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Deformation prediction by a feed forward artificial neural network during mouse embryo micromanipulation

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In this study, a neural network (NN) modeling approach has been used to predict the mechanical and geometrical behaviors of mouse embryo cells. Two NN models have been implemented. In the first NN model dimple depth (w), dimple radius (a) and radius of the semi-circular curved surface of the cell (R) were used as inputs of the model while indentation force (f) was considered as output. In the second NN model, indentation force (f), dimple radius (a) and radius of the semi-circular curved surface of the cell (R) were considered as inputs of the model and dimple depth was predicted as the output of the model. In addition, sensitivity analysis has been carried out to investigate the influence of the significance of input parameters on the mechanical behavior of mouse embryos. Experimental data deduced by Flückiger (2004) were collected to obtain training and test data for the NN. The results of these investigations show that the correlation values of the test and training data sets are between 0.9988 and 1.0000, and are in good agreement with the experimental observations.

Keywords: artificial neural network; biological cells; error back propagation algorithm; sensitivity analysis

1. Introduction

Living cells are always exposed to mechanical stimulation in the human body. Often, it is important for us to investigate how cells react mechanically to physical loads and how the distribution and transmission of these mechanical signals are ultimately converted to chemical and biological responses in the cells (Lim et al. 2006; Lee and Rhee 2009). Consequently, to understand the cell functions and behavior, the relationship between cellular deformations and mechanical forces in living cells is important. In order to study the biomechanical properties of biological cells, recently there has been an extensive interest in the literature. Because of the heterogeneous nature of biological cells, different experimental techniques are used and devised to probe the response of cells such as atomic force microscopy (AFM) (Sen et al. 2005; Lulevich et al. 2006), laser/optical tweezers (Dao et al. 2003), microplate stretcher (Thoumine and Ott 1997), micropipette aspiration (Vaziri and Kaazempur Mofrad 2007) and tapered micropipette (He et al. 2007).

These different experimental techniques have led to a variety of different mechanical models developed by various researchers to interpret and explain the experimental data such as cortical shell liquid core models (or liquid drop models), solid models, fractional derivative models, cytoskeletal models for adherent cells, a spectrin-network model for erythrocytes, etc. (Lim et al. 2006).

On one hand, although these experimental techniques have been a significant influence in biological cell studies, hey have problems such as difficult implementation, poor controllability, high cost, etc. (Tan et al. 2010). On the other hand, in some cases it is reported that using different mechanical models for the same type of cells has led to differing mechanical properties. For example in studying neutrophils, derived mechanical properties using the Newtonian liquid drop model and the Maxwell model are different (Lim et al. 2006).

Other methods which are usually used in cell indentation experiments are the contact mechanics models, including the Hertzian model and the Sneddon model. These models cannot be used where large deformations are considered because large deformations violate the small deformation assumption of the contact mechanics models. Furthermore, in contact mechanics models only a local dimple geometry change is taken into account and the global geometry of the deformed cell remains unchanged. Other limitations of the contact mechanics models in large deformations have been reported elsewhere (Sun et al. 2003; Kim et al. 2008).

In previous investigations on biological cells (Sun et al. 2003) a point-load model has been proposed to predict the indentation force of biological membranes, with its analytical solution given as follows:

$$F = \frac{2\pi Ehw^3}{a^2(1-\nu)}\left[\frac{3-4\zeta^2+\zeta^4+2\ln\zeta^2}{(1-\zeta^2)(1-\zeta^2+\ln\zeta^2)^3}\right] \quad (1)$$

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Where $\zeta = \frac{c}{a}$, c is the indenter radius and a is dimple radius of the cell. Here, ν, E, h and F are the Poisson ratio, Young's modulus, thickness of membrane and measured force, respectively.

Some limitations of point-load models are as follows: this model assumes that membrane stress within the dimple is uniform. Also, residual stress of the membrane is assumed to be zero, which is not the case in reality (Sun et al. 2003). On the other hand, it has been assumed that the interaction of the cytoplasm and membrane is uniform, which it is not in reality. Furthermore, as can be seen, Eqn. (1) is somewhat complicated, and it may be subject to variations due to parametric uncertainties.

Hence, the need is felt for simpler, cheaper and more precise models that can relate the deformed cell configuration to external applied force and do not include incorrect assumptions.

