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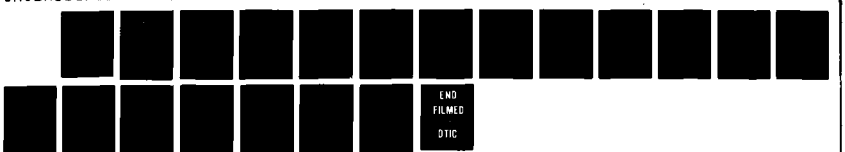

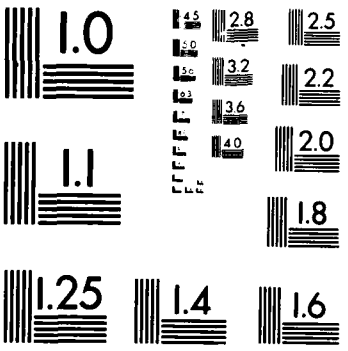

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. ABSTRACT (Continue on reverse if necessary and identify by block number)

The overall objectives of this research were to analyze the properties of identified neurons and neural circuits in Aplysia at exhibit nonassociative and associative plasticity and to examine the role of neuronal plasticity in learning. Two interrelated)proaches were used, one empirical and the other modeling. Between August 1, 1987 and September 30, 1990, progress was ade in six areas. First, experiments examined the modulation of membrane currents and critical second messengers that)ntribute to neuronal plasticity in the sensory neurons that mediate nonassociative learning and classical conditioning of the il withdrawal reflex. Second, mathematical formalisms of the cellular processes that underlie plasticity in sensory neurons were veloped and incorporated into a real-time model of a neuron-like adaptive element. This single-cell model demonstrated the)ility to simulate features of nonassociative learning and classical conditioning. Third, this single cell model was incorporated :o small neural networks that simulated some higher-order features of classical conditioning. Fourth, a form of the single cell odel was incorporated into a small pattern generating neural network that simulated features of operant conditioning. Fifth, Hodgkin-Huxley type of model of biophysical and cellular processes underlying rhythmic bursting patterns of activity in the :uron R15 was developed. Sixth, experiments have identified neurons that are elements of the central pattern generator that)ntrols feeding behavior and that may mediate operant conditioning behavior.

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I. Summary

The overall objectives of this research were to analyze the properties of identified neurons and neural circuits in *Aplysia* that exhibit nonassociative and associative plasticity and to examine the role of neuronal plasticity in learning. Two interrelated approaches were used, one empirical and the other modeling. Between August 1, 1987 and September 30, 1990, progress was made in six areas. First, experiments examined the modulation of membrane currents and critical second messengers that contribute to neuronal plasticity in the sensory neurons that mediate nonassociative learning and classical conditioning of the tail withdrawal reflex. Second, mathematical formalisms of the cellular processes that underlie plasticity in sensory neurons were developed and incorporated into a real-time model of a neuron-like adaptive element. This single cell model demonstrated the ability to simulate features of nonassociative learning and classical conditioning. Third, this single cell model was incorporated into small neural networks that simulated some higher-order features of classical conditioning. Fourth, a form of the single cell model was incorporated into a small pattern generating neural network that simulated features of operant conditioning. Fifth, a Hodgkin-Huxley type of model of biophysical and cellular processes underlying rhythmic bursting patterns of activity in the neuron R15 was developed. Sixth, experiments have identified neurons that are elements of the central pattern generator that controls feeding behavior and that may mediate operant conditioning of feeding behavior.

II. Research Objectives

The research that was proposed in AFOSR Grant 87-0274 had four specific aims: **1)** to analyze the membrane properties of sensory neurons and to incorporate this information into our neuron-like model of learning, **2)** to examine the ability of our neuron-like model of learning to simulate higher-order features of classical conditioning,. **3)** to analyze the properties of facilitatory and inhibitory interneurons that might contribute to associative learning, and **4)** to develop a cellular preparation that is amenable to the cellular analysis of operant conditioning, and to simulate features of operant conditioning in small neural networks. Two interrelated approaches were used, one empirical and the other modeling. The empirical approach utilized cellular neurophysiological techniques in order to analyze the particular ionic conductances and cellular processes that underlie forms of neuronal plasticity. The modeling approach involved formulating mathematical descriptions of the neuronal mechanisms and neural circuits, and examining whether simulation of the resultant model simulated the empirical data and features of learning. The two approaches were interrelated in that empirical data were used to constantly test and improve the quality of

the models, and predictions of the models were used to guide the design of new experiments.

III. Status of Research (Progress Report)

Progress during the past 38 months has been in six areas. First, the experimental analysis of the cellular mechanisms contributing to neuronal plasticity. Second, the development of quantitative, real-time models of neuron-like adaptive elements that simulate simple features of nonassociative and associative learning. Third, the implementation of our neuron-like model for learning into small networks and simulation of higher-order features of classical conditioning. Fourth, the simulation of features of operant conditioning with a neuron-like model of learning that was originally derived in order to simulate classical conditioning. Fifth, the development of a quantitative, real-time model of the bursting neuron R15. Sixth, identification of neuronal elements of the central pattern generator that controls feeding behavior and that may contribute to operant conditioning of feeding behavior.

