Using a Hopfield Iterative Neural Network to Explain Diffusion in the Brain's Extracellular Space Structure

Abir Alharbi
Department of Mathematics, King Saud University, P.o Box 22452, 11495 Riyadh, Saudi Arabia

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Abstract: Many therapies for drug delivery to the brain are based on diffusion, and diffusion in this extracellular space is based on micro-techniques that can be modelled with classical differential equations such as the point source diffusion equation. In this paper an energy function is constructed using a finite-difference approximation to the governing diffusion equation and then minimized by a Hopfield neural network. The synergy of Hopfield neural networks with finite difference approximation is promising. The neural network approach is capable of giving insight to the complex brain activity better than any other classical numerical method and the parallelism nature of the Hopfield neural networks approach is easier to implement on fast parallel computers and this will make them faster than the traditional methods for modelling this complex problem. Moreover, the effect of the involved parameters on the diffusion distribution and drug delivery in the ECS is investigated.

1 INTRODUCTION

Diffusion plays a crucial role in brain function. The space between cells, Extracellular space (ECS), is like a foam and many substances move with in this complicated region. Diffusion in this interstitial space is modeled with classical differential equations and quantified from measurements based on micro-techniques. Theoretical and experimental approaches rely on classical diffusion theory in porous media. The brain is a very complex structure of interwoven, intercommunicating cells, and is considered an area of research in medical science (Sykova, 1997). The classical laws of diffusion applied in porous media theory can give an accurate description of the way molecules are transported through this tissue. Diffusing molecules have random movements that cause collision with membranes and affect their concentration distribution (Nicholson and Tao, 1993). Diffusion is an essential link in many processes, ranging from the delivery of glucose to cells to intercellular communication. Besides delivering glucose and oxygen from the vascular system to brain cells, diffusion also moves informational substances between cells, a process known as volume transmission (Nicholson, 2001). Diffusion is also essential to many therapies that deliver drugs to the brain. In treating brain disorders, where diffusion is often compromised, understanding the transport of molecules can be crucial to effective drug delivery and treatment. The diffusion generated concentration distributions of well-chosen molecules also reveal the structure of brain tissue. This structure is represented by the volume fraction represented by (α), which is a dimensionless quantity and is defined as the ratio between the volume of the ECS and the total volume of the tissue. There is also the tortuosity (λ) parameter, which is a hindrance to diffusion imposed by local boundaries or local viscosity. Analysis of these parameters also reveals how the local geometry of the brain changes with time or under pathological conditions. Experiments has shown that the ECS in adult brain has $\alpha = 0.2$ which is about 20% of the total brain volume, the tortuosity is defined as

$$\lambda = \sqrt{D / D^*} \ ,$$

where D is a free diffusion coefficient and D^* is the apparent diffusion coefficient in the brain. As a result of tortuosity, D is reduced to the apparent diffusion coefficient $D^*=D/\lambda^2$. Thus, any movement of a substance diffusing in the ECS is bombarded by a number of obstacles or diffusion barriers. Moreover, substances released into the ECS are transported across membranes by concentration-

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dependent uptake (k') e.g., cellular uptake, loss across blood vessels or washout from brain slices (Sykova, 1997).

The diffusion of substances in a free medium is described by Fick's laws. In contrast to free medium, diffusion in the ECS is hindered by the presence of membranes, macromolecules of the ECS and by cellular uptake. To take into account these factors, it was necessary to modify Fick's original diffusion equations (Nicholson and Phillips, 1981; Nicholson and Sykova, 1998) to include macroscopic diffusion in a porous material which is described by the same fundamental differential equation as diffusion in a free medium (Fick's second law)

$$\frac{\partial c}{\partial t} = D^* \frac{\partial^2 c}{\partial r^2} + \frac{s}{\alpha} - k'c \qquad (1)$$

