Journal of Solid Mechanics Vol. 2, No. 2 (2010) pp. 190-198

Cell Deformation Modeling Under External Force Using Artificial Neural Network

M.T. Ahmadian[1,*], G.R. Vossoughi[1], A.A. Abbasi[2], P. Raeissi[3]

[1]*Center of Excellence in Design, Robotics and Automation (CEDRA), School of Mechanical Engineering, Sharif University of Technology, Tehran, Iran*
[2]*School of Mechanical Engineering, Sharif University of Technology, Tehran, Iran*
[3]*Iran University of Medical Sciences, Tehran, Iran*

Received 21 June 2010; accepted 23 July 2010

ABSTRACT
Embryogenesis, regeneration and cell differentiation in microbiological entities are influenced by mechanical forces. Therefore, development of mechanical properties of these materials is important. Neural network technique is a useful method which can be used to obtain cell deformation by the means of force-geometric deformation data or vice versa. Prior to insertion in the needle injection process, deformation and geometry of cell under external point-load is a key element to understand the interaction between cell and needle. In this paper, the goal is the prediction of cell membrane deformation under a certain force and to visually estimate the force of indentation on the membrane from membrane geometries. The neural network input and output parameters are associated to a three dimensional model without the assumption of the adherent affects. The neural network is modeled by applying error back propagation algorithm. In order to validate the strength of the developed neural network model, the results are compared with the experimental data on mouse oocyte and mouse embryos that are captured from literature. The results of the modeling match nicely the experimental findings.

Keywords: Biological cells; Artificial neural network; Error back propagation algorithm

1 INTRODUCTION

LIVING cells are always exposed to mechanical stimulations in the human body. Often, it is important for us to investigate how cells mechanically react to physical loads and how the distribution and transmission of these mechanical signals are ultimately converted to chemical and biological responses in the cells [1]. 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, there has recently been extensive concentration in the literatures. Because of the heterogeneous nature of these biological cells, different experimental techniques are used and devised to probe the response of cells such as: atomic force microscopy (AFM) [2, 3], laser/optical tweezers [4], micro plate stretcher [5], micropipette aspiration [6],tapered micropipette [7]. 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 model, cytoskeletal models for adherent cells, spectrin-network model for erythrocytes [1].

Artificial neural networks (ANNs) are computational networks that try to simulate the processes that happen in the human brain and nervous system during pattern, identification, information filtering and functional controls [8]. In conjunction with the statistical approaches, this manner is one of the most powerful modeling techniques. In order

* Corresponding author. Tel: +98 021 6616 5503; fax: 021 6600 0021.
E-mail address: ahmadian@sharif.edu (M.T. Ahmadian).

to predict the mechanical alloying outputs, it seems this model is perfectly appropriate. The subtraction of cost and time in all the experimental activities is the advantage of ANN modeling [9]. In this paper, utilizing neural network technique, on one hand, cell membrane deformation under a certain force is predicted; and on the other hand, the cell membrane geometries are used as input and related indentation force is predicted. In order to achieve this purpose, the neural network input and output parameters are associated to a three dimensional model with no adherent affects. The neural network is modeled by applying error back propagation algorithm. In order to validate the strength of the developed neural network model, the results are compared with experimental data on mouse oocyte and mouse embryos that captured from reference 16. The results of the modeling match nicely the experimental findings. The accuracy and simplicity of the neural network model would enable scientists to develop a platform for investigation and understanding of cell mechanics in cellular biology and tissue engineering.

In this paper, in the first step cell indentation experiment is presented and experimental data are to be used for training the applied neural network that are extracted. In the second step, artificial neural network foundation is explained and range of the data implemented to the neural network is defined. Results and conclusion of implementing the neural network to embryo and oocyte are presented in the last part of the paper.

2 CELL INDENTATION EXPERIMENT TECHNIQUES

In order to study biological cell mechanics, another class of experimental techniques is cell-indentation experiment .In this experiment, cell displacement controlled indentation under external force that applied by a micropipette or another cell poker on the surface of an individual cell is investigated. In other words, controlled displacement is vertically applied to the top portion of a single cell and the displacement gradually increases and then corresponding reaction force due to the cell to indenter is measured [11].

From experimental observations [see Fig. 1], the deformed cell can be shown in Fig. 2[10] .In this figure, three geometric parameters, a, w and R are used to characterize the deformed cell shape.