One engineering approach for prediction of the indentation force or dimple depth is based on the utilization of artificial neural networks (ANNs). A neural network consists of many processing elements which operate in parallel and are connected by several links with variable weights and biases, which are typically adjusted during the training process (Bahrami et al. 2005).

Our approach includes the following aspects: first, an ANN model proposed previously (Ahmadian et al. 2010) is reviewed and further extended. Second; some untrained samples are preserved for testing proposes to present the prediction capability of the ANN model. Third, sensitivity analysis is performed to investigate the parameters influencing indentation force and dimple depth. Fourth, the results of thesensitivity analysis are compared with previous analytical analysis to further verify the results of the ANN modeling approach.

2. Artificial neural network technique

Artificial neural networks (ANNs), also called 'neural networks', are collections of small individual interconnected processing units with weights and biases associated with each connection. Learning is the first step necessary in including intelligence in neural networks. During the learning process, the network autonomously adjusts the connection weighs and biases among the processing units according to imposed learning rules and, thereby, obtains unique knowledge from the data. In the second step, the learned neural network generates accurate output from the input data and, thereby, the network model is prepared for subsequent applications (Bahrami et al. 2005).

In these investigations, the feed-forward multilayer perceptron has been used and trained with the error back propagation algorithm (Nguyen et al. 1944). The activation function that has been used between the processing elements is a hyperbolic sigmoid transfer function as follows:

$$f(x) = \frac{1 - e^{-x}}{1 + e^{-x}} \tag{2}$$

Since the normalizing operation depends on the selected activation function, the data were normalized within the range of ± 1 (Bahrami et al. 2005):

$$X_n = \frac{X - X_{\min}}{X_{\max} - X_{\min}} \tag{3}$$

Where $X_{\min}$and $X_{\max}$are the minimum and maximum values of X; X_n is the normalized value and n is the number of the data set. The output $y_i$produced by the neuron $i$in the layer l is given by the following relationship (Jajarmi and Eivani 2009):

$$y_i = f(\sum_{j=1}^{n} w_{ij} + b) \tag{4}$$

Here $f$is the activation function, n is the number of elements in the layer $l-1$, $w_{ij}$is the weight associated with the connection between the neuron i in the layer $l$and the neuron j in the layer $l-1$, whose output is w_i, and $b$is the offset or bias which shifts the activation function along the basic axes. An iterative algorithm adjusts the weights of connections while the y response of the output neurons can be close to the desired response t, which can be tested by minimizing the learning error in each training (i.e. epoch), defined by mean square error (MSE) (Dashtbayazi et al. 2007):

$$MSE = \frac{1}{N}\sum_{i=1}^{N}(t_i - y_i)^2 \tag{5}$$

Where N is the total number of training patterns, $t_i$the target (i.e. desired) output value, and y_i is the network output value. The performance of the developed network was evaluated with the help of Bahrami et al. 2005; Jajarmi and Eivani 2009; Yazdanmehr et al. 2009:

1. Drawing a scatter diagram of estimated versus experimental values.
2. Computing mean absolute error (MAE) using:

$$MAE = \sum \frac{|x - y|}{n} \tag{6}$$

Where $x = X - X'$, X is the target output and X' is the mean of $X$and $y = Y - Y'$, Y is the network output and Y' is the mean of Y.

3. Sensitivity analysis

Sensitivity analysis is used to determine the relative importance of each of the input parameters on the model outputs. In other words, this analysis can help to identify input parameters influencing the model behavior. In the case of cell properties the available NN models have been used to identify more important input parameters for predicting deformation of the mouse embryo. In this study two techniques are used to identify the most sensitive factors influencing predicted deformation: relative strength of effect (RSE) and relative importance (RI) methods.

3.1. Relative strength of effect (RSE)

This technique was proposed by Yang and Zhang (1997). According to this technique, if there is a trained neural network with a given sample data set, this method can be used to recognize the most important parameters in the model, hierarchically. Based on this criterion, inputs with higher RSE have a stronger effect on the model outputs.

