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REACTION-DIFFUSION CELLULAR NEURAL NETWORK MODELS*

Angela Slavova

In this paper receptor-based Cellular Neural Network model is considered. Dynamics and stability of such model are studied by applying describing function technique. Comparison of the obtained results with the classical ones is made as well.

1. Introduction to Cellular Neural Networks (CNNs). Spatial and spatio-temporal patterns occur widely in physics, chemistry and biology. In many cases, they seem to be generated spontaneously. These phenomena have motivated a great deal of mathematical modelling and the analysis of the resultant systems has led to a greater understanding of the underlaying mechanisms. Partial differential equations of diffusion type have long served as models for regulatory feedbacks and pattern formation in aggregates in living cells. In this work we propose receptor-based models for pattern formation and regulation in multicellar biological systems. The systems describing our models are composed of both diffusion-type and ordinary differential equations. Such systems cause some difficulties, since both existence and behavior of the solutions are more difficult to establish. Many aspects of qualitative behavior have to be investigated numerically. For this purpose, we apply the Cellular Neural Networks (CNN) approach for studying such models.

CNN is simply an analogue dynamic processor array, made of cells which contain linear capacitors, linear resistors and linear and nonlinear controlled sources. Let us consider a two-dimensional grid with 3×3 neighborhood system as it is shown on Fig.1.

The squares are the circuit units-cells, and the links between the cells indicate that there are interactions between linked cells. One of the key features of a CNN is that the individual cells are nonlinear dynamical systems, but the coupling between them is linear. Roughly speaking, one could say that these arrays are nonlinear but have a linear spatial structure which makes the use of techniques for their investigation common in engineering or physics attractive.

We will give the general definition of a CNN which follows the original one:

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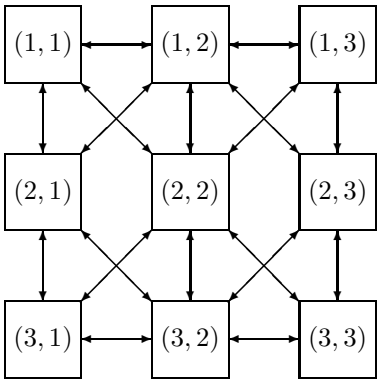


Fig. 1. 3×3 neighborhood CNN.

Definition 1. *The CNN is a*

a) 2-, 3-, *or n-dimensional array of*

b) *mainly identical dynamical systems, called cells, which satisfy two properties:*

c) *most interactions are local within a finite radius r, and*

d) *all state variables are continuous valued signals.*

Definition 2. *An $M \times M$ cellular neural network is defined mathematically by four specifications:*

1) *CNN cell dynamics;*

2) *CNN synaptic law which represents the interactions (spatial coupling) within the neighbor cells;*

3) *Boundary conditions;*

4) *Initial conditions.*

Suppose for simplicity that the processing elements of a CNN are arranged on a 2-dimensional (2-D) grid (Fig. 1). Then, the dynamics of a CNN, in general, can be described by:

$$\dot{x}_{ij}(t) = -x_{ij}(t) + \sum_{C(k,l)\in N_r(i,j)} \tilde{A}_{ij,kl}(y_{kl}(t), y_{ij}(t)) + \sum_{C(k,l)\in N_r(i,j)} \tilde{B}_{ij,kl}(u_{kl}, u_{ij}) + I_{ij}, \tag{1}$$

$$y_{ij}(t) = f(x_{ij}), \quad 1 \le i \le M, 1 \le j \le M, \tag{2}$$

x_{ij}, y_{ij}, u_{ij} refer to the state, output and input voltage of a cell $C(i,j)$; $C(i,j)$ refers to a grid point associated with a cell on the 2-D grid, $C(k,l) \in N_r(i,j)$ is a grid point (cell) in the neighborhood within a radius r of the cell $C(i,j)$, I_{ij} is an independent current source. $\tilde{A}$ and $\tilde{B}$ are nonlinear cloning templates which specify the interactions between each cell and all its neighbor cells in terms of their input, state, and output variables.

Moreover, as we mentioned above the cloning template has geometrical meanings which can be exploited to provide us with geometric insights and simpler design methods.