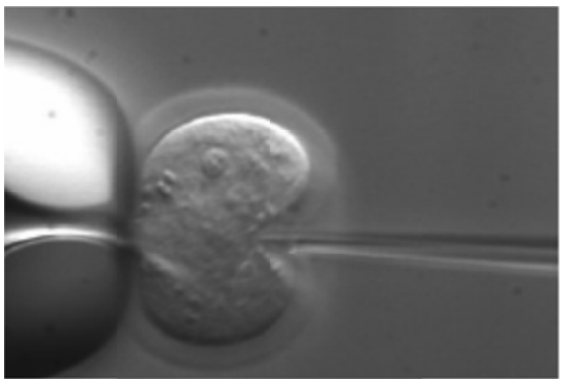

Fig. 1.
Image from experimental observation of mouse oocyte in cell indentation experiment in Ref.10.

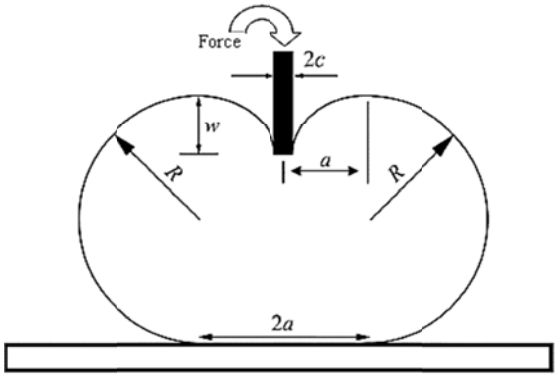

Fig. 2
Indentation of a single cell by a micropipette in Ref.10

In Fig. 2, c is the radius of the cell indenter tip and w, a and R are dimple depth, dimple radius and radius of the semi-circular curved surface of the cell, respectively. Therefore, the relation between force and dimple depth is

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

where $\xi = c/a$. In Eq. (1), ν, E, h and F are Poisson ratio, Young's modulus, thickness of membrane and measured force, respectively [10]. This equation is complicated and a simpler equation is needed to explain the relationship between indentation force and dimple depth. One of the methods by which this relationship could be simplified is the method of the neural network.

3 FUNDATION OF ARTIFITIAL NEURAL NETWORKS

Artificial neural network (ANN) is a model that tries to simulate the brain and its education process. In this model, processing essentials that interconnected to each other are called neurons or nodes which have weights associated with each connection. A structure of ANN with different neurons (nodes) and layers is shown in Fig. 3.The relative influence of the various neuron inputs to other neurons is represented by changing these weights [12]. There are many different types of ANN. Among them, the feed-forward neural network - which the information is transmitted in a forward direction - is common and suitable for modeling of a static (time in varying) train between input and output signals. The input –output relationship between each node of the hidden layers is given by [9]:

$$y = f(\sum_j w_j x_j + b) \tag{2}$$

where x_j is the output from the jth node of the previous layer, w_j the weight of the connection between the jth node and the current node and b is the bias of the current node. f is a function that can be nonlinear, e.g. log-sigmoid (Eq. (3a)) or hyperbolic sigmoid (Eq. (3b)).

$$f(x) = \frac{1}{1+e^{-x}} \tag{3a}$$

$$f(x) = \frac{1-e^{-x}}{1+e^{-x}} \tag{3b}$$

The input-output relationship of the output nodes is similar to that defined by Eq (2). Although the function f can be of a different type, e.g., a linear function. In this paper, due to non-linearity of the structure the hyperbolic sigmoid activation function is used (Eq. (3b)) between hidden layers and also for the input and output layers. Learning phase and working phase are two different manipulating phases of ANN. In the learning phase, the network is trained during a continuous process of simulation.

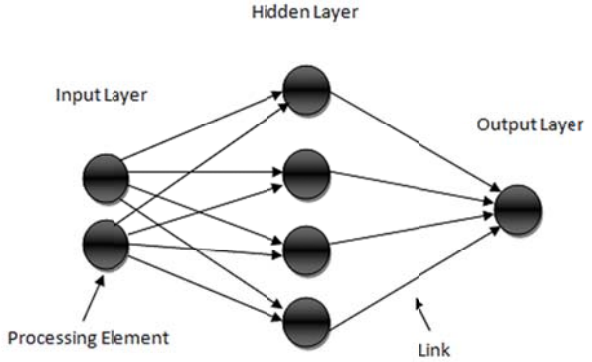

Fig. 3
Schematic representation of ANN.