A. Experimental Analysis of the Modulation of Membrane Currents and Critical Second Messengers that Contribute to Neuronal Plasticity in Tail Sensory Neurons

1. Serotonergic Modulation of Two Potassium Currents in Pleural Sensory Neurons 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 simple forms of learning. Previous analyses of the biophysical mechanisms of plasticity in the sensory neurons of *Aplysia* have focused on a serotonin (5-HT)-sensitive K^+ current, which is termed the S current ($I_{K,S}$). Application of 5-HT reduces the magnitude of $I_{K,S}$ via cAMP-dependent protein phosphorylation that closes the channel.

We demonstrated a novel action of 5-HT on membrane currents in somata of sensory neurons. The modulatory effects of 5-HT on the membrane currents were revealed by computer subtraction of current responses elicited in the presence of 5-HT from current responses elicited prior to the application of 5-HT. The complexities of the resulting 5-HT difference currents ($I_{5\text{-HT}}$) suggested that 5-HT modulated at least two components of membrane current. At membrane potentials more negative than 0 mV, application of 5-HT suppressed a component of membrane current that had properties identical to those previously found for $I_{K,S}$. This relatively voltage-independent component of $I_{5\text{-HT}}$ was active at or near the resting potential, did not inactivate, increased in a time-dependent manner during depolarization, was

relatively insensitive to the K^+ channel blockers 4-aminopyridine (4-AP) and tetraethylammonium (TEA), and was suppressed by bath application of cAMP. At membrane potentials more positive than 0 mV, 5-HT modulated an additional component of membrane current that had properties characteristic of the delayed or voltage-dependent K^+ current ($I_{K,V}$). This component had complex kinetics, was highly voltage-dependent, and was blocked by moderate concentrations of either 4-AP or TEA. We concluded that 5-HT modulated $I_{K,V}$, possibly by slowing its kinetics of activation and inactivation. These results indicate that the modulation of membrane currents by 5-HT is more complex than was originally thought. Given that more than one membrane current is modulated, a key issue becomes the quantitative extent to which modulation of specific currents contributes to modulation of spike parameters and plasticity of the sensory neurons (see Sections III.A.2. and III.B.3).

2. Differential Effects of cAMP and Serotonin on Membrane Currents, Action Potential Duration, and Excitability in Pleural Sensory Neurons of *Aplysia*. Since 5-HT modulates more than one component of membrane current, an additional question is whether modulation of the second component ($I_{K,V}$) is mediated via cAMP as is the first ($I_{K,S}$). In order to determine whether the modulation of $I_{K,V}$ by 5-HT is also mediated via cAMP, we compared the effects of a membrane-permeable and phosphodiesterase-resistant analogue of cAMP on membrane currents with those of 5-HT. At all voltage-clamp potentials examined (-40 to +30 mV), the addition of cAMP to the bath reduced the amplitude of the membrane current at the end of the voltage-clamp pulse. The cAMP-sensitive component of membrane current was relatively voltage-independent, increased slowly during the voltage-clamp pulse, did not inactivate, and was active at or near the resting potential. These properties are consistent with those of $I_{K,S}$, but are not indicative of a modulation of $I_{K,V}$ by cAMP. Indeed, the presence of cAMP did not occlude modulation by 5-HT of $I_{K,V}$. These results indicated that $I_{K,S}$ is modulated by cAMP, whereas $I_{K,V}$ is not.

In order to gain insight into the relative contributions of cAMP-dependent and cAMP-independent components to the serotonergic modulation of the electrophysiological properties of sensory neurons, we first examined the effects of cAMP on the duration of action potentials and neuronal excitability and then examined the effects of the subsequent addition of 5-HT to the bath, which still contained cAMP. The application of cAMP increased the duration of the action potential by an average of 24%. The subsequent addition of 5-HT to the bath, which still contained cAMP, dramatically increased the duration of the action potential to an average of 234% of the control duration. Thus, a cAMP-independent modulation of membrane current by 5-HT appeared to be critical for regulating the duration of the action potential. In contrast to a modest enhancement of the duration of the action

potential produced by cAMP, application of cAMP doubled the number action potentials elicited during a 1 s, 2 nA current pulse. The subsequent addition of 5-HT to the bath, which still contained cAMP, failed to produce any further increase in excitability. Thus, the presence of cAMP appeared to occlude any further modulation of neuronal excitability by the subsequent addition of 5-HT.

