SECURITY CLASSIFICATION OF THIS PA

AD-A277 423

Approved for public release; distribution unlimited

1a. REPORT SECURITY CLASSIFICATI

Unclassified

MARKINGS

2a. SECURITY CLASSIFICATION AUTHORITY

3. AVAILABILITY OF REPORT

2b. DECLASSIFICATION/DOWNGRADIN SCHEDULE

DTIC ELECTE MAR 28 1994 S B D

Approved for public release; distribution unlimited.

4. PERFORMING ORGANIZATION REPORT NUMBER(S)

5. MONITORING ORGANIZATION REPORT NUMBER(S)

AFOSR-TR- 94 0095

94-09429

6a. NAME OF PERFORMING ORGANIZATION
The University of Texas Medical School of Houston

6b. OFFICE SYMBOL (If applicable)

7a. NAME OF MONITORING ORGANIZATION
AFOSR, Bolling Air Force Base

6c. ADDRESS (City, State and ZIP Code)
Department of Neurobiology and Anatomy
P.O. Box 20708
Houston, Texas 77225

7b. ADDRESS (City, State and ZIP Code)
Washington, DC 20332

421
449

8a. NAME OF FUNDING/SPONSORING ORGANIZATION
AFOSR

8b. OFFICE SYMBOL (If applicable)
AFOSR/NL

9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBE
AFOSR-91-0027

8c. ADDRESS (City, State and ZIP Code)
Bolling Air Force Base
Washington, DC 20332

10. SOURCE OF FUNDING NOS.

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT NO.
61102F	2312	A1	

11. TITLE (Include Security Classification)
Professor

12. PERSONAL AUTHOR(S)
John H. Byrne

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Yr., Mo., Day)	15. PAGE COUNT
Final Technical Rept	FROM 90-10-01 TO 93-09-30	94-01-10	12

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB. GR.	
0616			Learning, Memory, Information Storage, Artifical Intelligence
0603			

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The overall objectives of this research were to investigate mechanisms underlying neural plasticity, learning and memory. Between October 1, 1990 and September 30, 1993, progress was made in eight areas: (1) Voltage-clamp experiments analyzed membrane currents in a neuron that is modified during learning. (2) These data were incorporated into a single-cell model of associative learning. (3) The single-cell model was incorporated into a small neural network and simulations examined the functions of interneurons and the consequences of plasticity at multiple sites. (4) Additional simulations with the single-cell model examined potential cellular mechanisms for operant conditioning. (5) As a first step toward identifying additional loci for learning-induced modifications, the synaptic interactions were characterized among neurons that function as a central pattern generator (CPG). (6) Experiments also characterized how transmitters modulated the properties of the neurons and synaptic connections in the CPG and altered the electrical activity in the CPG. (7) These data were used to develop a model of the CPG and simulations examined the mechanisms underlying the generation of rhythmic neural activity. (8) A realistic model of a bursting neuron was used to examine mechanisms underlying the generation and modulation of endogenous rhythmic neuronal activity. In addition, a computer program that is a general-purpose simulator for neural networks and action potentials was developed and has been made available to others. These results have provided general insights into information processing and storage in the nervous system.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT

UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS ☐

21. ABSTRACT SECURITY CLASSIFICATION
Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE NUMBER (Include Area Code)	22c. OFFICE SYMBOL
Dr. Haddad	(202) 767-5021	NL

DD FORM 1473, 83 APR EDITION OF 1 JAN 73 IS OBSOLETE.

24 JAN 1994 SECURITY CLASSIFICATION OF THIS PAGE

Final Technical Report

Grant Number: AFOSR-91-0027

Grant Title: Analysis and Synthesis of Adaptive Neural Elements and Assembles

Principle Investigator: John H. Byrne

Period of Report: 1 October, 1990 to 30 September, 1993

I. Summary and Research Objectives

The overall objectives of this research were to investigate mechanisms underlying neural plasticity, learning and memory. Both empirical and modeling studies were used to analyze the properties of identified neurons and neural circuits that mediate two behaviors (a reflex response and feeding) which are both modified during learning. Between October 1, 1990 and September 30, 1993, progress was made in eight areas: (1) Voltage-clamp experiments quantitatively analyzed membrane currents in a neuron that is modulated during learning-induced modification of a defensive withdrawal reflex. (2) These data were used to make extensions to an empirically derived single-cell model of associative learning by incorporating quantitative descriptions of membrane currents and their modulation. (3) This single-cell model was incorporated into a more complete model of the circuit underlying this reflex and simulations examined the contributions of additional interneurons and loci for plasticity to adaptive responses of this behavior. (4) Additional simulations with this single-cell model examined potential cellular mechanisms underlying operant conditioning in neural network which produced spontaneous patterned activity. (5) As a first step toward identifying potential loci for learning-induced modifications of feeding, the synaptic interactions were characterized among neurons that function as a central pattern generator (CPG) mediating aspects of this behavior. (6) Experiments also characterized how transmitters, which effect feeding behavior, modulated the activity in this CPG and the properties of the neurons and synaptic connections in the circuit. (7) These data were used to develop a realistic computational model of the neural circuit and simulations examined the mechanisms underlying the generation of rhythmic neural activity in the CPG. (8) A realistic model of a bursting neuron was used to examine mechanisms underlying the generation and modulation of endogenous rhythmic neuronal activity. In addition, a computer program that is a general-purpose simulator for neural networks and action potentials was developed and has been made available to others.

