		Mean squared error, MSE	Standard error, RMSE (output unit)
	all samples	*test samples*		
Initial age	85.9%	87.0%	45.56	6.75 years
Optimised age	96.3%	91.2%	11.70	3.42 years
Optimised strength	97.4%	96.6%	3.52	1.88 MPa

The initial ANN performance across the entire dataset was compared to the regression factors produced during IPSA for each input parameter. As illustrated in Fig. 2, the ANN model is most sensitive to the absence of compressive strength and least sensitive to the absence of porosity. Compressive strength factor accounts for 71% of the ANN predictive power, whereas exclusion of porosity decreases performance by 27%.

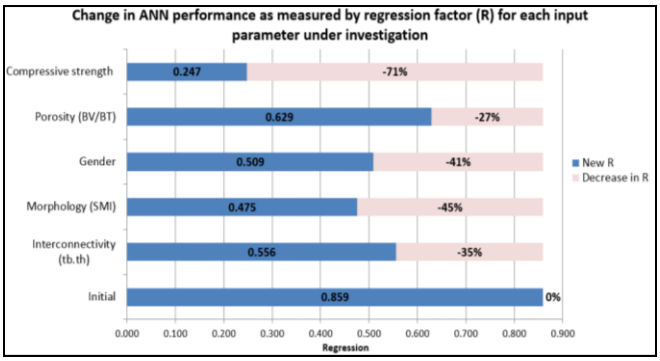

Figure 2. Decrease in ANN performance as measured by regression factor

Optimisation for the available dataset markedly improved the ANN performance. The linear regression analysis yielded R = 91.2% and R = 96.3% for test and all samples respectively (Fig. 3). The model was able to predict age of the specimens with the MSE = 11.70 (Fig. 4).

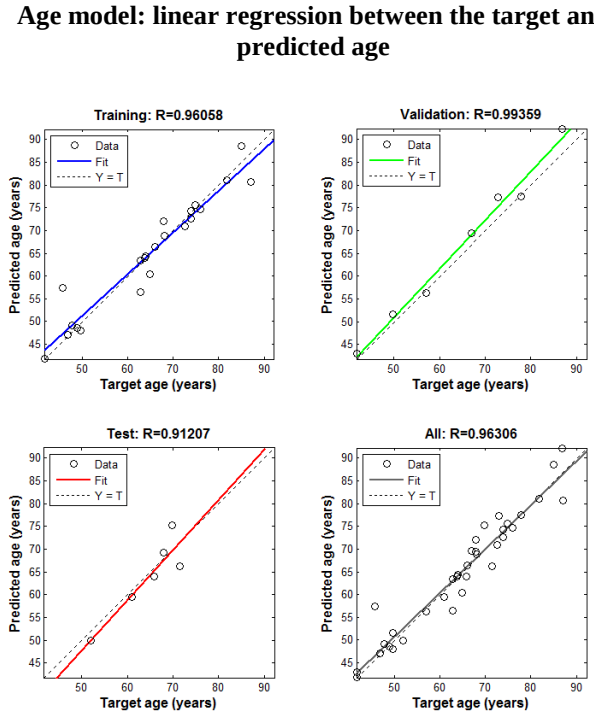

Figure 3. Optimised age model performance for training, validation and test samples.

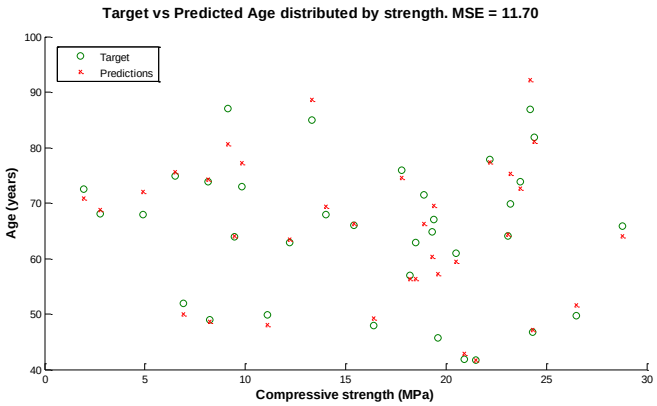

Figure 4. Scatter plot of target and predicted age for all samples (distributed by compressive strength)

The ANN model was reconfigured to use age parameter as one of the inputs and compressive strength of the trabecular tissue as an output. It was subsequently trained, cross validated, optimised and tested.

Optimised compressive strength model achieved regression factors between the predicted and target strengths of R = 97.4% for tests and R = 96.6% across the entire dataset. (Fig. 5).

