The Role of Chemical Mechanisms in Neural Computation and Learning

by

Martha Jean Hiller

S.B., Massachusetts Institute of Technology (1987)
S.M., Massachusetts Institute of Technology (1987)

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Signature of Author ....
Department of Electrical Engineering and Computer Science
May 13, 1993

Certified by..
Rodney A. Brooks
Associate Professor, EECS
Thesis Supervisor

Accepted by ....
Arthur C. Smith
Chairman, Departmental Committee on Graduate Students

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Abstract

Most computational models of neurons have assumed that their electrical characteristics are of paramount importance. The speed of electrical transmission relative to most chemical and metabolic processes combined with the apparently binary nature of action potentials has biased the field toward neglecting other aspects of the neural substrate as irrelevant. However, examples abound in the neuroscience literature in which chemical mechanisms, slow as they are, serve important roles in modulating the cell's electrical properties. In addition to mediating all long-term changes (e.g. the underlying mechanisms for learning processes), chemical mechanisms can have short-term effects that modify the processing of inputs received while those effects last. Both mechanical and chemical mechanisms also play important roles in the creation of the brain's anatomical structure during development, interacting with electrical mechanisms that determine the detailed connectivity between neurons.

The topic of this dissertation is the interaction between electrical and chemical mechanisms in neural processing, especially as they relate to learning and development. The emphasis on learning recognizes the prevalence of plasticity at all levels in the brain, and its central role in the establishment of the brain's structure and function.

My central thesis is that chemical mechanisms must be taken into account if we are to build accurate models of neural computation. To demonstrate their role, two neural systems are modelled in some detail. The first is a circuit controlling the gill withdrawal reflex in Aplysia, a marine snail. This circuit has been extensively studied to elucidate the mechanisms underlying observed habituation, sensitization, and associative learning in the reflex. These mechanisms display an intricate interaction between electrical conductances and chemical processes inside the synaptic terminals.

The second simulation models the formation of ordered topographic connections between different structures in the early visual pathway. These connections form

over long distances, and initially they are highly disordered. The process of sorting the axonal projections to produce a detailed topographic correspondence between the retinal image and the images projected on other visual structures also makes use of a combination of chemical and electrical mechanisms. The behavior of individual neurons is simplified in this model so that their interactions in networks can be studied; however, some care is taken to remain compatible with experimental results and with what is known about the biological mechanisms.

Thesis Supervisor: Rodney A. Brooks
Title: Associate Professor, EECS

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When I finished my master's thesis, I didn't feel grateful to much of anyone, so I left out the acknowledgements page. This time around, things are a lot different.

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The Genealogy of Brigid

Brigid of the mantles,
Brigid of the peat heap,
Brigid of the twining hair,
Brigid of the augury,
Brigid of the white feet,
Brigid of calmness,
Brigid of the kine,
Brigid, daughter of the Dagdah:
I am under the shielding
of Good Brigid each day,
I am under the shielding
of Good Brigid each night.
Brigid is my companion woman,
Brigid is my maker of song,
Brigid is my helping Goddess,
my choicest of women,
my guide.

Every day and every night
that I recite the genealogy of Brigid,
I shall not be killed,
I shall not be harried,
I shall not be put into a cell,
I shall not be wounded,
I shall not be anguished,
I shall not be ravaged,
I shall not be blinded,
I shall not be left bare
or forgotten.

No fire shall burn me,
Nor sun shall burn me,
Nor moon shall blanch me,
Nor lake shall drown me,
Nor flood shall drown me,
Nor briny sea shall drown me,
Nor dart of faerie sting me,
Nor seed of faerie lift me,
Nor earthly being destroy me.

For I am the child of Poetry,
Poetry, child of Reflection,
Reflection, child of Meditation,
Meditation, child of Lore,
Lore, child of Research,
Research, child of Great Knowledge,
Great Knowledge, child of Intelligence,
Intelligence, child of Comprehension,
Comprehension, child of Wisdom,
Wisdom, child of Brigid.

