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# Artificial neural networks capable of learning spatiotemporal chemical diffusion in the cortical brain

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ABSTRACT

Neurochemical and pharmacological studies of the central nervous system are important in understanding normal brain function and discovering effective treatments for brain diseases. Imaging systems are capable of providing large spatiotemporal chemical information, but they require the subject to remain still during recording. Implantable chemical sensors can be used in freely behaving animals and are able to provide higher resolution than imaging systems, but only in close proximity to the sensor.

The aim of this research was to design and evaluate an artificial neural network capable of generating 3D chemical information over time using data acquired from a limited number of chemical sensors that could eventually be recorded from a freely behaving animal. The results show that the spatiotemporal neural network is capable of learning ion diffusion in a model of the cortical brain, in ideal or noisy conditions, and that network simulations of sensor data are as accurate as mathematical simulations.



## 1. Introduction

Neural disease and disorders affect approximately 100 million Americans every year with costs estimated to be more than $500 billion [1]. Although much has been learned about components involved in neural function and disease, the dynamics of chemical mechanisms in the brain have not been fully characterized. More effective research into the underlying causes of disease and development of treatments would, in the long term, benefit millions of people and decrease costs by treating the disease instead of its symptoms.

The study of brain neurochemistry and pharmacology often involves research with animal models to determine the mechanisms of learning, memory, neurodegenerative diseases, and mental illnesses, to name a few [2]. Current tools available for studying neurochemicals *in vivo* include non-invasive imaging techniques and implanted chemical sensors. While the former are used predominantly in medical diagnosis, the latter are widely used in animal research. This is primarily due to the fact that diagnosis of disease in humans typically avoids invasive exploration unless absolutely necessary (e.g., biopsies). Small rodents such as rats or guinea pigs are used in most animal studies due to their relative low cost while being acceptable research models. Their brain is relatively small (~2 g) compared to the human brain (1300–1400 g) [3]. Resolution limitations on non-invasive imaging tools, along with movement of the animal, inhibit their use in animal research. Table 1 summarizes uses and limitations of current imaging systems.

Sensors can be implanted in the animal's brain for studies over long periods, although the data only provide a local concentration without the 3D images that the non-invasive imaging technologies are capable of producing. Problems such as inflammation at the insertion point and signal drift in chronic studies are being addressed by research into the sensor shape, insertion technique, and inflammation-resistant coatings or drugs [4–11]. In addition, many different implantable sensor arrays have been reported, which could provide more spatial information [12–15].

The aim of this research is to develop an artificial neural network capable of learning spatiotemporal chemical diffusion in the cortical brain. Such a network could eventually be coupled with chemical sensor arrays in order to measure the chemical function locally in the brain of a freely behaving animal. Successful development of this network could significantly enhance the ability to investigate neurochemical and pharmacological mechanisms in brain function and disease.

## 2. Neural networks

Artificial neural networks (ANN) have the potential to learn from the measurements of sensors and predict values at locations

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**Table 1**
Uses and limitations of existing functional imaging technologies [39].

