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In Search of A Unified Theory of Biological Organization: What Does the Motor System of A Sea Slug Tell Us about Human Motor Integration?

I. ABSTRACT

We summarize the behavioral, electrophysiological, and immunohistochemical findings in the sea slug, *Pleurobranchaea*, and compare these finding to those obtained in other invertebrate animals, in higher animals, and in humans. The findings show that there is "massive" distribution and sharing of information occurring, respectively, through diverging and converging network connections.

We examine the findings of reductionist approaches and find them inadequate to answer the problems arising from such widely distributed, multifunctional, and highly converging networks whose activity may be variable. Such findings indicate that "cooperative" actions among groups of neurons may arise dynamically and nonlinearly in shifting contexts or "consensuses" of response in which individual neurons may have different functions, even during times when the behaviors are similar. Control of these systems is emergent, "fuzzy", and error-prone rather than being reflexive or following explicit causes and effects that can be read from the "switchboard" circuit of the connections between neurons.

A unified theoretical perspective is needed that accounts for both the emergent and switch-board systems. Two problems apply in both cases: First, animals may have evolved highly specialized behaviors whose underlying neural networks may not necessarily reflect generally applicable principles. Second, owing to their complexity, it may not be possible to characterize biological networks in sufficient detail to permit an understanding of the system through simulation of the system itself. Thus, we use biological information only as indications or points of departure to identifying first principles that are not initially intended to account for a particular behavior, but to provide insights into generally-applicable self-organizing processes at the local-neuron level that can then be used to understand how large-group action emerges.

We discuss a number of these avenues to examine computationally and biologically, e.g: (1) Error and variation may not only be products of but may be causally related to the generation system dynamics. (2) The possibility that attractors provide avenues for energy- or error-minimization yields mechanisms from which emerge many important building blocks, e.g: the ability of groups of synapses to encode different categories of information simultaneously; threshold effects that enhance system function; and input signal dynamics which not only carry encoded information but also provide a variety of search strategies for locating attractor basins. (3) Minimal network architectures may be identified that permit bifurcation into different dynamical states. (4) Computer graphical analysis of spatio-temporal activity may show how different attractors are established and move and merge in space and time. (5) Competition between synapses may continuously sculpt and readjust network connections to changing conditions.

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In Search of a Unified Theory of Biological Organization: What Does the Motor System of a Sea Slug Tell Us about Human Motor Integration?

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2. Has the Table of Contents been removed? This is chapter is very long. It covers many different research fields, and provides many critiques. It would be beneficial to readers to see at a glance what the chapter will cover.

Therefore I strongly recommend that you include the TABLE OF CONTENTS.

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II. INTRODUCTION: GRAND UNIFICATION THEORIES

Much of our discussion here will address the functional meaning of divergence and convergence of connections among neurons. At the simplest level, both are anatomically definable: divergence occurs when a single neuron sends synaptic[1] projections to many other neurons, and convergence occurs when many neurons send projections onto a common follower neuron. A more functional definition is to say that divergence distributes information, whereas convergence produces sharing of information. The consequence of divergence is to increase the size of the co-functional group of neurons, but this alone would only produce a set of independent processors. In parallel programming, the programmer breaks down a problem into different components and then assigns each component to a different processor;

[1] We use the terms "synaptic projections" and "connections" to refer both to well-defined pre- and postsynaptic structures involving localized transmitter release and to morphologically indistinct structure involving diffuse transmitter release.

the programmer distributes the components, but the processors act independently. Similarly, there may be multiple sites of learning, perhaps arising from divergence of input-stimulus pathways onto many different cells, and each site may involve different cellular mechanisms, but unless there is some interaction or convergence, each site processes information independently. Because of its potential for sharing information, convergence forces many neural sites to work interdependently. Thus, convergence lies at the heart of our definition of parallel processing in biological systems,[37,141] as it does in simple connectionist neural networks[83] that have little resemblance to biological ones.

In attempting to understand the functional implications of divergence and convergence even in small networks, Pribram's[155] analogy to holography for distributed memory storage seemed a possibility,[141] particularly, as Mpitsos and Cohan[37] later reported, since some networks are able to reorganize similar motor output patterns of activity after neurons are removed that appear to control the pattern of activity going to motor neurons. In these studies, the neuron was removed from taking part in the motor pattern by hyperpolarizing it below its firing threshold. This produced two types of errors: cessation of firing in the motor neurons that it controlled, and cessation of all motor activity. Eventually, the original pattern recovered even though the hyperpolarized neuron, and the motor neuron(s) it drove, did not take part in the reformed motor pattern. Since the overall firing pattern in the reformed activity in the motor roots appeared similar to the original pattern, it seems reasonable that the error was *somehow distributed* throughout the generator network. By analogy to holography, the "picture" of activity emerging from the memory distributed among the pattern-generating neurons exhibited graininess when bits of information were lost rather than exhibiting holes or gaps in some regions while retaining high resolution in others as would occur in some neural networks.[134] We use "graininess" here because fewer neurons became involved in the reformed pattern than in the original one, yet the overall structure of the pattern seemed the same. There are problems even with the notion of holography, and in carrying the analogy of graininess too far, but for the present purposes, the real question that these studies point to is one of memory storage and control in high-dimensional systems. The high dimensionality that we refer to is not just in the number of interacting components. It also includes, as we shall discuss, the storage of different forms of information within the same set of synapses and nonlinear ways of addressing it.

While it is easy to see high dimensionality, and the consequences of it, in the human cortex, it has not been so easy to admit that it exists in animals that neuroscience persists in calling "simple." A world view that polarizes animals into simple and complex (into generalizations relating to invertebrate and vertebrate phyla) emerged; e.g., see comment in Edelman.[51] A wide variety of factors, including the technology of intracellular microelectrode recordings,[108] the ability to use these recording methods on cells that can be identified in different experimental preparations, findings showing that activity is encoded within the central nervous system itself for generating patterned motor activity,[188] the importation of the ethologist's[112] fixed-action pattern (FAP), identification of functional types of cells such as command neurons that control central pattern generators and stereotyped

behaviors or FAPs,[46,102] and the related findings showing that much of this activity is genetically encoded,[19] worked together to entrench reductionism. Though each finding remains useful in its own right, concepts developed from reductionist single-neuron methods have proved inadequate to understand distributed, multifunctional, and variable systems.

It is an interesting discovery that many biological systems, being potentially high dimensional, may generate complex behavior that is governed by relatively low-dimensional dynamics.[2] Choatic systems fall into this category, and, because of their complex response dynamics, have been a subject of considerable attention over the past ten years.[42,152,156,170] We shall summarize some of these efforts. But rather than dealing with the verifiability of chaos itself or of any dynamic process, which has already been addressed sufficiently elsewhere,[131] what we wish to do here is to address common features of all nervous systems which give rise to or exclude the ability of the systems to produce particular response dynamics. This is to say that the important features are not so much whether repetitive activity, as one example, is generated by limit-cycle or chaotic dynamics, as it is of the system characteristics that permit different activities to arise.

It may be useful to forewarn the reader that our own perspective of brain function, or of the function of systems composed of aggregates of nonlinearly interacting components, has two parts, one experimental and the other philosophical. It is essential, of course, that the philosophy or theory one holds about the actions of a system must have a foundation on hard biological fact. However, problems arise when doing only that. Take just one example: *All visual systems use on-responses* to respond to the onset of light, and off-responses to respond to the off-set of light. But knowing the cellular and physiological mechanisms that generate off-responses in some molluscs would lead one completely astray about the mechanisms that produce them in vertebrate animals.[130,186] Evolutionary selection mechanisms tend to optimize the adaptive[3] mechanisms in each organism. Thus, owing to diversification and optimization, it is often difficult to determine what features permit generalization across organisms, or for that matter, across integrative systems within an organism because the various systems may have developed under different evolutionary constraints. It is possible to argue in favor of comments one might find in print, which

[2]There is often no need to go beyond its definition of dynamics simply as "time-dependent variations of activity," though there are different forms of dynamics. Rather than presenting a formal definition, we shall introduce various ideas that modify our standard working definition as they arise in the course of the discussion.

[3]The term "adaptive" implies some conformation of a system (biological or computational) that allows it to survive in its environment. The process of conforming, as we shall discuss in detail in section VIII, may represent a gradient descent in the error of the response with respect to the response required for survival, or in the energy required to generate the response. That there may be local minima in such conformations indicates that there may be non-optimal ways of responding, and, conversely, it indicates that there may also be an absolute minimum representing some optimal way that the system might respond for a given environmental demand, though local minima may be sufficient for survival.

go something like this: Owing to the observation that evolution conserves mechanisms, what we understand of mechanisms of learning in a simple animal such as a sea slug will allow us to understand the mechanism of learning in humans. But to take that argument is to forget the equally important fact that diversification is a crucially important driving force in biological evolution, not only through variations arising from random factors, but also through deterministic low-dimensional factors whose dynamics gives them a life of their own.

As neurobiologists, we are interested in the integrative mechanisms of sea slugs, crayfish, insects, leeches, lampreys, or humans. But from a broader perspective, we wish to ask whether there are scale-independent principles, namely, ones that apply to different levels of organization, from chemical processes to cellular, organismal, and social ones. The question is: Can we identify unifying principles, as one might say of the attempts to establish grand unification theories (GUTs) in physics? Unfortunately biological systems are too complex and uncontrollable to permit such a synthesis presently, as we shall try to show in the present paper. One possibility is to conduct computer simulations of models that reduce a particular biological system within the bounds of definable characteristics. While this may give insight into mechanisms pertaining to that system, it may not provide much insight into general principles.

An alternative simulation approach is to use biological information as "points of departure" to conduct computer simulations that do not necessarily attempt to replicate the structure or function of any particular biological system. We go further to suggest that it might be useful to use simulation systems that are actually extreme caricatures of biology, but which nonetheless might generally give insight into biology. Eventually, what we hope to do is to obtain some idea about how network architecture incorporates various linear and nonlinear interactions between neurons to allow the network, as a whole, to generate different types of response dynamics. We want also to understand how these fundamental network principles become sculpted selectively to produce the neural responses observed in individual animals. The neural architecture in individual organisms may retain more or less of these primal features, as required or permitted by the tasks presented for adaptive fitness. Thus, by seeking to identify common principles from which different mechanisms may emerge, we are joining a call to reconsider the importance of comparative biology,[22] a subject which has suffered as research has become entrenched in animal-specific encampments. But, as we hope will become apparent, our efforts will not be to determine, for example, whether command processes are the same in different animals or to define the command process more exactly. As important as such issues are, we shall nonetheless aim to address comparisons at a broader or more abstract level. Much of our discussion here will center on making analogies through commonality in dynamical principles rather than in mechanisms.

There are, of course, many people who, in one way or another, have addressed the question of how cooperative action arises among groups of intercommunicating individuals. The works of Grossberg, for example, on neural networks and the mathematical foundation of many of psychological phenomena are too numerous even to summarize adequately.[71,72] It is a theme of modern neural network

connectionism,[150] in studies of chemical dynamics,[6,53,165] and in mammalian nervous system.[170] In many biological aspects, it can be traced back to Darwin,[40] and to Aristotle.[180] Such works notwithstanding, we shall attempt to show in the present discussion that a unifying theory of how neurons (or individuals of any type) act cooperatively within a group is presently lacking. Along the way we shall also attempt to identify ways for continuing the search for unifying principles.

In the course of this paper we shall first describe the behavioral, physiological, and immunohistochemical studies in our experimental system the sea slug *Pleurobranchaea*, and then compare these results to those obtained in other invertebrate animals and in vertebrates. Another gastropod mollusc, the sea slug *Aplysia*, has been the focus of reductionist researches in many laboratories that have attempted to explain animal behavior and associative learning in terms of definable reflexes. Section VII deals with reductionism; we examine these findings, show the difficulties that have arisen, and then reassess them from the point of view of parallel-distributed processing. Given growing interest in nonlinear dynamics in model mathematical and physical models, we examine the viability of applying tools arising from these studies to biological systems. In section IX, we suggest computer methods which might give some insight into how the integrated activity of large numbers of neurons might arise from interactions occurring locally between individual neurons. Thanks to the work of René Thom,[180] we use a call from Aristotle[7] to summarize the intent of our own work begun two decades ago: "~~what is this supposed to be?~~," namely, "Now let us make a fresh start," at least to point out what it is that traditional thinking in neurobiology does not address sufficiently, and what the problems are in progressing further.

"Ἄλλην ἀρξὴν ἀρξόμενοι,"

Ed this is a sentence in Greek from Aristotle

III. FINDINGS IN A SEA SLUG

1. BEHAVIOR

Pleurobranchaea is a large sea slug, a member of the opisthobranch gastropod molluscs, ranging in size from a few millimeters to tens of centimeters, depending on its age. Its general body features resemble a snail, though like land slugs, it has no shell (see photographs in Mpitsos[140,141,143,145]). The animal exhibits a relatively large repertoire of behaviors,[4] including, righting when turned upside down, defensive withdrawal, mating, egg-laying, feeding and a variety of other mouth-related behaviors involving the mouth, lips, jaws, and radula (a structure analogous to

[4] The ensuing discussion also relies on the term "behavior," and identifies a number of behaviors within the repertoire of what the animal can do. For the moment, we use "behavior" to refer specifically to a definable response of the animal, or generically to some unspecified but potentially identifiable response. We shall see by section III.7, however, that the definition of behavior, of behavioral repertoire, and of behaviorally multibehavioral or multifunctional systems (ones that can produce different behaviors using the same sets of neurons) needs to be revised to take into account the consequences of variation in "contexts" of neuronal group action.

a tongue). Feeding behavior usually has dominance over the other behaviors. For example, animals normally withdraw from tactile stimuli applied to their head regions, but in the presence of food, withdrawal responses are suppressed in feeding-motivated animals.[45,143] The most obvious feature of the feeding behavior is the rapid bite-strike response in which the entire jaw structures comprising the proboscis are rapidly thrust out to bite at a food object and then rapidly withdrawn. Feeding also consists of bite-ingestion movements in which food is grasped and then sequentially drawn into the mouth cavity largely through cyclical inward and outward movements of the radula and coordinated movements of the anterior regions of the jaws and mouth. A third stage of feeding consists of swallowing movements in which food is passed from the buccal cavity through the esophagus and then into the stomach. The bite-ingestion and swallow components of feeding[14] are excellent for neurophysiological work because of their oscillatory characteristics, much as might happen in humans during opening and closing of the jaws and related movements of the tongue. Because of the sequence of oscillations, the behavior persists and is amenable to analysis, whereas single-shot behaviors such as withdrawal are more difficult to analyze. However, as in humans, the number of cycles that the animal may exhibit during a single bout of bite-ingestion and swallow is often short and possibly nonstationary in its temporal characteristic, which, as discussed below, pose difficult problems in studies aimed at understanding the dynamics of the behavior.

The jaws, radula, mouth, and lips of the animal generate many different and variable behaviors.[136] These include several components of feeding, regurgitation, defensive biting, among others.[34,122,123,124,125,136] The animal also exhibits self- and inter-animal gill grooming,[146] but we presently have no way to evoke gill-grooming behavior reliably. However, of all its behaviors, inter-animal gill-grooming is particularly interesting because *Pleurobranchaea* is cannibalistic, raising questions into the mechanisms that turn carnivorous feeding mouth, radula, and jaw movements into cleaning movements.

2. NEUROPHYSIOLOGY

A. KEY FEATURES OF ALL MOUTH-RELATED BEHAVIORS CAN BE EXAMINED THROUGH A SMALL POPULATION OF NEURONS, THE BCNS The cerebropleural ganglion ("brain") of *Pleurobranchaea* innervates the mouth and anterior head regions, whereas the buccal ganglion innervates the muscles that move the jaws and radula. Thus, coordination of buccal-oral behaviors, namely ones that involve both the buccal structures and the mouth and lips, must happen through these ganglia.