According to Yang and Zhang (1997), the RSE can be defined as follows:

$$RSE = C \sum_{jn} \sum_{jn-1} \ldots \sum_{j1} W_{j_n k} G(e_k) W_{j_{n-1} j_n} G(e_{j_n}) \\ W_{j_{n-2} j_{n-1}} G(e_{j_{n-1}}) W_{j_{n-3} j_{n-2}} G(e_{j_{n-2}}) \ldots W_{ij_1} G(e_{j_1}) \quad (7)$$

Where C is the normalized constant which controls the maximum absolute value of RSE as unit, G denotes the differentiation of the activation function, W is the connected weight and e_k is the input signal which comes into layer k.

3.2. Relative importance (RI)

This index which is referred to as relative importance, RI, evaluates the contribution of each input variable to the output by interpreting the interconnection weights of the neural network model (Mandal et al. 2009). If a well-trained multilayer neural network model with an $m \times n \times 1$architecture (i.e. m input nodes, n hidden nodes and 1 output node) is considered, the following procedure can be used to calculate the relative importance of input variables as follows:

Step 1: a row vector, M $(1 \times n)$, for the interconnection weights between the hidden layer nodes (n nodes) and the output layer nodes is constructed.
Step 2: a $m \times n$ matrix, W, for the interconnection weights between the input layer nodes (m) and the hidden layer nodes (n) is constructed.
Step 3: the row vector, $R = MW^T$, in which $R = [r_1\ r_2\ r_3\ \ldots\ r_m]$, is calculated.
Step 4: the relative importance, RI, of an input node is calculated as follows:

$$RI_i = \frac{|r_i|}{\sum_{i=1}^{m} |r_i|} \times\ 100\ (\%),\ i = 1 \sim m. \quad (10)$$

4. The data base

The data used for this investigation were captured from experimental observations by Flückiger (2004). These experimental data were generated by Yu Sun and his co-workers (Sun et al. 2003) and come from multiple indentation tests which have been done on a single embryo. The detailed experimental observations of the mouse embryo cell are presented in Table 1. To become further familiar with the method of sample preparation, the readers can refer to Sun et al. (2003). Among these experiments, 70% of the data set (eight samples) was randomly selected for training the ANN models while 30% percent of the remaining data sets

Table 1. Experimental data sets fom mouse embryo (Flückiger 2004).

Data Number	Dimple Radius(um)	Dimple Depth(um)	Radius of the Semi-circular Curved surface of the cell(um)	Measured Force (uN)
1	18.375	11.754	12.76	1.052
2	18.7S5	13.887	12.54	2.379
3	19.572	15.039	12.24	3.418
4	19.866	16.425	11.76	4.511
5	20.412	17.289	11.52	5.655
6	20.748	17.496	11.14	6.013
7	22.113	19.017	10.68	6.762
a	22.512	21.006	10.13	8.148
9	22.879	22.905	10.10	9.664
10	22.932	24.399	9.860	11.96
11	23.079	25.155	9.650	13.39

(three samples) were used to validate the ability of the ANN models to predict the indentation force and dimple depth of the mouse embryos. In the first NN model used for indentation force prediction samples 2, 5 and 10 were randomly selected while in the second NN model samples 3, 6 and 9 were randomly selected to predict cell deformation.

5. Results and discussion

5.1. Neural network results

Two ANN models with one hidden layer have been used and trained using the error back propagation algorithm (Nguyen et al. 1944). The inputs of the first ANN model are dimple depth, dimple radius and radius of the semi-circular curved surface of the cell and indentation force is considered as an output, while in the second ANN model indentation force, dimple radius and radius of the semi circular curved surface of the cell are used as inputs and dimple depth is predicted in the output. The network's state of knowledge can be determined by the weight and bias values when MAE reaches the minimum value. Therefore, the optimum number of hidden units can be learned.

The architectures of the ANN models that have been used for prediction of indentation force and dimple depth are presented in Table 2a and 2b, respectively.

MAE values for various hidden units in the models that have been used for prediction of indentation force and dimple depth were calculated. According to these calculations, for the model used for prediction of indentation force, the ANN with one hidden layer and 13 hidden units yields the smallest MAE (8.3556%) while in the corresponding model used for prediction of dimple depth, the smallest MAE is yielded when the model has one hidden layer and five hidden units (6.2965%). In the first neural network model, samples 2, 5 and 10 were randomly selected for testing purposes, and the remaining samples were used for training the network, while in the second investigation,

Table 2a. Key neural network model parameters for indentation force prediction.

