A Computer Model of the Neural Substrates of Classical Conditioning in the *Aplysia*

Mark A. Gluck & Richard F. Thompson
Stanford University

"In experiments extending over the past thirty years, I have been trying to trace conditioned reflex paths through the brain or to find the locus of specific memory traces" -- Karl Lashley

When the essential neural circuit of a memory trace has been defined in sufficient detail as a biological system, it becomes necessary to determine if the circuit will in fact generate the phenomena of learning and memory that it is presumed to model. Even in elementary circuits, it is not always evident what the outcome of a given set of stimulus and training conditions will be at a qualitative-logical level of analysis. We report here an initial attempt at such modeling, utilizing the general approach of associative network modeling from cognitive science. We utilize the circuit of the *Aplysia* that exhibits elementary associative learning as identified by Kandel and associates (Hawkins, Castelluci, and Kandel, 1981; Kandel and Schwartz, 1982; Carew, Hawkins, Abrams, and Kandel, 1985).

The immediate goal of our research was to implement a computational model of the basic *Aplysia* circuit. By doing so, we hoped to arrive at an appropriate level of analysis in terms of the degree to which the biological properties of the neurons in the circuit are described that will allow realistic characterization of the behavior of the circuit. Our long-term goal is to utilize this level of computational analysis to account for the phenomena of learning and memory exhibited by the more complex memory trace circuits in the mammalian brain, particularly the cerebellar circuit that appears to be the essential memory trace circuit for the learning of discrete, adaptive behavioral responses (McCormick & Thompson, 1984a, 1984b; Clark, McCormick, Lavond & Thompson, 1984; Lavond, McCormick & Thompson, 1984)

The basic reflex studied in the *Aplysia* is withdrawal of the siphon, mantle shelf and gill to tactile stimulation of the siphon or mantle shelf. If weak stimulation of the sensory nerves (CS) is followed by strong shock to the tail (US), the synaptic potential of the motor neurons to the CS is facilitated. If repeated paired trials are given, this enhancement persists, yielding the basic phenomenon of classical conditioning, a persisting associatively induced increase in response of motor neurons to the CS. This conditioning

---

For their insightful comments and suggestions, we are indebted to Joseph Steinmetz, Leon Cooper, Mortimer Mishkin, Nelson Donegan, Misha Pavel, Stephen Kosslyn, and Terry Sejnowski. The assistance of Audrey Weinland and Katie Albiston is also gratefully acknowledged. This research was supported by ONR grant #N00014-83K-0238. Please address correspondence to: Mark A. Gluck, Department of Psychology, Stanford University; Bldg. 420, Stanford, CA 94305.

depends critically on the time between presentation of the CS and the US, as noted above. The tail shock US pathway involves interneurons which are thought to exert the US presynaptic action on the sensory nerve terminals. Hawkins and Kandel (1984) propose that conditioning results from the interplay of habituation and sensitization in a manner very similar to the dual-process view of habituation suggested by Groves and Thompson (1970).

Level of Analysis

Our primary focus in this modeling effort was on the behavioral conditioning data. We began by specifying the level of description of the data in which we were interested, as opposed to specifying, *a priori*, what level of biological detail we wanted to include in the model. Our basic goal was to account for the effects of the temporal relations between input events (**CS** and **US**) on the magnitude of output events (**MN**). In this paper we focus only on short-term learning and exclude longer-term effects. Our strategy is to be only as biologically precise as necessary in order to explain the relevant behavioral phenomena. We began by starting with the simplest possible representation of the circuit. After implementing this, and understanding what behavioral phenomena it did--and did not--account for, we added complexity, *constrained* by the neurobiological data.

Components of basic model

The initial circuit is composed of three neurons and three synapses, as represented in Figure 1(a). The neurons include: a (to be) conditioned stimulus: (**CS**), an unconditioned stimulus (**US**) and a motor neuron (**MN**). One fiber originates at the conditioned stimulus and terminates as a synpase on the motor neuron (**CS→MN** synapse). Two fibers originate at the unconditioned stimulus; one terminates as a synapse on the motor neuron (**US→MN** synapse), and one terminates as a synapse on the **CS→MN** synapse (**US→** {**CS→MN**} synapse).