The only way this can happen is through the buccal-cerebral neurons (BCNs), of which there are approximately 15–20 in each half of the two buccal hemiganglia. The BCNs are unique because they are: (1) the only cells in the buccal ganglion that project to the brain, except for two bilaterally paired giant neurons whose function is presently unknown, and (2) that are either directly involved in generating the central pattern generator for the buccal behaviors or intimately involved in

controlling it.[33,34,137] There may be other oscillators located in the brain, but by comparison to the effect of the BCN oscillator, other oscillators have weak effects. The BCNs and the two giant cells are the only sources of information to the brain about processes in the buccal ganglion. All of the behaviors involving movements of the mouth and lips in coordination with the tongue and jaws must act through BCNs, and since the BCNs are part of the central pattern generator, they do more than perform coordination of the different motor centers.

Although the various mouth-related behaviors may involve thousands of neurons, key features of the information required to generate these behaviors may be obtained from much smaller subsets of neurons consisting primarily of the BCNs and some of the neurons with which they interconnect. Thus, the BCNs acting individually and as a group are *multifunctional* because they must generate activity pertaining to multiple behaviors.

B. CONNECTIVITY OF THE BCNS Figure 1 summarizes the BCN connections. The evidence for these connections have been described in several publications.[32,33,34,137] The present evidence indicates that they connect with one another primarily polysynaptically, as indicated by the interneurons in Figure 1; however, many of these polysynaptic connections may be through other BCNs. In a few cases there may be mutual inhibitory connections between the BCNs, but the exact connectivity, if it can be defined, remains for further study. As indicated schematically in Figure 1, many BCNs converge onto the same target motor neurons, and individual BCNs diverge onto different motor neurons. In turn, the motor neurons neurons feed back to the BCNs that drive them. An identified group of neurons in the brain, the paracerebral neurons (PCNs), converge onto the BCNs, and the BCNs feed back to the PCNs.[65,66,137]

The actual biological network is much larger and more interconnected than shown in Figure 1. For example, there are different pools of neurons that send axons out of the brain through the various motor roots, of which there are approximately a dozen on each side of the brain, though some motor neurons send axons out different roots. Additionally, it is necessary to consider that there are numerous pools of interneurons. Thus, the number of converging and diverging connections in the brain and buccal ganglion is quite large. Moreover, just as there are interactions between the brain and buccal ganglion, there are interconnections between the brain and other ganglia. Therefore, the extended network consisting of neurons affecting the BCNs, and ones that the BCNs affect, involves hundreds of neurons.

What we hope to achieve in our present line of work is to add neuron pools to the core model shown in Figure 1. We want especially to obtain the temporal relationships in the firing of as many of the neurons as possible, partly to use the data to reassess the conclusions we have already reached, and partly to use it to obtain some insight into how such large numbers of neurons interact with one another. The time of firing of all BCNs and PCNs is being extracted from multiple

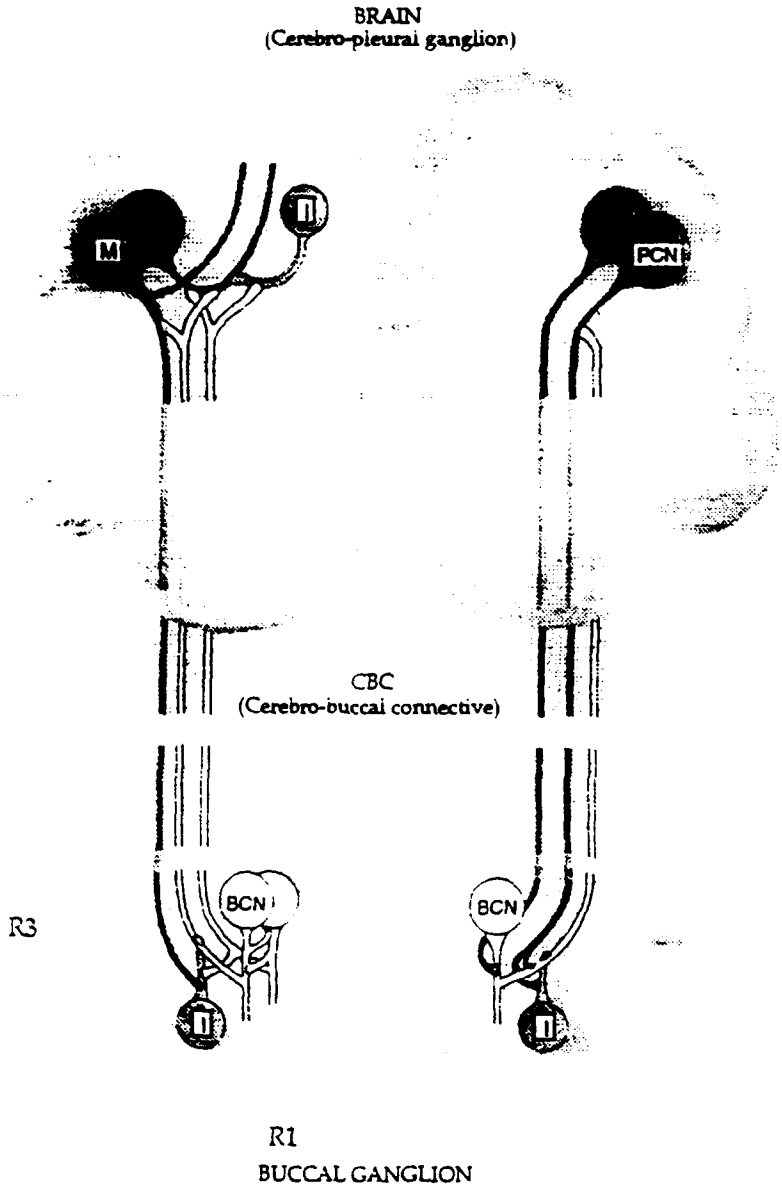

FIGURE 1 Cartoon showing central features of converging and diverging connections in *Pleurobranchaea* nervous system. BCN: buccal-cerebral neurons. I: interneuron.

FIGURE 1 (cont'd.) M: Motor neuron. PCN: Paracerebral neuron. Size of each of these pools of neurons is about 10 to 20 units each. There are many more motor neuron pools, one for each motor root; some cells send axons out multiple roots. R1: motor root that innervates muscles for opening jaws. R3: motor root for closing jaws. Motor roots of brain are not shown. For clarity of presentation, the BCN-motor neuron connections are shown on the left, and BCN-PCN connections are shown on the right. (Illustration here has been modified from Figure 1 in Mpitsos[135].

recordings conducted simultaneously at different extracellular sites along the nerves that connect the brain and buccal ganglia (the cerebro-buccal connectives, CBCs). Since activity occurs in both directions in the CBC, the multiple recording sites allows us to determine the direction of propagation of firing in different nerve fibers, and thereby to distinguish between the BCNs and other neurons. It is only a matter of extended labor to include the time of firing of motor neurons in the different motor roots.

The point of all of this work, however, is not to obtain a complete network, but to use the data to assure that our computer simulations of different model assumptions will provide activity that reflects the activity in the biological system. A particularly important aspect of this work will be to obtain an indication of the types of variations and motor pattern blending that the system generates.

Owing to similarities in their gross neuroanatomical features, which distribute different functions to the buccal ganglion and to the brain, the principles obtained in *Pleurobranchaea* may hold in many other snails and slugs. Moreover, it is likely, though not demonstrated sufficiently, that neurons analogous to the BCNs in *Pleurobranchaea* may have similar functions in all snails and slugs. But it is not clear presently whether other snails and slugs generate as many mouth-related behaviors as *Pleurobranchaea*, and whether the behaviors in these other animals are as variable.

IV. DISTRIBUTED FUNCTION, MULTIFUNCTIONALITY, AND VARIATION

1. RATIONALE FOR CHANGE IN CONCEPTUAL FRAMEWORK: SINGLE CELLS TO CONTEXTUAL GROUPS

Our initial aim for studying this "simple" sea slug was to understand the cellular basis of learning. The many control experiments in the studies of Mpitsos and Collins[140] and Mpitsos, Collins, and McClellan[141] were the first to demonstrate that sea slugs are capable of Pavlovian and avoidance associative learning, and even earlier work, though not as extensively controlled, promised that associative learning could be examined in isolated nervous systems.[143] However, work begun in the mid

1970s. closely examined the motor patterns and behaviors, and showed that networks are multifunctional in being capable not only of generating different behaviors and that similar motor patterns can yield different behaviors.[32,122,123,124,125,136,137] More importantly the motor patterns of different behaviors often blend with one another and the underlying motor patterns of neural and muscular activity are quite variable[32,136,137] As discussed below, rather than a definable reflex system, it seemed possible that networks of neurons work by flexible contexts of action. The variations in the contexts might involve linear regroupings or might arise from nonlinearities that cause rapid shifts or bifurcations in the patterns of activity generated by the network. It became apparent that attempts to attribute specific function to a given neuron, or to locate the engram of a learned behavior to a particular synapse could fail.

Consequently, we had to backtrack, to reassess how it is that even innate or "unlearned" motor patterns arise in such systems before we could address the problem of how newly learned information is incorporated into the network. Although we continued to conduct learning studies after the observations made in the mid to late 1970s, our rationale for doing them has not been to find the locus of learning at specific synapses, but to determine whether learning could actually be identified in the responses of reduced preparations.[136,138,139] Additionally, given the indication that information may be distributed over many neurons it was necessary to develop the technology for identifying populations of neurons that are involved in specific aspects of learning among which we could examine how learning affected cooperative actions among neurons in the population.[145,148,149,172]

The idea of cooperativity, which Freeman and coworkers[170] have used to advantage in their studies of rabbit olfactory bulb, resembles what we refer to as "*contexts*" in neuronal group function. Much of the discussion in this paper will attempt to present our understanding of functional contexts. Early in the development of the idea of command neurons (cells that evoke stereotypic behaviors), Davis and Kennedy[42,43] showed that each command neuron of the lobster swimmeret system produces characteristically different effects and selectively controls different motor neurons, indicating that the command process arises from group action in which each command neuron performs specific subtasks of the command process and activates a particular set of motor neurons. Later work, such as the finding in *Pleurobranchaea* that command neurons receive feedback connections from the motor network that they drive,[65] blurred functional distinctions that may be attributed to single neurons because function seemed to be shared. Davis[41] used the term "consensus" to refer to the emergent actions that might arise among groups of interacting neurons. In studies on locust walking, Kien[89,91] used "consensus" to refer to variable activity in ensembles of neurons. Our thinking on the ability of groups of neurons to act contextually includes variation in the effects produced by individual neurons, by the group as a whole, and in the neurons that constitute the group. For the present discussion we use the idea of "contexts" interchangeably with "consensus," partly because we, too, are inclined to believe that its meaning of "all or most" is descriptive of what may often take place in the number of neurons that become active during normal behavior.

Although there are similarities between our use of the "contexts/consensus" and Davis' and Kien's use of "consensus," there are also some important differences which we shall address. Our definition relies on many factors other than the number of neurons that become active. Therefore, we hold off a definition, which is given in section IV.8, until have first presented behavioral examples, and provided discussions of principles relating to variation, dynamics, and nonlinear function.

2. CONTEXT OF NEURONAL GROUP ACTION: INFERENCES FROM BEHAVIORAL CHOICE

The following example may help to explain our use of the term "consensus" (or "context"): One of the original purposes for studying *Pleurobranchaea* was to examine how animals "choose" to perform a particular behavior when confronted simultaneously by many stimuli that often require conflicting responses, as might occur in the natural environment.[44] For example, turning an animal upside down evokes righting behavior having a definable duration. Presenting food to the animal produces several components of feeding behavior at definable thresholds. When turning the animal upside down and presenting food simultaneously, righting times significantly increase, but feeding thresholds remain constant. By such simultaneous presentations of different stimuli to evoke pairs of behaviors, it is possible to define a behavioral hierarchy,[45] and to view the process of establishing the hierarchy as a reflex system where one behavior inhibits another.[98]

It is necessary, however, to go one step further. Early studies on behavioral "choice"[146] indicated that some behaviors seem to blend into one another, as Kirsti Bellman[18] was to show later in lizards. In *Pleurobranchaea*, for example, the anterior portion of the foot may start to twist in order to right, but, at the same time, it may begin to cup around the descending solution of the food stimulus. The anterior foot appears to be attempting to perform two contradictory behaviors at the same time. Even when righting behavior starts, it is slowed because the foot's motor-system is still receiving conflicting activities, one for righting and one for feeding. We do not deny that reflexes involving inhibition can be found, but doing that alone places one's concepts on the side of the razor's edge in which behavior, and the underlying neurointegrations, are viewed as set and repeatedly definable structures. The important issue to us is the process of forming the behavioral "choice" during the time that the animal is presented multiple stimuli rather than a stereotyped behavioral hierarchy. The two approaches speak about the same behaviors but give different explanations. The contextual approach views behavior as arising fluidity among many different and blendable behaviors. The reflex approach views the animal as a generator of a set of fixed-action patterns (FAPs; e.g., Gillette[64]), each relating to definable ar ' repeatedly identifiable responses in the animal. The definition of behavioral hierarchy forces one to think of behaving animals as concatenations of reflexes or FAPs that are repeatedly definable. In the extreme situation in which an inverted animal lies motionless, neither feeding nor righting, the definition of behavioral hierarchy would lead one to develop experiments showing inhibition between

feeding and righting sensory-motor systems, as shown for the interaction between feeding and withdrawal.[38] It would also lead one to identify a particular locus in the nervous system at which such inhibition takes place. The variability of activity in *Pleurobranchaea*, and the high degree of converging and diverging connections in its nervous system lead us to believe that such localization of mechanism may be misleading. By contrast, when taking these factors into account, one's focus is directed to dynamically shifting contexts of activity in which the identity and location of the underlying mechanism for a behavior is not fixed, just as the behavior may not be fixed and always distinguishable from others. One is more apt to think of variably emerging networks rather than "switchboard" reflexes.

Thus, although the definition of behavioral hierarchy is useful for categorization, and although it is defined using the behavioral choice paradigm, it dangerously excludes the dynamics within choice-making processes. To be sure, reflex actions are indications of a process, but the reflex approach leads one to examine the structure of the network itself whereas an approach that deals with the dynamics of interactions leads one to examine principles of interaction from which networks emerge not only variably but also nonlinearly, as we shall try to illustrate in section VII, when dealing with reductionism, and in section IX when dealing with computer simulations. Inhibitory interactions between motor systems may be used by both explanations, but the dynamical approach uses inhibition either as a potential explanation that may or may not actually take place, or as a participating variable in a system that expresses the dynamics. In either of these non-reflex explanations, the role of *inhibition may not be discernible* from the structure of the network itself, though dynamical explanations must also account for conditions that actually express reflexes.

3. CONTEXT OF ACTION IN THE BUCCAL-ORAL SYSTEM

The buccal-oral system of *Pleurobranchaea*, consisting of the lips, mouth, radula, and jaws, seems to magnify variation and behavioral blending because, as noted above, it is capable of generating many different behaviors and variants within individual behaviors. Moreover, blending happens among the various mouth-related behaviors themselves, as well as with behaviors produced by other motor systems. A number of studies have provided criteria for identifying motor patterns relating to particular buccal-oral behaviors. McClellan[122,124,125,126] and Croll and Davis[38,39] have established specific motor pattern differences in electrical recordings made from muscles and nerves to distinguish between feeding, regurgitation, and rejection behaviors, but even McClellan's studies demonstrated that different behaviors can be generated by similar motor patterns.