Minimizing of an error function is the goal of this stage and during this minimization procedure, connection weights and biases are set. In this process, the outputs must be equal or close to targets. Using series of data sets that captured from actual system's behavior is the most convenient method for training a neural network. The learning algorithm may be categorized into two different paradigms called: supervised learning and unsupervised learning. In supervised learning, which is used in this paper, an external teacher is required that can provide an adequate mapping knowledge between the input and output signals. For each given input, the teacher provides the learning system with desired outputs which is memorized by minimizing the discrepancy between the neural network outputs and actual outputs. In this method, an optimization technique such as least square technique is used to minimize the overall evaluation function. If we use least square method as an optimization method for neural network while evaluation function is discrepancies between actual output signals and appropriate network output's signals, this method is called "delta method" or "error back propagation method" that is implemented in this work [13], [14]. On the other hand, unsupervised learning does not rely on an external teacher for guiding the learning process. The teacher can be considered as a built in mechanism to learn method [14]. Improvements in better converges of neural network model depends on better selection of initial conditions such as learning momentum, learning rate, initial weights and thresholds, increasing the number of layers and increasing the number of neurons in each layers [15]. For example, in order to avoid the local minimum and reach to global minimum, learning rate can play an important role [15], [13].

4 DATA COLLECTION

The input neural network parameters associated with the indentation experiment are dimple radius, dimple depth, radius of the semi-circular curved surface of the cell and the external force which exerted to the cell that are denoted by a, w, R and f, respectively. These parameters obtained from two sets of data associated to mouse oocyte and mouse embryos. The ranges of input variable data used for the model are shown in Table 1 (for mouse oocyte) and Table 2 (for mouse embryos). These tables are exerted from experimental observations by YU SUN and his co-workers [16]. These experiments are performed statically; therefore a static neural network structure is implemented.

5 ARCHITECTURE OF THE NEURAL NETWORK MODEL

Architecture of the neural network model is summarized in Table 3. The model includes an input layer, a single hidden layer and an output layer as shown in this table. In this model, six neurons are used in hidden layer and one neuron in output layer. The initial weights and thresholds are generated randomly. Since the normalizing operation depends on the selected transfer function, which adjusts the sum of the weights into an output, we normalized the data between -1 and 1for hyperbolic sigmoid transfer function. Inputs and outputs are normalized as follows:

Table 1
Input variable data ranges used for mouse oocyte

Input variable	Mouse oocyte	
	Minimum value	Maximum value
Indentation's force (μN)	0 2.172	07.211
Dimple depth(μm)	10.51	22.00
Dimple radius (μm)	13.35	18.20
Radius of semi-circular curves(μm)	11.96	15.80

Table 2
Input variable data ranges used for mouse embryos

Input variable	Mouse oocyte	
	Minimum value	Maximum value
Indentation's force (μN)	0 1.052	13.390
Dimple depth(μm)	11.754	25.155
Dimple radius (μm)	18.375	23.079
Radius of semi-circular curves(μm)	9.650	12.76

Table 3
Key neural network model parameters for back propagation algorithm

Key parameter	Value
Layers	3
Hidden layer	1
Neurons in hidden layer	6
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

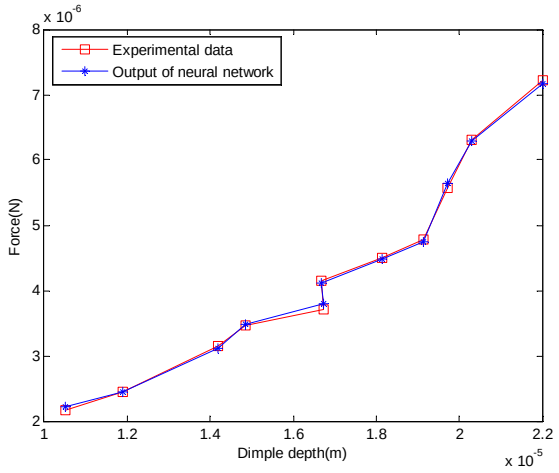

Fig. 4
Comparison of the predicted force and experimental data versus the dimple depth for mouse oocyte.