II. Status of Research (Progress Report)

A brief summary of the progress made during the funding period is provided below. Additional details can be found in the collection of reprints that are included as an appendix to this Final Technical Report.

A. Analysis of the Modulation by Serotonin of the Voltage-Dependent Potassium Current in Sensory Neurons that Mediate the Tail Withdrawal Reflex of *Aplysia*

The serotonergic modulation of membrane currents is an important mechanism contributing to presynaptic facilitation of transmitter release from sensory neurons, which in turn, is thought to

be a cellular mechanism contributing to several forms of learning. Previous work supported by the AFOSR demonstrated that 5-HT modulates a highly voltage-dependent K^+ current ($I_{K,V}$). During this reporting period, these observation were extended by quantitatively examining the effects of 5-HT on $I_{K,V}$. $I_{K,V}$ was described using a Hodgkin-Huxley type model. The parameters necessary to develop the model of $I_{K,V}$ where determined by using a nonlinear curve fitting program and voltage-clamp records of $I_{K,V}$, which where obtained with and without 5-HT present. Application of 5-HT decreased the maximum conductance of $I_{K,V}$ by about 50%. In addition, 5-HT slowed the time constants for activation and inactivation of $I_{K,V}$ by about 25% and 100%, respectively. To examine how this modulation of $I_{K,V}$ contributes to 5-HT-induced changes in the electrophysiological properties of sensory neurons, these experimental observations were incorporated into a single-cell model of a sensory neuron (see Section B). These results indicated that the serotonergic modulation of $I_{K,V}$ was primarily responsible for 5-HT-induced spike broadening, whereas modulation of another K^+ current, the S-K^+ current ($I_{K,S}$), was primarily responsible for 5-HT-induced increases in neuronal excitability.

B. Simulations of Action Potentials, Excitability and the Effects of Serotonin on Sensory Neurons in *Aplysia*

Plasticity in the sensory neurons of *Aplysia* has been used extensively as model system in which to study the cellular and molecular mechanisms of simple forms of learning. In particular, the serotonergic modulation of transmitter release and membrane currents are important mechanisms contributing to presynaptic facilitation in sensory neurons, which in turn, is thought to be a cellular mechanism contributing to sensitization and classical conditioning. Previously, a single-cell model of associative learning was developed that simulated many features of synaptic plasticity in sensory neurons. This model, however, did not include realistic descriptions of the membrane currents and their modulation by 5-HT. During this reporting period, a quantitative analysis of the K^+ currents in sensory neurons and of the effects of 5-HT on the parameters governing these currents was performed (see Section A). This single-cell model of associative learning was extended by incorporating these data into realistic descriptions of the biophysical, biochemical and electrophysiological properties of sensory neurons. A Hodgkin-Huxley type membrane model of an *Aplysia* sensory neuron was developed. The membrane currents in the model, as well as their modulation 5-HT, were based on voltage-clamp data from the sensory neuron soma. In addition, a model for the intracellular levels and regulation of Ca^{2+} and models of transmitter release and of intracellular levels of second messengers were included. Simulations of voltage-clamped sensory neurons produced a good fit to the waveforms and maximum amplitudes of all ionic currents that have been identified in sensory neurons to date and simulations of individual action potentials and of neuronal excitability also produced a good fit to the empirical data. Moreover, simulations of voltage-clamped sensory neurons produced a good fit to the waveforms and maximum amplitudes of excitatory postsynaptic potenitals (EPSPs) under normal, depressed and facilitated conditions and simulations of action potentials also accurately predicted the resultant spike-induced EPSP. The simulations illustrated that the serotonergic modulation of $I_{K,V}$ contributed significantly to spike broadening, but not to enhanced excitability. On the other hand, the modulation of other currents, namely $I_{K,S}$ and the slow Ca^{2+}-dependent K^+ current, were responsible for the increase in excitability. In addition, simulations illustrated that in addition to its effects on membrane currents, 5-HT must have a facilitatory effect on transmitter mobilization.