B. Mathematical Models and Simulations of Cellular Processes Underlying Neuronal Plasticity in Sensory Neurons

1. Single Cell Model of Associative Learning. One of the useful aspects of the *Aplysia* system has been the ability to combine modeling approaches with empirical ones. Indeed, predictions from the models have led to the discovery of additional processes contributing to presynaptic facilitation. Our approach has been to transform the various biochemical and biophysical mechanisms that contribute to nonassociative and associative plasticity within the sensory neurons into mathematical formalisms, assign values to the parameters that agree with published data, and fit the components together to create a model of transmitter release at the sensory to motor synapse.

Briefly, the model includes differential equations describing two pools of transmitter, a releasable pool (P_R) and a storage pool (P_S). Vesicles of transmitter are mobilized from the storage pool to the releasable pool via three fluxes, one driven by diffusion (F_D), one driven by Ca^{2+} (F_C), and one driven by cAMP (F_{cAMP}). The storage pool is replenished by the synthesis of new vesicles (F_N). Differential equations also describe the regulation of intracellular levels of both Ca^{2+} and cAMP. Simulated action potentials (all-or-nothing 3 ms depolarizing pulses) lead to the influx of Ca^{2+} (I_{Ca}) into an intracellular pool (Ca^{2+} Pool), the Ca^{2+}-mediated release of transmitter (T_R), and Ca^{2+}-mediated mobilization of transmitter. Sensitizing or reinforcing stimuli (US) lead to the release of facilitatory transmitters, which in turn lead to the synthesis of cAMP, the mobilization of transmitter, and to an increase in the duration of the action potential; thus allowing greater Ca^{2+} influx and enhanced release of transmitter. The effect of the conditioned stimulus (CS) (Ca^{2+} entry during spikes in the sensory neuron) on levels of cAMP is simulated by making the concentration of cAMP dependent on the intracellular concentration of Ca^{2+}. This dual regulation of the cyclase by the modulatory transmitter and the CS (Ca^{2+} entry) permits the formation of an association between the 'neuronal trace' of the CS and the unconditioned stimulus (US).

Our simulations have illustrated that this neuron-like element accurately simulates many aspects of the nonassociative plastic properties of the sensory neurons. For example, repetitive action potentials in the model result in the cumulative inactivation

of I_{Ca}, depletion of transmitter in P_R, and thus, depression of synaptic transmission. This synaptic depression is the neuronal analogue of habituation. In addition, the single-cell model accurately simulates presynaptic facilitation, which is the neuronal analogue of dishabituation and sensitization.

This neuron-like element also simulates many aspects of associative plastic properties of sensory neurons, which are believed to be cellular mechanisms contributing to classical conditioning. Moreover, it predicted an interstimulus interval (ISI) function very similar to that observed behaviorally in *Aplysia* and other animals. The simulated ISI function in the neuron-like element is a direct consequence of the kinetics of the buffering of intracellular Ca^{2+}. When the ISI is short, high levels of Ca^{2+} are present at the time of the US and therefore the CS-mediated amplification of the effects of the US are greatest. As the interval between the CS and US increases, Ca^{2+} levels are buffered; consequently with longer ISIs, there is less amplification of the effects of the US. Thus, the elevation of intracellular Ca^{2+} levels produced by the CS serves as a "trace" that becomes associated with a closely paired US. The higher levels of cAMP result in greater presynaptic facilitation.

2. Mathematical Model of Cellular Mechanisms Contributing to Presynaptic Facilitation. Presynaptic facilitation of transmitter release from sensory neurons is an important mechanism contributing to nonassociative and associative learning in *Aplysia*. As described above (Section III.B.1.) we concluded that enhancement of the postsynaptic potential (PSP) during presynaptic facilitation is mediated by at least two processes; spike broadening, which has been observed experimentally, and a process that we modeled as mobilization of transmitter. In an effort to gain insight into the relative contribution of these two mechanisms of presynaptic facilitation, we have extended our earlier model to include more detailed descriptions of: a) the kinetics of the Ca^{2+} channel, b) the diffusion of Ca^{2+} through the cytoplasm, c) the process of transmitter release, and d) the PSP. This extended model provides an accurate description of the input-output relationship for synapses of sensory neurons, and predicts changes in the shape of postsynaptic potentials as a function of mobilization and spike broadening. The results confirm and extend previous experimental studies and indicated that cellular analogs of sensitization (facilitation of nondecremented responses) is mediated primarily by spike broadening; whereas, analogs of dishabituation (facilitation of depressed of responses) require mobilization.