where $c(r,t)$ is the concentration of the diffusing substance, and s is the source density. Equation (1) is a model of the concentration of the diffusing molecules in the ECS at a radial distance r, it is a parabolic partial differential equation studied in the theory of some biological context (Berg, 1993). Equation (1) plays an important role in drug therapy and in curing major brain diseases such as Parkinson's and brain tumours, and solving it with different approaches has been an appealing subject to many researchers for many years and it proofed to be not an easy task to do. Some researchers presented analytic solutions as in ([Nicholson and Freeman 1975, Saftenku, 2005), and some found approximate solutions by numerical methods as in (Nicholson 1985, Chen and Nicholson 2000). In this paper Eq.(1) is solved by a numerical method based on a neural network approach called the Hopfield Finite Difference method (HFD) and that is because neural networks are dynamic and were originally designed to operate in a similar way as the brain functions therefore this approach can give us insight on the complex diffusion in the ECS of the brain more than any other classical simple numerical method. In section 2 a description of the governing equation is given, and in section 3 the neural network solution to this equation is presented. The results will be given and examined in section 4 followed by conclusions and plans for our future studies.

2 DIFFUSION EQUATION IN THE ESC

Currently, the most widely used diffusion paradigm is the release of a substance from a point source into the ECS. In this study, the ion source which is an ionophoretic electrode or pressure ejection approximates a point source. Moreover, assuming spherical symmetry and adopting the spherical coordinate system, with the source density s = Q (source strength in mol/s), Eq. (1) becomes the point source equation as given in (Nicholson and Phillips, 1981)

$$\frac{\partial c}{\partial t} = \frac{D^*}{r}\frac{\partial^2 (rc)}{\partial r^2} + \frac{Q}{\alpha} - k'c \qquad (2)$$

In the source term Q is characterized by Q = n I / F; where I (amp) is the iontophoretic current, F is the Faraday constant (96485 C/ mol), and n is the transport number. Analytic solution to Eq. (2) is well known and has the form (Crank, 1975)

$$c = \frac{Q}{8\pi D^* \alpha r} \exp\left[r\sqrt{\frac{k'}{D^*}}\right] \operatorname{erfc}\left(\frac{r}{2\sqrt{D^* t}} + \sqrt{k't}\right) + e^{-r\sqrt{\frac{k'}{D^*}}} \operatorname{erfc}\left(\frac{r}{2\sqrt{D^* t}} - \sqrt{k't}\right)\Bigg] \qquad (3)$$

in which erfc(.) is the complementary error function. The common choice of ion for measuring diffusion is TMA+ (Nicholson, 1993). One example of its use is when research requires the use of experimental models in which a defined population of cells can be brought together into an epileptic state. One way to do this is by locally injecting a drug that causes seizure-like activity and after injection the drug will diffuse in the ECS with the usual characteristics determined by D, α and λ. This leads us to an important question, what is the concentration distribution that is required to produce an epileptic focus? To resolve the distribution problem, two types of information are required; the value of D and D* for the drug used and a description of the concentration distribution at the instant when nerve cells begin seizure-like activity. Among agents that produce epileptic models are penicillin, valproate and pentylenetetrazol (PTZ). In principle, to determine the concentration distribution that induced

seizure, one would employ appropriate drugs for the epileptogenic agent, measure concentration at the time that the cells began to display epileptic activity and then calculate the drug distribution. Unfortunately, such drugs do not perform well and are fairly insensitive so they are not suitable for work at the low concentrations that produce seizure. Consequently, TMA+ was added to the epileptogenic agent and both pressure ejected. Then the distribution of the TMA+ could be measured and, knowing the relative diffusion coefficients of TMA+ and the drug, the drug distribution could be calculated. It was also shown that values of λ, obtained from D and D* from the combination of TMA+ and the drug were similar to those previously obtained with TMA+ alone. Using this approach (Lehmenkuhler et al., 1991) were able to show that neurons within a sphere of about 150 μm radius must be exposed to penicillin to produce seizure. Therefore, studying the diffusion of the ion TMA+ is needed, and in our study we will present the solution of the point source diffusion equation of the ion TMA+ in the ECS of brain, together with an analysis of all the involved parameters.