$$x_n = \frac{x - x_{\min}}{x_{\max} - x_{\min}} \tag{4}$$

In the first step, the network is trained to adjust the weights and thresholds between layers until output of network are close to actual output and in the second step we used these adjusted weights and thresholds in our network model. The error calculated in the output layer is the difference between the network output and the actual output and for the model is the half of mean square (HMS) as follows:

$$\text{HMS} = \frac{1}{2}\sum_{i}^{n}\left[Y_i - Y_i^d\right]^2 \tag{5}$$

6 RESULTS AND DISCUSSIONS

In order to predict the dimple depth due to an arbitrary exerted force on mouse oocyte and mouse embryos two sets of networks are designed and tested. In these simulations, indentation force acts as one of inputs of the network and the dimple depth is predicted in the output of the network .In a similar manner, to predict indentation force for a certain dimple depth in mouse oocyte and mouse embryos also two sets of networks are designed. In these models, the dimple depth is used as one of network's input while the indentation force would be the output of the network. Plots of the predicted force versus dimple depth in comparison with the experimental data for mouse oocyte and mouse embryos are shown in Figs. 4 and 5, and their related error values versus the number of epochs (each time of network's training) also shown in Figs. 6 and 7 , respectively.

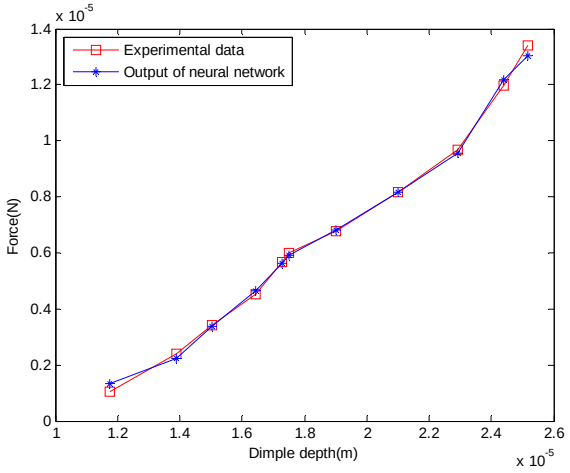

Fig. 5
Comparison of the predicted force and experimental data versus the dimple depth for mouse embryos.

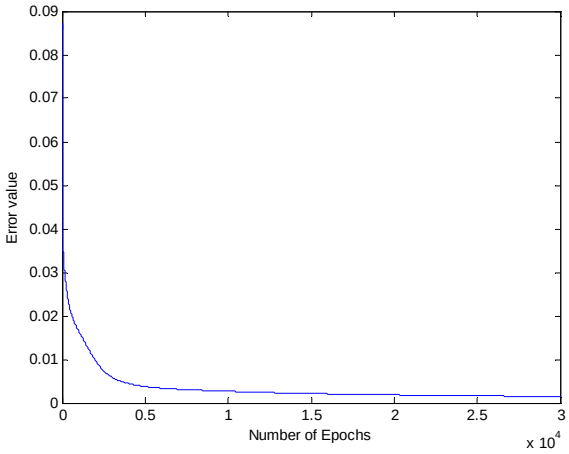

Fig. 6
Error values versus the number of epochs in the prediction of indentation force for mouse oocyte.

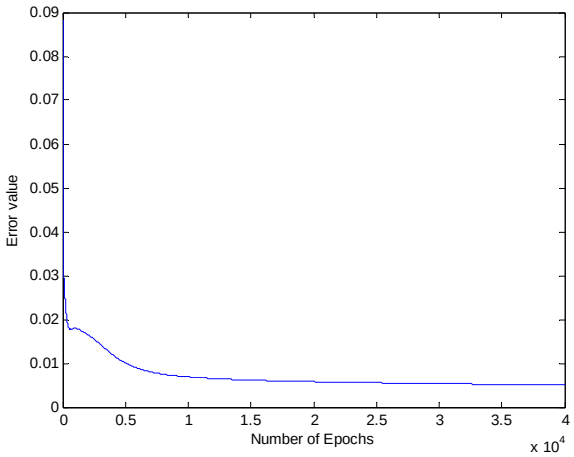

Fig. 7
Error values versus the number of epochs in the prediction of indentation force for mouse embryos.

According to Fig. 6, the smallest error value after 30000 epochs has reached to 0.0015 for mouse oocyte and this value, in Fig. 7, has reached to 0.0051 after 40000 epochs for mouse embryos. There is not any gap between the experimental data and neural network's output and good prediction occurs in both cases (Figs. 4 and 5). Plots of predicted dimple depth versus indentation force in comparison with the experimental data for mouse oocyte and

mouse embryos are also shown in Figs. 8 and 9, and their related error values versus the number of epochs are shown in Figs. 10 and 11, respectively.