3. Mathematical Model of Serotonergic Modulation of Electrophysiological Properties of Sensory Neurons. The voltage- and current-clamp experiments described above, Section III.A., indicate that the effects of 5-HT on the duration of the action potential and on the excitability in sensory neurons is due to the modulation of at least two

membrane currents, $I_{K,S}$ and $I_{K,V}$. In order to assess the quantitative contribution that each current makes to the overall modulatory effects of 5-HT, we constructed a Hodgkin-Huxley type membrane model of the somata of the sensory neuron. The model consists of a membrane capacitance, a leakage conductance with its associated equilibrium potential, and differential equations that describe eight ionic currents with their associated conductances and equilibrium potentials: the Na^+ current (I_{Na}), a Ca^{2+} current with a high threshold component ($I_{Ca,N}$) and low threshold component ($I_{Ca,L}$), $I_{K,S}$, $I_{K,V}$, the fast K^+ current (I_A), and a Ca^{2+}-activated K^+ current with a slow component ($sI_{K,Ca}$) and a fast component ($fI_{K,Ca}$). In addition, the model includes a description of intracellular Ca^{2+} concentrations. Parameter values for many of the current were estimated from voltage-clamp data from sensory neurons, while values for the remaining parameter were adjusted to qualitatively simulate features of excitability and spikes in sensory neurons.

One action of cAMP is to initiate the closure of S-channels, which results in a reduction in the amplitude $I_{K,S}$. Thus we simulated the cAMP-dependent actions of 5-HT on membrane current by reducing the maximum conductance of $I_{K,S}$ in the model. Although the mechanism underlying the cAMP-independent modulation of $I_{K,V}$ by 5-HT is not yet known, we have speculated that 5-HT may lead to a slowing in the rates of activation and inactivation of $I_{K,V}$. Thus we simulate the cAMP-independent actions of 5-HT on membrane current by altering the voltage-dependent time constants for activation and inactivation of $I_{K,V}$ in the model. The simulated membrane currents and their modulation by cAMP and 5-HT were similar to those observed experimentally.

Given a reasonable fit of the normal electrophysiological properties of sensory neurons, we then adjusted the parameters of those membrane currents that are modulated by 5-HT separately to try to gain insights into the specific role they play in regulating spike broadening and excitability. Reducing only $I_{K,S}$ in the model produced a modest (10%) broadening of the simulated spike. In contrast, modifying $I_{K,V}$ produced a dramatic increase in spike duration (200%). While reducing $I_{K,S}$ did not significantly increase spike duration, it did produce a significant increase in excitability. In contrast, simulations in which $I_{K,V}$ was also altered did not show any further increase in excitability.

These initial simulations must be repeated after more detailed information on the properties of the sensory neuron membrane currents is available. Nevertheless, the results of these simulation are remarkably similar to the physiological actions of cAMP and 5-HT. These simulations support the hypothesis that the cAMP-dependent modulation $I_{K,S}$ by 5-HT plays a key role in regulating excitability of sensory neurons,

while the cAMP-independent modulation of $I_{K,V}$ by 5-HT appears to be critical for regulating the duration of the action potential.

C. Empirically Derived Neuron-Like Elements and Neural Networks Simulate Higher-Order Features of Classical Conditioning

As described above (Section III.B.1.) we developed a model of a neuron-like element that incorporates descriptions of cellular processes that contribute to plasticity of the sensory neurons. Our simulations have illustrated that this neuron-like element is capable of predicting features of nonassociative learning and simple features of classical conditioning. We extended these observations by examining the ability of small neural networks that include this neuron-like element to predict more complex features of associative learning, such as higher-order features of classical conditioning.

We implemented two small neural networks that are derived from the characteristics of the neural circuit mediating withdrawal reflexes of *Aplysia*. In each network, two sensory neurons (SN1 and SN2) with identical properties make synaptic contact with a motor neuron (MN). Activity in the individual sensory neurons represents separate pathways for conditioned stimuli (CS1 and CS2). The amplitude of the EPSPs at the sensory-to-motor synapses represent the ability of each CS to activate the response system and produce a conditioned response (CR). A key aspect of the architecture of this network is that the sensory neurons also make excitatory synaptic connections with a facilitatory interneuron (FN). This connection has two consequences, one practical and the second theoretical. First, from a practical point of view, the circuit can be simplified by removing the motor neuron and using the EPSP at the sensory-to-facilitatory synapse as measure of changes in the synaptic strength of the CS. Second, from a theoretical point of view, a sensory neuron can 'take control' of the facilitatory interneuron as the strength of its sensory-to-facilitatory synapse increases. This possibility has fundamental implications with respect to neural models of higher-order features of classical conditioning. Because there is little experimental data on the properties of the facilitatory neuron, it is modeled as an element that simply sums its synaptic inputs, and if the inputs are equal to or exceed a threshold, a simulated action potential is initiated. An important assumed property of the facilitatory neuron is that its output diminishes or accommodates rapidly, and that its recovery from accommodation is relatively slow. Normally, the presentation of the unconditioned stimulus (US) always activates the facilitatory interneuron and stimulates the release of the facilitatory transmitter, which in turn activates an adenylate cyclase in the sensory neuron.