2.1 The Diffusion Equation in ECS by the Hopfield Neural Networks

Continuous Hopfield neural networks were developed by Hopfield and Tank to solve constrained optimization problems. The nets are recurrent where the weights are fixed to represent the constrain and the quantity to be optimized. The activations of the units iterate to find a pattern of outputs that represent a solution to the problem and correspond to the minimum of an Energy function (Hopfield, 1982). Hopfield network can be easily implemented on fast parallel computers, because of its parallel nature. Therefore it is applied to many optimization problems where complex computation is needed, such as the traveling salesman problem, map coloring, space allocation (Hopfield and Tank, 1985) and many more. Another area for using Hopfield nets is combining it with the finite difference method to solve partial differential equations (PDE), this is done by minimizing an energy function constructed to represent the total squared error measuring how well the finite difference quotients satisfy the PDE. This approach is called the Hopfield Finite Difference method (HFD), and it has the advantage of working in a parallel mode and giving fast and accurate results. The HFD method has been used to solve the classical Wave, Heat (Diffusion), Poisson equations (Alharbi, 1997, 2010, 2012), and to systems of PDEs (Alharbi and Alahmadi, 2008).

We will use the HFD to solve the point source diffusion equation in the ECS described in the last section. However, before the method is applied there are preliminary procedures to be done. First, a neural representation of the problem is needed so that the neurons in the network model the node points in the mesh grid of the finite difference procedure, i.e. each unit in the HFD neural net corresponds to a node point in the mesh grid, and the activation of unit (i, j) gives the approximate solution at (iΔr, jΔt) where i and j are integers and Δr, Δt are the step sizes in r and t respectively. Second, the Hopfield neural net is designed to be a fully connected net with symmetric weights. The weights are fixed to represent the differential equation and the initial conditions. The activation function is the identity function since continuous range of outputs is desired. The design of the HFD neural net goes through two stages: first, the finite difference scheme for radial diffusion in spherical coordinates is used on the grid points denoted $c_{i,j}$ at (iΔr, jΔt), with the equations

$$\frac{\partial^2 (rc)}{r\partial r^2} = \frac{1}{i\Delta r^2}[(i+1)c_{i+1,j} - 2ic_{i,j} + (i-1)c_{i-1,j}]$$

for i≠0, and for i=0

$$\frac{\partial^2 (rc)}{r\partial r^2} = \frac{6}{(\Delta r)^2}(c_{1,j} - c_{0,j}) \qquad (4)$$

Substituting these equations in the diffusion equation (2) and using the central finite difference scheme for the time derivative we get

$$\frac{c_{i,j+1} - c_{i,j}}{\Delta t} = \frac{D^*}{i\Delta r^2}[(i+1)c_{i+1,j} - 2ic_{i,j} + (i-1)c_{i-1,j}] + \frac{Q}{\alpha} - k'c_{i,j} \qquad (5)$$

Second, the finite difference method produces a linear system of equations for *i=1,2,...n,* and *j=1,2,...,m*. A design for the HFD net is made using the energy function representing the total squared error from the finite difference quotients, given by

$$E = \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{m}\left[\frac{c_{i,j+1} - c_{i,j}}{\Delta t} - \frac{D^*}{i\Delta r^2}[(i+1)c_{i+1,j} - 2ic_{i,j} + (i-1)c_{i-1,j}] - \frac{Q}{\alpha} + k'c_{i,j}\right]^2 + E_2 \qquad (6)$$

where E_2 comes from the initial nodes with *i=0*,

$$E_2 = \frac{1}{2}\sum_{j=1}^{m}\left[\frac{c_{0,j+1}-c_{0,j}}{\Delta t} - \frac{6D^*}{\Delta r^2}(c_{1,j}-c_{0,j}) - \frac{Q}{\alpha} + k' c_{0,j}\right]^2 \quad (7)$$

We want to update the time step approximation unit $c_{i,j}$, therefore we differentiate the energy function with respect to $c_{i,j}$ and consider only the closest previously initialized units. The updating equations for the activity of unit $c_{i,j}$ are given in Eq.(8).