Contents

List of Figures

List of Tables

Chapter 1

Introduction

A study of the brain's architecture and learning mechanisms can be extremely useful in understanding the nature of intelligence and adaptive behavior. However, in the past, the usefulness of biological examples has been limited by the primitive state of our understanding of both computational systems and neuroscience, and by the limited interaction between computational modellers and experimentalists.

Neuroscience research has progressed rapidly in recent years, and now more than ever, maintaining communication between these fields can be beneficial to both. Computational modelling in neuroscience helps to understand and integrate experimental data and to test hypotheses about the function of neural circuits, and it provides a framework to focus the direction of future research. In artificial intelligence and connectionist research, the articulation of underlying principles of development in neural systems can provide important insights and design principles for the construction of intelligent systems.

This thesis describes mathematical and computational models of several known biological learning mechanisms. What can these mechanisms tell us about the nature of computation in the brain? What classes of algorithms has it evolved? What does its structure reveal about biological approaches to adaptive behavior? What can we learn from the brain about effective ways of interacting with the world?

1.1 Motivations

My primary reason for choosing this topic was a deep curiosity about the brain and how it works, particularly with regard to the nature of neural computation. One of the most interesting aspects of my undergraduate education was the explication of all the layers of abstraction in computers, from the internal electrical properties of a silicon transistor to a high-level programming language. I started this work with the goal (however unrealistic) of doing the same with the brain: understanding all the layers of neural processing from the underlying chemical processes to its higher-level functioning.

Just as the nature of the underlying hardware directs and constrains the character of computer languages, the nature of the neuronal substrate constrains the character of the computational primitives and "programming languages" used in the brain. For this reason, characterizing the behavior of neurons is crucial for developing an understanding of neural computation. Mechanisms involved in learning and development are emphasized throughout this work in recognition of the prevalence of plasticity at all levels in the brain, and its central role in the establishment of the brain's structure and function.

Learning, in the context of traditional neural networks research, is conceptualized as permanent synaptic changes in response to information encoded in the neuron's electrical activity. However, neurons and their synaptic connections change over time in a wide variety of ways, only a few of which fit this model. Although neural plasticity is often activity-dependent, many other processes in the cell, such as chemical and mechanical properties, also play important roles in the cell's development over time.

Learning in the brain is thus a far richer and more complex phenomenon than is recognized by traditional models. A primary thesis of this work is that a recognition of the multiplicity of mechanisms for plasticity in the cell is essential to understanding the way the system functions as a whole. Because most previous models of the functional characteristics of neurons have concentrated exclusively on their electrical properties, the focus here is on chemical mechanisms.

1.2 Goals

The goal of this research is to better understand the relationship between structure and function in the nervous system: that is, between the biological mechanisms underlying different types of learning and their computational properties.

The questions I am interested in include:

1. What mechanisms underlie different forms of learning and memory? What kinds of algorithms can be implemented efficiently in biological systems? What is the nature of the primitive computational operations in the brain?

2. How do the biological processes within individual neurons contribute to their computational properties, as compared to the contribution of the network of connections in the corresponding brain structures?

3. In what ways can learning be incorporated into structured networks? Which aspects of behavior are learned?

4. How are biological learning mechanisms similar to or different from current computational learning models?

This dissertation answers these questions for a few specific cases, laying the groundwork for a more general analysis. The methodology is to construct computer models of example systems utilizing two types of learning, classical conditioning phenomena in *Aplysia*, and long-term potentiation (LTP) in mammals. These circuits are studied both in terms of chemical interactions within and between neurons and overall network structure. Their capabilities and limitations are explored through simulation and analysis.

This work is, of necessity, speculative, and serves primarily to sketch out an area of study and identify some interesting problems, and fill in a few details that point the way toward the kind of answers that are likely to be found as more work is done in this area.

1.3 Modelling in Neuroscience

The field of neuroscience has progressed very rapidly in the past few years. A range of new experimental techniques allows researchers to probe the internal mechanisms of neurons in far more detail than was possible even five or ten years ago.