Having observed considerable motor-pattern variations, Mpitsos and Cohan[136,138,139] devised a series of associative learning experiments to determine whether a learned response persisted in even minimally dissected animals. The results clearly showed that the behaviors of the undissected and dissected, behaving animals were identical, as determined by direct observation of what the animal

did in response to the applied experimental and control stimuli that were used in training. However, when examining the electromyographic data alone, obtained simultaneously while observing the behaviors, it was not possible to identify consistent differences in the firing patterns of muscles during feeding, regurgitation, and rejection. The information had to reside within these patterns, but the information itself could not be read simply by examining the temporal orchestration of activity in the recorded motor patterns. An alternative explanation is that the information resides in the dynamics of the neuromuscular system as a whole, i.e., in the combination of interactions between the motor output, in the nonlinear loading presented by the muscles and mouth and jaw structures, and in the effect of sensory feedback to the central nervous systems. Such systems may have qualities similar to damped-driven oscillators whose dynamics are sensitive to changes in parameter-constants that control the effects of different variables (e.g., see the description of the Duffing oscillator in Thompson[181]). Not inconsistent with this is that the animal can perform a given behavioral effect successfully using combination of patterns. In neural activity, it may be sufficient to have reached an approximating and variable "consensus" or "context" of action rather than requiring an explicit stereotyped pattern.

The neural sources of some of this variation were identified in studies of isolated nervous systems that were used in order to remove the influence of sensory perturbations. For example, neural patterns reemerge even when BCNs that were initially responsible for generating patterned activity are reversibly removed from the coactive networks (Figure 5 in Mpitsos[137]), showing that different combinations of neurons generate similar responses. Similarly, the firing of some BCNs shift variably between completely opposite phases of the cycle of opening and closing of the jaws (Figure 16 in Mpitsos[137]). Graded intermediates may occur as the nervous system generates patterns of rhythmic activity and spontaneously shifts into another pattern.

Our view is that the intermediate and variable forms of activity give crucial information about integrative mechanisms. Variations that occur within group action must arise from variations at the level of individual neurons. To present these ideas, the next two subsections discuss "attractors" and "attracting states," and the role that different forms of variation and error have in the response properties of biological systems.

4. DEFINITIONS: MODES OF COOPERATIVITY

A. ATTRACTORS AS DISSIPATIVE STRUCTURES An intuitive definition of attractor may be given by examining the property of attraction. Suppose for the moment that we are dealing with a process governed by three variables. The state of the system at any given time is represented by the values of the these variables. The progression of these values over time define the parameter state space of the activity of the system. Plots of these variables, one variable in each coordinate of three-dimensional space, defines the phase space. The flow or trajectory from one

point to another provides a view of the phase portrait of the dynamics of the activity. For continuous periodic activity, the trajectory is a closed loop. A brief external perturbation, applied to one or any combination of the variables, will move the state of the system away from the closed loop. If the trajectory then collapses asymptotically back toward the closed loop, the system may be considered to be governed by an attractor. The set of all possible perturbations, and subsequent dissipative responses shown by the asymptotic recovery, define the inset to the attractor or its *basin of attraction*. In the case of periodic activity the attractor is a *limit cycle*. The activity could also be generated by *chaotic attractors* whose trajectories are not represented by a limit set either before or after perturbations, but by an attracting set. An indication of this set may be viewed through the geometry of the topological manifold in which the trajectories mix. Examples of the mixing geometry of attractors in *Pleurobranchaea* responses and model systems in our own work may be found in Mpitsos[135,142] and Andrade et al.,[6] respectively. Though we have used phase portraits to obtain an intuitive view of attractors, a single dynamical system may have phase portraits containing multiple, competing attractors.[181]

The above-cited work from our laboratory also discusses a variety of geometrical and computational tools that may be used to determine whether the activity is generated by limit-cycle or chaotic attractors. In either case, the most useful for determining whether the system is generated by an attractor is to conduct the perturbation experiments described above, which a major focus of our present efforts in both biological and model systems. Much experimental work needs to be done in this way, but it is quite likely that attractors underlie much biological function, as shown, for example, by perturbation experiments designed to test for resetting of the phase of oscillatory activity (an example of an externally applied current pulse to one of the BCNs in *Pleurobranchaea* is shown in Figure 3 in Mpitsos[137]).

B. LOW DIMENSIONALITY IN HIGH-DIMENSIONAL SYSTEMS As the system evolves to dissipate perturbations, one would observe that the ensemble of points in state space decreases over time, i.e., that there is volume contraction. Volume contraction simplifies the topology of the structure defined by the trajectories, and as pointed out by Thompson and Stewart,[181] "*This can often mean that a complex dynamical system with even infinite-dimensional phase space...can settle to final behavior in a subspace of only a few dimensions*" p. 1.

This phenomenon is particularly important in biological systems because they are inherently high dimensional. A single cell in the visual cortex of the mouse, for example, receives inputs from approximately 5000 other cells,[21] each of which may be a controlling variable. Numerical analyses of spontaneous cortical neuron activity,[156] of EEGs in olfactory bulb,[170] cortex,[4,9,171] and of motor patterns in *Pleurobranchaea*,[135,142] all indicate that the activity is generated by relatively few variables. One of the tasks facing work in animals such as *Pleurobranchaea*, and of correlative computer simulations, is to identify the variables, out of the many available, that become active in low-dimensional activity, and to identify the conditions among these variables that permit low dimensionality to arise. Part of the

goal of our computer simulation is to define minimal structures that permit the generation of different types of attractors, and to determine how different attractors might arise at different times within the same high-dimensional space. An interesting possibility is that what determines which sub-space is occupied may simply be a matter of what attractor becomes established first. In a sense, there may be a type of competition such that the same behavior at some different times may be generated by a somewhat different attractors arising from variable subsets of the available high-dimensional possibilities.

C. TURBULENCE, "ATTRACTING STATES, AND SELF-ORGANIZING CRITICALITY"

Thus, given weak connections, which are common in the *Pleurobranchaea* nervous system,[137] it is not inconceivable that different limit-cycle and chaotic attractors may emerge simultaneously within the same network, moving and blending in space and time, and giving rise to the blending seen in whole-animal behavior[136] and in some motor patterns.[137] These conditions may provide the opportunity for analogs of *turbulence* to occur.[131] As discussed in the computer studies described in section IX, we believe that large groups of neurons need not all act in a coordinated fashion, particularly when a large number of relatively weak synapses are distributed throughout the network. The statistical properties of the network and the effect of weak coupling may permit conditions under which different subsets of the extended network are able to begin acting cooperatively within themselves. Yet owing to extensive convergence and divergence of the underlying connectivity, one subset of neurons may influence the coordinated firing of other subsets. In this way, small foci of coordinated firing may move spatially, blend, or separate in to different foci, much as one might envision of vortices in hydrodynamic turbulence. Instructive examples of such phenomena in physical models have been presented in laboratory simulation[175] and computer simulations of the formation of the large red spot of Jupiter.[115] Videotapes showing the evolution of vortices in the hydrodynamic model and in the computer simulations were seminal in solidifying our own intuition about what may happen in neural systems.[178] In considering the possibility of turbulence in neural systems, our own feeling is that the definition of "attractor" in such cases may not be as suitable as in more definable spatio-temporal structures. We prefer to use the term "*attracting states.*"

Attracting states may have some resemblance to mechanisms of *self-organizing criticality* (SOC) proposed by Bak and coworkers.[10,11,12,15,31,185] The ideas have been applied to models of turbulence in forest fires[14] and the production of unpredictable avalanches that occur when attempting to build mounds of sand by piling one grain of sand over another.[13] Local effects are deterministic and easily observed but the global effects are not predictable from such local information, and partly for these reasons, systems governed by SOC seem to be acting near the "boarder of chaos."[10] To our knowledge, SOC has not been applied to nervous systems. We envision that conditions that would allow SOC to take place would retain the deterministic character of monosynaptic actions between neurons, but given weak interactions, would also permit statistical or random spatio-temporal long-range effects through polysynaptic action.

5. CHAOS AND OTHER FORMS OF VARIATION

A. BIFURCATION PARAMETERS AND CHAOS We shall examine bifurcation parameters in more detail in a section IX. It is sufficient to state briefly that they are parameter constants that control how a system (or its defining set of equations) expresses its nonlinear characteristics. When the system is far from critical points, changes in bifurcation constants have relatively little effect on the dynamics of the system. At or near critical points, small changes in bifurcation parameters produce rapid changes (bifurcations) in the response of the system. Within certain ranges in the values of these parameters, the system may exhibit rapid shifts between different types of periodic activity and chaos as the parameter is successively changed.[6,181]

The simplest definition of chaos is that it is completely deterministic at each step of its temporal evolution, yet over the long term, its response is not predictable. An example we shall discuss later is the logistic equation, given by $X_{n+1} = R(1 - X_n)X_n$ where R is the bifurcation constant. This equation has no random factor in it, yet, for certain values of R, it is not possible to predict the evolution of the time series several iterations into the future given some initial starting value. Despite its long-term equivalence to random noise, the organized geometry in plots of X_n versus X_{n+1} clearly show the deterministic, non-random character of chaos.[121,134,181]

It is difficult to prove that biological systems generate chaotic attractors, owing primarily to their short-lived and apparently nonstationary behavior.[131] However, computer simulations have clearly shown that Hodgkin-Huxley membranes[29,30] and the parabolic burster neuron, R_{15}, in the abdominal ganglion of *Aplysia*[25] may be capable of bifurcating into a broad spectrum of simple periodic and chaotic activity. Our previous studies on the implications of attractors and variation, and of their implication in the generation of contexts of interrelated firing in groups of neurons, have been discussed in behavioral and neurophysiological studies.[136,137,144] And there is some evidence for chaos in the responses of individual BCNs and motor neurons in *Pleurobranchaea*.[135,142] Other activity of single neurons is more consistent with noisy limit cycles.[133,146]

The lessons to be gained from chaos are: (1) as illustrated by the logistic equation, variations arising from chaos are not "noise" superimposed on the information-carrying signal; they themselves represent the information. (2) The information in chaotic systems is always increasing with respect to information available at a given initial time. This is to say that if chaos is to represent behavior, it is necessary to use the long-term phase-space geometry of the attractor driving the system to gain a view of what the behavior is like. Given equal noise-free conditions, the behavior represented by periodic activity can be defined in a single orbit. (3) Periodic or limit-cycle activity dissipates perturbations differently than chaotic systems. As pointed out by Conrad,[37] limit cycles in biological motor systems dissipate perturbations in ways equivalent to heat loss through the body structures innervated by the neural system in question, whereas chaotic attractors dissipate the perturbations by generating new variations. Limit-cycle attractors always return to doing behaviors in the same stereotyped ways. Chaotic attractors generate new variations naturally in response to perturbations because their sensitivity to initial conditions

always forces them to generate the behaviors in different ways, which is to say that behaviors are always different in chaotic systems. (4) Mpitsos and Burton[134] have shown that chaotic discrete processes, much as might occur in spike trains communicating between networks, allow simple networks to perform complicated tasks that would require considerably more complex networks to perform if the signals were generated by nonchaotic discrete processes or by continuous periodic or continuous chaotic processes. (5) It was also shown that the inherent variations of chaotic discrete processes permits networks that receive such signals to optimize their responses either in transmitting the signal one-for-one or in performing computations on them. That is, the deterministic character of chaotic discrete processes allows them to convey information, yet their long-term randomness provides sufficient variation to allow the responding network to learn rapidly. As we shall discuss below, random noise may be used advantageously to perform such optimizations. But random noise has the disadvantage of being high dimensional, and high-dimensional processes are difficult to generate because they must represent many degrees of freedom. Chaotic processes are long-term equivalent to random noise, yet the expression of chaos can be easily controlled using low-dimensional systems and simple adjustments to a single control parameter, as in the logistic equation. In multibehavioral systems such as *Pleurobranchaea*, the combined informational content and variation of chaos may be useful in accessing the different response possibilities.[134]

B. BIFURCATION-INDUCED VARIATIONS Another form of low-dimensional variation arises when systems approach bifurcation points. An intuitive understanding for this may be given by recalling the above discussion on the demonstration of attractors lying in three-dimensional space, and using this example to understand what happens to Lyapunov exponents as the system approaches bifurcation points. In a system governed by three variables, there are three exponents. (A useful discussion of Lyapunov exponents and numerical methods for estimating them are presented in Wolf[190]). A negative Lyapunov exponent indicates that there is contraction in a given direction in phase space. If all three exponents were negative, the flow of points in phase space would collapse in all directions into a single point. For continuous, bounded systems not at a fixed point, at which the system remains at equilibrium at some non-changing parameter state (see definition in Thompson and Stewart,[181] p. 194), Haken[73] has shown that one of the exponents must be zero. In a simple limit cycle governed by three variables, the remaining exponents must be negative. The negativity in the sum of the exponents assures that there is an overall contraction in the flow of points in phase space to keep the system bounded. The summed negativity also assures that the system will dissipate perturbations if they are not so large as to push the state beyond the attractor's basin of attraction. Bifurcations into chaos introduce a positive exponent, but retain the criteria of one zero-valued exponent and that the sum of the exponents be negative. The positive exponent shows that the state of the system in the corresponding dimension of phase space is always expanding. Having a zero-valued Lyapunov exponent indicates that the growth in phase space is neither contracting nor expanding over time. Thus, the

rate of growth of a three-variable[5] system in phase space is given by $2^{(\lambda_1+\lambda_2+\lambda_3)t}$, where λ_1, λ_2, and λ_3 are the corresponding Lyapunov exponents for growth in each direction of phase space, and t is time. Since the exponential change is given as base 2, the exponents express the rate of change of growth in phase space as information in bits per second. Thus limit cycles lose information as they evolve with respect to some initial state,whereas chaotic systems gain information.

As a system approaches bifurcation points, some of the Lyapunov exponents approach zero values, as we show herein for the catalytic network model of Andrade et al.[5,146] Setting the bifurcation parameter, μ, to a value of .02, generates a one-period limit cycle far from a bifurcation point, and λ_1, λ_2, and λ_2, have values, respectively, of 0, -2.8, and -43. Adjusting μ to .0125, well past the bifurcation into a two-period limit cycle, the exponents have values of 0, -3.6, and -43. However, setting μ to .0149, which is near the bifurcation point, the exponents are 0, -.05, and -46: λ_2 vanishes. Thus, as the system approaches bifurcation points, a greater number of Lyapunov exponents approach zero than when the system is farther away from these points. Perturbations in directions of phase space governed by exponents having small negative values would be dissipated slowly. Even in model systems having no extraneous injected noise, transient variations are often difficult to remove when attempting to locate bifurcation points.

Kelso, Schlultz, and Schöner[58] have given the term "critical fluctuations" to the variations observed in human finger movements during phase transitions, or, in our terminology, at critical bifurcation conditions. We have observed similar fluctuations in our own studies using sinusoidal current to drive individual neurons in *Pleurobranchaea* and *Aplysia*.[67] Moreover, since the *Pleurobranchaea* buccal-oral system appears to sit metastably near transitions into different patterns of activity (as shown, for example, by frequent spontaneous transitions of activity in isolated nervous systems; e.g., see Mpitsos[142]), we should expect to see variations in activity simply because of the tendency of the system to pass through bifurcation conditions. In model networks, it is possible to generate activity in the system long enough to get rid of transients. But biological systems, which generally do not have such long-term luxury, should exhibit considerable variation simply because of bifurcation effects, unless they lie far from critical points.

[5]The need for three variables in continuous systems that can generate chaos may be viewed intuitively by examining the flow of trajectories in phase space and their ability to mix as they course through the attractor surface; a typical trajectory will visit every vacinity. Evidence for mixing can be obtained by cutting a Poincare section through the phase portrait and noting the interrelated positions of the crossings of the trajectory through the section.[181] If one places a string on a flat surface defined by two variables, it is possible to conform the shape of the string to flow to a fixed point, to form a variety of self-similar spirals,[166], or to connect the two ends of the string to form limit cycles. However, it is not possible to have nearby lengths of the string diverge from one another and eventually mix in their interrelated positions without causing the string to cross on itself somewhere unless the trajectories flow into a third dimension and then fold back onto a thickened plane; i.e., however imperceptible, there must be a thickness to the surface of the attractor composed of countless layers arising from continuous stretching and folding which brings distant trajectories close together. Discrete processes, on the other hand, can generate chaos in a single dimension, as shown by the logistic equation.