The HFD net iterates to find the minimum of the energy function given in equations (6) and (7) using these updating equations given in (8). The net will converge to a stable minimum of the Energy function whenever the activity of each neuron changes according to the equations of motion (8). The parameters in the HFD net must be carefully chosen to make sure the HFD finds the minimum of E and captures all the dynamics of the diffusion in the ESC. One of these parameters is the time step δ which should be set to a small value, depending on the parameters of the problem being solved, and usually specified by trial and error. If we use a too small value, the learning slows down, increasing the number of epochs and the time needed to solve the problem. Moreover, if we increase the grid size, then δ must be accordingly decreased to maintain a balanced updating of the activations.

$$c_{i,j}^{(p+1)} = c_{i,j}^{(p)} - \delta(\beta_1)\left[\frac{c_{i,j+1}-c_{i,j}}{\Delta t} - \frac{D^*}{i\Delta r^2}[(i+1)c_{i+1,j} - 2ic_{i,j} + (i-1)c_{i-1,j}] - \frac{Q}{\alpha} + k' c_{i,j}\right]$$

$$c_{0,j}^{(p+1)} = c_{0,j}^{(p)} - \delta(\beta_2)\left[\frac{c_{0,j+1}-c_{0,j}}{\Delta t} - \frac{6D^*}{\Delta r^2}(c_{1,j}-c_{0,j}) - \frac{Q}{\alpha} + k' c_{0,j}\right]$$

$$s.t. \quad \beta_1 = \left(\frac{-1}{\Delta t} + \frac{2D^*}{\Delta r^2} + k'\right), \qquad \beta_2 = \left(\frac{-1}{\Delta t} + \frac{6D^*}{\Delta r^2} + k'\right) \quad (8)$$

The choice of initial activations influences the rate of convergence. Starting with a suitable range of random initialized units decreases the number of epochs the net needs to reach the desired activations, hence reducing the time consumed in solving the problem. On the other hand, choosing an initial state that does not fall into the domain of any stable point will cause the units to go through more epochs seeking the closest minimum and converging. In our case the net is initialized with zeros since the concentration starts impulsively from rest, and then activated seeking a minimum of the energy function, by changing according to the updating equations (8). The original Hopfield net described by Hopfield and Tank uses random order to update the activations of the neurons and this technique is utilized here too to give the net its randomness similar to real neurons in nature. An epoch consists of all units in the system updating their activation. The net goes through as many epochs as needed for it to converge to a minimum, that is reaching a stable set of activations, and hence finding the approximate solution of the TMA^+ point source diffusion equation.

3 DISCUSSION

The work done in this paper is theoretical and only provides an approximate solution to the modelled point source equation given in the last section from a mathematical point of view, therefore the values of the involved parameters in this model equation were set according to an experiment conducted by (Nicholson, 1993) in the specialized labs; where the transport number of the electrode is 0.5 with the effective diffusion coefficient used $D^* = 5.07 \times 10^{-6}$ $cm^2\ s^{-1}$, $\alpha = 0.2$, $k' = 0.0025\ s^{-1}$ and $\lambda=1.6$. The Hopfield neural network used in this study is designed to minimize the energy function given in Eq.(6) with parameters set as :m=15, n=20 , Δt =10s, Δr =10 μm, δ =0.005, and Q=0.0005 nmol/s, and the net is activated to update the neurons according to Eq.(8). After only 500 epochs the net converges to a stable set of activations and the approximate solution describing the TMA+ concentration c (μM) is shown in Fig.1. As we can see the results are excellent in terms of speed and accuracy compared to the exact solution obtained from Eq.(3) and to results published by Nicholson 1993. The total squared error plot given in Fig. 2 confirms the HFD accuracy after only 500 epochs. Table 1 compares results obtained from the HFD approach described in this work with numerical results obtained by the classical finite difference method (FD).

As we can see in Table 1 the results are very close in terms of accuracy and that makes the HFD approach reliable even if it goes through more steps and calculations because brain activity is a very complex dynamic area and it needs a dynamic approach such as neural networks to capture its

Table 1: Comparison of results from the Neural networks HFD and the numerical method FD.