C. The Role of Interneurons in Controlling the Tail-Withdrawal Reflex in *Aplysia*: A Network Model

The neural circuit that mediates the tail-withdrawal reflex in *Aplysia* is a useful system for studying the cellular and molecular mechanisms contributing to simple forms of behavior, learning and memory. The tail-withdrawal reflex is mediated, at least in part, by a monosynaptic circuit consisting of sensory neurons and motor neurons. The strength of the connection between the sensory and motor neurons is modulated by several forms learning. Although the relationship between the magnitude of this monosynaptic connection and the magnitude of the reflex response is fairly well understood, little is known about the determinants of response duration in motor neurons. For example, it is difficult to explain how brief (<1 s) trains of monosynaptic EPSPs evoked in motor neurons by activity in sensory neurons can drive the extended (>10 s) activity in motor neurons and how observed changes in the amplitudes of these EPSPs produce the observed changes in the duration of motor neurons responses. To examine quantitatively the determinants of the conversion of stimulus intensity into the duration of motor neuron responses, the computer program SNNAP (see Section VI) was used to construct a model representing the interactions among neurons of the tail-withdrawal circuit. Membrane conductances of model neurons were described by Hodgkin-Huxley type equations. Parameters were derived from electrophysiological studies.

Simulations indicates that monosynaptic connections from a number of sensory neurons to a single motor neuron contribute only to the first 600 ms of the motor neuron response, even when synaptic efficacy was greatly enhanced. In order to simulate long-duration motor neuron responses, it was necessary to include elements representing recently described excitatory interneurons that elicit slow, decreased-conductance EPSPs in motor neurons. Disynaptic connections via as few as two interneurons led to an extended (about 20 s) response duration in motor neurons at average spike rates of about 2 spikes/second. Furthermore, the polysynaptic circuit simulated empirically observed neural plasticity in both the magnitude and duration of the motor neuron response. Enhancement by 100% of the amplitudes of the synaptic connections from sensory neurons led to an 85% increase in the number of spikes fired by the motor neuron and a 25% increase in the duration of the motor neuron response. Augmentation of the connections from interneurons to the motor neuron had effects very similar to those of enhancement of connections from sensory neurons. The circuit could account for the effects of enhancement of depressed synapses as well. Effects of plasticity in sensory neurons and interneurons were cumulative. In summary, interneurons evoking slow PSPs can transform information regarding stimulus intensity into the duration of a response. The gain of the amplitude-to-duration conversion was adjustable via physiologically realistic synaptic modulation. These simulations provided general insights into information processing in the nervous system by illustrating mechanisms for intensity to duration conversion.

D. Simulations of Operant Conditioning in a Biologically Realistic Neural Network

One of the fundamental problems in neurobiology is to understand events occurring within individual neurons and within networks that contribute to learning and memory. An equally important and related problem is to determine the mechanistic relationships between different forms of learning. These issues were addressed with simulations of neural networks with biologically realistic properties. Previously, a mathematical model of an *Aplysia* sensory neuron was developed that reflects the subcellular processes underlying activity-dependent neuromodulation. This single-

cell model simulated many features of nonassociative learning, such habituation, dishabituation and sensitization, and of a simple of associative learning, classical conditioning. Moreover, when incorporated into a small neural network, the activity-dependent neuromodulation learning rule could simulate some higher-order features of classical conditioning, such second-order conditioning and blocking. During the reporting period, simulations were used to test the hypothesis that activity-dependent neuromodulation could also support operant conditioning. A network of six neurons, two of which were adaptive elements with an associative learning rule based on activity-dependent neuromodulation, was constructed. A two-neuron central pattern generator (CPG) drove the network between two output states. Operant conditioning was simulated by delivering reinforcement when one selected output occurred. The network exhibited several features of operant conditioning, including extinction and sensitivity to reversed contingencies, the magnitude of reinforcement, the delay of reinforcement, and contingency. These simulations indicated that there need not be fundamentally different cellular mechanisms for the two forms of associative learning. Rather, any differences in the neural mechanisms for the two forms of learning may reside in some characteristic features of the network in which the cellular plasticity is embedded.

E. Synaptic Interactions Among Pattern Generating Neurons in Buccal Ganglia of *Aplysia*

Feeding is one of three behaviors in *Aplysia* that has been shown to be modified by operant conditioning. As a first step toward investigating the cellular mechanisms of operant conditioning, experiments are beginning to: 1) identify rhythmic patterns of neuronal activity generated in the buccal ganglia (The buccal ganglia of *Aplysia* controls the movements of several components of the forgut, such the buccal mass and the esophagus.), 2) identify and characterize neurons that are elements of the central pattern generator (CPG) producing the rhythmic neuronal activity; 3) characterize the synaptic connectivity among these neurons; and 4) examine the effects of transmitters, which modulate feeding behavior, on the neurons and synaptic connections within the CPG.