Now, in terms of definition 2 we can present the dynamical systems describing CNNs. For a general CNN whose cells are made of time-invariant circuit elements, each cell $C(ij)$ is characterized by its CNN cell dynamics

$$\dot{x}_{ij} = -g(x_{ij}, u_{ij}, I^s_{ij}), \tag{3}$$

where $x_{ij} \in \mathbf{R}^m$ and u_{ij} is usually a scalar. In most cases, the interactions (spatial coupling) with the neighbor cell $C(i+k, j+l)$ are specified by a CNN synaptic law:

$$I^s_{ij} = A_{ij,kl}x_{i+k,j+l} + \tilde{A}_{ij,kl} * f_{kl}(x_{ij}, x_{i+k,j+l}) + \tilde{B}_{ij,kl} * u_{i+k,j+l}(t). \tag{4}$$

The first term $A_{ij,kl}x_{i+k,j+l}$ of (4) is simply a linear feedback of the states of the neighborhood nodes. The second term provides an arbitrary nonlinear coupling, and the third term accounts for the contributions from the external inputs of each neighbor cell that is located in the N_r neighborhood.

2. Reaction-diffusion CNNs. It is known that some autonomous CNNs represent an excellent approximation to nonlinear partial differential equations (PDEs). In this paper we present the receptor-based model by a reaction-diffusion CNNs. The intrinsic space distributed topology makes the CNN able to produce real-time solutions of nonlinear PDEs. Consider the following well-known PDE, generally referred to us in the literature as a reaction-diffusion equation:

$$\frac{\partial u}{\partial t} = f(u) + D\nabla^2 u,$$

where $u \in \mathbf{R}^N$ and $f \in \mathbf{R}^N$, D is a matrix with the diffusion coefficients, and $\nabla^2 u$ is the Laplacian operator in $\mathbf{R}^2$. There are several ways to approximate the Laplacian operator in discrete space by a CNN synaptic law with an appropriate A-template.

As a first example of CNN models we consider the Fisher equation. Sixty years ago Fisher showed that the propagation of a mutant gene can be modeled by a nonlinear reaction-diffusion partial differential equation (PDE):

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + f(u). \tag{5}$$

where $f(u) = qu(1-u)$. This classic equation, also known as the "diffusional logistic" equation, has been found to be useful in many other applications and has been widely studied. In chemical media the function $u(t,x)$ is the concentration of the reactant, D represents its diffusion coefficient, and the positive constant q specifies the rate of the chemical reaction. In media of other natures u, D, q can represent different quantities. In general, medium described by (5) is often refered to as a bistable medium, because it has two homogeneous stationary states: $u = 0$ and $u = 1$. Observe the case when $f(u) = u(u-1)(u-E)$ in which $f(u)$ has three zeros: at $u = 0, E$ and 1. This generalized model arises in many areas of ecology, including selection-migration models and other bistable population models. It is also found in a degenerate form of Nagumo's equation.

After rescaling the time $t' = qt$ and space coordinate $x' = (q/D)^{1/2}x$, and dropping the prime, in one-dimensional space (5) becomes:

$$u_t = u_{xx} + u(1-u). \tag{6}$$

As we mentioned, Fisher equation (6) can be precented by a reaction-diffusion auto-

nomous CNN where the cells are a degenerate special case of Chua's oscillator. We will map $u(x,t)$ into a CNN layer such that the state voltage of a CNN cell $x_{kl}(t)$ at a grid point (k,l) is associated with $u(kh,t)$, $h=\Delta x$. Therefore, an one-dimensional Laplacian template is of the following form:

$$A_1 = (1,-2,1),$$

and the CNN model in this case is:

$$\frac{du_k}{dt} = (u_{k-1} - 2u_k + u_{k+1}) + u_k(1-u_k), \tag{7}$$

$k=1,\ldots,n$, $n=M.M$, where we have $M\times M$ cells.