Ed: Note that reference has been added

(also see discussion of the Jordan curve theorem and the theorem of Poincaré-Bendixon in Hofbauer and Sigmund (1988).)

A rather interesting problem of bifurcation-induced variations occurs in regions of the controlling parameter that cause chaos. Such regions are filled with subregions that lead to periodic activity, as can easily be demonstrated by examining the bifurcation parameter of the logistic equation at expanded scales.[181] Therefore, small changes in a control parameter may actually lead to rapid shifts between chaos and periodicity, with each state being accompanied by transient variations. Clearly, there is a need to understand how biological systems cope with the sensitivity in the adjustment of bifurcation parameters and with the different forms of variations that arise from such adjustments. One possibility may be that the large number of converging and diverging connections among neurons may buffer unwanted bifurcation conditions by lifting the controlling effect from residing in single neuron or a few of them and distributing it over a large number of neurons. In this way, the bifurcation conditions emerge from group action, though individual neurons may exhibit near critical behavior. This may also be a reason for the observation of the wide distribution and convergence of neurotransmitters and modulators.

C. RANDOM NOISE Other variability in *Pleurobranchaea* seems to be high-dimensional, or even random, as shown by the response of a single neuron in Figure 1 of Mpitsos[133] and by the analysis of electromyograms in Mpitsos.[136] It has long been known that a little random noise may help systems to avoid local minima which may be defined for the present purposes as non-optimal responses (see Figure 8 in Burton and Mpitsos[23] for a diagrammatic demonstration of local minima). The physicochemical properties of DNA provide an example of one use of noise in biological studies.[49] Heating solutions of DNA (injecting noise into the system) breaks the two complementary strands apart. If the solution is cooled too rapidly, the original complementary bonds between base pairs is not completely restored; i.e., the system has fallen into a local minimum. If the solution is cooled slowly, the strands recombine optimally, forming the absolute minimum. Thus, the terms "local minima" and "absolute minimum" may be used to refer to number of characteristics, such as information storage, reconstruction of an original template, and energy level. Such processes of noise control are time dependent, and usually control noise by decreasing it exponentially. The method is referred to as *simulated annealing*. Kirkpatrick, Gelatt, and Becchi[92] discuss simulated annealing and apply it to several optimization problems, including the placement of computer chips on a circuit board, in which the goal is to minimize wire length and bends, and the traveling salesman problem, in which the goal is to minimize the distance traveled between cities if each city is visited only once. Simulated annealing is time dependent because it requires the noise in the system to have a decay rate, and once the noise has died out, it is necessary to introduce noise into the system again in order for it to be ready to respond to a new situation. Biological systems are generally event dependent, not time dependent. It may be difficult or impossible to determine in advance when the next challenge to survival will occur or what it will be, and when to re-inject noise into the system. Once a challenge has presented itself, there may not be enough time to adjust the rate of decay of noise.

As a step in determining how random noise might be used in adaptive systems, Burton and Mpitsos[23] devised time-independent noise algorithms (TINA) that control noise through the response of the system, as would occur in natural environments, rather than through predefined time schedules. To demonstrate the algorithm, Burton and Mpitsos used simple nonbiological neural networks that were required to learn to transmit or manipulate chaotic input signals, much as might occur if networks communicated with one another with chaotic spike trains. Networks were trained using an error-backpropagation algorithm.[164] Random noise was added to the learning-induced changes in synaptic weights and thresholds, but the level of the injected noise was adjusted on the basis of the amount of error generated each time the network responded to an input event. By such adjustments it was possible to avoid local minima and speed the process of reaching maximal levels of learning.

D. VARIATION-DEPENDENT OPTIMIZATION IN MULTIFUNCTIONAL SYSTEMS Thus, random noise, chaos, and possibly variations arising from bifurcation conditions may provide conditions leading to two different methods of optimizations. The effect of chaotic discrete processes was shown under conditions in which chaos would act as a transmitter of information between networks, whereas the effect of noise was shown when it was added to changes in synaptic weights and thresholds during learning when the network had to respond to the chaotic signal. However, chaos is only short-term deterministic. The long-term statistics of chaotic discrete processes, as might occur in spike trains, are identical to random noise. For systems such as *Pleurobranchaea* or the mammalian olfactory bulb[170] that are multifunctional or contain multiple information within the same set of connections, variations that allow the system to search for one of many attractors or attracting states may be essential.

The three types of variation mentioned above involve different search strategies and control methods. Chaos has a deterministic search strategy and can be controlled through bifurcation parameters in membrane dynamics,[25,29] synaptic release (see the interesting suggestion in Kriebel et al.[99]) and, as we shall discuss in section IX, in synaptic strengths. Neural systems may be able to approximate randomness simply by using weak synapses and by taking advantage of the large number of connections between cells. For example, connections between 10–100 neurons may provide sufficient degrees of freedom to approximate the high dimensionality of Gaussian noise. A number of activity-dependent changes in synaptic strengths or in the probability of transmitter release[37] might provide methods to control noise naturally and in time-independent ways. Some of the "noise" or variations that occur near bifurcation points are deterministic and self-controlled because they are transients that die out asymptotically as the activity evolves over time. Decreases in the value of Lyapunov exponents near bifurcation points would also allow random effects to become amplified, but as the system passes through bifurcation, both the transient effects and random variations diminish.

Variation, not chaos. The point, then, in thinking about adaptive mechanisms is to understand the use of a spectrum of variational types. Owing to its interesting

phase-space geometry and its long-term unpredictability, chaos has received much press. The important issue, however, is not chaos, but variation and its control, and the way variation affects the ability of the system to access different dynamical states. The neural architectures that support the generation of these variabilities and ones that lead to control are unexplored. We provide suggestions in section IX.

6. ERROR AS AN INTEGRATIVE PRINCIPLE

A system that has evolved to meet only one adaptive need can be highly tuned to perform that task well, but when confronted with new adaptive needs, such systems may prove extremely fragile. Alternatively, if the system is naturally variable the output may never be exactly "right" for a given task, but it may be right enough for the system to adapt successfully to different situations. Moreover, given a limited number of neurons, a greater range of outputs may be possible when the system has variable and blendable outputs than when the system contains a rigidly fixed number of output patterns.

Error may not only be a product of system dynamics, it may also be influential in the establishing the dynamics. The first indication of this was in studies of hypercycle catalytic networks originally devised to account for the first steps in chemical or prebiotic evolution.[53,104] Schnabl, Stadler, Frost, and Schuster[165] recently showed that error, expressed as mutual intermutation between reactive molecular species significantly affects the ability of a system to bifurcate into complex, chaotic oscillations. Andrade et al.[6] provide a more biologically plausible model of error utilization in catalytic networks that may be modifiable for application to studies of neural networks. In this model, error arises from faulty replication; i.e., in mutual intermutation the error is transformed into information contained in another reactant species, whereas in faulty replication, information is simply removed from the system. Although the generation of complex (chaotic) behavior in this latter model is less sensitive to changes in error than the mutual intermutation model, analysis of both models using the level of error as the bifurcation parameter shows that error plays a role in the dynamics occurring among the catalytic interaction.

7. DEFINITIONS: DYNAMICS, BEHAVIOR, AND MULTIFUNCTIONALITY

The above discussions provide the background for us to present several working definitions. In the most general terms, we take the term "dynamics" to imply the generation of cooperative activity among a group of interacting components of a system. There may be many different dynamical mechanisms: linear shifts in the aggregates of coactive components, bifurcations, limit-cycle and chaotic attractors, attracting states, turbulence, and self-organizing criticalities are just a few examples that we mentioned. As we shall attempt to illustrate further in section IX, our definition of "neurocircuits" relies heavily on dynamics rather than network architecture.

In much of the preceding discussion, we have used the term "behavior" in the sense that the behaviors are identifiable, as if feeding, regurgitation, righting, and other behaviors in the animal's repertoire, are definable. Indeed, the notion of a repertoire, seems to indicate that they are definable. However, our above discussion of "contexts" and "consensuses" shows that we do not believe that behaviors need be repeatedly the same. For example, the animal ingests food, it may regurgitate it, and it may right when inverted. Yet the animal may perform these behavioral effects in many different ways. If we are correct in our assessment of variations in neural activity and contexts, it is possible that the kinematics of the behavioral effect are always changing. Given this blurring of what the term "behavior" may mean, it is obvious that systems capable of generating many different behaviors using the same neurons must be defined in ways that include variation. Therefore, multifunctional networks to us implies patterns of activity and behavioral effects that lead variably from one effect to another as well as the generation of distinctly different behaviors.

8. DEFINITION OF CONTEXTS IN GROUP ACTION: LINEAR AND NONLINEAR ORGANIZATION

To gain some perspective on our definition of contexts in group function, the above subsections provide some of the necessary background on what we mean by behavior and what we mean by nonlinear dynamics and attractors, different modes of cooperative action, and optimization and its relationship to different forms of variation as these factors play on attractors and on turbulence-like phenomena. The discussion has introduced the importance of local minima and error. The heart of all of these response phenomena lies in the anatomy of convergence and divergence. It is easy to refer to behavior, but once closely examined, we have realized that behavior may not be as definable as presumed, though we do not deny that definable behaviors do exist.

We began this section using references to studies that have considered how distributed interactions among neurons lead to behavior, and which have proposed that the appropriate behavior arises when a large number of neurons, or perhaps all or most of them, become active.[41,89,90,91,187] This is part of what we mean by "contexts" and "consensuses." Linear summations such as implied by "large number" do not address two important problems. First, if attractors or other nonlinear phenomena arise, it is not necessary for the majority, or a large number of neurons, to become active. That is, coherent activity may take place among a minority of neurons, but if the coherence is strong enough, we believe that its effect may override activity that is less strongly organized, though both coherent and noncoherent activity probably affect the actual expression of the resultant behavior. The question, then, is not how many neurons become active but how strong the coherent activity is above a "noise" level. Second, even if the interactions are linearly related, or if robust, stable attractors have not organized, adaptive responses may still take

place, though the effect may not be as strong as in cases when the majority of neurons act together or when there are strong attractors.

V. BEHAVIORAL AND NEUROPHYSIOLOGICAL FINDINGS IN OTHER ANIMALS

1. INVERTEBRATES

A. OVERVIEW OF MULTIFUNCTIONALITY AND VARIABILITY Taking advantage of well-defined connections between four identifiable cells in the buccal ganglion of *Aplysia*, Gardner[60] has shown that synaptic effects between identified neurons vary widely from animal to animal. Drawing an analogy to connectionist neural networks, Gardner points out that the importance of a network is not so much in what its synaptic strengths are but rather in what the set of synapses together can do in expressing the information in an *algorithmic process*. The difference between biological networks and neural networks is that the temporal interrelationships in the firing of neurons may shift, and that the same network may be able to generate different patterns of activity.[136,137] Thus, in Gardner's terms, a set of connections may contain the information for many different algorithms. Our modification to this is that one must not consider the algorithm as being repeatedly the same; i.e., the algorithm is itself variably expressed.

Recent findings in the sea slug *Aplysia*[106,193] and in lobsters[26,75,76,77,106,107] are consistent with the notion that the same network can produce activity relating to different behaviors (i.e., they are multifunctional), as is the work on yet another sea slug *Tritonia*,[52,63] although only the work on *Aplysia* has taken notice of variation.[192] An important paper describes leech locomotion, and asks what it is that the "central pattern generator" really mediates since a variety of variable behaviors were observed.[8] Kien[89,90,91] has published a series of insightful papers on locust walking, and has addressed the notion of variation through observations indicating that different groups of neurons become active to produce a behavior. Variability has also been reported in walking motor patterns in cockroaches.[47]

By the late 1970s the notion that "hard wired" networks can explain behavior had received strong support form studies on genetically inherited ability to generate patterned activity in a many animals.[19] Nonetheless, ten years later, Getting[62] voiced the following interesting conclusion from his work in *Tritonia*. "Networks with similar connections can produce dramatically different motor patterns, and, conversely, similar motor patterns can be produced by dramatically different networks," just as one can read from the work in *Pleurobranchaea*[36] that, "*Organized activity emerges or self-organizes such that different contexts of the same coactive neurons become involved in generating the same or different motor pattern.*" Much evidence in neurobiology has shown that it is possible to ascribe particular function to identified neurons, and criteria of how to do that have been extensively

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discussed.[16,102,103,158] Some of the same researchers have also put forth the contrasting notion recently that conditions might exist under which it may not be possible to ascribe function to particular neurons.[100]

Thus, although the classical perspective still seems to hold, and much evidence exists to support it, there is a growing awareness of alternative possibilities. Our feeling is that it may be difficult to make direct comparisons between animals, even if there seem to be many similarities, as there are, for example, in the general neuroanatomical features of the nervous systems in snails and slugs indicating that their nervous systems contain neurons such as the BCNs in *Pleurobranchaea*. It may be, for example, that feeding systems in animals that evolved to utilize relatively stable and predictable food sources may be less variable than ones having to cope with unpredictable ones. One might envision such a comparison between certain herbivores and carnivores, though the defining experiments have not been done. What is most important in all of this is that people have begun to address the issues, and quite likely the most illuminating comparisons will be ones that involve different response dynamics. Our bias is that variation should be a common observation. In cases not exhibiting variation, the question then has to do with the mechanisms that control variation.

B. BIFURCATION AND RESPONSE MODALITY IN THE LOBSTER STOMATOGASTRIC SYSTEM The recent discovery of the ability of the stomatogastric ganglion in lobsters to generate different behaviors[75,76,77] shows clearly that one must not assume that even the simplest networks produce only single responses. The findings of Cardi et al.[26] are worth casting in our frame of reference relating to bifurcation. The stomatogastric ganglion in lobsters contains a subset of 14 neurons that comprise the pyloric network which acts as a central pattern generator. Of particular interest in this network is a further subset of three pacemaker neurons that form the oscillator. Another oscillator lying in the commissural ganglion sends projections to the stomatogastric ganglion. By using sucrose-block techniques on the nerve interconnecting the two ganglia, it was possible to reversibly interrupt the connections between the two oscillators. When the projections were blocked, systematic injection of depolarizing and hyperpolarizing current into one of the three pyloric pacemaker neurons resulted in continuous variation in the period of oscillatory bursts of activity in the pyloric rhythm. But when these projections were not interrupted, the period varied discontinuously, and, for some ranges of the injected current, two modes of oscillation emerged at a particular level of injected current. Overall the results show that the timing between the two oscillators affected the modes of integration in the pyloric network, and that the commissural projections also exerted neuromodulatory control over the pyloric network.

There are two ways to look at this data. The first is that there is some reflex circuit change that alters the oscillations in the pyloric network when the connection between the two pattern generators is intact. This seems reasonable if one considers that neuromodulation may be capable of adjusting which neurons participate in the oscillatory interactions or their interrelated timing (e.g., Marder[117,118,119]). Using

John's[81] terminology, the network may use "switchboard" factors to control whether the network produces unimodal or bimodal firing in its burst patterns.

A broader perspective holds that the role of transmitters and modulator is to raise the network closer to a critical point for bifurcation. Small, systematic adjustments in the current injected into one of the three pattern-generating neurons push the system beyond the critical point allowing the network as a whole to oscillate in two modes, or to jump discontinuously from one period to another. When that transmitter (or transmitters) is not present, as when the connections between the oscillators are interrupted, the system settles into a state that is far from the bifurcation point. In this case, no amount of injected current will push the network close enough to the critical point to permit bifurcation to take place. What does happen is that the period varies continuously as a function in the strength of the injected current. This is precisely what happens when one varies the bifurcation parameter in a system that is far from a critical point (e.g., see Thompson[181] and Andrade[6]). There are two potential bifurcation parameters in the study of Cardi et al.[26] The way the experiments were conducted uses the polarization state (amount of injected current) of one of the pattern-generating neurons as the bifurcation parameter. However, if there were sufficient knowledge of the cells in the commissural ganglion that project to the pyloric ganglion, their level of firing could be used as the bifurcation parameter for each level of applied polarization in the pattern-generating neuron.