At t = 50 s and Selected values of r	c(μM) in HFD	Total squared Error in HFD	c(μM) in FD	Total squared Error in FD
10 μm	1.9625	5 x10^{-4}	1.9626	5.9x10^{-4}
50 μm	0.3924	-1x10^{-4}	0.3923	-2x10^{-4}
100 μm	0.1962	-1.5x10^{-5}	0.1963	5 x10^{-5}
150 μm	0.1308	-1x10^{-4}	0.1306	-3.7x10^{-4}

behaviour rather than a simple classical mathematical method such as FD. Neural networks have the capability to accurately model the neural activities and its different structures and tasks since this was the original objective of creating neural networks. Another feature of HFD that make it exceed other classical numerical methods is that the parallelism nature of the Hopfield neural networks approach is easier to implement on fast parallel computers and this will make them faster than the traditional methods for modeling this complex problem.

To look at the concentration of TMA+ as a function of time t, Fig. 3 shows the concentration at r= 100, 150, and 300 μm. As we can see at closer radial distances from the point source (r =100 μm) the concentration reaches higher values and then gradually decreases to values still much higher than all the other distances. Moreover, at farther radial distances such as r =300 μm the concentration does not exceed 0.0654 μM for all time periods, this means if a drug is injected into the brain and allowed to diffuse for a few seconds, at a location greater than 300 μm away from the source, the concentration will be very low, and maybe too low to activate any receptors or neurons there.

Figure 4 shows the concentration as a function of radial distance r at times t = 20, 40, and 60s. As we expect concentration has a higher value at earlier times of the diffusion and gradually decreases as the distance from the source grows further. Therefore, as an example after just 150 seconds from injecting a drug in the ECS at t =0, the drug will diffuse and the concentration of the drug will be negligible at any spherical distance from the source. The effect of the initial concentration or source density on the diffusion of TMA+ is shown on Fig.5, with D*=0.5 x10^{-5} cm^2/s, and r = 150 μm. It is evident that the higher the concentration initially released the higher the values of the concentration at each t. This is evident at the highest initial source Q =0.001 nmol/s, where a higher concentrations for all t is reached and manages to reach the farthest before all of the TMA+ diffuses away.

To study the influence of different diffusion coefficients on the concentration of TMA+ Fig.6 shows plots at Q=0.0005 nmol/s and r =150 μm away from the iontophoretic source for D* = 0.5, 0.7, and 0.2 x10^{-5} cm^2/s. As we can see the smaller the diffusion coefficient the slower the concentration reaches its highest and it takes longer time to diffuse. It is also evident the larger D* reaches the highest concentration earlier on and decreases concentration faster. The diffusion coefficient D*=0.7 x10^{-5} cm^2/s starts at a higher concentration than the other two but drops faster to lower concentrations.

From all the observations noted in the earlier graphs, and if we consider different combinations of initial density source and diffusion coefficients, we can conclude that using D*=0.5x$10^{-5}$$cm^2/s$ and Q=0.0005 nmol/s starts low in concentration but manages to give higher concentrations for a larger radial diffusion distance. For that reason, we use this combination in most of our study here. Hence, if our analysis should present recommendations to efficient

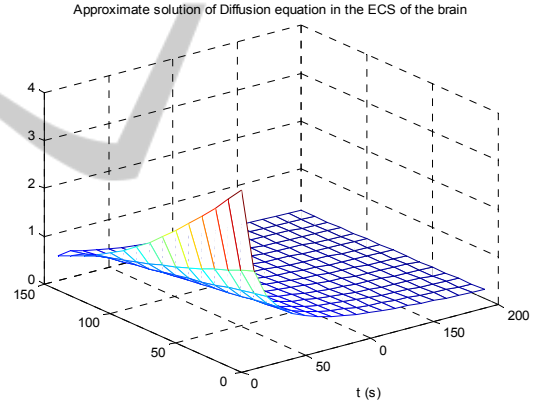

Figure 1: The approximate solution of diffusion equation by HFD for r = 0 to 150 μm and t = 0 to 200 s.