Neurons are represented continuously by an **Activation** which ranges from 0 to 1. This value is interpreted discretely during each time cycle as a binary value --*fired* or *not fired*-- determined probabilistically from the activation. Synapses are represented continuously by a **Strength**, which ranges from 0 to 1 and also has a probabilistic interpretation. It represents the probability of a synaptic terminal passing a "pulse" to the post-synaptic neuron if the pre-synaptic neuron has fired. Each **CS** synaptic terminal has the potential to be modified in a pairing specific manner which peaks some time after the synapse receives a pulse. The time course of this potential determines the possible *Inter-Stimulus-Intervals*. At this level of modeling we assumed that the **CS** synaptic terminals have this temporal information **without** specifying the chemical or biological source.

The simulation begins by reading the input activation levels of the **CS** and **US** neurons. From these activations the states of the neurons (e.g. *fired* or *not fired*) are probabilistically determined. If an input neuron has fired, then with a probability determined by the appropriate synaptic strengths, a pulse is received by the **MN**. Thus, if the **MN** receives a pulse from either input neuron, then **MN** Activation increases exponentially, proportional to 1 minus the current Activation, at a rate determined by the *Activation Increment Rate*. If no pulse is received by the **MN**, its Activation decreases exponentially towards 0, at a rate determined by the *Activation Decrement Rate*. Every time a synaptic

terminal passes a pulse, the strength of that synapse decreases exponentially at a rate determined by the *Habituation Rate*. If the **US→{CS→MN}** synaptic terminal passed a pulse, then with probability **CS**-Plasticity-Potential (as determined by the *Plasticity Parameter*) it will sensitize the **CS→MN** proportional to 1 - **CS.Strength**.

Simple Associative Learning

The model successfully models the basic associative learning phenomena: In the initial state, the **US** produces a large amount of activity in the **MN** compared to only a small amount produced by the **CS**. After repeated presentations of the **CS** followed by the **US** at an optimal Inter-Stimulus Interval (ISI), the **MN** response produced by the **CS** increased significantly. Following the removal of the **US**, both the **CS→MN** strength and the **MN** activity during presentation of the **CS** decay back to their initial state, resulting in the behavioral phenomena of extinction.

With simultaneous presentation of **CS** and **US** (e.g. ISI=0), little or no learning occurs because the Sensitization Potential of the **CS→MN** synapse is at 0 when the **US** fires. With an ISI that is longer than optimal, some learning occurs, but less learning than with an optimal ISI.

More Complex Associative Learning

In addition to simple conditioning, we would like to model the mechanisms responsible for differential conditioning, second order conditioning, and blocking. In differential conditioning an animal learns to respond specifically to one conditioned stimulus and not to another unconditioned stimulus. In the *Aplysia*, a *CS+* is presented to the siphon paired with a US while an unpaired *CS–* is presented to the mantle (or visa versa). In second-order conditioning a CS_1 is first conditioned via pairing with the *US*. After this training is complete, the CS_1 can serve as a reinforcing stimulus to condition a new stimulus CS_2. Blocking is a process whereby an animal learns not only about the contiguity of stimuli, but also about their predictive contingency. If the CS_1 is conditioned to predict the *US* then the addition of a second stimulus CS_2, simultaneous with the CS_1, does not produce conditioning to the CS_2 alone.

Following Hawkin & Kandel (1984) we added a second **CS** and a **Facilitator Interneuron**--see Figure 1(b)--whose behavior mimics the **MN** and which sensitizes all **CS→MN** synapses. Given these additions, the circuit model produces successful simulations of second order conditioning of CS2 to CS1, but fails to produce a blocking effect.