The advantage of using bifurcation analysis may not be appreciated in studies of most experimental biological systems because of their complexity and of the difficulties they pose in permitting selective control of a single parameter. The utility of the analysis becomes more obvious, however, in computer simulations. Not the least utility of bifurcation analysis is that it may provide some predictability. For example, Feigenbaum[59] observed that the succession of period-doubling bifurcations occurs in a universally predictable way. The ratio of differences in successive bifurcations is given by $\mathcal{F}_i = (\mu_i - \mu_{i+1})/(\mu_{i+1} - \mu_{i+2})$, where μ is the value of the bifurcation parameter in the sequence of bifurcations from $i = 1, \ldots, \infty$. For many bifurcation maps, $\mathcal{F}_i$ quickly converges to 4.6692 to the fourth decimal place. The pyloric network may be small enough to permit the use of computational methods. The major task will be to determine what parameter to control, though information from neurohumoral experiments may point to candidate factors. Different bifurcation states may use the underlying network architecture in different ways. The way the network expresses the various firing patterns among its constituent neurons is not predictable from knowledge of the bifurcation parameter itself nor of the anatomy of the neuronal connections. Predictability of these functional or emergent networks is even more difficult in large networks or if variability is a factor. If there are many weak synapses, there may be insufficient synaptic power to control how the activity traverses the connections among the neurons. Previous activity in the network may alter how the neurons participate in the future to produce similar overall patterns of activity. Both factors have been observed in *Pleurobranchaea*.[137] and may affect how the network responds during bifurcation.

2. MAMMALS

The importance of variation in brain function was, to our knowledge, noted first in mammalian studies. The work of Adey and coworkers (see summary in Adey[3]), done over twenty years ago, on the chimpanzee and human electroencephalogram (EEG), and on firing of cortical neurons in cats, clearly expressed the need to consider that noise may have a crucial role in the organization of brain function. Adey noted that while information must be contained in structure, the way the information is expressed quite likely is not obtainable from knowing the connections of structure itself. At about the same time, John[81] discussed the problem of considering cortical structure as statistical rather than as "switchboard" circuits that can be deciphered simply by examining the connections. The ideas expressed by Adey and John were seminal in solidifying reservations in our own laboratory about the viability of ascribing whole-animal behavioral phenomena to simple neurocircuits.[141] Wetzel and Stuart[187] clearly favored a variable neuronal group hypothesis to account for vertebrate walking. More recently, Braitenberg[21] examined ~~that~~ connectivity of visual cortex and suggested that activity flowing through it may resemble a random walk. Rapp et al.[156] analyzed spontaneous firing in cortical neurons and suggested that the variations observed in cortical may not be random, but rather may arise from deterministic low-dimensional mechanisms such as chaos. Variation appears to be an important avenue for self-organization of cooperative activity occurring simultaneously over the entire surface of olfactory bulb. ~~as~~ Freeman and Skarda[170] have proposed. The dynamical state of the bulb shifts from chaotic baseline variations into memory-specific limit cycles that are evoked when the animal inhales odors.

All of these findings are consistent with our own findings in *Pleurobranchaea*, and, in turn, our findings suggest that the different variational types may provide for response optimization into different attractors. Although the work in *Pleurobranchaea* represents the first demonstration that chaotic activity underlies adaptive responses in animals, it is necessary to take the evidence extremely cautiously, as has been pointed out.[131,135,142] ~~To be sure, the responses are often variable, and that is the more important issue than chaos itself~~. However, to the extent that chaos does hold to be the case in *Pleurobranchaea*, and in the various observations described above in mammals, then it may prove a general principle to pursue further that the variations may not only convey information for a behavior but also may provide for one of the methods for response optimization discussed in section IV.

3. DIVISIONS OF THE MAMMALIAN MOTOR SYSTEM: RELATIONSHIP TO DIVERGENCE AND CONVERGENCE

Mammalian motor behavior may be classified as involving the pyramidal system (PS) or the extrapyramidal system (EPS). According to the classical view, execution of all voluntary movement in mammals is initiated by motor cortex acting through the PS, which constitutes a two-neuron chain. The upper motor neuron descends from the cortex and synapses in the spinal cord with the lower motor neuron, which innervates the muscle. Going backwards, each muscle fiber is innervated by a

single lower motor neuron, which is contacted by only a few, perhaps a single upper motor neuron. So, each skeletal muscle of the body has a topical representation in a specific zone of the motor cortex. Stimulation of a specific region results in a stereotype response, which, if the stimulus is focal, includes one muscle fiber only. A given cortical neuron can act in two different states depending on the context defined by preceding impulses from the associative cortex.[179] This seems much like a switchboard, showing a precise structure-function correspondence. It can function as such, but the result is not the kind of movement we'd like to perform. We get an idea of what kind of movements the PS can produce by itself by watching patients with dysfunction of the cerebellum or the basal ganglia, as in the case of Parkinson's disease. Their movements are coarse, as if the limb-moving is not quite sure of the goal. They have often heavy tremor, suggesting an imbalance of muscular tone at rest. Similar imbalance during movement is indicated by rigidity, suggesting that processing of the sensory information about continuously altered position is not occurring fast enough or precisely enough. We might say that the PS does not tolerate nearly as much error as the EPS. It is interesting to emphasize that in cases of cerebellar infarcts or in Parkinson's disease, the spinal cord with all its reflexes is supposed to be intact and functioning the best it can perform. Therefore, the PS may exhibit considerably less convergence of overlapping information and less distributed action. The one-to-one mapping allows the PS to execute precise control of movement but may make it extremely error prone should a particular line fail, whereas the EPS may exhibit less precise control yet may be less error prone when its components fail.

Although the physiological showing that given muscular responses can only be obtained by stimulation of certain cortical neurons indicates that there is little convergence, histochemical data suggest that multiple transmitter systems, presumably from the EPS and spinal cord, converge onto the lower motor neuron. The substances involved include dopamine, noradrenaline, serotonin, histamine, substance P and TRH.[79] The upper motor neuron shows some degree of divergence, since its collaterals contact with EPS neurons and spinal cord interneurons before synapsing with the lower motor neuron.

Classically, anything regulating motor functions other than the PS is defined collectively as the EPS. It includes the basal ganglia, the vestibular system, and the cerebellum, and it is thought to be responsible for coordination of movements. Its components connect indirectly with the PS both at cortical and spinal cord levels. The components of EPS are highly interconnected, although the precise circuitry is incompletely known, a high degree of convergence and divergence are likely to occur in the EPS, as suggested by the morphology of, e.g., the cerebellar Purkinje cells and basket cells. By contrast, the PS has significantly fewer connections among its constituent neurons.

This distinction between PS and EPS, however, may not be immutable, as indicated by motor learning. Consider a musician learning a new piece or a jongleur learning a new number. Initially, the motor pattern is established under cortical control. This always happens relatively slowly and, once it gets fast enough, the cortex cannot handle it and may even inhibit the pattern. Where is the pattern

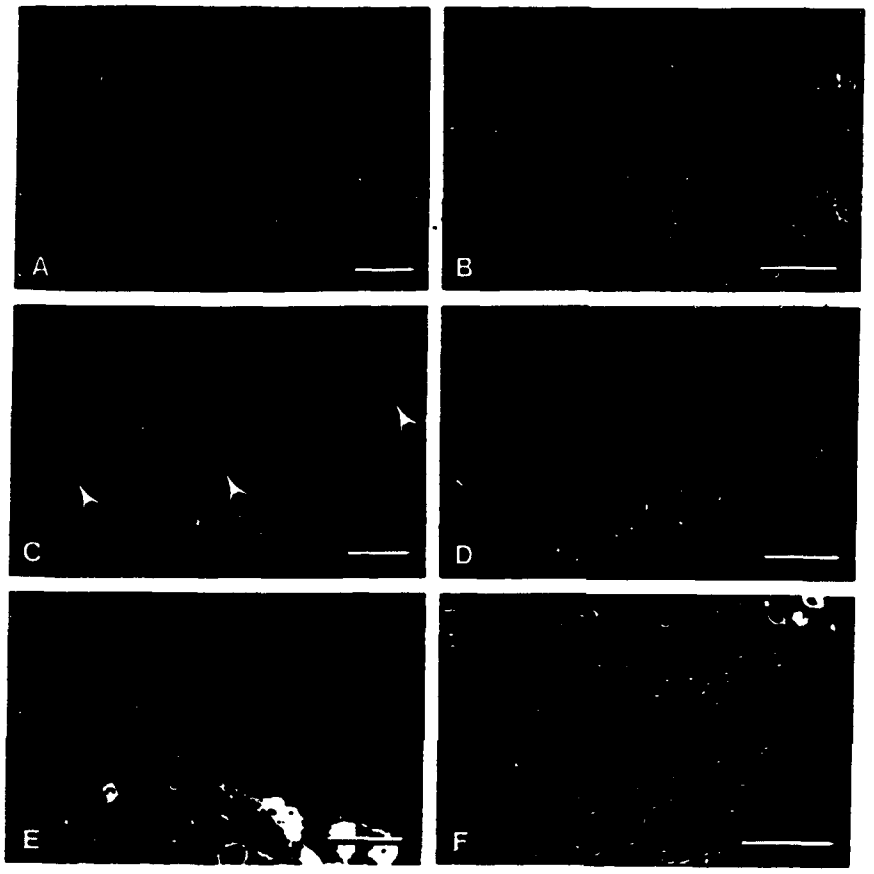
transferred to? It must be some subcortical level that takes over the pattern. All we know is that the control levels must be above the lower motor neuron, which is the final common pathway and that the pattern must be processed by the EPS. Control can be switched back and forth between the different levels, but the PS and EPS seem almost to have switched their functional categorization. To be sure, learning may model EPS to conform to convergence architectures that exhibit less convergence and variation, as discussed below in relation to Figure 4.

The diffuse reticular activating system (RAS) is perhaps most apropos to discussions of convergence and divergence, and adds a control factor that must be considered with all somatic motor functions. We know from everyday experience that rather sophisticated motor activity can take place at the lowest states of activation (sleepwalking) or rather gross errors may occur, if the state of activation is overly high. The structure classically thought to be related to the state of activation is the RAS of the brain stem. Interestingly, this is not really a structure in the sense of the nuclei or the cortex. Rather, its neurons are diffusely spread over a large proportion of the brain stem. Considering the anatomical fact that most of the vital regulation centers are located in that region over a very small space, RAS must be in contact with just about everything. It has been thought that RAS controls mainly autonomic vital functions. However, it has turned out that a reticular system is found all over the spinal cord as well. So it is reasonable to expect that RAS is intimately involved with motor functions too. (Our guess is that the RAS extends over all the cortex as well, if we only had markers to identify the cell types.) Thus, a better understanding of differences in the connectivity and function of the PS, EPS, and RAS, and their interactions, may shed some light on the functional significance of convergence and divergence.

VI. NEUROMODULATION

1. CONVERGENCE AND DIVERGENCE OF NEUROTRANSMITTER SYSTEMS

A. INVERTEBRATES In the classic view, experimental manipulation of individual neuromodulators often generates predictable effects, as has long been demonstrated in other animals.[114,116,117,147] Our own work began with a similar intention: to identify behavior-specific neurotransmitter evidence relating to associative learning. There is good pharmacological evidence for the classically defined type of cholinergic muscarinic receptors (and of a new form) in *Pleurobranchaea*.[148] Behavioral evidence shows that muscarinic receptors have a role in associative learning.[145] Development of immunofluorescence methods for detecting the transmitter for these receptors, acetylcholine (ACH), has allowed us to identify the location of presynaptic cholinergic neurons.[172,173] Using complete serial histological sections to examine



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It is important that micrographs in Figs 2 & 3 come out properly. Do you think I should see final Figure?

FIGURE 2 A-F: Photomicrographs of the neuropil region of *Aplysia* buccal ganglion showing immunoreactivity for (A) histamine, (B) serotonin, (C) ACH, (D) GABA (gamma-aminobutyric acid), (E) VIP (vasoactive intestinal peptide), (F) FMRFamide (Phe-Met-Arg-Phe-NH_2), cross in (C) indicates immunoreactive neuropil, and the arrowhead shows immunoreactive terminals around nonreactive neurons. Bar = 100 μm (A,D,E,F) or 50 μm (B,C). (G)-(I) (now labeled (A)-(C); will be changed): Photomicrographs of the neuropil region of *Pleurobranchaea* buccal ganglion showing immunoreactivity for (G) histamine, (H) GABA, (I) FMRFamide. Bar = 100μm. Note the extensiveness of the immunoreactive coverage throughout the neuropil in all tissues from both animals. Positive immunoreactivity is indicated by the white profiles that are extensively distributed over the black nonreactive areas. For reference, in Figure 2(I), FMRF-amide covers the entire neuropil of the buccal ganglion. The large cell at the right is the buccal giant, and the commissure leading to the left half of the buccal ganglion

FIGURE 2 (cont'd.) is at the left margin. The anterior margin of the ganglion is delineated by the row of dimly stained cells at the top of the micrograph, and the posterior margin is shown at the bottom edge of the neuropil. The area between the neuropil and the row of dimly stained cells contains cell bodies which are not seen because they contain no immunoreactivity. (Modified from Soinila and Mpitsos.[172])

the full extent of the projections led us to the finding that we should have expected from our physiological work, but, interestingly, we did not. The histology showed that a relatively few cells diverge perfusely throughout the nervous system, hardly leaving any portion of the neuropil untouched.

This led us to examine the distribution of over a dozen putative neurotransmitters in complete serial sections of all ganglia in both *Aplysia* and *Pleurobranchaea*.[172,173,174] Examples of these findings are shown in Figure 2 (A-F) for *Aplysia* and in Figure 2 (G-I) for *Pleurobranchaea*. Each transmitter we examined involved a few neurons that diverged and converged extensively over the same target areas of the neuropil, and on individual neurons. The alternative possibility that neurotransmitters projected selectively onto different areas was seldom seen. Our present working hypothesis, which is being examined physiologically, is that there may be little motor specificity in the projection of neuromodulators, though

there may be differences in their actions. Recent physiological findings in *Aplysia*[128] support this hypothesis since individual bath-applied transmitters and neuromodulators appear to affect all motor systems examined.

Given the physiological finding of the extensive convergence and divergence in *Pleurobranchaea*,[137] and the corollary finding in *Aplysia* that sensory stimulation activates perhaps the majority of neurons in a ganglion,[193] the interesting possibility arises that conditions may often arise when many or possibly all neurotransmitters may become active at the same time. In this case, the classic view of neuromodulation that has been generated using selective applications of single transmitters may not provide adequate insight into the physiological effects produced under normal behavioral conditions. The classic view comes, we believe, dangerously close to making an unstated assumption that the effects of the individual transmitters on common target neurons sum linearly. But if conditions arise when the interactions are nonlinear, the classic experimental approach provides us with little insight into how neuromodulation acts to control network function in normally behaving animals.