Even so, biological structures are so complex, and biochemical interactions are so intricate and difficult to isolate, that many aspects of the physical system must still be inferred from insufficient data. This is one of the major challenges of the field, and it limits the uses to which modelling can be put.

Until biological systems are understood far better than they are at present, a biological model, however rigorous it may be mathematically, is at best a working hypothesis. The question of whether a particular model is "correct" is therefore of far less interest than that of whether it is useful. How well does it reveal the gaps in our knowledge, and suggest questions to direct further experimentation?

At worst, a biological model is simply wrong. It can be difficult to keep track of the many many details of what is known about a neural system, and integrate them into a model that remains compatible with the current state of experimental research. The goal of biological modelling is to organize this information in a way that reveals some underlying structure or functional principle while maintaining a plausible correspondence between the mathematical properties of a simulation and its supposed biological substrate.

1.4 Is it Real or is it Artifact?

It can often be difficult to distinguish, when looking at a system in which everything interacts with everything else, whether a given effect is an integral part of the system's functional design, or an artifact that is due to undesired but unavoidable constraints of the physical substrate. However, there are a number of properties which can be examined to help distinguish between these situations.

- One question we can ask is how many cellular resources participate in producing the effect, or would be necessary in order to avoid it. An effect which requires the coordination of many different processes is more likely to be significant than one which results from a single mechanism. Conversely, if a large number of cooperating processes would be necessary to prevent an effect from occurring, or if there is evidence for the presence of processes which minimize the effect, this would be a strong argument for classification of that effect as an unavoidable artifact.

- Another question is whether the behavior results from a cellular mechanism whose function in other systems is well established. Protein phosphorylation as a response to extracellular signals, for example, was first studied in the control of glycogen metabolism, and has been established as an important mechanism for modulating a wide variety of metabolic processes in many different cell types [51]. This mechanism is therefore a likely candidate for mediating a neuron's metabolic responses to neurotransmitters.

- Given some parameter which activates and deactivates a particular process, a correspondence between the range of variability necessary to control the process and the observed range of variability of that parameter *in vivo*[1] may be an indication of functional significance.

  Two examples involving the NMDA receptor, a protein involved in interneuronal communication, illustrate this point. The action of NMDA receptors is strongly potentiated in response to very small concentrations of glycine [23]. However,

[1] That is, in the living animal, as opposed to the petri dish.

this effect saturates even with trace amounts of glycine, comparable to the basal levels found in the extracellular fluid, so there is no evidence for a differential response to a controlled variation in the glycine concentration *in vivo*. This does not, however, rule out the possible significance of glycine potentiation, as there may be controlling processes which have not yet been discovered.

Basal levels of magnesium also affect the NMDA receptor, by blocking its activity. However, this activity block is removed when the cell is depolarized to levels which are often reached in the course of its normal functioning [34]. In this case, therefore, there is evidence for the functional significance of the magnesium block.

- Another indication that may be useful in determining whether a mechanism is functionally important is its magnitude relative to other mechanisms affecting the same behavior. An example would be a comparison of synaptic depression to habituation. In synaptic depression, neurotransmitter release is reduced by only ten or fifteen percent following prolonged firing. In habituation in *Aplysia*, by contrast, synaptic transmission is reduced to thirty percent of its initial value by only a few training trials [30].

  The absence of a large effect, however, does not necessarily rule out the functional significance of a candidate cellular mechanism. The lack of positive evidence could be due to limitations in the experiment. For example, localized effects may be lost in the noise if the measuring technique is not specific enough.

- A highly specific response to a particular chemical, and lack of response to other similar chemicals, may also indicate functional significance.

Although none of these arguments is conclusive, and in many cases new experiments may provide evidence which counters our current intuitions, they nonetheless can improve our ability to distinguish important effects from artifacts. The mechanisms discussed in this dissertation all match at least one of these indications for a functionally significant effect.