Previously, a pattern of electrical activity in neurons of the buccal ganglia, termed Pattern 2, was identified. In addition, several cells on the caudal surface of the buccal ganglia, termed B31/32, B33, B34, B35, B36 and B37, were identified as being part of a CPG for Pattern 2. In cells B4/5, Pattern 2 was characterized by a burst of action potentials superimposed on a sustained depolarization. Perhaps the clearest distinguishing feature of Pattern 2 was the presence of a depolarization in cells B31/32 preceding activation of B4/5. Previous work indicated that B31/32 were crucial to Pattern 2. Hyperpolarization of B31/32 blocked the initiation of Pattern 2 normally produced by stimulation of the radular nerve, whereas direct depolarization of B31/32 elicited Pattern 2 activity. Two additional cells, B51 and B52, on the rostral surface also appeared to be involved in Pattern 2. Both B51 and B52 were active during patterned neuronal activity elicited by radular nerve stimulation, and sustained depolarization of B51 elicited a complex pattern of activity in B4/5 and B31/32.

During the reporting period, experiments began to characterize the synaptic interactions among B4/5, B31/32, B35, B51 and B52 in order to further examine how these neurons might function as a CPG. A preparation was developed in which simultaneous intracellular recordings could be made from cells on caudal surface of the left buccal ganglion and from cells on rostral

surface of the right buccal ganglion. Up to four cells could be recorded from simultaneously and the synaptic connections were examined by intracellularly stimulating one of the neurons while monitoring the membrane potentials in the other three. For example, intracellular stimulation of B35 produced EPSPs in B52 and B4/5 and inhibitory postsynaptic potentials (IPSPs) in B51. Numerous pair-wise intracellular recordings and stimulation experiments defined the complex pattern of the synaptic interactions among these neurons. This pattern of connectivity was only one of the factors determining how this neural circuit may function as a CPG. Additional factors, such as the intrinsic properties of the neurons, also must be considered. The simulation program SNNAP was used to construct a model representing the intrinsic properties and synaptic connections of these identified neurons, and to examine how this neural circuit may function as a CPG (see Section G).

F. Modulation of Neural Circuitry Controlling Aspects of Feeding Behavior in *Aplysia*

Experiments also were began to analyze how transmitters, which affect feeding behavior in *Aplysia,* modulated this CPG. In particular, experiments examined the effects of 5-HT and the peptide SCP_b on the B31/32 induced neuronal activity. Results indicated that 5-HT inhibited the B31/32 induced pattern of neuronal activity, whereas SCP_b excited it. In addition, 5-HT inhibited the initiation of Pattern 2 activity by the direct depolarization of B31/32 . Concentrations of 2.5 to 50 μM 5-HT were examined and all inhibited Pattern 2 activity. SCP_b initiated the B31/32 pattern of neuronal activity from a quiescent state. Concentrations of 0.5 to 8 μM of SCP_b were examined. Lower concentrations did not initiate spontaneously occurring Pattern 2, but they did increase the likelihood that weak nerve stimulation would elicit Pattern 2. Higher concentrations reliably induced sustained Pattern 2 activity in the absence of nerve stimulation. In addition, 5-HT antagonized the actions of SCP_b. When 5-HT was added to the bath, which still contained SCP_b, the level of SCP_b-induced activity was dramatically reduced.

The actions of these two transmitters appeared to be quite complex. For example, the actions of 5-HT included: 1) decreasing the excitability of some elements in the CPG (e.g., B31/32 and B4/5), while increasing the excitability of others (e.g., B35); 2) enhancing the synaptic connections between some elements in the CPG (e.g., B35 to B4/5) while inhibiting others (e.g., B4/5 to B31/32); and 3) inducing subthreshold oscillations in the membrane potentials of B31/32. Thus, 5-HT appeared to modulate both the intrinsic biophysical properties of the neurons and the strength of their synaptic connections. The actions of 5-HT, however, varied dramatically between cells.

G. Network Model of a Central Pattern Generator (CPG) in the Buccal Ganglia of *Aplysia*

To understand the mechanisms that produce and modify rhythmic neuronal activity, SNNAP (see Section VI) was used to simulate a CPG in the buccal ganglia of *Aplysia* (see Section E). Development of this network involved four stages. First, the intrinsic properties of identified cells, which are elements of the CPG, were simulated. Thus, models of B4/5, B31/32, B35, B51, and B52 were developed and theses models of each element reflected the unique features of the individual cells. For example, the model B31/32 cell did not support over-shooting action potentials, was electrically coupled to B35 and brief depolarizations elicited a plateau potential. Second, the known synaptic connections among these cells were simulated. Moreover, the characteristics of each