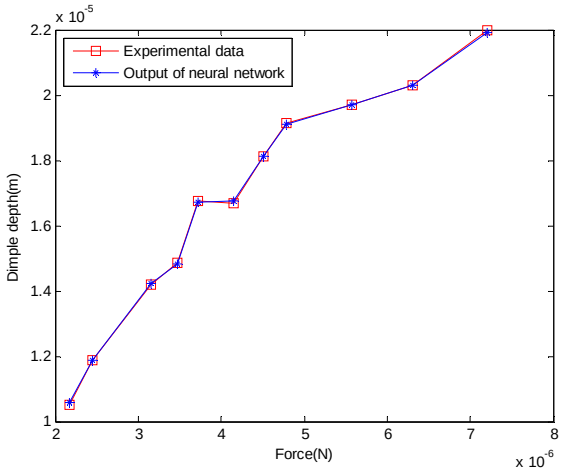

Fig. 8
Comparison of the predicted dimple depth and experimental data versus indentation force for mouse oocyte.

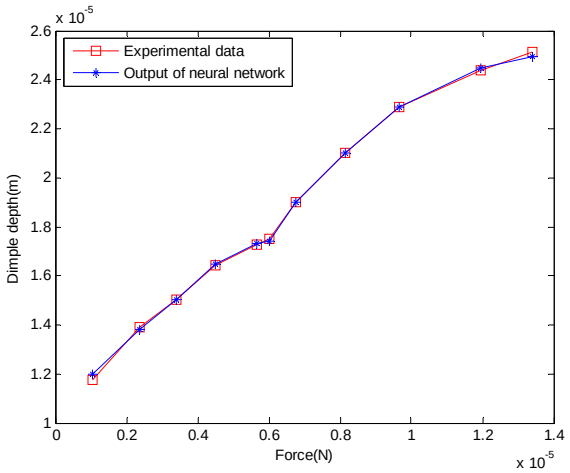

Fig. 9
Comparison of the predicted dimple depth and experimental data versus indentation force for mouse embryos.

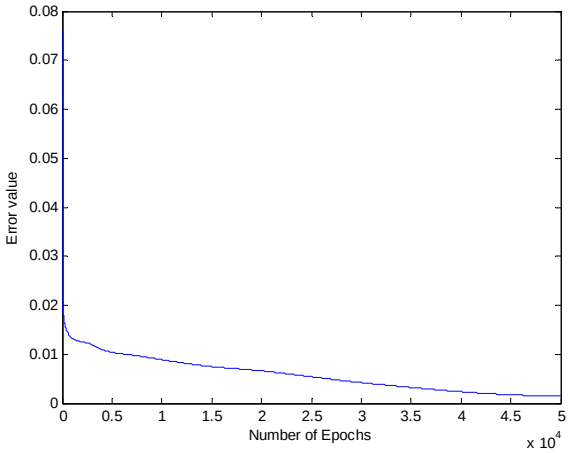

Fig. 10
Error values versus the number of epochs in the prediction of dimple depth for mouse oocyte.

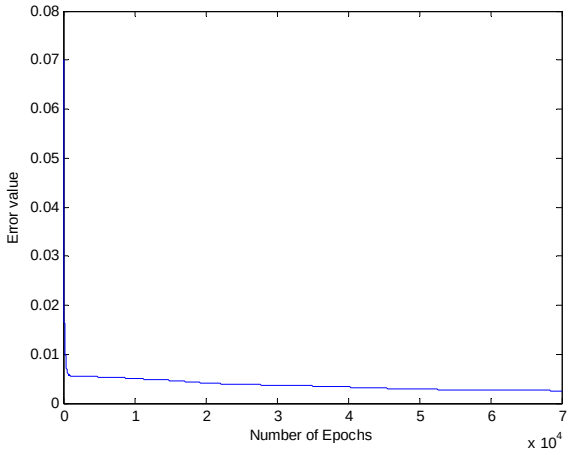

Fig. 11
Error values versus the number of epochs in the prediction of dimple depth for mouse embryos.

In Fig. 10, the error value has decreased to 0.0014 after 50000 epochs for mouse oocyte and this value for mouse embryos, in Fig. 11, has reached to 0.0026 after 70000 epochs. The very good agreement between the experimental data and neural network's output also occurs in prediction of dimple depth for mouse oocyte and mouse embryos (Figs. 8, 9). Consequently, the accuracy of ANN model in estimation is visibly confirmed in these figures.

