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**FINAL REPORT (1986-1989)**

AFOSR GRANT 86-0076

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**AFOSR-TR- 89-0809**

**ABSTRACT**

**Overview of experimental categories:** Work over the three-year tenure of this grant has dealt with interrelated studies of (1) neuropharmacology, (2) behavior, and (3) distributed/parallel processing in the generation of variable motor patterns in the buccal-oral system of the sea slug *Pleurobranchaea californica*. (4) Computer simulations of simple neural networks have been undertaken to examine neurointegrative principles that could not be examined in biological preparations. The simulation work has set the basis for further simulations dealing with networks having characteristics relating to real neurons.

**Goal:** All of the work has had the goal of developing interdisciplinary tools for understanding the "scale-independent" problem of how individuals, each possessing only local knowledge of group activity, act within a group to produce different and variable adaptive outputs, and, in turn, of how the group influences the activity of the individual. The pharmacologic studies have had the goal of developing biochemical tools with which to identify groups of neurons that perform specific tasks during the production of a given behavior but are multifunctional by being critically involved in generating several different behaviors. *Keywords:*

**General conclusion:** *The brain is a Darwinian engine in that it diversifies its output while the environmental conditions determine or select the form of the output that is appropriate at any given time.* In addition to sensory-induced variations, the brain itself generates its own variability. As shown by analysis of spike trains recorded intracellularly and extracellularly in identifiable groups of neurons, some forms of variability may represent low-dimensional chaos, while other forms may represent high-dimensional "thermal noise". Chaos may aid both in response diversification and response stability, while "thermal" noise may aid in response optimization. Optimization procedures used by other people generally involve some form of time-dependent control of noise, as occurs in simulated annealing. Time-dependent algorithms may work well for optimization of responses to single events, but are difficult to apply to adaptive systems that must respond to sequences of unexpected environments. To overcome this problem, we have developed event-dependent algorithms that use constant levels of noise. *b* 1473

The pharmacological/behavioral studies have shown that a highly specific muscarinic cholinergic antagonist, scopolamine, but not the agonist, oxotremorine, enhances one-trial food-aversion learning. Receptor binding studies have shown that membranes of neural tissue in our experimental animal contain binding sites having pharmacologic characteristics resembling those of muscarinic receptors in mammalian cortex. We are now examining the possibility that scopolamine enhances learning by upregulating the synthesis of receptors. In immunohistochemical studies, we are developing methods for visualizing the input and target neurons of the muscarinic cholinergic nervous system. This information will then provide the foundation for neurophysiological studies that compare the dynamics of the identified group with other already identified groups of neurons, all affecting the same motor system of the animal.

**Publications:** During the three-year tenure of the grant 6 publications have appeared, and numerous papers were given at national and international meetings; 5 more papers are presently being written for publication whose foundation arose from work funded by this grant.

**FINAL REPORT (1986-1989)**

AFOSR GRANT 86-0076

George J. Mpitsos, Ph.D.  
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**A. Overview of Experimental Categories:**

Work over the three-year tenure of this grant has dealt with interrelated studies of (1) neuropharmacology, (2) behavior, and (3) distributed/parallel processing in the generation of variable motor patterns in the buccal-oral system of the sea slug *Pleurobranchaea californica*. (4) Computer simulations of simple "connectionist" networks have been undertaken to examine neurointegrative principles that could not be examined in biological preparations. These simulation studies have also laid the foundation for further simulations dealing with networks having realistic neuronal characteristics.

**B. Progress In Each of the Four Areas Noted in Section A:****Areas 1 and 2: Behavior and Pharmacology:**

The purpose of the biochemical/pharmacologic work has been to develop biochemical probes with which to identify groups of neurons having specific jobs in generating behaviors. These groups will then be used to ascertain the first principles by which groups produce "cooperative" activity relating to the specified behavior. The activity in these newly identified neurons will be contrasted against the activity in a group of neurons that has already been identified in our previous work, and whose responses have led us to include variability and chaos in brain function as critical neurointegrative principles.

Single, low-dose injections of the muscarinic antagonist scopolamine enhances one-trial food-aversion learning in the sea slug *Pleurobranchaea*. Receptor binding studies using a new ligand, the <sup>125</sup>I-form of quinuclidinyl-benzilate, have uncovered two classes of muscarinic receptors: one found typically in other species, and in high concentration in vertebrate cortex, and a new form not encountered in other animals. Invertebrate tissues usually contain low densities of muscarinic receptors, but the density of the new form in nervous tissues is similar to the density of muscarinic receptors in mammalian cortex. The new receptor form may be a precursor to the other.