In a two-dimensional isotropic medium Fisher's equation (5) in rescaled variables is:

$$u_t = u_{xx} + u_{yy} + u(1-u). \tag{8}$$

The solution $u(x,y,t)$ of (8) is a continuous function of the time t and the space variables x, y. We shall approximate the function $u(x,y,t)$ by a set of functions $u_{jk}(t)$ which are defined as

$$u_{jk}(t) = u(jh_x, kh_y, t),$$

where h_x and h_y are the space intervals in the x and y coordinates. Then, two-dimensional discretized Laplacian A template takes the following form:

$$A_2 = \begin{pmatrix} 0 & 1 & 0 \\ 1 & -4 & 1 \\ 0 & 1 & 0 \end{pmatrix}.$$

The CNN model for two-dimensional Fisher's equation (8) is:

$$\begin{aligned} \frac{du_{jk}}{dt} &= (u_{jk-1}(t) + u_{jk+1}(t) - 4u_{jk}(t) + u_{j-1k}(t) + u_{j+1k}(t)) \\ &+ u_{jk}(t)(1-u_{jk}(t)) = (u_{jk-1}(t) + u_{jk+1}(t) - 4u_{jk}(t) \\ &+ u_{j-1k}(t)u_{j+1k}(t)) + n_{jk}(t), \end{aligned} \tag{9}$$

$1\le j\le M$, $1\le k\le M$.

Another most widely studied nonlinear reaction-diffusion partial differential equation (PDE) is the Brusselator equation, whose dimensionless equation is:

$$\begin{aligned} \frac{\partial u}{\partial t} &= a - (b+1)u + u^2v + D_1\nabla^2 u \\ \frac{\partial v}{\partial t} &= bu - u^2v + D_2\nabla^2 v, \end{aligned} \tag{10}$$

where $\nabla^2 = \dfrac{\partial^2}{\partial u^2} + \dfrac{\partial^2}{\partial v^2}$ is a two-dimensional Laplacian operator in $\mathbf{R}^2$, a, b are coefficients of the chemical reaction which give the concentration of initial substances and D_1, D_2 are diffusion coefficients. The Brusselator equation (10) is well known in chemical kinetics as an ideal system for studying the dissipative structures. In some sense this system behaves as harmonic oscillator.

Our CNN model for the Brusselator equation (10) with A_2-template can be written in the following form:

$$(11)\quad \begin{aligned} u_{jk} &= a-(b+1)u_{jk}+u_{jk}^2v_{jk}+D_1[u_{j+1k}+u_{j-1k}+u_{jk+1}+u_{jk-1}-4u_{jk}] \\ v_{jk} &= bu_{jk}-u_{jk}^2v_{jk}+D_2[v_{j+1k}+v_{j-1k}+v_{jk+1}+v_{jk-1}-4v_{jk}], \end{aligned}$$

$1 \le j \le M$, $1 \le k \le M$.

The other model we consider is a more general form of the Hodgkin-Huxley model for the propagation of the voltage pulse through a nerve axon which is referred to as the FitzHugh-Nagumo equation:

$$(12)\qquad u_t - u_{xx} = u(u-\Theta)(1-u) - b\int_0^t u(s,x)ds,$$

$0 < x,t < 1$, $0 < \Theta < 1/2$, $b \ge 0$. The proposed equation (12) is a nonlinear parabolic integro-differential equation, in which u_t is the first partial derivative of $u(t,x)$ with respect to t, u_{xx} is the second derivative of u with respect to x and u is a membrain potential in a nerve axon. The steady state $u = 0$ represents the resting state of the nerve.

Now, if we map $u(x,t)$ into a CNN layer such that the state voltage of a CNN cell $v_{xkl}(t)$ at a grid point (k,l) is associated with $u(kh,t)$, $h = \Delta x$ and use the one-dimensional discretized Laplacian template A_1, then it is easy to design the CNN model of the proposed FitzHugh-Nagumo equation (12):

(1) CNN cell dynamics:

$$(13)\qquad \frac{du_j}{dt} - I_j^s = u_j(u_j-\Theta)(1-u_j) - b\int_0^t u_j(s)ds.$$

(2) CNN synaptic law:

$$(14)\qquad I_j^s = \frac{1}{h^2}(u_{j-1}-2u_j+u_{j+1}).$$

Let us assume for simplicity that the grid size of our CNN model is $h = 1$ and let us denote the nonlinearity $n(u_j) = u_j(u_j-\Theta)(1-u_j)$. Substituting (14) into (13), we obtain:

$$(15)\qquad \frac{du_j}{dt} - (u_{j-1}-2u_j+u_{j+1}) = n(u_j) - b\int_0^t u_j(s)ds, 1 \le j \le N.$$

Equation (15) is actually an integro-differential equation which is identified as the state equation of an autonomous CNN made of $N \times N$ cells.