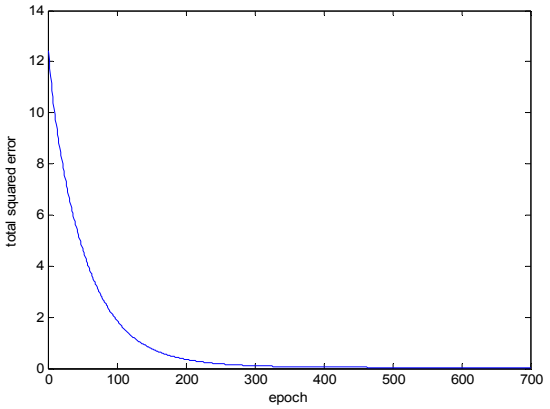

Figure 2: The total squared error plot of the HFD solution for the diffusion equation.

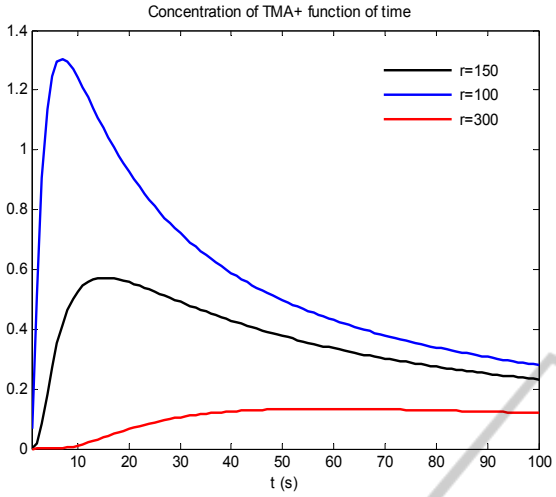

Figure 3: The diffusion of TMA^+ at different radial distances.

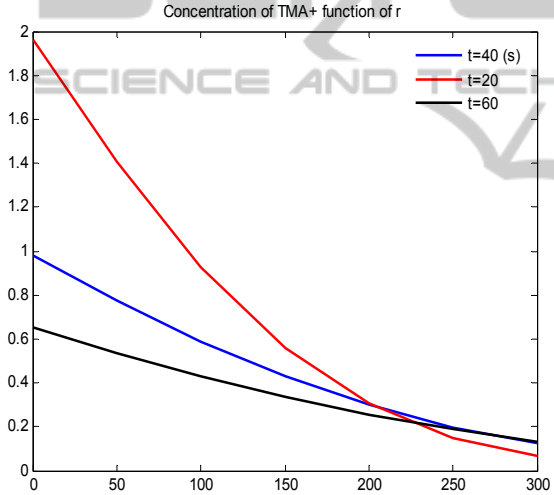

Figure 4: The Diffusion of TMA^+ at different times.

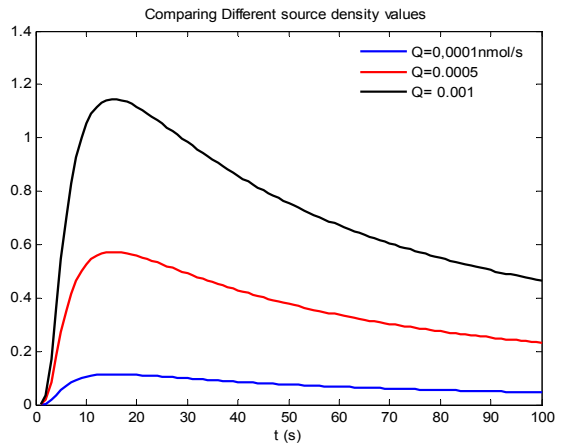

Figure 5: The concentration of TMA^+ at different source density values.