We are examining the possibility that exposure to scopolamine upregulates the synthesis of receptors, and are developing immunohistochemical methods for visualizing both the presynaptic cholinergic neurons and the postsynaptic neurons having muscarinic receptor sites.

*The purpose of these studies is not to lead us to specific synapses to which we can attribute learning (as is presently being done in other "simple" animals), but rather to determine how distributed changes affect the functioning of groups of neurons. In fact, we believe that individual synaptic changes acquired during learning can take part in several different behaviors. This point of view sets us philosophically far apart from all other laboratories dealing with learning in "simple" systems.*

Finally, taking the view that the neurochemical basis of behavior is as dynamical and variable as the neurophysiological one, we have also been examining other neurotransmitters that impinge on the same motor system.

### **Area 3: Variability in Motor Patterns:**

Our neurophysiological and neurobehavioral studies have shown that the activity of neurons is variable, as are the behaviors in which they take part in generating. Traditionally, neurobiologists have attempted to attribute identifiable functions to individual neurons or groups of neurons. However, we have found that the functional role of a given cell is time- and context-dependent. Neurons can have a multiplicity of functions, each of which is determined by the context of activity in other neurons that become coactive with it. *Thus, the underlying circuitry does not determine the behavior, but rather the potentiality of many different and variable behaviors; the appropriate response emerges dynamically from the underlying circuitry. Moreover, the factor that determines the results of such dynamical processes is the selective pressure applied by the environment. This view is Darwinian in that it posits that adaptive brain function arises by means of diversification and selection, not by centrally preset motor programs.*

We have shown over the past three years that some of this variability may be produced by the central nervous system itself in the form of chaos. Some researchers have identified chaos with pathologic states such as seizure EEGs or with deep sleep EEGs, while other researchers have proposed that chaos may represent transitional attractors leading to limit cycles whose predictable properties then carry information relating to specific olfactory odors. *Our work was the first to indicate that chaotic attractors themselves may underlie adaptive behaviors.* Other laboratories have recently reinterpreted their own work in the same light.

We have also been among the early few to show and discuss the problems associated with application of chaos theory to biological systems whose responses are both short-lived and nonstationary. The causes of nonstationarities are generally unknown, but, as we shall be presenting in June of 1989 at the Annual Meeting of the Bioelectromagnetic Society in Tucson, nonstationarities in neural systems may arise through time- and activity-dependence of bifurcation parameters (e.g.,  $K^+$  conductance). It may be possible to view the state of these parameters as arising from the distributed system of coactive neurons, with each neuron contributing a portion of the total effect. In the same way that the activity of a given neuron might not be a useful indicator of the motor output as a whole, the

parametric set of individual neurons may not be a useful indicator of the parametric setpoint of the network. The understanding of how such global bifurcation parameters emerge from the underlying neuronal components, and whether changes in their parametric state can usefully explain network nonstationarities, will initially have to come from computer simulations studies.

#### Area 4: Computer Simulations:

To avoid problems of dealing with unknown variables in biological systems, and to examine the ability of networks to process chaotic activity, we have turned to computer simulations. One paper, dealing with the ability of a network simply to transmit a chaotic signal from one network to another, has already appeared on this subject. We are presently writing two papers for publication showing that networks can also perform a variety of manipulations on chaotic signals.

*Two important aspects of this work deal, first, with the use of noise to control the ability of the network to learn or respond, and, second, with the relationship between network architecture and holographic or other forms of memory storage.*

In the first part of these new studies, we have used noise to enhance the response/learning rate of a network. This work compares time-dependent decay of noise, as in simulated annealing, with our event-dependent algorithms that use constant levels of noise. The reason for developing new noise-control algorithms is that while simulated annealing may be useful for optimization of a single response, adaptive systems must produce many responses to meet unpredictable environmental events--*i.e., adaptive systems are event-driven not time-driven.* The second part of our computational studies examines different diverging and converging networks to determine how the structure of neural circuits affects the way memory is stored. That is, the work examines how the amount of convergence and divergence of connections in the circuit affects the relative information-carrying capacity of individual synapses.

All of the work on simple connectionist networks will be extended to simulations involving realistic neuron properties and relating specifically to our physiological system.

#### C. Publications:

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- Mpitsos, G. J., Burton, R. M., Creech, H. C., and Soynila, S. O. (1988) Evidence for chaos in spike trains that generate rhythmic motor patterns. *Brain Res Bull* 21: 529-538.

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- Mpitsos, G. J., and Murray, T. F., Creech, H. C., and Barker, D. L. (1988) Muscarinic cholinergic action in one-trial food-aversion conditioning: Scopolamine enhances experimental-control differences in the mollusc *Pleurobranchaea*. *Brain Res Bull* 21: 169-179.
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