3. Receptor-based models. This work is devoted to mathematical modelling of pattern formation. Partial differential equations of diffusion type have long served as models for regulatory feedbacks and pattern formation in aggregates of living cells. We propose new reseptor-based models for pattern formation and regulation in multicellular biological systems. The idea is that patterns are controlled by specific cell-surface receptors which transmit to the cells signals responsible for their differentiation. The main aim of this work is to check which aspects of self-organization and regeneration can be explained within the framework of CNNs.

The simplest model describing receptor-ligand is given in the form of three equations. It takes into consideration the density of free receptors, of the bound receptors and of the ligands. We use a representation of this simplest receptor-based model that is as generic as possible and based on the scheme shown in Fig. 2.

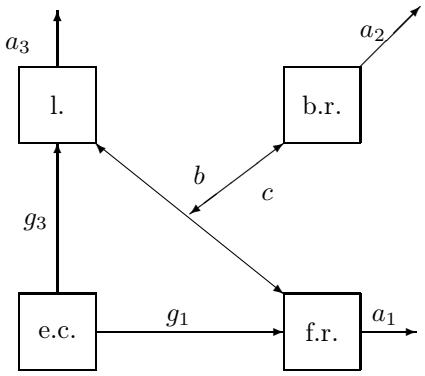


Fig. 2. General scheme of the simplest receptor-based model

The abreviations in Figure 2 are as follows: l. – ligands, b.r. – bound receptors, e.c. – epithelial cells, f.r. – free receptors. We assume that new ligands and new free receptors are produced on cell surface through a combination of recycling (dissociation of bound receptors) and *de novo* production within the cell. Then a ligands binds to a free receptor reversibly which results in a bound receptor that is internalised into the cell. Bound receptors also dissociate. Both ligands and free receptors undergo natural decay.

We consider one-dimensional epithelial sheet of length L. We denote the concentration of ligands by $w(x,t)$, where x and t are space- and time-coordinates, with x increasing from 0 to L along the body column. The bound and free receptors densities are denoted by $u(x,t)$ and $v(x,t)$, respectively. For simlicity we assume that all binding processes are governed by the law of mass action without saturation effects. The model is described by the following dynamical system:

$$\begin{aligned} \frac{\partial}{\partial t}u &= f_1(u,v,w) \\ \frac{\partial}{\partial t}v &= f_2(u,v,w) \\ \frac{\partial}{\partial t}w &= d\frac{\partial^2}{\partial x^2}w + f_3(u,v,w), \end{aligned} \tag{16}$$

where $u,v,w : [0,1] \times \mathbf{R}^+ \to \mathbf{R}^+$, the functions $f_i, i = 1,2,3$, are nonnegative for nonnegative arguments and they have the following form:

$$\begin{aligned} f_1 &= -a_1u + g_1(u,v) - buw + cv, \\ f_2 &= -a_2v + buw - cv, \\ f_3 &= -a_3w - buw + g_3(u,v) + cv, \end{aligned}$$

$a_i > 0, i = 1,2,3$, $b,c > 0$. We suppose that the functions $g_i, i = 1,3$ are of quadratic form, i.e. $g_i(u,v) = g_iu^2$. The model has biological interpretation for such functions [7]. a_1 is the rate of decay of free receptors, a_2 is the rate of decay of bound receptors and

a_3 is the rate of decay of ligands, the function g_1 defines the rate of production of new free receptors, the function g_3 defines the rate of production of ligands, cv is the rate of dissociation of bound receptors, b is the rate os binding of ligands and free receptors and d is the diffusion coefficient for ligands.