1.5 Selecting a System for Modelling

There are a number of properties which, when known for a biological system, make it easier to model learning phenomena in that system. Some of these are:

1. a description of the input and output behavior of the circuit, both before and after learning.

2. a description of the internal and external connections in the circuit.

3. information about the behavior of the synapses, for example, the strength of the connections, whether they are excitatory or inhibitory, and what forms of learning are present.

4. a high-level description of the function the system performs.

5. evidence for the presence and importance of learning phenomena found in the system.

The *Aplysia* gill withdrawal reflex and map formation in the early visual system were chosen for study because they have been extensively studied and are relatively well-understood. Because many of the mechanisms involved are widespread in other brain regions and across species, it is expected that the principles discovered here will generalize to other learning situations as well.

1.6 Chapter Organization

The central chapters of this document take a detailed look at two neural systems which illustrate a variety of learning processes in neurobiology.

Chapter 2 describes a circuit controlling the gill withdrawal reflex in *Aplysia*, a marine snail, and presents a simulation and and analysis of the mechanisms underlying observed habituation, sensitization, and associative learning in the reflex. These mechanisms display an intricate interaction between electrical conductances and chemical processes inside the synaptic terminals.

The *Aplysia* circuit has been extensively studied, and is unusually well understood. The results demonstrate that biological learning is complex and many-faceted, rather than working via a single general-purpose mechanism. Even what appears as a single mechanism, in a high-level description, is made up of many component processes. These processes, which can be very different from one another, work together to regulate the process so that it is stable and robust and produces consistent, meaningful behavior.

The second simulation models the formation of ordered topographic connections between different structures in the early visual pathway. Connections between these structures (e.g. from the retina to the optic tectum and to the lateral geniculate nucleus (LGN) in the thalamus, and from the LGN to the visual cortex) must form over long distances, and initially they are highly disordered. The process of sorting these connections to produce a detailed topographic correspondence between the source and target images involves an interaction between chemical and electrical mechanisms.

Chapter 3 describes a simulated model of topographic map formation in the visual system, and Chapter 4 presents a mathematical analysis of the system and the constraints necessary to ensure its success.

The final chapter draws the various parts of this research together and summarizes the insights into the particular brain systems studied. It discusses principles that are common to the different systems, and which may turn out to be more generally true of biological systems that mediate adaptive behavior.

Part I

Classical Conditioning in Aplysia

Chapter 2

Synaptic Plasticity in Aplysia

This chapter presents a simulation and analysis of mechanisms underlying short-term learning in the marine snail *Aplysia*.

One purpose of this work is to test the conceptual models described by neurobiologists to discover whether the hypothesized mechanisms are adequate to explain the observed learning phenomena. The simulation demonstrates that the mechanisms described in the literature can produce some simple aspects of the experimental results, but there are many details which it cannot explain. For example, inconsistencies in learning and recovery rates when different training protocols are used require a more complex explanation.

Two specific mechanisms are analyzed in detail to explore the relationship between the macroscopic behavior of the system and the underlying mechanisms. These are the process which governs the relationship between Ca^{++} influx and transmitter release and the chemical cascade which controls the effect of the inter-stimulus interval (ISI) on the strength of associative learning. The analysis predicts certain parameters of those processes, such as chemical reaction rates, that could be tested experimentally.

Studies of learning in *Aplysia* provide evidence for a specific biological implementation of classical conditioning phenomena, which makes use of both chemical and electrical properties of the synapses. However, they also point to a more general use of chemical changes in neurons as a mechanism for short-term memory. Processes similar to those described here may be used to control a broad range of neural responses. Both calcium ions (Ca^{++}) and cyclic AMP are important mediators of *Aplysia*'s learning responses. These chemicals are used throughout the animal kingdom as cellular *second messengers*, controlling many different metabolic processes [51].

The effect of a second messenger on a cell is determined, in part, by the differential expression of proteins which respond to it. They can also be controlled by limiting the distribution of the second messenger within the cell; for example, if it remains localized within a single synapse, only the proteins in that synapse will be affected, and other parts of the cell will remain unchanged. A third mechanism for control is the use of additional processes which modulate the responsiveness of different proteins to a particular second messenger.