To produce blocking, we needed a mechanism to turn off the **US**'s ability to sensitize when it has already been predicted by some **CS**. Hawkins and Kandel (1984) suggest that the interneuron goes into a refractory period after being activated, which is longer than the possible ISI. This was implemented computationally by creating an additional variable, the **Refractory State**, which is set to a constant when the interneuron activation exceeds a threshold (.9 in the simulations shown), and then decays towards zero according to an ogive (e.g. S-shaped) function. The **Refractory State** affects the interneuron by probabilistically governing the growth of interneuron activation in the following manner: if any synapse passes a pulse to the interneuron, then activation increases with probability equal to the lesser of 0 and 1 minus the **Refractory State**. To produce the

appropriate blocking behavior the decay of the **Refractory State** was set so that the refractory period would be longer than than the potential ISI. If, however, the interneuron is in a refractory period when the **US** fires, a direct **US→MN** connection is needed in order to get an appropriate unconditioned response. Repeated attempts, however, to get this circuit simulation to produce blocking, **failed** to do so.

We were initially convinced that the circuit really should produce blocking. We tried, without success, to vary all the parameters in an attempt to produce blocking. This highlights a methodological difficulty inherent in the use of computer models for making claims about circuitry: By simulating a circuit, one can demonstrate what a circuit can do, but one cannot prove, based solely on the inability to *simulate* a desired behavior, that the real circuit is *unable to produce* this behavior. If, however, the insights gained from the "hands on" experience of building the circuit can be translated into a convincing logical demonstration of the circuit's information processing limitations, then a simulation can contribute to making an argument about a particular circuit. We outline below why we believe that the circuit simulation will not produce blocking.

The Blocking Paradox

If the activity of the **F. Int** determines both the acquisition of new conditioned pathways and the retention of previously learned pathways, then the **F. Int** must, during the presentation of a "predicted" **US**, have a differential effect on the **CS #1** and the **CS #2** for it to sensitize the **CS #1** sufficiently to retain the previously learned association but not sensitize the **CS #2** enough to acquire this new association. The current formulation of the blocking mechanism is not sufficiently detailed to give rise to these behaviors. This is not to say, however, that the current circuit could not generate blocking. Rather, the interaction between the mechanisms for blocking and habituation is more subtle than previously realized. The paradox exists not so much in the circuit, but in the current level of detail at which the circuit's mechanisms are specified, at least in our simulation.

The locus of the paradox lies in the fact that no special mechanism for the decay of a learned response is proposed. Instead, following the Groves and Thompson model, decay of learned responses during **CS** alone trials is controlled by the background phenomena of habituation. Previous theoretical models, such as Sutton and Barto (1981), have missed this paradox because--following Rescorla and Wagner (1972)--they propose an active process which extinguishes the learned association during **CS** alone trials.

Possible Solutions

A resolution of this paradox will involve specifying mechanisms of pairing specific sensitizitization which robustly predict the blocking of the **CS #2** and yet at the same time, retain the **CS #1** association. We consider here two alternatives: the first involves modeling the current circuit anatomy at a more detailed level, and the second involves postulating additional circuitry described at the current level of detail. We emphasize that these extensions are not predictions for the *Aplysia* circuit, rather they are an attempt to understand the limitations of the current circuit by exploring what extensions to the circuit might, in theory, produce blocking.

If both retention and acquisition are governed by the same Interneuron--as Hawkins and Kandel suggest--then the activity of the **F. Int**, during the presentation of a "predicted" **US**, must be sufficient to retain the **CS #1** association, but insufficient to acquire the **CS #2** association. A learning mechanism which required a stronger pulse to acquire an association than to retain an association could perhaps give rise to the desired circuit behavior. An implementation of this mechanism produced successfull, but *weak*, blocking.

An alternate method for differentiating between retention and acquisition is to posit different neural mechanisms governing retention and acquistion. Consider the addition to the circuit of a second interneuron which does not go into a refractory period (i.e. mimics the **MN**) and which sensitizes proportional to the current learned association. This interneuron would counteract the effect of the habituation of an already learned association but would would have no effect on an unlearned association. We implemented this possibility and the resulting circuit exhibited a strong blocking effect.

CONCLUSIONS

Our computational model of the basic neural circuit of the *Aplysia*, as proposed by Kandel and colleagues, is sufficient to produce basic associative learning phenomena, namely acquisition, extinction, differential conditioning, and second-order conditioning. There are, however, problems with the computational circuit in accounting for blocking. The mechanisms proposed for blocking are not sufficiently detailed to explain both blocking and the habituation (extinction) of learned responses.