After the seminal paper of Turing [7], the study of patterns arising through bifurcation has been prevalent in the modelling literature, especially regarding morphogenesis. Again we restrict our attention here to bifurcation solutions. Diffusion-driven instability is also a mechanism of pattern formation in the activator-inhibitor models. The results of *de novo* pattern formation from the dissociated cells and of the cutting experiments suggest that there exists an organising centre which creates a global structure of the set of solutions. Thus, a natural approach is to study at first the diffusion-driven instabilities (Turing type instability). We show that a three-variable receptor-based model (16) can produce diffusion-driven patterns only under assumption that the number of free receptors increases nonlinearly by some kind of positive feedback (autocatalysis). Also production of ligands must depend on free receptors. In the next sections we outline the results concerning stability of the solutions of such reaction-diffusion equations. Diffusion-driven instability (Turing-type instability) arises when there exists a spatial homogeneous solution which is asymptotically stable in the sense of linearised stability in the space of constant functions, but is unstable with respect to inhomogeneous perturbation. We study the linear instabilities of the homogeneous steady state to classify the patterns which may grow.

4. Dynamical behavior of the CNN model. Describing function approach. As we mentioned above, there are several ways to approximate the Laplacian operator in discrete space by a CNN synaptic law with an appropriate A-template [2]. In our case we take one-dimensional discretized Laplacian template:

$$A : (1, -2, 1).$$

Therefore, the CNN representaion for our reseptor-based model (16) is the following:

$$\begin{aligned} \frac{du_j}{dt} &= -a_1 u_j + g_1 u_j^2 - b u_j w_j + c v_j \\ \frac{dv_j}{dt} &= -a_2 v_j + b u_j w_j - c v_j \\ \frac{dw_j}{dt} &= -a_3 w_j + d(w_{j-1} - 2w_j + w_{j+1}) - b u_j w_j + g_3 u_j^2 + c v_j, \end{aligned} \tag{17}$$

$1 \leq j \leq N$. The above equation is actualy ordinary differential equation which is identified as the state equation of an autonomous CNN made of N cells. For the output of our CNN model we take the standard sigmoid function [2].

In this section we introduce an approximative method for studying the dynamics of CNN model (17), based on a special Fourier transform. The idea of using Fourier expansion for finding the solutions of PDEs is well known in physics. It is used to predict what spatial frequences or modes will dominate in nonlinear PDEs. In CNN literature this approach has been developed for analyzing the dynamics of CNNs with symmetric templates [4, 5].

In this paper we investigate the dynamic behavior of a CNN model (17) by use of Harmonic Balance Method well known in control theory and in the study of electronic

oscillators [5] as describing function method. The method is based on the fact that all cells in CNN are identical [2] and, therefore, by introducing a suitable double transform, the network can be reduced to a scalar Lur's scheme [5].

We study the dynamics and the stability properties of (17) by using the describing function method [5]. Applying the double Fourier transform:

$$F(s,z) = \sum_{k=-\infty}^{k=\infty} z^{-k} \int_{-\infty}^{\infty} f_k(t) \exp(-st) dt,$$

to the CNN equation (17) we obtain:

$$\begin{aligned} sU &= -a_1 U + g_1 U^2 - bUW + cV \\ sV &= -a_2 V + bUW - cV \\ sW &= -a_3 W + d(z^{-1}W - 2W + zW) + g_3 U_b^2 UW + cV. \end{aligned} \tag{18}$$

Without loss of generality we can denote $N(U,V,W) = g_i U^2 - bUW + cV$ and then we obtain from (18):

$$\begin{aligned} U &= \frac{1}{s+a_1} N \\ V &= \frac{1}{s+a_2} N \\ W &= \frac{1}{s+a_3 - d(z^{-1} - 2 - z)} N. \end{aligned} \tag{19}$$

In the double Fourier transform we suppose that $s = i\omega_0$, and $z = \exp(i\Omega_0)$, where ω_0 is a temporal frequency, Ω_0 is a spatial frequency.

According to the describing function method, $H(s,z) = \dfrac{s+a_1}{s+a_3 - d(z^{-1} - 2 + z)}$ is the transform function, which can be expressed in terms of ω_0 and Ω_0, i.e. $H(s,z) = H_{\Omega_0}(\omega_0)$.