An interesting, though considerably more speculative, aspect of this research is the question of which parameters of these chemical processes are actively modulated by neural cells. Answering this question would shed light on the kinds of primitive operations the cell has available to it for computational control.

2.1 The Nature of the Beast

Aplysia is a marine gastropod mollusc, also known as a “sea slug”. Eric Kandel, one of the more prominent experimentalists working with *Aplysia*, describes the creature as follows:

> As is readily appreciated from its proud gait, illustrated in Figure 2-1, *Aplysia californica* is a large, attractive, and obviously intelligent beast. It is just the sort of animal one would immediately select for studies of learning. [28, page 6]

Aplysia is currently in demand for studies in neuroscience for two major reasons.

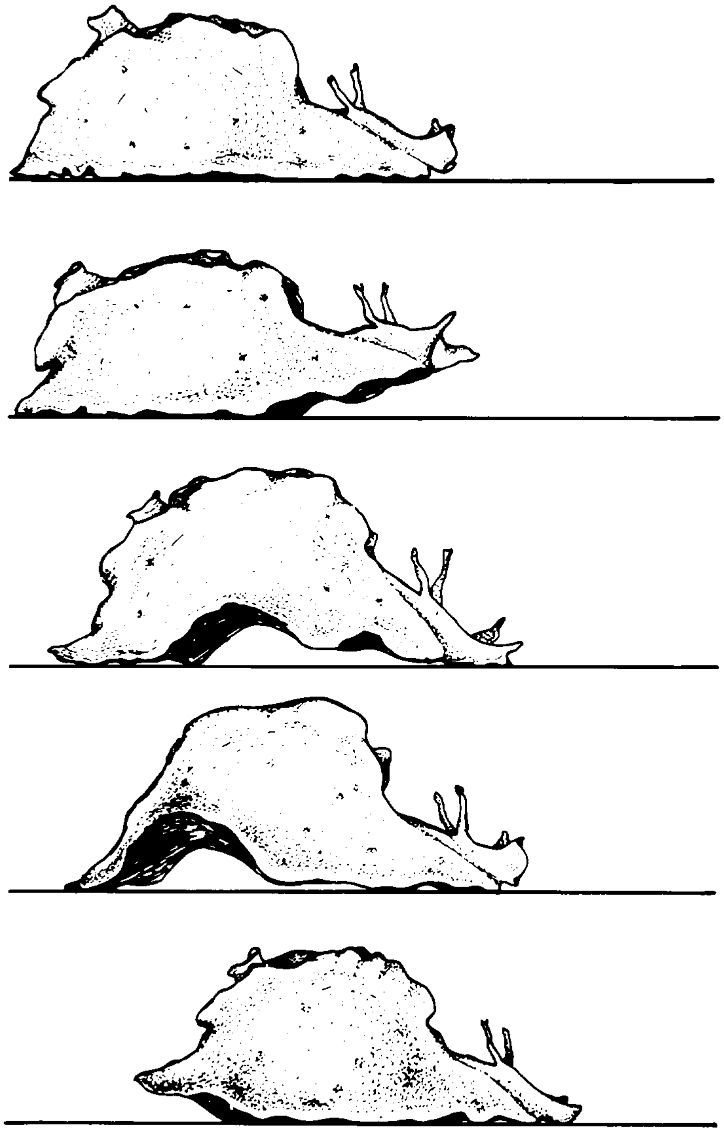

Figure 2-1: Aplysia's "proud gait" (From [28, page 7].)

The first is that its nervous system has a number of properties that make it easy to study[27]. Its neurons are relatively large, and the organization of its nervous system is consistent enough that individual neurons can be reliably identified from one animal to the next. Synapses are electrically close to the cell body, so intracellular recording of synaptic potentials is possible. This means that the interneuronal connections — the "wiring diagram" — of the animal can be determined through intracellular recording at the cell body.