synapse, such synaptic depression or a combination of fast and slow synaptic potentials, were simulated. Third, simulations of the complete network were used to determine whether the present assemble of identified neurons could function as a CPG. Preliminary simulations, indicated that the neural circuit, as previously understood, could not account for Pattern 2 activity. Fourth, additional neuronal elements were incorporated into the neural network and simulations were used to predict what cellular and network features would be necessary to produce Pattern 2 activity. An additional element was included that had regenerative properties, received excitatory input from B35 and inhibited B31/32, B35, and B52 and excited B4 and B51. The modified neural network more accurately simulated Pattern 2. Thus, the model predicated that at least one critical element of the CPG was missing from the current assemble of identified cells. This unidentified cell is responsible for the large IPSP that repolarizes B31/32 and B52 and it drives the activity in B4/5 and B51. (Subsequent experimental work identified the missing CPG element and this newly identified cell was termed B64.)

H. Simulation of the Bursting Activity of Neuron R15 in *Aplysia*: Role of Ionic Currents, Calcium Balance, and Modulatory Transmitter

Endogenously bursting neurons are often critical components within neural circuits underlying rhythmic behaviors. In isolated preparations of the *Aplysia* abdominal ganglion, R15 is the prototypical endogenous burster, and has been used extensively to study the mechanisms underlying bursting and its modulation. During the reporting period, the development of a Hodgkin-Huxley type model of R15 was completed. This model more accurately reflected the known properties of R15 by incorporating two significant improvements over previous models of R15. First, the model incorporated quantitative and realistic descriptions of most of the membrane currents that are known to exist in the soma of R15. Second, the model incorporated a fluid compartment that provided for a Ca^{2+} balance within the cell. The intracellular levels of Ca^{2+} play critical roles in a number of processes in R15, such as modulating membrane currents and modulating the activity of second-messenger and enzymatic systems. The model simulated the actual magnitudes and time courses of fluctuations in intracellular Ca^{2+} that have been observed experimentally; and predicted many features of the activity of bursting neurons, including transitions between an endogenous bursting mode, a silent mode, and a beating mode as a function of applied current. The model provided insights into the ability of bursting neurons to exhibit different modes of activity and which parameters were critical for determining the characteristics of bursting activity. Thus, the model can be used to simulate and to examine a wide range of electrochemical activities in R15 and provides general insights into the generation of rhythmic neuronal activity.

III. Publications

During the reporting period, 9 abstracts, 5 articles in refereed journals, 2 invited articles in journals, 5 chapters, and 1 manuscript in preparation were sponsored by AFOSR-91-0027. These publications are listed below.

A. Abstracts

1. Baxter, D.A. and Byrne, J.H. Synaptic interactions among pattern generating neurons in buccal ganglia of *Aplysia*. *Society for Neuroscience Abstracts*, **17**: 124, 1991.

2. Canavier, C.C., Baxter, D.A., Clark, J.W. and Byrne, J.H. Simulations of action potentials, transmitter release, and plasticity of sensorimotor synapses in *Aplysia*. *Society for Neuroscience Abstracts*, **17**: 1590, 1991.

3. White, J.A., Cleary, L.J., Ziv, I. and Byrne, J.H. A network model of the tail-withdrawal circuit in *Aplysia*. *Society for Neuroscience Abstracts*, **17**: 1590, 1991.

4. Ziv, I., Baxter, D.A. and Byrne, J.H. Simulator for neural networks and action potentials (SNNAP): application to a central pattern generator. *Society for Neuroscience Abstracts*, **17**: 125, 1991.

5. White, J.A., Baxter, D.A. and Byrne, J.H. Quantitative analysis of the modulation by serotonin of the voltage-dependent potassium current in pleural sensory neurons of *Aplysia*. *Society for Neuroscience Abstracts*, **18**: 714, 1992.

6. Ziv, I., Baxter, D.A. and Byrne J.H. Network model of a central pattern generator in the buccal ganglia of *Aplysia*. *Society for Neuroscience Abstracts*, **18**: 1279, 1992.

7. Kabotyanski, I. Ziv, D.A. Baxter and J.H. Byrne. Metabolic precursors of dopamine and serotonin modulate rhythmic neural activity in the buccal ganglia of *Aplysia*. *Society for Neuroscience Abstracts*, 19: 350, 1993.

8. Baxter, D.A., I. Ziv and J.H. Byrne. Simulator for neural networks and action potentials (SNNAP): use of computer simulations as a supplement for undergraduate and graduate courses in neurobiology. *Society for Neuroscience Abstracts*, 19: 208, 1993.

9. Baxter, D.A. and J.H. Byrne. Serotonin inhibits rhythmic neural activity mediated via neurons B31/32 in the buccal ganglia of *Aplysia*. *Society for Neuroscience Abstracts*, 19: 349, 1993.