B. VERTEBRATES As in the above discussion, we provide only selected examples here. Extensive innervation by nerve fibers staining for a large number of transmitters, such as ACH, dopamine, serotonin, histamine, GABA, taurine, glutamate, enkephalin, angiotensin, cholecystokinin, TRH, and vasoactive intestinal polypeptide, has been described in the mammalian striatum.[70] Likewise, multiple transmitters (ACH, serotonin, noradrenaline, glutamate, GABA) have been localized throughout the cerebellar cortex.[167] The wulst ("bulge") is a structure in the avian brain that resembles the mammalian neocortex. It is bipartite and runs the length of the dorsomedial portion of the hemisphere. A medial portion is similar to the mammalian hippocampus (wulst regio hippcampalis, Wrh), and a lateral portion is similar to regions of the somatosensory neocortex (wulst regio hyperstriatica, Whs). Both structures are laminated, permitting experiments that can determine whether neurotransmitters are differentially distributed between and within laminae. Shimizu and Karten[169] examined the immunohistochemical location of cell bodies and fibers containing serotonin, ACH (through localization of choline acetyltransferase, ChAT, and nicotinic ACH receptors, nAChR), catecholamine (through localization of the enzyme tyrosine hydroxylase), GABA (through localization of the enzyme glutamic acid decarboxylase, GAD, and the $GABA_A$ receptor), and the neuropeptides substance-P (SP), leucine-enkephalin (L-ENK), neuropeptide Y (NPY), neurotensin (NT), somatostatin releasing-inhibiting factor (SRIF), corticotropin releasing-factor (CRF), vasoactive intestinal polypeptide (VIP), and cholecystokinin (CCK). Although these substances exhibited laminar specificity, evidence was obtained showing that many regions of the Whs contained overlapping transmitters and neuromodulators. For example, in some portions of a large region, the hyperstriaticum accessorium, evidence was obtained for all substances except CCK, though the density of distribution for each substance was different.

An ideal structure to use for such purposes in vertebrate animals is the retina because of its well-known function and neuroarchitecture, and the ease with which

its various cell types can be identified.[50,186] Present findings indicate that many neurotransmitters and neuromodulators are located in the various cells of the retina,[84] but the methods do not show clearly enough how much divergence and convergence among the cells in the retina or wuist, and how much occurs from the retinal ganglion cells onto other brain areas. A better method of analysis is to use evidence from the location and distribution of transmitter receptors. Progress in the laboratory of Professor Harvey J. Karten[35] at the Department of Neuroscience, University of California at San Diego, indicates that individual retinal cells contain receptors for many different neurohumoral factors, and that many cells stain for the same receptors, indicating that there is extensive convergence and divergence of neurotransmission and neuromodulation. Because of its experimental approachability and well-known function, the retina may provide a rich experimental source for understanding how multiple converging factors interact to control neuronal function.

In human physiology, Parkinson's disease is probably the best-known example of a transmitter-specific defect in human motor function. Its cause is considered to be a decrease in the activity of the dopaminergic nigrostriatal tract. Clinical neurology has established that when the amount of dopamine is too low, the action of the dopamine antagonist, the cholinergic system of the basal ganglia, becomes too strong. The treatment, l-dopa, increases dopamine levels to retain the balance between the two systems. However, there is nothing in here to prove that the action of the dopamine-ACH system is necessarily based on fixed circuits and that it acts individually in normal brain function. Although dopamine is found in a specific tract, we do not know how much divergence or convergence is involved in that system, and what the effects may be when many neurons and transmitters act together.

Although the pituitary is not a classically definable motor organ, it provides an excellent example of multi-humoral control. The intermediate lobe is a morphologically homogeneous group of cells that all contain the same hormones, melanocyte stimulating hormone and beta-endorphin. The question is why are so many different transmitters needed for the simple regulation of inhibition-excitation. Stimulatory (serotonin, ACH) and inhibitory (dopamine, opioids, probably GABA) actions have been described for one substance at a time, but we have no idea how these substances act together. Since the output is so simple and easily measurable (hormone secretion), this tissue may provide a model to study the implications of divergence and convergence of multiple neurotransmitter inputs.

Figure 3 summarizes some of our findings in rat pituitary. The data clearly support the possibility of high convergence onto the same target areas, but since there is presently no morphometric evidence of how many neurons provide the innervation, we cannot presently provide an estimate of the ratios of convergence and divergence. The pituitary is particularly interesting since the output of the system in response to converging actions is neurohumoral rather than electrical.

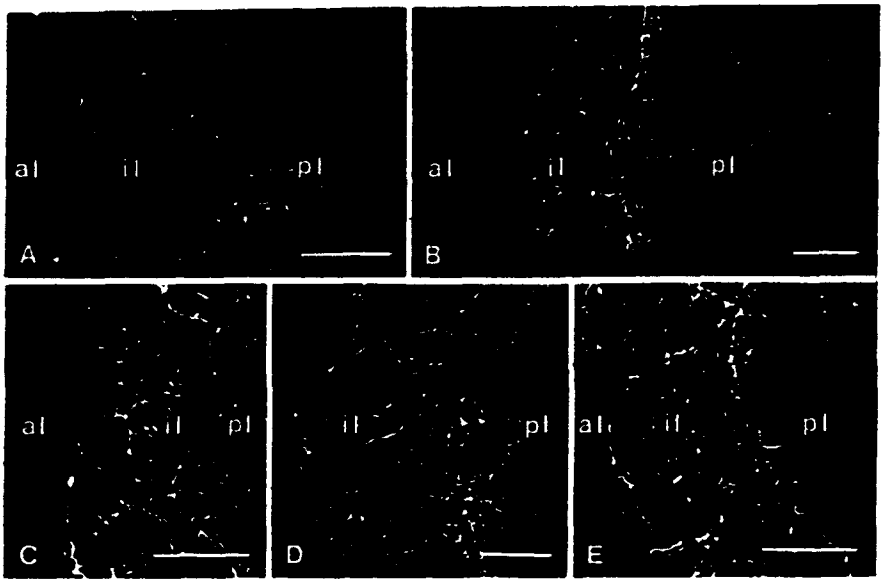

FIGURE 3 Photomicrograph of rat pituitary. al: Anterior lobe. il: intermediate lobe. pl: posterior lobe. (A) Acetylcholine. (B) MEAGL (Met^5-enkephalin-ARG^6-GLY^7-LEU^8. (C) Serotonin. (D) GABA. (E) Tyrosine hydroxylase, the dopamine-synthesizing enzyme. Note convergence of these substances onto similar areas of the intermediate and posterior lobes, as shown ~~above in~~ neural tissues of *Aplysia* and *Pleurobranchaea*.

In Fig 2 p21

In conclusion, we suggest that the properties of nonlinearity, distributed function, variability, multifunctionality, convergence/divergence, and the likelihood that the system is error-prone, all of which we have attributed to the electrical neurocircuit, may also be ascribable to neuromodulation. It may be possible to obtain repeatable effects when controlling certain transmitters, but what the effects may be or how to conceptualize the interaction of many transmitters (acting at very low concentrations) is presently unclear. If the dynamics of target processes (electrical or chemical) are far from bifurcation points, the nonlinearities (or any effect) may not be observable. But given that the bifurcation points are accessible, the number of possible effects arising from electrical nonlinearities and from the effects of transmitters, cotransmitters, and neurohormones become enormous. If we are to believe that neurohumoral agents act variably and in concert, then we must envision further that the subcellular mechanisms that each of these receptors and channels activates, may lead to converging and diverging nonlinear actions within the cell itself. Thus, it is conceivable that the clarity of the mechanisms presented for a single neurotransmitter or a single second-messenger system may be somewhat misleading. The point that needs to be examined further is that there may be many different sites of converging interactions in biological systems that process the

same information in parallel, and perhaps in different ways, but may be capable of sharing the results of such processing. Thus, systems may exist in which it may not be possible to ascribe unique function to any motor, cellular, or subcellular process.

VII. REDUCTION AND EMERGENCE IN CONTROL MECHANISMS

How are these widely distributed physiological and neurohumoral processes controlled? We suggest that many are not, at least not explicitly. It would be too costly, for the same reasons that it would be too costly to devise neurocircuits for each behavior. It seems better to allow the system to be error-prone. As discussed in studies on *Pleurobranchaea*,[131,136,137] some looseness may actually be beneficial since systems needing to be highly tuned to specific tasks may prove to be brittle in variable, unpredictable environments. Put differently, it seems better to allow the interaction between the organism and the environment to determine the behavior than to "hard-wire" encode all of the behaviors that an animal can perform.

1. TRANSMITTERS CONTROL NETWORK FUNCTION AND ARCHITECTURE

There are, of course, demonstrable control mechanisms that we need to remember that show hard-wiring. For example, as we have mentioned previously, it has been shown that selective application of neurotransmitters evokes different patterns of activity in simple ganglia,[48,109,117] just as there is a vast textbook literature showing evidence of the classical "neurocircuit."[82] Most published evidence weighs heavily in this direction. Thus, good evidence exists to show that "*Each neurotransmitter or neurotransmitter system may...be able to elicit, from the same neuronal circuit, a characteristic and different 'operational state.' In this way it would be possible to obtain a wide range of stable neuronal outputs from a single circuit.*"[119]

A remarkable series of experiments by Kater and coworkers (e.g., Kater and Mills[86] and Lipton and Kater[109]), begun initially in the fresh water snail *Helisoma* and now extended to mammalian neural tissues, shows the ability of transmitter receptors to control neuronal growth, plasticity, and even survival of neurons. The work has examined a spectrum of neurotransmitters and neuromodulators, including ACH, GABA, dopamine, glutamate, norepinepherin, serotonin, somatostatin, and VIP. Taking advantage of cell culture of identified neurons, the work has been able to provide a strong basis of control experiments. As one example in *Helisoma*, serotonin retards neurite outgrowth whereas the addition of ACH prevents the serotonin-induced inhibition. The transmitters work through the depolarization state of the cell. For example, presenting an excitatory transmitter alone retards the normal neurite outgrowth, but superimposing hyperpolarizing current on transmitter-induced excitation allows the neurite to resume its normal growth rate. The transmitters may act either through voltage- and receptor-activated channels

on a common intracellular messenger, calcium. As Lipton and Kater[109] summarize, neuronal architectures (and therefore neurocircuits) are determined by a fine *balance* in the activation of these two types of channels through an interplay of excitatory and inhibitory transmitters (though different mechanisms may be used in other neural systems: see Garyantes[51]).

The term "balance" clearly indicates that Lipton and Kater are aware that control in natural biological systems may be high-dimensional since neural tissues are known to contain many transmitters. The problem, then, is to determine how the high dimensionality is expressed. One possibility is that there is simple linear summation of the effects produced by the various transmitter. However, it is well known that the electrogenic properties of the postsynaptic cell can easily change a simple synaptic input into a nonlinear response. Twenty years ago, Wilson and Cowan[189] conducted computer simulations on a population model to illustrate that groups of cells intercommunicating through excitatory and inhibitory connections exhibit damped oscillations, multiple stable states, and, under certain constraints, stable limit-cycle oscillations in the number of excitatory and inhibitory neurons firing per unit time. A rather interesting feature of the model is that local interactions were essentially random, yet the long-range effects were quite organized. Another interesting feature of the model that is pertinent to the present discussion is that the population of excitatory and inhibitory cells were homogeneous: differences arose statistically through use and refractory period. In even simpler networks involving one-shot activation between converging inputs to a common neuron can lead to linear and nonlinear effects in the postsynaptic cell.[5,96] In single neurons, it may be possible to generate many different periodic and aperiodic firing patterns by means of fine adjustments to a single ion channel.[29] This latter study also showed that intracellular calcium concentration may fluctuate differentially and nonlinearly in each dynamical state. Therefore, the controlling balance between converging transmitters and neuromodulators that affect neuronal structure need not be a simple linear affair. What may seem a linear balance, under some parameter ranges of the neuronumoral state, can easily switch to drastically different conditions at critical bifurcation conditions.

The dynamics of interactions arising in population of cells need not employ the full high-dimensional space. Going back to our notion of attractors, the different dynamics that a network will allow determine the characteristics of temporal visitation of activity at any given neuron in the coactive group; i.e., a set of connections will be activated differently by the types of attractors that it can sustain. Although a developing network at some primitive state may exhibit different dynamical capabilities than a finely tuned, mature one, the same questions of nonlinear conditions arise in both. Finally, if attractors arise either in the responses of single neurons or in networks of them, the high-dimensionality we see in the number of transmitters present may not necessarily be expressed as a high-dimensional process. It is an interesting possibility, raised by numerical studies, that coordinated activity in potentially high-dimensional systems often results in low-dimensional attractors.[142,170] From a simple listing of the number of transmitter resulting from experiments in which transmitters are applied one at time or in pairs, it is not evident how the

system dynamically collapses into low-dimensional control, and which of the transmitters become involved. Even in small model networks in which all of the driving differential equations are known, it is not obvious from the equations themselves, nor presently from the connectivity, how it is that a lower dimensionality arises from a larger possible set of available variables unless the system is examined after activating it.[5]

Given a linear system, it may be possible to say that neurotransmitters are architects of neural structure. But, as we shall discuss later in section IX when dealing with bifurcation in minimal networks, conditions may arise when the activity itself is what fine tunes a network, and in turn, the network redefines the type of activity that can emerge. There is a dialectical interplay between the two elements, and this dialect, we believe, can act as an architect of neurons and circuits. The chain of events that we might envision of the events that control cell structure is as follows: The dynamics of firing in individual neurons and in networks of them acts on structure through transmitters; the transmitters act on the cell through calcium. The dynamics of changes in intracellular calcium sets up a chain of events that affect cell growth. But cell growth redetermines what the dynamics will be, and so forth recursively. Other factors may contribute, such as synaptic competition. If the notion that many neurons act in close temporal association, or in coordination, is correct, we must then add the complication that the system as a whole is extremely high-dimensional and that many types of nonlinearities may occur. As we shall speak below of the locus of learning, there may be no *sine qua non* balance of neurohumoral agents for a given architecture to appear. Although there may be many systems in which there is always a precise connection between a balance between a particular set of chemical elements and structure, understanding these systems gives little insight into others in which variability is an issue.

Thus, while the scientific method at our disposal provides elegant connections between cause and effect, much as Descartes and Euclid would like us to believe, the possibility of high-dimensional space, of nonlinearities, and of the dialectic between structure and dynamics indicate that our view of complex systems may be too simple. However, the scientific methods, as they are, are nonetheless the only ones we have. Therefore, our concern is not that the methods and conclusions are simplistic but rather it is that they do not address fundamental questions that need to be asked. Moreover, the clarity of some of these reductionistic methods and the importance of the resulting findings have overshadowed the need to go beyond them and to develop methods of data collection that may be useful in taking that step.

2. CONTROL OF WHOLE-ANIMAL BEHAVIOR: REDUCTIONIST EXPLANATION OF LEARNING IN APLYSIA

A. SYNAPSE-SPECIFIC CONTROL OF BEHAVIOR A tradition in invertebrate neurobiology holds that an advantage of using invertebrate animals is that once a behavior is identified with a particular motor pattern, the same behavior can then be studied neurophysiologically in the motor patterns of isolated nervous systems. As discussed

briefly in section IV.3, this is quite difficult to do in *Pleurobranchaea*.[136] However, the most elegant example of such reductionist approaches has been the identification of site-specific learning in the gill-withdrawal response in *Aplysia*.[27,58,83,144] A long series of studies have attempted to show how changes at monosynaptic sites between sensory neurons and motor neurons can explain whole-animal phenomena such as sensitization, dishabituation, and associative learning. The mechanism involves serotonin as a neurotransmitter in the reinforcing pathway. The original series of experiments showed that activation of serotonin receptors on sensory neurons leads to a chain of events involving adenosin 3′,5′-monophosphate (cyclic AMP) that depress a potassium current when the cell fires. This exposes an inward calcium current that broadens the action potential, and, owing to the increase in intracellular calcium, leads to increased transmitter release onto the follower motor neuron. A group of sensory cells, referred to as the LE-neurons, which are usually activated electrically in isolated ganglia, provides the input to identified motor neurons of which neuron L_7 is perhaps the most important in terms of its effect on the movement of the gill. A group of cells, referred to as L_{29}, provides the serotonergic input.