The second reason, as mentioned above, is that it learns.

2.1.1 What Does *Aplysia* Learn?

The learning phenomena observed and studied in *Aplysia* and other gastropod molluscs fall under the category of classical conditioning responses. Classical conditioning builds on innate reflex responses, which are modified in response to experience. A reflex consists of a sensory stimulus for which the animal exhibits a characteristic behavioral response.

The Phenomena of Classical Conditioning

First-order classical conditioning responses[1] include habituation, dishabituation, sensitization, associative learning, extinction and recovery [9]. In habituation, repeated application of a stimulus results in attenuation of the reflex response. This attenuation can last for an extended period. Dishabituation and sensitization are very similar, as both involve an enhancement of the reflex response following a strong stimulus. This stimulus need not be the same as the one that normally elicits the reflex response. The difference between the two is that dishabituation acts on an already-habituated response, whereas sensitization can act regardless of whether the reflex is habituated.

[1] That is, responses which involve only a single conditioned stimulus.

Associative learning is the best-known phenomenon of classical conditioning. There are two stimuli involved in associative learning, called the unconditioned stimulus (US) and the conditioned stimulus (CS). The US naturally evokes the reflex response (UR). If the US and the CS are paired in a sequence of learning trials, the CS alone will begin to evoke the reflex response (CR).

In extinction, a CR gradually disappears following repeated application of the CS unpaired with the US. After a CR has been extinguished, it often reappears after a period of rest. This response is called recovery.

Higher-order classical conditioning phenomena include second-order conditioning (where a new stimulus is conditioned using an already conditioned stimulus-response pair in place of a primary reflex response), generalization of various kinds, and blocking (where an already conditioned stimulus prevents conditioning of a new stimulus).

The Gill Withdrawal Reflex

One of the more prominent features of the molluscan body is the *mantle*, located on its back (see Figure 2-2). The mantle consists of a cluster of organs including a siphon and gill for breathing. Light tactile stimulation of the siphon induces a protective reflex, in which the siphon and gill are contracted and withdrawn into the parapodium (see Figure 2-3.) Tactile stimulation at a point on the siphon activates about 8 sensory neurons, each of which fires 1 to 2 spikes [28].

This gill withdrawal reflex has been shown to exhibit several forms of first-order conditioning [30, 21]. The reflex habituates after repeated tactile stimulation of the siphon, and sensitization occurs following an electrical shock to the tail [28]. Simple associative learning has also been found [1], using the tail shock as the unconditioned stimulus (US), and tactile stimulation of the siphon as the conditioned stimulus (CS). The response to tactile stimulation is initially fairly weak. It is strengthened somewhat by sensitization, and this effect is greatly enhanced by pairing the two stimuli.

All of these effects have a short-term form, lasting a few hours, and a long-term