Key parameter	Value
Layers	3
Hidden layer	1
Neurons in hidden layer	13
Neurons in input layer	2
Neurons in output layer	1
Learn rule	Delta rule
Transfer function	Hyperbolic sigmoid
Learning momentum	0
Learning rate	0.15

Table 2b. Key neural network model parameters for dimple depth prediction.

Key parameter	Value
Layers	3
Hidden layer	1
Neurons in hidden layer	5
Neurons in input layer	2
Neurons in output layer	1
Learn rule	Delta rule
Transfer function	Hyperbolic sigmoid
Learning momentum	0
Learning rate	0.15

samples 3, 6 and 9 were randomly selected for testing and the remaining data were used for training the model. The correlation values between experimental and trained data are calculated as 1.0000 and 0.9999 for the models that have been used for prediction of indentation force and dimple depth, respectively. Moreover, the corresponding MAEs of the indentation force and dimple depth are 1.60% and 6.01%, respectively. As can be seen, the NN models are successful in prediction of indentation force and dimple depth.

The predicted indentation force and dimple depth by ANN models versus experimental values for testing sets are shown in Figures 1 and 2, respectively. The test data sets were only used for testing purposes and are not involved in the model training process.

Consequently, the precision of the ANN models in prediction is obviously confirmed by their performance on the testing data sets. The correlation value and MAE for the testing data set in prediction of indentation force are 0.9999 and 4.65%, respectively, and the corresponding values in prediction of dimple depth are 0.9988 and 16.52%, respectively. These results validate that a good

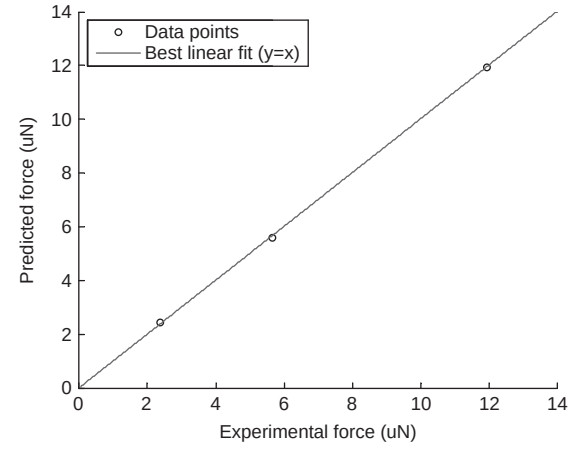

Figure 1. Comparison of the predicted and experimental indentation force values using testing data.

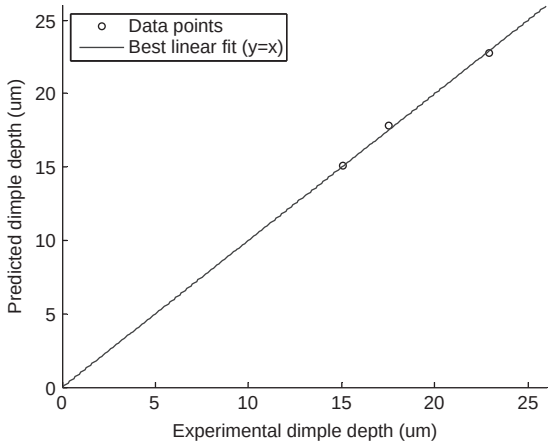

Figure 2. Comparison of the predicted and experimental dimple depth values using testing data.

correlation occurred between experimental and predicted observations.

As can be seen from these results, for a given cell deformed by an indenter this simple ANN model together with the experimental data is capable of accurately predicting the external applied force in an online process without needing a force sensor or, vice versa, can be used to predict the deformed cell shape without needing a visual or displacement sensor and can reduce experimental cost. However, the price that must be paid for this simplicity and low-cost implementation is that we cannot measure the mechanical properties of biological cells such as Young's modulus by this modeling approach.

5.2. Sensitivity analysis results

The results of sensitivity analysis using the trained ANN for deformation prediction are presented in Figures 3 and 4. Figure 3 shows the significance of the input parameters on predicted deformation using the RSE method while the corresponding results using the RI method are shown in Figure 4.