Strength model: linear regression between target and predicted compressive strength

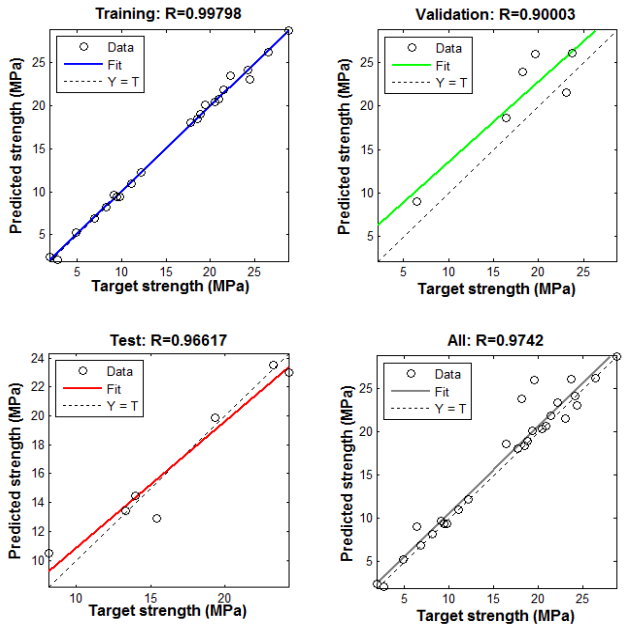

Figure 5. Optimised strength model performance for training, validation and test samples

As shown in Fig. 6 the actual (target) values of the compressive strength and those predicted by the ANN for each individual sample were closely aligned (MSE = 3.52) across the entire dataset. This corresponds to the standard error of less than 2 MPa.

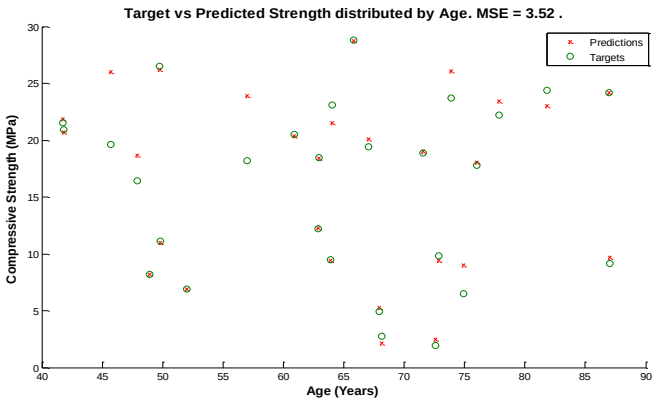

Figure 6. Scatter plot of target and predicted compressive strength for all samples (distributed by age of the specimen)

IV. Discussion

The strong correlation that was observed between the ANN predictions and target age is an indication that the mechanical and structural properties of the human trabecular bone depend on the age for the osteoarthritis affected patients. Such correlation was not previously established by using bivariate linear regression analysis between the age and each individual property of the bone [7]. Instead, the ANN model developed here provides an instrument for a multivariate non-linear regression analysis, investigating correlation of age and all of the input mechanobiological parameters combined.

The outcomes of the IPSA revealed that all five input parameters, including compressive strength, porosity, gender, trabecular thickness and structure model index, are significant contributors to the ANN predictive power. Thus, the dimensionality of the model cannot be reduced without compromising its accuracy.

Within the limitations of the optimisation process, the results demonstrated that the ANN model can be utilised as a predictive tool for the age of the specimens from the selected input of mechanobiological parameters related to the trabecular bone. This level of accuracy is similar to that achieved by expert systems in medical diagnosis [16, 17]. It is, however, required to further assess the performance of the ANN on a larger set of test data for the model to be recommended for clinical applications.

The high accuracy of the compressive strength model enables prediction of bone fracture risk based on the structural and biological parameters that can be derived without invasive tests on the specimen. This ANN model of femoral trabecular bone is of a particular value to hard tissue engineers when designing bioscaffolds that mimic the natural trabecular tissue [18-20]. It is important to re-iterate that as with many data-driven machine learning models, this ANN based 'black-box' approach could not be used with the objective to determine, in exact mathematical terms, the nature of the causal relationship between the inputs and outputs [21, 22]. Nevertheless, tissue engineers, by being able to predict how compressive strength correlate with bone volume fraction, trabecular thickness and structure model

index for specimens of various age and gender groups, could tailor their scaffold designs for an individual patient to match the trabecular tissue at the site of implantation.

V. Conclusion

Primary findings are:

(1) The age of the osteoarthritic patients positively correlates with the 5-dimensional vector of mechanobiological parameters of their trabecular bone, including compressive strength, bone volume fraction BV/TV (indication of porosity), structure model index (a measure of morphology of the trabecular network), trabecular thickness factor (measure of interconnectivity) and the gender of the specimen.

(2) All input parameters are significant in the multidimensional correlation with age. Compressive strength accounts for 71% of the ANN predictive power.

(3) When optimised for the dataset, the ANN determines the age of the specimens with standard error of 3.42 years. For test samples the model achieved the regression factor between predicted and target age of 91.2%.

(4) When re-configured to predict compressive strength from the structural and biological indicators, the ANN yielded standard error of 1.88 MPa and the regression factor of 96.6% for test samples. This model has a direct practical application for estimating the bone fracture risk and optimising bioscaffold designs.

In the context of the future data availability and ongoing methodology validation based on physical approximations and surrogate data, this exploratory study created a precedent for applying machine learning models to small experimental datasets in hard tissue engineering. By virtue of its imbedded learning algorithms, these ANN models were designed to improve their generalisation with every new data sample. The ability to evolve with additional training makes the ANN models promising versatile tools for a range of hard tissue engineering and associated clinical applications.

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