In summary, ANN has the ability to accurately predict the mechanical behavior of biological cells .It seems that this model could be extended to other experimental methods in biological cell studies .By means of this model, the need for detailed experimental analysis of the processes can be reduced drastically. Since the governing equation between measured force and dimple depth (Eq. (1)) is somewhat complex and subject to variations due to parametric uncertainties, neural network modeling has been shown to be potentially capable of modeling such problems.

7 CONCLUSIONS

In this paper, the neural network model is applied to extract and estimate mechanical behaviors of mouse oocyte and mouse embryos. In order to learn the underlying complex relationships between input and output cell membrane geometries of normalized experimental data acquired from published literature, the neural network model is implemented and trained. In one hand, the changes of the cell membrane dimple depth under a different indentation forces is predicted and on the other hand, indentation force is estimated by the means of changing in the dimple depth. Since the biological cell modeling studies are very challenging, the neural network modeling is used in this study because of its ability in mimicking complex input-output relationships. The obtained mechanical properties using the neural network model are in excellent agreement with the experimental observations.

REFERENCES

[1] Lim, C.T., Zhou, E.H., Quek, S.T., 2006, Mechanical models for living cells - a review, *Journal of Biomechanics* **39**: 195-216.

[2] Sen, S., Subramanian S., Discher D.E., 2005, Indentation and adhesive probing of a cell membrane with AFM: Theoretical model and experiments, *Biophysical Journal* **89**: 3203-3213.

[3] Lulevich V., Zink T., Chen H.Y., Liu F.T., Liu G.Y., 2006, Cell Mechanics using atomic force microscopy - based single-cell compression, *Langmuir* **22**: 8151-8155.

[4] Dao M., Lim C.T., Suresh S., 2003, Mechanics of the human red blood cell deformed by optical tweezers, *Journal of the Mechanics and Physics of Solids* **51**: 2259-2280.

[5] Thoumine O., Ott A., 1997, Time scale dependent viscoelastic and contractile regimes in fibroblasts probed by microplate manipulation, *Journal of Cell Science* **110**: 2109-2116.

[6] Vaziri A., Kaazempur Mofrad M.R., 2007, Mechanics and deformation of the nucleus in micropipette aspiration Experiment, *Journal of Biomechanics* **40**: 2053-2062.

[7] He J.H., Xu W., Zhu L., 2007, Analytical model for extracting mechanical properties of a single cell in a tapered micropipette, *Applied Physics Letters* **90**: 023901.

[8] Sterjovski Z., Nolan D., Carpenter K.R., Dunne D.P., Norrish J., 2005, Artificial neural networks for modelling the mechanical properties of steels in various applications, *Journal of Materials Processing Technology* **170**: 536-544.

[9] Dashtbayazi M.R., Shokuhfar A., Simchi A., 2007, Artificial neural network modeling of mechanical alloying process for synthesizing of metal matrix nanocomposite powders, *Materials Science and Engineering A* **466**: 274-283.

[10] Sun Y., Wan K.T., Roberts K.P., Bischof J.C., Nelson B.J., 2003, Mechanical Property Characterization of Mouse Zona Pellucida, *IEEE Transactions on Nanobioscience* **2**: 279-286.

[11] Zahalak G.I., McConnaughey W.B., Elson E.L., 1990, Determination of cellular mechanical properties by cell poking, with an application to leukocytes*, Journal of biomechanical engineering* **112**: 283-294.

[12] Bahrami A., Mousavi Anijdan S.H., Madaah Hosseini H.R.,2005, Effective parameters modeling in compression of an austenitic stainless steel using artificial neural network, *Computational Materials Science* **34**: 335-341.

[13] Yazdanmehr M., Mousavi Anijdan S.H., Samadi A., Bahrami A., 2009, Mechanical behavior modeling of nanocrystalline NiAl compound by a feed-forward back-propagation multi-layer perceptron ANN, *Computational Materials Science* **44**: 1231-1235.

[14] Samarasinghe S., 2006, *Neural Networks for Applied Sciences and Engineering: From Fundamentals to Complex Pattern Reorganization,* Auerbach Publications, Taylor & Francis Group, Boca Roton, New York.

[15] Sarangapani J., 2006, *Neural Network Control of Nonlinear Discrete-Time Systems*, CRC Press ,Taylor & Francis Group, Boca Roton, London, New York.

[16] Flückiger M., 2004, *Cell Membrane Mechanical Modeling for Microrobotic Cell Manipulation*, Diploma Thesis, ETHZ Swiss Federal Institute of Technology, Zurich, WS03/04.