According to these figures, indentation force is the most effective parameter for predicted deformation, whereas the radius of the semi-circular curve (R) has not so much effect on output. In this figure, the radius of the semi-circular curve has negative RSE and RI values, which means that with increasing values of R the predicted deformations are decreased while with decreasing the values of R the predicted deformations are increased. These figures show that radius of the semi-circular curve has a negligible effect on output and it can be removed from the model inputs.

These results have a good agreement with previous analysis reported by Flückiger (2004). For a better understanding of the results of sensitivity analysis, the

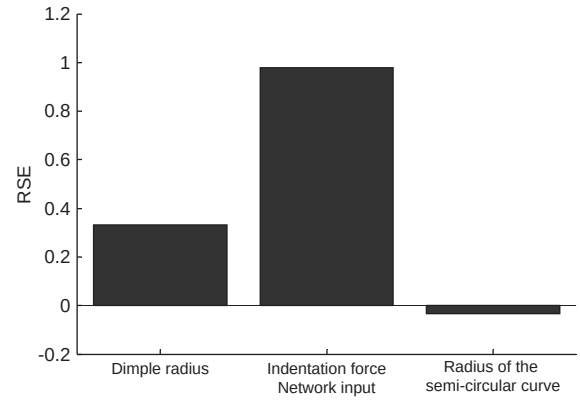

Figure 3. Significance of the input parameters on deformation using the RSE method.

force-deformation diagram of mouse embryo according to the analysis of Flückiger (2004) in comparison with the experimental data is presented in Figure 5.

As can be seen from this figure, the force-deformation curve of the analysis which includs the effect of semi-circular curved surface (R) is the same as that which ignores this effect.

These results are another validation of the correct implementation of ANN models.

6. Conclusion

In the present paper, ANN modeling has been applied to predict the geometrical and mechanical behavior of mouse embryos in a cell injection experiment. The predicted values obtained using the ANN approach are in good agreement with the experimental observations. Moreover, in order to ascertain the importance of each input parameter on the predicted deformation, sensitivity analysis has been also done. Results of the sensitivity analysis show that indentation force is the most important parameter in prediction of deformation

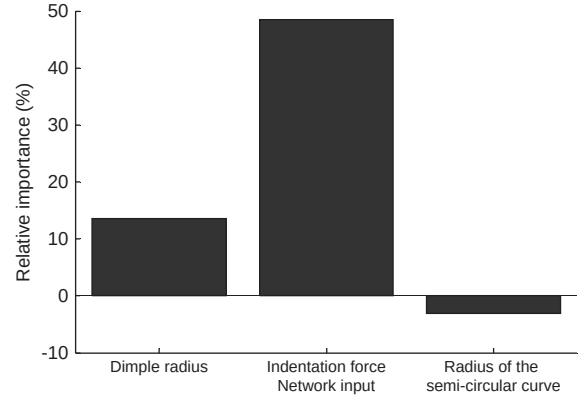

Figure 4. Significance of the input parameters on deformation using the RI method.

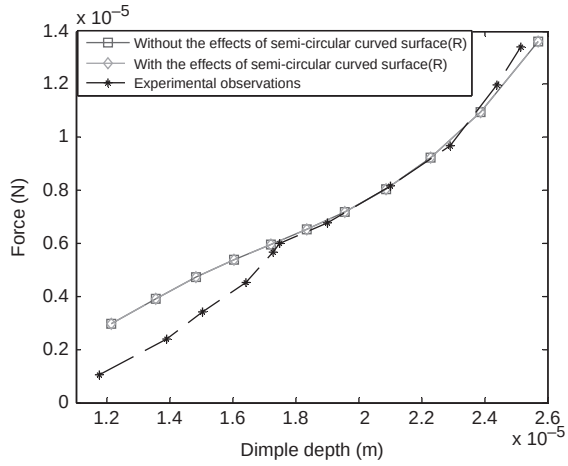

Figure 5. Investigation of effects of the semi-circular curved surface (R) using the force-deformation curve from previous analysis (Flückiger 2004).

of the mouse embryo and the semi-circular curved surface of the cell has negligible effect on the predicted deformation. The developed models are suitable for computing accurate reaction force on tools (for example in cell manipulation tasks) and for computing deformation of biological cells for the virtual reality-based medical simulations.

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