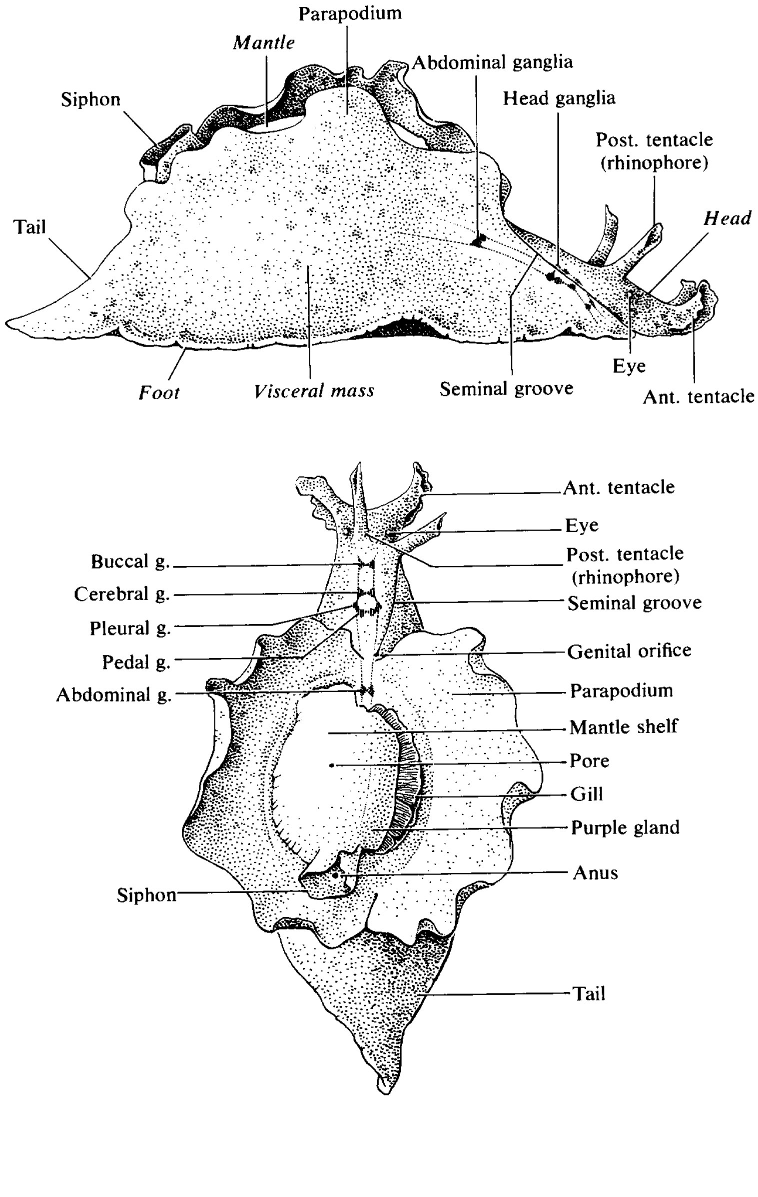

Figure 2-2: Aplysia's body (From [27, page 76].)

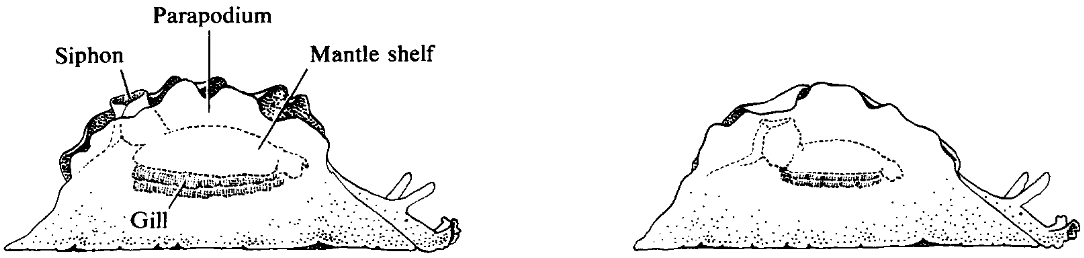

Figure 2-3: The gill withdrawal reflex (From [27, page 85].)

form which can last for at least several weeks.

Some types of higher-order conditioning have also been found in *Aplysia* or its close relatives [21, 57].

2.1.2 Why Does *Aplysia* Learn?

One might wonder just what it is that a sea slug has to learn about, being a simple grazing animal with no natural predators. As the marine neurobiologist is a relatively recent arrival on the scene, it can hardly be expected to have evolved these abilities for the sole purpose of showing off in a petri dish.

However, even the life of such a gentle beast is fraught with circumstance. Many of these creatures live in the littoral, or intertidal, zone of the ocean. In Kandel's words,

> Animals living in the littoral zone are often exposed to the air for several hours a day and are buffeted about by the tides. These animals must withstand wide and rapid changes in temperature, humidity, salinity, pressure, mechanical stimulation, and wind, and survive repeated exposure to air and immersion in the sea. [27, page 74]

These circumstances offer many dangers, and it is easy to see why a creature living in such an environment might evolve the capacity to learn. If a gentle tactile