Our analysis illustrates the complexities that arise in trying to understand a simple circuit involving only four neurons that generates phenomena of associative learning. Our results illustrate the need for computationally implemented quantitative theories of neuronal circuit function. If the functioning of even this simple circuit is not evident at a logical-qualitative level of analysis, then the more complex circuits that code, store and retrieve memories in the mammilian brain will certainly require quantitative modeling.

References

Carew, T. J., Hawkins, R. D., Abrams, T. W., & Kandel, E. R. (1985). *Journal of Neuroscience.*

Clark, G. A., McCormick, D. A., Lavond, D. G., Baxter, K., Gray, W. J., & Thompson, R. F. (1984). Effects of lesions of cerebellar nuclei on conditioned behavioral and hippocampal neuronal responses. *Brain Research, 291,* 125-136.

Davis, W. J. & Gillette, R. (1978). Neural correlates of behavioral plasticity in command neurons of Pleurobranchaea. *Science, 199,* 801-804.

Groves, P. M. & Thompson, R. F. (1970). Habituation: A dual-process theory. *Psychological Review, 77,* 419-450.

Hawkins, R. D., Castellucci, V. F., & Kandel, E. R. (1981). Interneurons involved in mediation and modulation of gill-withdrawal reflex in Aplysia. I. Identification and characterization. *Journal of Neurophysiology, 45,* 304-314.

Hawkins, R. D. & Kandel, E. R. (1984). Is there a cell-biological alphabet for simple forms of learning?. *Psychological Review, 91,* 376-391.

Hoyle, G. (1980). Learning, using natural reinforcements, in insect preparations that permit cellular neuronal analysis. *Journal of Neurobiology, 11,* 323-354.

Kandel, E. R. & Schwartz, J. H. (1982). Molecular biology of learning: Modulation of transmitter release. *Science, 218,* 433-443.

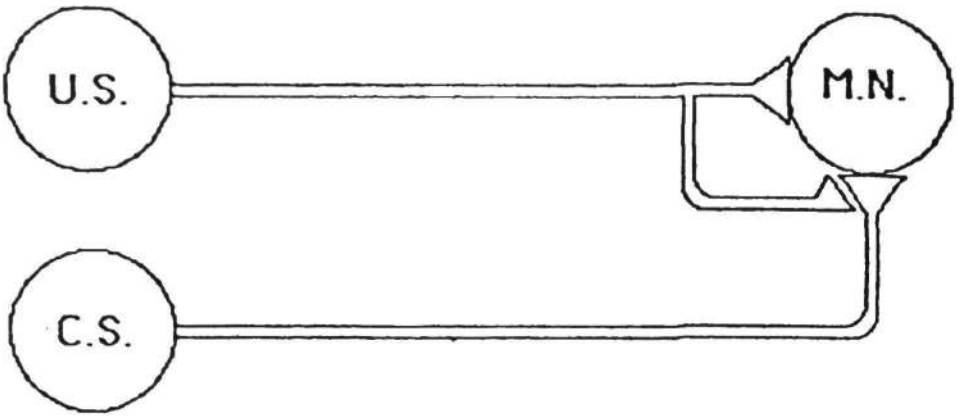
Lavond, D. G., McCormick, D. A., & Thompson, R. F. (1984). A nonrecoverable learning deficit. *Physiological Psychology, 12,* 103-110.

McCormick, D. A. & Thompson, R. F. (1984a). Cerebellum: Essential involvement in the classically conditioned eyelid response. *Science, 223,* 296-299.

McCormick, D. A. & Thompson, R. F. (1984b). Neuronal responses of the rabbit cerebellum during acquisition and performance of a classically conditioned nictitating membrane-eyelid response. *Journal of Neuroscience, 4,* 2811-2822.

Sutton, R. S. & Barto, A. G. (1981). Toward a modern theory of adaptive networks: Expectation and prediction. *Psychological Review, 88,* 135-170.

(A)



(B)