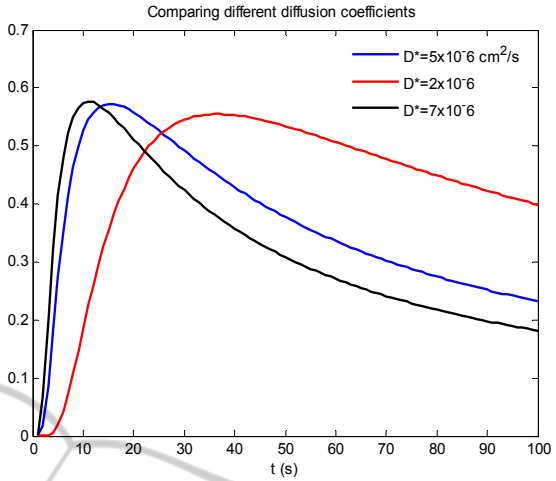

Figure 6: The concentration of TMA^+ with different Diffusion coefficients.

drug delivery based on our results, then a carefully chosen combination of D* and Q is needed for a drug to reach neurons within a sphere of a specified radius. Similarly, if the experiment combines the ion TMA+ with another drug then a corresponding joint D* and Q must be carefully chosen.

4 CONCLUSIONS

In this research a solution to the point source diffusion equation in the ESC of the brain by a Hopfield finite difference neural network. A finite difference approximation in spherical coordinates is used to form an energy function which represents how well these approximations model the problem. A Hopfield neural network is then designed to minimize this energy function. Results obtained from the Hopfield neural networks showed excellent performance in terms of accuracy and speed. Our study is done in a theoretical frame and is compared to actual results published by Nicholson 1993, and it needs to be extended by researchers in the drug therapy field to conduct the actual experiments and take these results to the next level of testing, experimenting and reaching the desired recommendations.

Our study of the effect of the parameters on the solution showed that if a drug is delivered to the brain by injection separately or with an ion, it will diffuse in the region and activate all nearby neurons with in a small sphere radius, and depending on the concentration value needed to activate these neurons. For example, if the ion TMA^+ was added to the drug and both were pressure ejected. Then the

distribution of the TMA^+ could be measured and, knowing the relative diffusion coefficients of TMA^+ and the drug, the drug distribution could be calculated. From our results we showed that neurons within a sphere less than 300 μm radius away from the point source must be exposed to the drug and they will produce a respond, and all neurons outside this area will be exposed to almost negligible concentrations and probably the drug will not show an effect on them.

Therefore, our study may help doctors and patients to attain efficient drug delivery, i.e. by choosing the appropriate drug knowing its density and diffusion factor and the location of the injection. Apart from the clinical relevance of these studies, they also provide a paradigm of how diffusion analysis can be used to address other types of question by using the co-diffusion of substances, one of which has a 'reporter' role. A major reason for introducing drugs is to fight cancerous tumors and many studies have involved chemotherapy agents. Tumors often have diffusion characteristics that differ from normal tissue and this has made it difficult to introduce many drugs that show an effect on them, including large antibodies, that could otherwise be effective agents (Lehmenkuhler et al., 1991). The delivery of Dopamine to alleviate Parkinson's disease is another area where much work has been done. Dopamine alleviates the effects of Parkinson's disease but, sadly, the treatment does not offer a permanent cure because, for unknown reasons, the treatment becomes ineffective after a period of some months or years. This led to attempts to implant sources of Dopamine in the brain directly, most notably grafts of tissue or encapsulated populations of dopamine-producing cells. Recently there has been interest also in the delivery of substances like nerve-growth factor (NGF) that may be capable of reversing some of the effects of Alzheimer's disease (Krewson et al., 1995). All of these reasons give us motivation for future work to conduct more research on the diffusion equation in the ECS, and on the concentration distribution with different parameter values and with different drug therapies and extend this work with specialists in the drug therapy research labs to transform these theoretical results to actual experimental results. Furthermore, the neural networks are originally designed to operate similarly to the brain's functions and that can give us more insight on diffusion in the ECS of the brain than any other numerical method, hence it will be beneficial in future work to use different neural networks as models of the ECS activities in the brain and fully make use of the dynamics and full potentials of neural networks in this area .

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