In a preliminary attempt to develop a network that incorporates recently described features of inhibition, we implemented a five-cell network that incorporates inhibitory

interneurons. As a first step, we assumed that the inhibitory interneurons only act on cellular processes mediating associative plasticity in the sensory neurons. This form of inhibition is a hypothetical mechanism that could occur at numerous loci, such as blocking the influx of Ca^{2+} or blocking the Ca^{2+} priming component of cAMP synthesis. In this simulation, we assumed that activity of the inhibitory neuron transiently blocks further Ca^{2+} priming of cAMP synthesis in the sensory neuron, but not priming that results from Ca^{2+} present before the onset of activity of the inhibitory neuron. We also assumed that the inhibitory neuron has a burst-like property. The duration of activity in the inhibitory neuron was a function of the amount of time its input remained above threshold. The output of the inhibitory neuron was constant during its activation.

When the single-cell model was incorporated into the three-cell network, we found that the constraints imposed by the empirical data limited the ability of the network to simulate second-order conditioning and blocking. On the other hand, we found that a detailed description of subcellular processes unmasked phenomena that were relevant to the simulation of blocking that were not captured by less detailed models. The five-cell network successfully simulated both second-order conditioning and blocking more readily than the three-cell network. These simulations demonstrated that neuron-like elements and network architectures that reflect the cellular processes contributing to activity-dependent neuromodulation can simulate higher-order features of classical conditioning.

D. A Classical Conditioning Learning Rule Simulations Features of Operant Conditioning in a Pattern Generating Neural Network

Despite operational distinctions, it is not known whether the cellular processes underlying classical conditioning and operant conditioning are fundamentally different or whether they share aspects of a common underlying mechanism. Recent theoretical studies indicate that the same neural networks and learning rules that can simulate features of classical conditioning can also simulate elementary forms of operant conditioning. Therefore, we were interested in determining whether a small network containing elements with the activity-dependent neuromodulation learning rule, which simulates features of classical conditioning, could also simulate features of operant conditioning. In order to test this hypothesis, we took the mathematical model of the sensory neurons in *Aplysia* and incorporated this neuron-like element into a small neural network and examined its ability to simulate features of operant conditioning.

Our simulations of operant conditioning were closely based on operant conditioning of head-waving behavior in *Aplysia*. Head-waving in *Aplysia* is a naturally occurring behavior in which the animals sweep their heads from side to side. *Aplysia* can be operantly conditioned to wave their heads preferentially to one side of their body.

Although the neuronal elements and circuit underlying this behavior are not yet known, we developed an artificial neural network that produced a pattern similar to the side-to-side movement in head-waving. This network contained three classes of elements: pattern generating elements (PGs), associative elements (AEs), and motor neurons (MNs). The pattern generating elements produced the spontaneous behavior that served as the target of operant training. Two spontaneously active and mutually inhibitory neurons (PG_A and PG_B) comprised a central pattern generator that drove the network between two 'behavioral' or output states (Output A or Output B). Each pattern generating neuron made an excitatory connection onto an associative element (AE). The properties of these associative elements were similar to our model of sensory neuron, but they were modified slightly in order to reduce the transmitter depletion that would otherwise occur during the prolonged periods of activity during these simulations. These associative elements were the only elements in the network that are capable of activity-dependent neuromodulation (*i.e.*, associative enhancement of synaptic strength). The motor elements (MN_A and MN_B) were driven by the associative elements. Activity in the motor elements served as the measure of network behavior, and it fed back onto the pattern generating elements. This excitatory feedback from the motor elements contributed to the maintenance of bursts of activity in the pattern generating elements. The neural pathways for reinforcement impinged on both associative elements. Positive reinforcement, like the US in the simulations of classical conditioning, facilitated the connection between the associative and motor elements. This synaptic facilitation was enhanced by prior activity in the associative element via the activity-dependent neuromodulation learning rule.

Our simulations demonstrated that an associative element and a learning rule, which were originally derived in order to simulate features of classical conditioning, could also simulate behavioral data on operant conditioning. Specifically, we were able to demonstrate a change in the time spent performing a reinforced behavior, and this change was dependent upon a contingency between the occurrence of that behavior and the occurrence of reinforcement. Our network also exhibited extinction and reversal learning. Thus, the results of these simulations illustrate that, at least in theory, the same cellular mechanisms that are believed to underlie classical conditioning in *Aplysia* could also underlie operant conditioning.