B. Refereed Articles in Journals

1. Canavier, C.C., Clark, J.W. and Byrne, J.H. Simulation of the bursting activity of neuron R15 in *Aplysia*: role of ionic currents, calcium balance, and modulatory transmitters. *Journal of Neurophysiology*, **66**: 2107-2124, 1991.

2. Raymond, J.L., Baxter, D.A., Buonomano, D.V. and Byrne, J.H. A learning rule based on empirically-derived activity-dependent neuromodulation supports operant conditioning in a small network. *Neural Networks*, **5**: 789-803, 1992.

3. White, J.A., Ziv, I., Cleary, L.J., Baxter, D.A. and Byrne, J.H. The role of interneurons in controlling the tail-withdrawal reflex in *Aplysia*: a network model. *Journal of Neurophysiology*, **70**: 1777-1786, 1993.

4. Ziv, I., Baxter, D.A. and Byrne, J.H. Simulator for neural networks and action potentials: description and application. *Journal of Neurophysiology*, **70(6)**: in press, 1993.

5. White, J.A., Baxter, D.A. and Byrne, J.H. Analysis of the modulation by serotonin of a voltage-dependent potassium current in sensory neurons of *Aplysia*. *Biophysical Journal*, **66(3)**: in press, 1994.

C. Invited Articles in Journals

1. Baxter, D.A. and Byrne, J.H. Ionic conductance mechanisms contributing to the intrinsic electrophysiological properties of neurons. *Current Opinion in Neurobiology*, **1**: 105-112, 1991.
2. Byrne, J.H., Baxter, D.A., Buonomano, D.V., Cleary, L.J., Eskin, A., Goldsmith, J.R., McClendon, E., Nazif, F.A., Noel, F. and Scholz, K.P. Neural and molecular bases of nonassociative and associative learning in *Aplysia*. *Annals of the New York Academy of Sciences*, **627**: 124-149, 1991.

D. Chapters

1. Byrne, J.H. and Crow, T. Examples of mechanistic analyses of learning and memory in invertebrates. In: J.L. Martinez, Jr. and R.P. Kesner (eds.), *Learning and Memory: A Biological View* (pp. 329-358). New York: Academic Press, Inc., 1991.
2. Byrne, J.H. Classical conditioning and operant conditioning. In: L.R. Squire (ed.) *Encyclopedia of Learning and Memory* (pp 44-47). New York: MacMillan Publishing Company, 1992.
3. Raymond, J.L and Byrne, J.H. Cellular and network schemes for higher order features of classical conditioning. In: L.R. Squire (ed.) *Encyclopedia of Learning and Memory* (pp 119-123). New York: MacMillan Publishing Company, 1992.
4. Byrne, J.H., Zwartjes, R., Homayouni, R., Critz, S., and Eskin, A. Roles of second messenger pathways in neuronal plasticity and in learning and memory: insights gained from *Aplysia*. In: S. Shenolikara and A. Nairn (eds.) *Advances in Second Messenger and Phosphoprotein Research Volume 27* (pp. 47-108). New York: Raven Press Ltd., 1993.
5. Baxter, D.A. and Byrne, J.H. Learning rules in neurobiology. In: D. Gardner (ed.), *The Neurobiology of Neural Networks* (pp. 71-106). Cambridge: MIT Press/Bradford Books, 1993.

E. Manuscripts in Preparation or Under Review

1. Canavier, C.C., Baxter, D.A., Clark, J.W. and Byrne, J.H. Simulation of action potentials, excitability, and the effects of serotonin on sensory neurons in *Aplysia*. In preparation, 1993.

IV. Professional Personnel

Baxter, Douglas A., Ph.D.
Byrne, John H., Ph.D.
Canavier, Carmen C., Ph.D.
White, John A., Ph.D.
Ziv, I., Ph.D.