| | Advantages | Disadvantages |
|---|---|---|
| ***CT*** | • Excellent images of skull, sulci, and ventricles.<br>• Volumetric and dynamic images can be obtained if spiral CT is used.<br>• Has proven useful in diagnosing certain brain disorders<br>• Relatively low scanning time. | • Artifacts often arise in regions containing very dense structures (e.g. areas close to bony interfaces).<br>• Patient is exposed to ionising radiation.<br>• Only transverse slices obtained<br>• In order to get different slices of the body, the patient and/or machine must be put into different positions.<br>• Cannot be used on patients allergic to the dye |
| ***fMRI*** | • Can map brain's functional responses to specific stimuli.<br>• Non-invasive and safe.<br>• Will help to learn more about neurophysiology in both disease and health.<br>• Reference anatomic images are simultaneously acquired with the functional data. | • Pacemakers, shell injury, plates, screws, or metallic implants are contraindications.<br>• Subjects have to remain still.<br>• Procedure may take ~45 min. to complete<br>• Price of scanner is expensive<br>• Artifacts near skull base limit its use.<br>• Resolution limited to 0.5 cm voxel |
| ***PET/SPECT*** | • Exact quantification of cerebral blood flow and metabolism.<br>• Whole head imaging is more reliable.<br>• Neuroreceptor concentration and affinity can be measured.<br>• Non-invasive alternative to biopsy.<br>• Available in most departments of nuclear medicine.<br>• Large numbers of radiotracers available.<br>• Cost effective. | • Radionuclide scanning technique<br>• Cannot be used repeatedly<br>• Need to inject isotope for each new task.<br>• Anatomic data need to be obtained separately<br>• Limited resolution<br>• Limited but growing availability.<br>• Absolute quantification is not possible, and bilateral symmetrical reduction is difficult to recognize. |
| ***MRS*** | • Direct investigation of phosphorhylated intermediate metabolites & neurotransmitters (e.g. GABA and glutamate).<br>• In certain situations, biopsy may be avoided (e.g. tumefactive lesion of demyelination mimics neoplasm = > spectra suggests destructive demyelination). | • Long procedure if one is interested in quantification at molecular level.<br>• Only limited substrates are measurable.<br>• Voxel size may be larger than lesion.<br>• Irregularly shaped lesions may not conform to voxel margins. |

where no sensors are present. One type of ANN, the recurrent neural network (RN) has bidirectional data flow, which allows the network to learn temporal information, such as speech [16], or spatial information, like in virtual reality [17,18].

Studies on combined temporal and spatial learning with neural networks in the areas of sea scattering signals [19], pattern learning and recognition [20,21], brain–machine interfaces [22], ground–water pollution [23], and vision [24] have been published. These networks either used unsupervised learning in 1–3D space or up to 2D with supervised learning. However, 3D spatiotemporal networks using supervised learning have not been thoroughly studied.

### 2.1. Elman networks

Recurrent neurons were the building blocks of this novel spatiotemporal network with parallel subnets joined together to provide a final output. The Elman network was used as the recurrent subnet in the network because of its simplicity. The Elman network is able to perform sequence-prediction tasks that are beyond the capability of a standard multi-layer perceptron by maintaining memory. It uses the least amount of computations of all the RNs; however, the Elman network usually requires more neurons in the hidden layer to learn a system compared to more advanced RNs.

The Elman network has at least three layers (input, hidden, and output) and a set of context units in the input layer [16,25]. Connections from the hidden layer go to the context units with a weight fixed at one. The input is fed forward at each time step and then a learning rule, such as back-propagation, is applied. The context units always maintain a copy of the previous value of the hidden units since they propagate over the fixed back connections before application of the learning rule.

For a basic Elman network, there is one hidden layer of neurons that apply a 'tansig' function, which compresses the magnitudes of its inputs to the range of $-1$ to 1 [25]. The output layer contains neurons with 'purelin' functions, which pass their input to the output unchanged. This unique combination enables Elman networks to approximate, with arbitrary accuracy, any function with a finite number of discontinuities [25].

### 2.2. A configuration of Elman networks for learning spatial and temporal patterns

This system employs Elman networks as subnets in a larger network with the aim to recognize both spatial and temporal informations. To accomplish this aim, the spatial information is input to the network, via the subnets, at each time step while the temporal information is learned by feeding inputs sequentially.

The networks were designed and evaluated in MATLAB using the Neural Network Toolbox (The MathWorks, Inc.). The structure of the complete spatiotemporal recurrent network (STRN) consists of two stages of networks. In the first stage, individual networks are trained by inputs from a given sensor. As illustrated in Fig. 1, a unique sequence of vectors is fed into the hidden layer of each Elman subnet. At each time step, the input vector consists of the value (e.g., concentration), the maximum and the minimum values from the current and four previous time steps, and a least squares value from the current and four previous time steps. All of these parameters are commonly used as inputs in neural networks. The minimum, maximum, and LSE provide information on the variability of concentration over time. In addition, $x$, $y$, and $z$ coordinates for concentration measurements from a given sensor relative to the sensor set as the origin for a particular subnet were included in the input vector to provide spatial information for the network to learn.