E. Mathematical Model of a Bursting R15 Neuron

The R15 cell in the abdominal ganglion of *Aplysia* is one of the most widely studied cells in the field of electrophysiology. Many models of this cell exist in the literature. All models attempt to mimic the endogenous bursting behavior of R15, since it is primarily this feature that makes the cell interesting. We extended these earlier efforts, and

developed a model of R15 that: 1) incorporated as much quantitative experimental data as possible into the model in a manner consistent with currently known mechanisms; 2) provided a calcium ion balance within the model; and 3) simulated the electrical behavior of R15 to the fullest extent possible. Our model was a lumped parameter electrical equivalent circuit (*i.e.*, a Hodgkin-Huxley type of model) with twelve state variables, including membrane potential, internal calcium concentration, calcium buffer occupancy and nine membrane gating variables. On the basis of available data, we developed a model that contains the following components: inward currents (fast sodium current, I_{Na}; background sodium current, $I_{Na,B}$; spiking calcium current, I_{Ca}; slow inward current, I_{SI}), outward currents (delay rectifier current, I_K; calcium-activated potassium current, $I_{K,Ca}$; anomalous rectifier, I_R), a non-specific cation current (I_{NS}), and pump and exchanger currents (sodium-calcium exchanger current, I_{NaCa}; calcium pump current, I_{CaP}; sodium-potassium pump current, I_{NaK}). The model proved to be capable of reproducing the bulk of the attributes of the R15 neuron, including endogenous bursting modes, rhythmic beating modes, and alterations in the waveform of the action potential during bursting activity.

We also used a model of R15 to study the emergence and mechanisms of chaos in neural systems. Chaos in neural systems can be defined operationally as activity that appears random but that is generated by a deterministic system rather than by additive noise. It has been suggested that chaotic discharge patterns may be involved in such large scale neuropathological phenomena as seizures, epilepsy, tremor and convulsions. In addition, it has been suggested that chaos in neural systems can have several advantages; for example, biological chaos may help to prevent various functional units in a neural system from becoming entrained, or phase-locked, into period activity. Our simulations of the model of R15 exhibited chaos. Thus, chaotic behavior can be a results of intrinsic properties of individual neurons and need not be an emergent property of neural assemblies. Although the existence of chaotic behavior in R15 has not been examined experimentally, our modeling results predict that the potential for such behavior exists.

F. Identification of Neuronal Elements of the Central Pattern Generator that Controls Feeding Behavior.

As a first step toward investigating the cellular and network properties that contribute to operant conditioning, we have begun to identify elements of the circuit that mediate feeding behavior. Although much is known about sensory neurons, motor neurons and modulatory interneurons in the feeding motor system, up until recently, little was known about the command neurons and pattern generators initiating feeding. Such information is critical for an understanding of the neuronal mechanisms of operant

conditioning, since the command and pattern generating neurons are possible loci for the conditioning.

Our approach was to characterize patterned neural activity in the isolated buccal ganglia and then find cells initiating the patterns. We used identified cell B4 and B5 as monitors of activity. We identified a two neurons, B31/B32, whose activity seemed crucial to initiate rhythmic firing in cells B4 and B5. These newly identified neurons provide a starting point for investigating factors that initiate and control different patterns of neural activity in the buccal ganglia. Since the buccal ganglia are involved in generating feeding behavior, further studies on the newly identified neurons may provide insights into the neural control of feeding behavior, and provide a neural substrate for studying modulation of feeding patterns by associative learning.

IV. Publications

A. Abstracts

1. Baxter, D.A. and J.H. Byrne. Modulation of membrane currents and excitability by serotonin and cAMP in pleural sensory neurons of *Aplysia*. *Soc Neurosci Abstr*, **13**: 1440, 1987.

2. Gingrich, K.J. and J.H. Byrne. Mathematical model of two cellular mechanisms contributing to dishabituation and sensitization in *Aplysia*. *Soc Neurosci Abstr*, **13**: 597, 1987.

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8. Baxter, D.A. and J.H. Byrne. Reduction of voltage-activated K^+ currents by forskolin is not mediated by cAMP in pleural sensory neurons of *Aplysia*. *J Neurophysiol*, **64**: 1474-1483, 1990.

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10. Byrne, J.H., D.A. Baxter, D.V. Buonomano, and J. L. Raymond. Neuronal and network determinants of simple and higher-order features of associative learning: experimental and modeling approaches. *Cold Springs Harbor Symp Quant Biol* **55**: in press.

11. Byrne, J.H., D.A. Baxter, D.V. Buonomano, L.J. Cleary, A. Eskin, J. Goldsmith, E. McClendon, F. Nizaf, F. Noel, and K. Scholz. Aspects of the neural and molecular bases of short- and long-term forms of nonassociative and associative learning in *Aplysia*. *Annals New York Acad Sci*, in press.

C. Manuscripts in Preparation or Under Review:

1. Raymond, J.L., D.V. Buonomano, D.A. Baxter and J.H. Byrne. A classical conditioning learning rule simulations features of operant conditioning in a pattern generating neural network. In preparation.