V. Interactions

A. Presentations to Professional Organizations, Special Meetings, and Invited Lectures

1. Dr. Baxter presented an abstract entitled "Mathematical modeling of the serotonergic modulation of electrophysiological properties of sensory neurons in *Aplysia*" at the Meeting on Cellular and Molecular Neurobiology of *Aplysia* on October 7, 1990.
2. Miss Raymond presented an abstract entitled "Activity-dependent neuromodulation can support operant conditioning in a small oscillatory network" at the Meeting on Cellular and Molecular Neurobiology of *Aplysia* on October 7, 1990.
3. Dr. Byrne presented the lecture entitled "Neural and Molecular Basis of Long-Term Sensitization in *Aplysia*" at the Meeting on Cellular and Molecular Neurobiology of *Aplysia* on October 6, 1990.
4. Dr. Baxter presented the abstract entitled "Mathematical modeling of the serotonergic modulation of electrophysiological properties of sensory neurons in *Aplysia*" at the 20th Annual Meeting of the Society for Neuroscience on November 2, 1990.
5. Dr. Canavier presented AFOSR-sponsored research at the Biophysical Society Workshop on Chaotic Dynamics in Biophysics on February 27, 1991.
6. Dr. Byrne presented the lecture entitled "Aspects of the Neural and Molecular Mechanisms of Short-Term Sensitization in *Aplysia*" to the Department of Zoology at The University of Texas at Austin on March 7, 1991.
7. Dr. Byrne presented two lectures entitled "Experimental and Modeling Approaches to Neural and Network Determinants of Learning" and "Neural and Molecular Mechanisms Underlying Short-Term and Long-Term Sensitization" to the Computational Neuroscience Program at Case Western on April 9-10, 1991.
8. Dr. Byrne presented a lecture entitled "Recent Advances in the Analysis of Learning" at the Annual Meeting of the American Association of Anatomists on April 22, 1991.
9. Dr. Baxter presented a lectured entitled "Serotonergic Modulation of Potassium Currents in Tail Sensory Neurons of *Aplysia*" to the Department of Zoology at The University of Texas at Austin on April 24, 1991.
10. Dr. Byrne presented AFOSR-sponsored research at the Mid-Year Short Course on "Neural Computations" in Mexico City on May 2-3, 1991.
11. Dr. Byrne presented AFOSR-sponsored research at the Gordon Conference on "Regulation of Synaptic Activity" on June 17-21, 1991.
12. Dr. Byrne presented AFOSR-sponsored research at the Cold Spring Harbor Laboratory Course entitled "Cellular and Molecular Biology of Learning and Memory" on July 14-28, 1991.
13. Dr. Byrne presented AFOSR-sponsored research at the Dahlem Workshop in Berlin on "Exploring Brain Function: Models in Neuroscience" on September 29 to October 5, 1991.

14. Dr. Ziv presented the abstract entitled "Simulator for neural networks and action potentials (SNNAP): application to a central pattern generator" at the 21st Annual Meeting of the Society for Neuroscience on November 11, 199 .

15. Dr. Baxter presented the abstract entitled "Synaptic interaction among pattern generating neurons in buccal ganglia of *Aplysia*" at the 21st Annual Meeting of the Society for Neuroscience on November 11, 1991.

16. Dr. Canavier presented the abstract entitled "Simulations of action potentials, transmitter release, and plasticity of sensorimotor synapses in *Aplysia*" at the 21st Annual Meeting of the Society for Neuroscience on November 15, 1991.

17. Dr. White presented the abstract entitled "A network model of the tail-withdrawal circuit in *Aplysia*" at the 21st Annual Meeting of the Society for Neuroscience on November 15, 1991.

18. Dr. Byrne presented AFOSR-sponsored research at the Bat-Sheva Seminar in Jerusalem entitled "From Neuron to Network" on November 22-30, 1991.

19. Dr. Byrne presented a lecture entitled "Neural and Molecular Bases of Simple Forms of Learning" to the Department of Biology at the Texas A & M University on 3 March, 1992.

20. Dr. Byrne presented a lecture entitled "Neural and Molecular Bases of Simple Forms of Learning" at the University of Pennsylvania on March 17-19, 1992.

21. Dr. Canavier presented the abstract entitled "Simulation of serotonin (5-HT)- induced modulation of the sensorimotor coupling in *Aplysia*" at the Tenth Annual Houston Conference on Biomedical Engineering Research on March 20, 1992.

22. Dr. White presented the abstract entitled "Analysis and simulation of amplitude-to-duration conversion in a simple reflex response in *Aplysia*" at the Tenth Annual Houston Conference on Biomedical Engineering Research on March 20, 1992.

23. Dr. Ziv presented the abstract entitled "SNNAP: Simulator for neural networks and action potentials" at the Tenth Annual Houston Conference on Biomedical Engineering Research on March 20, 1992.

24. Dr. Byrne presented AFOSR-sponsored research during a series of lectures at the Cold Spring Harbor Laboratory Course on Molecular Neurobiology on August 7-9, 1992.

25. Dr. Byrne presented a lecture entitled "Neural and Molecular Bases of Simple Forms of Learning" at the Third International Congress of Neuroethology on August 10-14, 1992.

26. Dr. Byrne presented a series of invited lectures and demonstrations entitled "Mathematical Models of Nervous Systems and Neural Networks" at the Frie University of Berlin on September 4-13, 1992.

27. Dr. Ziv presented an abstracted entitled "A simulation of a central pattern generator in the buccal ganglia of *Aplysia*" at the 11th Annual Conference on Biomedical Engineering Research in Houston on February 11-12, 1993.