B. COMPLICATIONS A number of important extensions and problems have arisen that both greatly illuminate and complicate this simple model system. We cite only a few examples:

1. *Peripheral nervous system.* From the beginning of work in the late 1960s, evidence has existed indicating that emergent effects may involve the peripheral nervous system which is distributed within the gill itself. Indeed, in many cases the abdominal ganglion seems not to be necessary for generating robust gill withdrawal responses and simple forms of learning.[144]
2. *Complex behavior.* The once-presumed simple withdrawal reflex has turned out not to be so simple, and consists of several different types of movements.[106]
3. *Neuronal function.* Some of the major identifiable motor neurons have variable function within the same experimental preparation within the same behavior.[107] This raises strong questions in *Aplysia* as to the veracity of assuming that identified neurons have consistently the same role in a given behavior, much as Mpitsos and Cohan[137] have raised regarding the function of neurons in *Pleurobranchaea*.
4. *Complex network.* Small, well-localized sensory taps activate perhaps half of the cells in the abdominal ganglion, showing that there is extensive divergence of sensory and possibly other effects.[193]
5. *Non-constant activity.* Cells partaking in successive taps are variable.[192] suggesting that localization of the network may be difficult or impossible.
6. *Source of serotonergic control is unidentified.* Activation of L_{29} produces enhanced transmitter release. Serotonin applied experimentally produces same effect. But L_{29}, which was thought to provide the serotonergic enhancement, apparently does not contain serotonin.[93,151]

Ed: subscripted "B" SCP_B

7. *Multiple neurohumoral factors enhance synaptic release.* We now know that at least two other transmitters, small cardioactive peptide A and B (SCP_A, SCP_B), broaden action potentials in LE cells and produce synaptic facilitation on their follower motor neurons,[2] but apparently they are not located in L_{29}.[101] Interestingly, SCPB produces spike broadening but not facilitation of transmitter release in depressed sensory neurons,[154] which may relate to mobilization of transmitter.
8. *Multiple subcellular processes.* There may be diverging cyclic AMP-dependent processes in different forms of synaptic facilitation.[68] Conversely, in both the gill-withdrawal system and the analogous tail-withdrawal system, cyclic AMP-dependent and cyclic AMP-independent subcellular processes may converge onto the same spike-broadening mechanisms in both the gill-[94] and tail-sensory neurons.[177]
9. *More than one group of sensory inputs.* The possibility has been raised that under some conditions, novel sensory neurons may be involved in modification of a siphon withdrawal response whose behavioral modification has been thought to be controlled by changes in the LE sensory neurons.[191]
10. *LE cell activity lacks timing to be primary site of learning.* Most importantly, it now appears that there is a second group of sensory cells that have lower thresholds than the LE cells,[36] and are probably more likely to activate than the LE cells during training of the gill withdrawal response itself. It has now been reported[36] that the latency of responses in mechanoactivated LE cells in all of the 32 preparations that were tested always occurred *after* the initiation of the discharge in the motor neurons. Their timing in the behavioral reflex has been difficult to determine.[24]

The problem, then, is if the *cellular basis of behavior* relies on the LE cells as the site of facilitated transmitter release, the responses of the LE cells must occur *before* the initiation of motor output for that behavior, but the recent findings show clearly that they do not.

3. EMERGENT CONTROL OF *APLYSIA* BEHAVIOR: PARALLEL DISTRIBUTED PROCESSING

A. DON'T WORRY, BE HAPPY: NEW SYNTHESIS It might be tempting to some interpreters of the above-mentioned complications in *Aplysia* to disparage the original conclusions about site-specific learning. We believe, however, that that would be a mistake. To dismiss the original conclusions would be to fall to the temptation

that has faced previous work on learning in *Aplysia*, and of most such attempts in other animals, that there is, in fact, some other reducible locus of learning, or some reducibly identifiable neurocircuit as the generator of behavior. But by making the dismissal, one would miss the more important issue that emerges from the findings, namely, that the data may be influential in redirecting the focus from reductionism to a higher level of analysis. It is not just that behavior may be different on different occasions. A general scheme appears to have emerged in all of the work on *Aplysia* that is not inconsistent with the findings we have obtained in our attempts to understand the integrative processes that generate behaviors in *Pleurobranchaea*. This scheme relates to our discussion above of parallel processing arising from the extensive distribution and sharing of information, as we summarize below in subsections B and C.

B. THE LOCUS OF LEARNING MAY NOT BE AT A UNIQUE CELLULAR SITE The evidence cited in the above list of complications may be reinterpreted as in the following general scheme: Different sites in the nervous system are capable of generating similar components of the same behavior, and each site is capable of affecting the other; i.e., there is apparently extensive convergence and divergence between different sensory and motor centers. Within a given sensory-motor system, divergence is an inherent effect of even small, highly localized stimulation. At the same time, different sensory pathways converge on the same motor neurons. Similar convergence occurs among neurohumoral systems and their subcellular effects.[172] Thus, mounting evidence indicates a cascade of diverging and converging chemical interactions that distribute sensory and motor effects widely, ~~in innate response and in responses arising from different forms of learning.~~

Evidence exists that supports these possibilities. For example, we know that weak, highly localized tactile stimulations, as used in training experiments to show learning, activates large numbers of neurons,[193] i.e., that divergence distributes information over many cellular loci. We also know that learning occurs in both the peripheral and central components of the nervous system of *Aplysia* (see review in Mpitsos and Lukowiak[144]). We also know from studies in isolated nervous systems and from more intact preparations that conditioning-related changes occur on LE sensory neurons that synapse on different gill motor neurons. Training-induced changes may occur at the neuromuscular junction.[50] Additionally, changes may occur during training that follow all of the criteria established for associative learning but which do not take place between the sensory neurons and their follower neurons. For example, Lukowiak and Colebrook[113] have obtained evidence of associative conditioning that excludes the major gill motor neurons. The conditioned stimulus (CS) consisted of weak tactile stimulation of the siphon skin. The unconditioned stimulus (UCS), in one set of experiments, consisted of strong electrical stimulation of the pedal nerve which connects the brain with the foot, and in another set of experiments, it consisted of strong tactile stimuli to the gill itself. During training, dual intracellular recordings were made from sensory neurons and major identifiable gill motor neurons (L_7, LDG_1, LDG_2, L_9). The movement of the gill itself was also monitored. In the course of training, the CS produced gill-withdrawal movements

that increased as a function of the number of training trials, and the efficiency of the sensory-to-motor neuron synapses increased. Appropriate control experiments showed that the effects were consistent with associative conditioning. However, the number of action potentials produced in the motor neuron in response to the CS correlated well with the actual movement of the gill only during the initial stages of training. But most of the amplitude changes in the gill-withdrawal response was not correlated with any changes in the number of action potentials generated in the motor neurons. In another set of experiments, designed to mimic associative learning observed whole-animal studies, evidence was obtained for associative learning in a significant number of reduced preparations in which there was an increase in the number of action potentials produced in the motor neurons, but there was no change in the amplitude of the gill-withdrawal response.

Findings such as these show that associative learning, and simpler forms of learning such as sensitization and habituation, may take place at many different loci. Thus, as regards the complication 10 noted above, it is not too big a jump to realize that learning could also happen in classes of sensory neurons other than the LE cells, and eventually to discover that learning-related physiological changes may also be shown postsynaptically in the motor neurons themselves, not just presynaptically in the sensory neurons. Additionally, as Mpitsos et al.[141] have pointed out in detailed control studies of associative learning in *Pleurobranchaea*, let us not be wedded dogmatically to a definition of associative learning that forces physiology to comply with a particular protocol of stimulus presentations applied by the experimenter to whole animals. Single-trial training in this study showed that, for short intervals between CS and the UCS, backward conditioning produced almost as strong conditioning as forward conditioning. Mpitsos et al. pointed out that what may be temporally controllable experimentally in the application of sensory inputs may not hold physiologically. The same set of subcellular mechanisms producing learning-related changes in forward between the CS and UCS (which is required by the definition of associative learning) may exist to some extent when the stimuli are presented in close temporal pairing but in reverse order. To us, changes arising from both the forward and backward temporal relationships between the CS and UCS can represent associative learning (though this does not exclude arguments for different mechanisms, should they occur, to account for backward conditioning). For these reasons, it also may not be too big a jump to accept the fact that learning may still take place in the LE neurons of *Aplysia*, even if their responses arising from stimulation of sensory skin do not occur until after the motor neurons are activated by other sensory neurons.

Thus, while it is possible that a unique "locus of learning," the engram in *Aplysia*, might still be found, the data indicate strongly that *the system seems to consist of many parallel, redundant, and possibly interacting components, none of which may be the* sine qua non *element in the learning process or in the generation of the motor responses, irrespective of whether or not they involves learning.*

C. THE NEUROCIRCUIT MAY NOT BE DEFINABLE Another tradition of reductionism in neurobiology, particularly in studies of invertebrate studies, has been the notion that cells and their function are repeatedly identifiable. We have already mentioned some of the problems in identifying function in *Aplysia*.[50,107] The recent computer simulations of simple neural networks relating to the feeding system of *Aplysia* have led to a similar conclusion that, "*...tests done on individual neurons can provide misleading information on the actual role of the neuron in generating behavior.*"[100] Compare this quote with one from Mpitsos and Cohan,[137] p. 538: "*...these findings indicate that the classic technique of driving a particular neuron in order to assess its effect in evoking activity or a behavior may be an insufficient criterion for identifying its functional role.*" That is, a given neuron's function depends on the context of activity in which it takes part. But, given variability in the activity in the firing patterns within such contexts or "mobile consensuses," even this might be an insufficient definition.[32,131,137]

The neurocircuit for a behavior is misrepresented by even the most complete mappings of identified neurons that we see in publications. Studies using voltage-sensitive dyes show that weak, localized stimulation of sensory skin of the siphon produces massive and variable activation of neurons in the abdominal ganglion of *Aplysia*.[132,193] As we have discussed of the simplified networks shown in Figure 1 for *Pleurobranchaea*, the connectivity the actual circuit of interacting neurons is quite large. The larger the overall pool, and the greater the number of weak synapses that exist, the greater will be the possibility that the actual network generating a behavior will be variable and undefinable.

D. DIFFERENT LEVELS OF LEARNING WITHIN DEFINABLE SETS OF SYNAPSES. Let us assume for the moment that a small group of neurons can be isolated functionally from the effects of other groups of cells. Can we then obtain sufficient information about the network to define it completely by looking at the network and knowing all of the connection parameters? We think not. Consider just one example relating only to the strength of synapses. In our own neural network simulations, the data indicate that synapses contain different forms of information.[23,132] One form of information ("knowledge") is task-specific relating to the computations of one or more functions that network must perform. Another form ("metaknowledge") has to do with the process by which that task was learned: it does not affect the network performance on the specific tasks, but only becomes evident when the network is confronted with new tasks. These conclusions were drawn from experiments that compared learning performance in networks that used random noise to optimize changes in synaptic weights against networks that were not exposed to noise. Both types of networks were allowed to reach the same level of learning on a given task, but the noise-exposed networks learned a subsequent task faster, even when noise was not included during training of the second task, than networks that did not use noise. Starting networks at different initial synaptic strengths at the beginning of a training session yields different final synaptic settings, but all final networks perform the same learned task equally well. Because of this, Burton and Mpitsos initialized networks using different synaptic strengths and thresholds.

Then, examination of a large number of networks at the end of the first training session revealed that the two types of training methods did not generate statistically significant differences in the means and standard deviations of the synaptic weight settings. Both types of networks contained the same information for generating equally accurate computations relating to the first task, but networks that were exposed to noise contained further information that permitted them to perform well on a second task. Each task has a particular error landscape associated with it (see Figure 8 in Burton and Mpitsos[23] and Figure 13 in Mpitsos[134] for examples of error landscapes and volumes). Burton and Mpitsos suggest that noise-exposed networks sample these error-structures more completely than networks that were not exposed to noise. Thus, when confronted with new tasks having any similarity in their error structures as the first task, the synaptic settings of networks exposed to noise already contain information about the new task and are able to navigate its error fields rapidly. By contrast, since networks that are not exposed to noise contain less of such information they are not able to navigate as rapidly through the new error structure.

The implication of these findings for the present discussions is that one may look for changes relating to a given task, but depending on the conditions under which that task has been learned, the aggregate of synapses within a pool of neurons may contain different types of information, where one type pertains specifically to one or more tasks that have been learned, and the second type pertains to more general conditions that do not affect the accuracy of the first, but nonetheless may camouflage the results that the experimenter is seeking to identify. The rabbit olfactory bulb[170] may be a useful example to contrast our findings. In this structure, odor-specific information is stored spatio-temporally, but apparently all neurons take part in expressing the code for each odor. Our simulation networks can also be constructed to encode information relating to multiple tasks,[134] but the noise-induced changes in the network represent an informational abstraction that goes beyond the information need specifically to perform well on previously learned tasks. Therefore, if our computer simulations of connectionist neural networks have analogs in biological systems, the understanding of synaptic modification and the information that the synapses contain cannot be deciphered simply by examining the synapses themselves as they relate to only one task. In their studies of Mauthner neurons, Faber, Korn, and Lin,[57] raise the related caveat, but for different reasons, that "...although it is possible to derive generalized rules of the operation of synapses, their variants may exert a major role in shaping the behavior of complex circuits."

Analogous problems as those described above and in the preceding two subsections may have beset Lashley[105] whose unsuccessful attempts to identify the locus of stored memories (engrams) in the cortex have been more inspiring and illuminating, at least to us, than were he to have found them. It is interesting that much of neuroscience has followed the same course as Lashley, but on the cellular level in attempting to identify behavioral phenomena in terms of single synapses and single neurons, ~~and in the process has generated equally instructive findings.~~ It is also interesting that Pavlov, before Lashley, was apparently discontent with the

possibility that learning could be localized to particular areas of the cortex since learning persisted in his animals even after they had suffered brain damage (see Boakes,[20] pp. 127–128).

4. "FUZZY" CONTROL

Thus, the "control" we seek to define for the physiological and neurohumoral aspects of the nervous system is oblique and emergent rather than being crisply Euclidean in postulating particular causes and effects as would be expected of reflexes. One feature of such emergence is that there may be many ways to do the same thing, and even gradations between these ways. We know, for example, that under some conditions, removal of a neuron from acting in a motor pattern can be compensated by shifts in the activity of other neurons.[137] Redundancy, arising from information sharing among convergent pathways, compensates for error or failure in some of its components, even if these components originally generated strong control over the other members of the coactive group. Are neurohumoral systems equally redundant, or does each of the ever-growing number neurotransmitters being identified daily have a unique task? Our own work leans heavily toward the first of these possibilities.[172] In the same sense that there may be "lazy" synapses in neural networks,[134] whose presence is required only under some conditions, are there "lazy" or even unnecessary transmitters? Some of what we see in a given system may represent baggage of evolutionary or developmental processes. This, however, provides for yet another form of variation that permits possible adventitious incorporation into further evolution or behavior.

5. IS OUR VIEW HOLISTIC?

No. Being concerned with mechanisms that generate global behavior is not necessarily being holistic. In our approach, global behavior depends on local rules followed by individuals acting within a large group. It is these rules that we seek to identify, though there may be different rules that relate to global behavior directly. Even in simple processes such as building of sand-grain mounds[13] and affine transformations,[16] the global consequences of local behavior are not predictable. Nevertheless, emergent function need not be a property of large groups of neurons.

It is interesting, however, that one of the best examples of work in artificial intelligence in many decades employed a top-down analysis in which a principle obtained from studies on the behavior of whole animals was used to gain insight into how that behavior might have emerged from individual neuronal units. The work we refer to is Klopf's[95] drive-reinforcement model of associative learning, which extends Hebb's[74] rule to account for Pavlovian conditioning. Hebb's rule states that, *"When an axon of cell A is near enough to excite cell B and repeatedly and persistently takes part in firing it, some growth or metabolic change takes place in one or both cells such that A's efficiency as one of the cells firing B is increased."* Before Klopf's

Ed: Note reference Klopf (1982)

model, computer simulations of Hebb's rule in simple networks were not successful in demonstrating learning that mimicked findings in biological systems.