2. Canavier, C.C., J.W. Clark and J.H. Byrne. A model of a bursting R15 neuron. In preparation.

D. Chapters

1. Baudry, M., D.L. Alkon, P.O. Andersen, T.V.P. Bliss, J.H. Byrne, T.J. Carew, J.-P. Changeux, H.M. Gerschenfeld, M. Ito, M.B. Kennedy, R. Nicoll, C. Mulle, R. Schmidt, R.F. Thompson and R. Willmund. Activity-dependent regulation of synaptic transmission and its relationship to learning. In: *The Neural and Molecular Bases of Learning*, Eds., J.-P. Changeux and M. Konishi, Dahlem Konferenzen. New York, John Wiley and Sons, pp 153-175, 1987.
2. Byrne, J.H., L. Cleary and A. Susswein. Analysis of associative learning in *Aplysia*: behavioral and cellular studies. In: *Growth and Plasticity of Neural Connections*, Eds., W. Winlow and C.R. McCrohan, Manchester University Press, pp 186-205, 1987.
3. Byrne, J.H., K.J. Gingrich and D.A. Baxter. Computational capabilities of single neurons: relationship to simple forms of associative and nonassociative learning in *Aplysia*. In: *Computational Models of Learning in Simple Neural Systems (Vol. 23 The Psychology of Learning and Motivation)*, Eds. R.D. Hawkins and G.H. Bower, New York, Academic Press, 31-63, 1989.
4. Byrne, J.H. and K.J. Gingrich. Mathematical model of cellular and molecular processes contributing to associative and nonassociative learning in *Aplysia*. In: *Neural Models of Plasticity: Experimental and Theoretical Approaches*, Eds. J.H. Byrne and W. Berry, Orlando, Academic Press, 58-72, 1989.
5. Baxter, D.A., D.V. Buonomano, J.L. Raymond, D.G. Cook, F.M Kuenzi, T.J. Carew and J.H. Byrne. Empirically derived adaptive elements and networks simulate associative learning. In: *Harvard Symposium on Quantitative Analyses of Behavior, Vol. 12: Neural Network Models of Conditioning and Action*, Eds., M.L. Commons, S. Grossberg and J.E.R. Staddon, Hillsdale, Lawrence Erlbaum Associates, Inc., in press.
6. Byrne, J.H.. Learning and memory in invertebrates. In: *Neurobiology of Comparative Cognition*, Eds., R.P. Kesner and D.S. Olton, Hillsdale, Lawrence Erlbaum Associates, Inc., in press.
7. Byrne, J.H., L.J. Cleary and D.A. Baxter. Aspects of the neural and molecular mechanisms of short-term sensitization in *Aplysia*: modulatory effects of serotonin and cAMP on duration of action potentials, excitability and membrane currents in tail sensory neurons of *Aplysia*. In: *The Biology of Memory*, Eds., L. Squire and E. Lindenlaub, Stuttgart, F.K. Schattauer Verlag, in press.

E. Books

Byrne, J.H. and W.O. Berry (Eds.). *Neural Models of Plasticity: Experimental and Theoretical Approaches*, Orlando, Academic Press, 1989.

V. Professional Personnel

Baxter, Douglas, Ph.D.

Buonomano, Dean (Graduate Student)

Byrne, John, Ph.D.

Canavier, Carmen (Graduate Student)

Gingrich, Kevin, M.D.

Raymond, Jennifer (Graduate Student)

Susswein, Abraham, Ph.D.

VI. Interactions: Presentations to Professional Organizations, Special Meetings, and Invited Lectures

1. Dr. Byrne presented aspects of this research at the *NATO Advanced Research Workshop on Modulation of Synaptic Transmission and Plasticity in Nervous Systems*, Il Ciocco, Italy, 1987.

2. Dr. Byrne presented aspects of this research at the *Gif Lectures in Neurobiology on the Neuronal Mechanisms of Long-Lasting Changes in the Nervous System: Facts and Perspectives*, Gif-sur-Yvette, France, 1987.

3. Dr. Baxter presented the abstract "Modulation of membrane currents and excitability by serotonin and cAMP in pleural sensory neurons of *Aplysia*" at the *17th Annual Meeting of the Society for Neuroscience*, New Orleans, LA, 1987.

4. Dr. Baxter presented aspects of this research at the *Review Meeting for Air Force Sponsored Basic Research*, San Antonio, TX, 1987.

5. Dr. Gingrich presented the abstract "Mathematical model of two cellular mechanisms contributing to dishabituation and sensitization in *Aplysia*" at the *17th Annual Meeting of the Society for Neuroscience*, New Orleans, LA, 1987.

6. Dr. Byrne presented aspects of this research at the *Bat-Sheva De Rothschild Foundation Seminar on Neural Network Models and Their Relevance to Biology*, Jerusalem, Israel, 1988.

7. Dr. Byrne presented aspects of this research at the *American Association for Artificial Intelligence Symposium on Parallel Models of Intelligence: How Can Slow Components Think so Fast?*, Stanford, CA, 1988.

8. As a speaker and conference co-organizer, Dr. Byrne presented aspects of this research at the conference on *Biotechnology of the Brain: Fundamental Discoveries and Clinical Applications*, Houston, TX, 1988.