28. Dr. Cleary presented an abstracted entitled "The role of interneurons in control of the tail-withdrawal reflex in *Aplysia*: characterization of LPl17 and its contribution to response duration at the Meeting on Neurobiology of *Aplysia* on April 21-25, 1993.

B. Consultative and Advisory Functions to other Laboratories and Agencies

1. Dr. Byrne was a member of Board of Visitors for Review of Division of Cognitive and Neural Sciences for the Office of Naval Research in 1991.
2. Dr. Byrne served as an *ad hoc* member of the Neurology B Study Section for the National Institute of Health during 1992.
3. Dr. Byrne served (1991-1993) as a member of the Evaluation Panel in Biomedical Sciences for the National Science Foundation Minority Graduate Fellowship Program.
4. Dr. Baxter serves (1991-present) as an outsider reviewer for the National Science Foundation.
5. Dr. Baxter serves (1987-present) as an outside review for the Medical Research Council of Canada.

VI. New Discoveries, Inventions, or Patent Disclosures and Specific Applications

Simulator for Neural Networks and Action Potentials (SNNAP)

As part of the modeling efforts during the reporting period, a computer program that is a general-purpose Simulator for Neural Networks and Action Potentials (SNNAP) was developed. SNNAP is easy to use and versatile, yet it is realistic and quantitative. The intrinsic voltage-dependent membrane currents of individual neurons are described as an equivalent electrical circuit with Hodgkin-Huxley type descriptions of voltage- and time-dependent ionic currents. The user can develop a library of input files that designate individual neurons, each with a unique combination of ionic currents and intrinsic biophysical properties. SNNAP is capable of simulating small networks of fully interconnected neurons. [Alternatively, SNNAP can be used to model a single neuron with multiple compartments, each with unique properties and synaptic inputs. The number of neurons in a network or compartments is limited by the amount of memory available in the computer.] The connections among neurons can be made by either electrical or chemical synapses. The chemical synaptic connections are capable of expressing several simple forms of plasticity, such as depression with repeated stimulation or increased release in response to presynaptic spike broadening. In addition, any given presynaptic neuron can make up to four synaptic connections with any given postsynaptic neurons. Thus SNNAP can simulate multicomponent synaptic connections. The user can develop a library of input files that designate individual networks, each with unique combinations of neurons and patterns of connectivity.

SNNAP also includes mathematical descriptions of intracellular second messenger systems. The synthesis and decay of second messengers are modeled as simple first-order processes in which the user can individually specify the rates of synthesis and decay for one or more second messenger systems in each neuron. The synthesis of second messengers is driven by the externally controlled application of a transmitter or by synaptic inputs. Thus SNNAP can simulate modulatory synapses as well as simulating experimental procedures such as a brief puff of transmitter to a single neuron at a specific time and/or the bath application of a transmitter to an entire neural circuit. The intracellular concentrations of second messengers, in turn, can be linked to one or more ionic conductances. Thus, SNNAP can simulate membrane currents that are modulated, either enhanced or inhibited, by one or more transmitter driven second messenger systems.

In addition to transmitter controlled synthesis of second messengers, SNNAP also includes mathematical descriptions of the intracellular levels of ions, such as Ca^{2+}. The accumulation of an ion is driven by the voltage- and time-dependent ionic current(s) for the particular species of ion. The user can specify the rate of removal (i.e., decreased concentration due to internal buffering) for individual intracellular ionic pools. The concentrations in each ionic pool, in turn, can be linked to one or more ionic conductances. Thus, SNNAP can simulate membrane currents that are either enhanced (e.g., Ca^{2+}-activated K^+ currents) or inhibited (e.g., Ca^{2+}-dependent inactivation of Ca^{2+} currents) by the of one or more ions.

Originally, a less comprehensive version of SNNAP was developed on Intel x86 based microcomputers. Recently a more comprehensive version of SNNAP was developed and was ported to the Sun SPARCstation minicomputer platform. This port allowed for faster operation, which is critical as the program becomes more sophisticated and the neural networks become more complicated. In addition, SNNAP was made easier to use by incorporating a Graphical User's Interface (GUI). In the Intel x86 version, the GUI is compatible with the Microsoft Windows environment, and in the SPARCstation version, the GUI is compatible with the MIT X11 environment.

At the 23rd Annual Meeting of the Society for Neuroscience, both versions of SNNAP were demonstrated. These two programs are available to scientists who wish to integrate computational methods into their research. To date, 21 copies of SNNAP have either been requested or distributed to individuals in this country as well as in Canada, France, Germany, and The Netherlands. The development of biologically realistic simulations is an increasingly important aspect of neuroscience, and it is likely that SNNAP can make an important contribution to this emerging field of computational neuroscience.

VII. Other Statements

None