We are looking for possible periodic state solutions of system (18) of the form:

$$X_{\Omega_0}(\omega_0) = X_{m_0} \sin(\omega_0 t + j\Omega_0), \tag{20}$$

where $X = (U,V,W)$. According to the describing function method we take the first harmonics, i.e. $j = 0 \Rightarrow$

$$X_{\Omega_0}(\omega_0) = X_{m_0} \sin \omega_0 t,$$

On the other hand, if we substitute $s = i\omega_0$ and $z = \exp(i\Omega_0)$ in the transfer function $H(s,z)$, then we obtain:

$$H_{\Omega_0}(\omega_0) = \frac{i\omega_0 + a_1}{i\omega_0 + a_3 - d(2\cos\Omega_0 - 2)}. \tag{21}$$

According to (21), the following constraints hold:

$$\begin{aligned} \Re(H_{\Omega_0}(\omega_0)) &= \frac{X_{m_0}}{Y_{m_0}}, \\ \Im(H_{\Omega_0}(\omega_0)) &= 0. \end{aligned} \tag{22}$$

Hence, we obtain the following constraints:

$$\omega_0 = \frac{1}{a_3 - a_1 + d(2\cos\Omega_0 - 2)} \tag{23}$$

$$X_{m_0} = \frac{4}{\pi}\left[X_{m_0}\arcsin\left(\frac{1}{X_{m_0}}\right) + \sqrt{1 - \frac{1}{X_{m_0}^2}}\right].$$

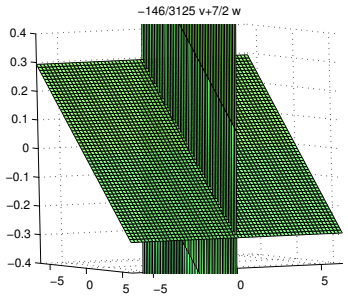
Suppose that our CNN model (17) is a finite circular array of N cells. In this case we have finite set of frequences:

$$\Omega_0 = \frac{2\pi k}{N}, \ \ 0 \le k \le N-1. \tag{24}$$

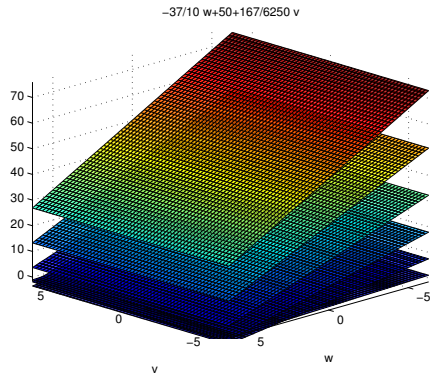
Thus, (22), (23) and (24) give us necessary set of equations for finding the unknowns X_{m_0}, ω_0, Ω_0. As we mentioned above, we are looking for a periodic wave solution of (18), therefore, X_{m_0} determines approximate amplitude of the wave, and $T_0 = \dfrac{2\pi}{\omega_0}$ determines the wave speed.

Proposition 1. *CNN model* (17) *of the receptor-based system* (16) *with circular array of N cells has periodic state solutions $x_j(t)$ with a finite set of spatial frequences $\Omega_0 = \dfrac{2\pi k}{N}$, $0 \le k \le N-1$.*

The following bifuraction diagrams are obtained for our CNN model:



Remark 1. For the Turing-type instability [7], the functions describing production of free receptors (f.r.) must depend on the density of f.r. and this dependence must be a power function of the order $\alpha + 1$, where $\alpha > 0$. Hence, Turing type patterns can occur if $g_1(u) = g_1 u^{\alpha+1}, \alpha > 0$. This function can depend also on the density of bound receptors (b.r.), but also it is critical here that it depends on the density of f.r. For numerical simulations the simplest function fulfilling the above condition is used, namely $g_1(u) = g_1 u^2$. To model the production rate of ligands (l.) g_3 we also take a function of the concentration of free receptors. In numerical simulations as a function similar to g_1 is used $g_3(u) = g_3 u^2$.



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Angela Slavova
Institute of Mathematics and Informatics
Bulgarian Academy of Sciences
Acad. G. Bonchev Str., Bl. 8
1113 Sofia, Bulgaria
e-mail: slavova@math.bas.bg

КЛЕТЪЧНО НЕВРОННИ МРЕЖИ НА РЕАКЦИЯ ДИФУЗИЯ

Анжела Славова

В тази статия са предствени клетъчно невронни модели на уравнения на реакция-дифузия, възникващи в биолигията, физиката, инженерството. Динамиката и устойчивостта на рецепторен модел са изследвани с метода на описващата функция. Направени са симулации на клетъчно невронния модел и резултатите са сравнени с класическите.