9. Dr. Byrne presented aspects of this research at the special interest dinner "Neural Networks: Real Life vs Parallel Computer" at the *18th Annual Meeting of the Society for Neuroscience*, Toronto, Canada, 1988.

10. Dr. Byrne presented the abstract "Small networks of adaptive elements that reflect the properties of neurons in *Aplysia* exhibit higher-order features of classical conditioning" at the *18th Annual Meeting of the Society for Neuroscience*, Toronto, Canada, 1988.

11. Dr. Baxter presented the abstract "Reduction of voltage-activated K^+ currents by forskolin is not mediated by cAMP in pleural sensory neurons of *Aplysia*" at the *18th Annual Meeting of the Society for Neuroscience*, Toronto, Canada, 1988.

12. Dr. Baxter presented the abstract "Analysis and Simulation of Cellular and Network Properties Contributing to Higher-Order Features of Associative Learning" at the Cold Spring Harbor meeting on the *Cell and Molecular Neurobiology of Aplysia*, 1988.

13. Dr. Byrne presented aspects of this research at the *12th Harvard Symposium on Quantitative Analyses of Behavior: Neural Network Models of Conditioning and Action*, Cambridge, MA, 1989.

14. Dr. Byrne presented aspects of this research at the *Symposium Medica Hoechst 23: The Biology of Memory*, Munich, FRG, 1989.

15. Dr. Byrne presented aspects of this research at the *Gordon Conference on Neuronal Plasticity*, Wolfboro, NH, 1989.

16. Dr. Byrne presented aspects of this research at the *Second International Congress of Neuroethology Symposium on Learning and Memory*, Berlin, FRG, 1989.

17. Mr. Buonomano presented the abstract "Simulation of Higher-Order Features of Classical Conditioning" at the *Houston Bioengineering Conference*, 1989.

18. Dr. Baxter presented the abstract "Operant conditioning can be simulated by small networks of neuron-like adaptive elements" at the *19th Annual Meeting of the Society for Neuroscience*, Phoenix, AZ, 1989.

19. Dr. Byrne presented aspects of this research at the *Symposium on Molluscan Neurobiology,* Amsterdam, Netherlands, 1990.

20. Dr. Byrne presented aspects of this research at the *Fifth Annual Spring Neuroscience Symposium on Mechanisms of Learning and Memory*, Emory University, 1990.

21. As the keynote speaker, Dr. Byrne presented aspects of this research at the *Conference on Activity-Driven CNS Changes in Learning and Development*, State University of New York at Albany, 1990.

22. Dr. Byrne presented aspects of this research at the *55th Symposium on Quantitative Biology on The Brain*, Cold Spring Harbor Laboratory, 1990.

23. As a faculty member, Dr. Byrne presented aspects of this research during the *Computational Neuroscience Course: Learning and Memory*, Cold Spring Harbor Laboratory, 1990.

24. Dr. Byrne presented aspects of this research at the Cold Spring Harbor meeting on the *Cell and Molecular Neurobiology of Aplysia*, 1990.

25. Dr. Baxter presented the abstract "Mathematical modeling of the serotonergic modulation of electrophysiological properties of sensory neurons in *Aplysia*" at the Cold Spring Harbor meeting on the *Cell and Molecular Neurobiology of Aplysia*, 1990.

26. Dr. Baxter presented the abstract "Mathematical modeling of the serotonergic modulation of electrophysiological properties of sensory neurons in *Aplysia*" at the *20th Annual Meeting of the Society for Neuroscience*, St. Louis, MI, 1990.

27. Ms. Raymond presented the abstract "Activity-dependent neuromodulation can support operant conditioning in a small oscillatory network", at the Cold Spring Harbor meeting on the *Cell and Molecular Neurobiology of Aplysia*, 1990.

VII. New Discoveries and Specific Applications

A number of scientific discoveries resulted from the research sponsored by the AFOSR Grant 87-0274. First, we found that in tail sensory neurons serotonin modulates not only $I_{K,S}$ but that it also modulates $I_{K,V}$. Since the serotonergic modulation of these sensory neurons is believed to contribute to simple forms of learning in *Aplysia*, this discovery provided new insight into the cellular mechanism of learning. Second, we identified neurons that are elements of the central pattern generator that controls feeding behavior in *Aplysia*. Feeding behavior in *Aplysia* has been shown to be modified by operant conditioning like training, and before a cellular analysis of the cellular mechanisms of operant conditioning can begin it necessary to identify the neurons underlying the behavior. Thus the identification of the pattern generating neurons is an important first step in the investigation of the cellular mechanisms of operant conditioning. In addition, our simulations have led to the development of biologically derived computational algorithms that simulate many features of nonassociative and associative learning. Although it is too early in the research to comment on specific applications of this research, these results are relevant to aspects of artificial intelligence and provide a starting point for developing machines having some of the information processing capabilities of the nervous system.

No inventions were made.