Hebb's rule may be interpreted as a three-cell network,[141] one input cell for the CS and one input cell for the UCS, both of which synapse on a common follower cell (cell B). Klopf made the following crucial modifications to the rule to make it work in such a simple system: (1) Temporal delay was added between the onset of the CS and UCS. (2) Synaptic modification was made proportional to the rate of change in the CS and UCS. (3) The follower cell (B) itself expressed a form of behavior analogous to tendencies that may be observed in whole animals: Whole animals seek to optimize some quality of their environment, such as avoiding pain and enhancing pleasure. Klopf made the simple, but crucial analogous assumption that cells tend to optimize excitation and reduce inhibition. Additionally, to account for excitation and inhibition, the follower cell received excitatory and inhibitory terminals in its CS input pathway.

(1988)

(1982)

The methodology for training the network is the same as for training the whole animal. In each training trial, a pulse is presented to the CS input, which initially produces little effect, and after a short delay, a pulse is presented to the UCS input. The only parameter that is arbitrarily set in the model is the constant for the rate of learning. Amazingly, training-induced changes in the synaptic effect of the CS input on the follower cell reproduced all of the known Pavlovian conditioning phenomena in experimental animals and in humans (e.g., backward conditioning, CS alone, UCS alone, trace conditioning, second-order conditioning, foreshadowing, blocking, conditioned inhibition, etc.).

The model has now been extended to account for instrumental conditioning.[129] The work also made progress in resolving the long-standing debate relating to the theoretical relationship between Pavlovian and instrumental conditioning since the instrumental conditioning effects in the model emerge from Pavlovian conditioning. Thus, computational methods may have resolved what psychological debate and experimentation in biological systems have not been able to do. The studies discussed in section IX pursue the same rationale of using simple rules to lead to understanding of global effects.

VIII. DOES A THEORY EXIST?

At least three important principles have emerged from dynamical systems studies that are important to biologists: (1) The notion of attractors. (2) A considerable amount of information about a system can be gained from bifurcation analysis. And (3) an understanding of the dynamics of a system can be obtained from the phase-space geometry of such attractors. By these methods, it is possible to discover much about a system without having to resort to the difficult if not impossible task of uncovering the sets of equations that actually run the system.

that distributed networks can generate

A long history of work has developed these ideas, from Poincaré to Lorenz, Crutchfield, Farmer, Packard, Rössler, Ruelle, Takens, Swinney, Shaw, Yorke, and others of the many recent contributors to the knowledge of nonlinear dynamics.[1,181] There are many theorems in the field of nonlinear dynamics and there are many discussions of how to handle the nonlinearities.[71,72,168] beautiful demonstrations of attractor topologies, bifurcations, and stability analyses, when these are in fact available. As important as these are, they do not constitute a unified theory, at least not as it *might* apply to brain function, though Bak and coworkers suggest that their mathematics or models of self-organizing criticalities.[10,11,12,13,15,31,185] which apparently account well for many physical and biological phenomena, may provide an encompassing dynamical theory.

One way to get around the theoretical problems, as is often suggested by physiologists and non-physiologists alike, is to perform computer simulations on systems whose state space is completely defined and parameterized, that is, to determine all of the connections between neurons, membrane properties, neurotransmitters, firing thresholds, and the like. However, one look at the complexity of the connections and at the wide divergence and convergence occurring in even "simple" systems should provide convincing evidence that this approach is hopeless.[35,137,172,193] Moreover, as discussed above, the reductionist neurocircuits that have been developed over the years to account for behaviors are but a caricature of the actual "network" that generate the behaviors in intact animals.

The possibility might also be suggested that insight into the integrative principles might be obtained from the mathematics describing the biological systems. This also seems an unlikely possibility at present, even in relatively small systems. Even in well-defined experimental systems, the first evidence of dynamical states and their bifurcations came from direct observations. One such example is the Belousov-Zhabotinsky reaction which consists of about 30 chemical constituents in which malonic acid is oxidized in an acidic bromate solution.[151,162] While it may be possible to define the various reactant species and list the reactions, it has not been possible, to our knowledge, to predict the dynamics of the system using the mathematics of the reactions. Another example is the demonstration of different dynamical states in yeast glycolysis.[120] As yet another example, near the turn of the century, Duffing extensively studied damped-driven oscillators, yet the full force of the dynamics in his simple model system was not uncovered until recently using computer simulations.[181,182] Lorenz's landmark paper[110] showing the first instance of persistent chaos in a simple mathematical model of fluid convection was found accidentally in computer simulations, not theory.

Finally, even the application of extant dynamical systems tools to time series of experimental data provides little recourse.[131] These tools have largely been developed using simple models whose responses can be generated sufficiently long to obtain an indication of their dynamics. Biological responses, by contrast, are often extremely short lived. For example, chewing and swallowing behaviors in humans as in *Pleurobranchaea* may be generated by robust attractors, but so few cycles are generated that characterization of their dynamics, whether they be limit-cycle or chaotic attractors, is not possible. Even in ideal systems, a certain amount of

guess-work needs to be done. For example, work in our laboratory has found that the Grassberger-Procaccia algorithm significantly overestimates the attractor dimension of limit cycles and underestimates it for chaotic systems, particularly as the dimension increases, even for model systems such as the Rössler hyperchaos.[159]

The positive side of all of these problems is that biology stands on an exciting albeit difficult threshold of growth in theories and concepts. And it is biology that will force further development of dynamical tools. The work of Ellner and coworkers on nonparametric methods to calculate Lyapunov exponents is an example.[54,55,56]

IX. COMPUTER SIMULATIONS: MINIMAL MULTIFUNCTIONAL NETWORKS

Computational analogies may provide insight where theory is lacking. Lorenz's[110] work on convection provides an excellent example of how computer simulations may spark insight into new methods for handling complex systems. The work of Klopf and coworkers,[95,129] which was discussed above under Reductionism, is another example in which computational methods have proved decisive in addressing an important problem in the theory of learning. In Lorenz's case, the outcome was unexpected. In Klopf's case, the outcome was planned because of the equivalence of the statement of drive reinforcement at both the unit and global levels. Both of these examples show that certain statements or assumptions about interacting systems can be used to address complex behavior through computational methods without having first to develop a proved theory about the global system. Put differently, given certain assumptions about local events, it may be possible to allow the system to generate itself. In the same way, we discuss here four topics that may be addressable computationally and which may eventually prove beneficial in understanding some of the complexities of biological organization.

1. NONLINEARITIES AND BIFURCATIONS IN SIMPLE NETWORK ARCHITECTURES

As we have referred to repeatedly above, we do not yet understand the functional meaning of convergence and divergence beyond the notion of reflexes,[134,137,172] or as Sperry put it,[176] of the "three-bodies problem." For many studies of associative learning and motor pattern generator, there is as much need now for a new language to handle the emergent properties arising from convergence as there was fifteen years ago.[141] But we can point at least to two small interrelated advancements: identification of the nonlinear interactions that arise from network architectures, and the identification of architectures that permit bifurcations to arise from such interactions. The discussion below uses several model systems to clarify what we

mean, and to inquire into the problem of continuous versus discrete processes in neuronal activity.

A. NONLINEARITY AND BIFURCATION IN MODEL SYSTEMS

Rössler and logistic. Nonlinearities are easy to see in simple models such as the Rössler system[160] of coupled ordinary differential equations that generate complex chaotic dynamics:

$$\frac{dx}{dt} = -y - z \qquad \frac{dy}{dt} = x + ay \qquad \frac{dz}{dt} = b_z x - cz\,,$$

where a, b, and c are constants. Here X is a function of Y and Z. Y is a function of X and itself, and Z is a nonlinear function of itself and X. Each of these variables is expressed nonlinearly through the others. The logistic equation, $X_{n+1} = R(1 - X_n)X_n$, is an even simpler example, where the new value on the left is generated by the nonlinear drive of the previous value on the right (initialized between 0 and 1), and is then reintroduced into the system to generate the subsequent number. For values of the constant R between 0 and about 3.55, the process of nonlinear action followed by recursive folding back into the equation produces periodic sequences of numbers, but for R greater than 3.55, the system generates chaotic sequences.[121] Successive, linear adjustments to a constant such as R may produce only minor changes in the system over a large portion of R's allowable range. But at critical points, very small alterations in R produce nonlinear shifts (bifurcations) in the sequence of numbers. At low R-scale resolutions, regions are observed at which only chaos appears to occur. By expanding the R-scale, one observes that chaotic regions contain periodic regimes.

Bifurcation in Hodgkin-Huxley membrane. Teresa Chay's[29] seminal paper examined a three-variable Hodgkin-Huxley membrane precisely in this way. The time variation of voltage in the model is given by

$$\frac{dV}{dt} = g_I^* m_\infty^3 h_\infty (V_I - V) + g_{K,V}^* n^4 (V_K - V) + g_{K,C}^* \frac{C}{1+C}(V_K - V) + g_L^*(V_L - V)\,.$$

I: mixed inward currents (sodium, calcium). K,V: voltage-sensitive potassium channel. C: internal calcium concentration. K,C: calcium-sensitive potassium current. L: leakage. n: probability of opening K,V. m,h: probabilities of activation, inhibition. g^*: maximal conductance divided by capacitance.

The three variables in the system are (1) membrane potential (V); (2) n, the probability of opening the voltage-dependent potassium channel; and (3) intracellular concentration of calcium (C). Intracellular calcium is voltage-dependent, as are sodium, one of the potassium channels, n, m, and h. It can be easily seen mathematically that all of these variables affect one another through voltage (as a consequence of their effects on currents), and that the system of such interactions is highly nonlinear, although examination of the equations would not necessarily give immediate insight into which parameters to use to control bifurcations. The bifurcation parameter is the calcium-dependent potassium conductance $g_{K,C}$, and,

as described above for the logistic equation, the membrane produces many different firing patterns when this conductance was systematically changed.

B. RELATIONSHIP BETWEEN BIFURCATION DYNAMICS AND NETWORK ARCHITECTURES. To illustrate the difficulties encountered in attempting to understand the dynamical capabilities of network architectures, and the direction we have taken in some of our computer studies, consider the (overly) simplified cartoons in Figure 4 that transpose the Rössler system and the Chay membrane into "realistic" analogs of neuronal networks. "Realistic" might include voltage-sensitive ion channels, calcium-dependent ones, transmitter release dynamics, transmitter re-uptake, and second messenger systems, and other processes one might want to include in an experimental system.

Given tonic excitatory input to X in Figure 4(a), and making X capable of post-inhibitory rebound, it may be possible for ~~X = Y and X = Z to oscillate~~ if there is sufficient accommodation in the firing of Z and/or Y. Figure 4(b) shows a network cartoon of a subset of the variables in the Chay membrane. Given Chay's simulations, it might be predicted that the synapse of K_{Ca} onto V would provide access to bifurcation dynamics. The nonlinearities in the Rössler and Chay systems are easily identifiable in the differential equations that compose them. And it is possible to see how the calcium-dependent potassium conductance can influence the dynamics of the Chay model. But it is considerably more difficult to identify analogous nonlinearities and bifurcation conditions in neuronal networks. It has long been established that synaptic activation of neurons leads to nonlinear responses because of the firing threshold in the driven neuron. It is also known how to simulate individual synapses using digital integration, by describing the kinetics

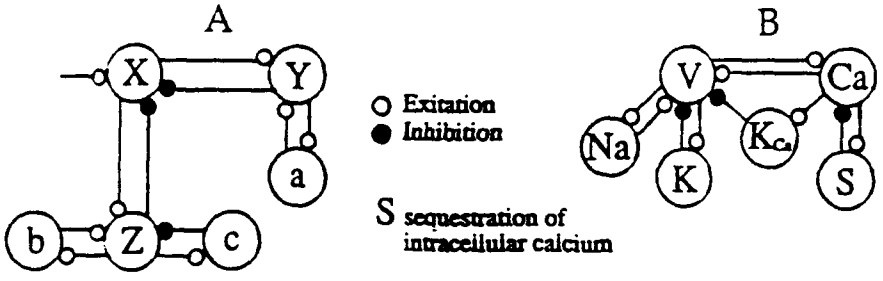

FIGURE 4 Cartoon of "minimal" neurocircuit transpositions of the three-variable Rössler system of coupled differential equations (A) and of the Chay's three-variable Hodgkin-Huxley membrane (B). See text.

mathematically, or by examining nonlinear interactions between different types of synapses.[36] But the dynamical implications of different network architectures and of the synapse characteristics that affect the dynamics of regenerative electrical activity of neurons in these networks are problems that remain largely untapped.

Along this line, present efforts in our laboratory are aimed at understanding what types of converging and diverging centers in minimal networks are required for bifurcations to occur. In the same way as Chay used the calcium-dependent potassium conductance to control the bifurcations, our efforts are to determine whether synaptic strengths can also be used as bifurcation parameters. The problem facing us in dealing with the biological system is much more difficult than that which faced Chay because: (1) our system has many more degrees of freedom. (2) Our system is not as smoothly continuous as the Hodgkin-Huxley membrane; i.e., the membrane responses may seem continuous, but cells usually receive information in short pulses or bursts. (3) There are no previous network examples for us to follow in which bifurcation have been demonstrated. Interestingly, the types of convergence centers that have proved capable of bifurcating into variable activity in our preliminary computer simulations, are ones having similar structures as the one shown in Figure 4(b).

As our knowledge grows of the connectivity among the BCNs and of their connections with other neuronal groups, we shall construct computer simulations of networks having increasing sizes. We shall then progressively introduce the effects of the many converging neurotransmitter systems. Additionally, by implementing early behavioral evidence of synaptic competition during learning in *Pleurobranchaea*,[141] and the evidence for synaptic competition in mammalian cortex,[127] we expect to see our networks remodel their connections overtime. Interactive groups may actually grow or shrink in time; large populations may split into subsets; the spatial boundaries between coactive groups may move in time; and network architectures may emerge that affect the amount of variation occurring in the network.

C. CONTINUOUS VS. DISCRETE PROCESSES. The Rössler and Chay model are both three-variable systems, as required of any continuous bounded system that is capable of generating chaos.[78] We summarized the reasons behind the need for three variables using mixing of trajectories in three-space and an examination of Lyapunov exponents in section IV.5.B. By contrast, discrete processes can generate chaos in one dimension, as in the case of the logistic equation, and coupled discrete processes can generate chaos in two-space, as shown by the Hénon system, where $X_{n+1} = 1aX_n^2 + Y_n$ and $Y_{n+1} = bX_n$.[78] Recall also that the issue is not whether a system generates chaos, but its ability to exhibit both simple and complex behaviors, depending on its bifurcations conditions arising from simple quantitative alterations rather than from qualitative changes in network structure. Moreover, if the bifurcation parameter is the driving frequency of an input signal, it is not necessary even for quantitative changes to occur in the network for simple and complex dynamics to appear.

The difference between continuous and discrete processes is of significance to neurobiologists. The neural networks studies of Mpitsos and Burton[134] indicate that

when signals between networks are chaotic discrete processes, simple networks are able to perform difficult tasks on these signals that would otherwise require more complex networks to perform if the mode of transmission used continuous periodic or ~~even~~ chaotic processes. Continuous processes are used in neural integration,[186] but the usual mode of information transfer is through trains of action potentials. Trains of action potentials in pacemaker firing cells are generated by continuous fluctuations in membrane potentials and in the dynamics of ionic species. Examples may be found in computer simulations of the parabolic burster neuron R_{15} in *Aplysia*,[25] and in the Chay model described above. The information in these spike trains, though generated by continuous processes, is in a pulse code. Therefore, there are a number of questions that need examination. For example, is there an informational difference between the dynamics of spike trains by comparison to the information contained in the continuous membrane processes that generate them? What happens in postsynaptic cells when they receive such spike trains, and when are we to consider the dynamics in the postsynaptic cells as continuous processes or analogs of discrete processes? The membrane potentials of these follower cells may appear continuous, but they are driven by discontinuous input events.

The differences between discrete and continuous processes pose problems in numerical analyses. Experimental data usually consists of the time series of one or several dependent variables, but the methods provide little knowledge of the number of dependent variables that actually drive the system. Numerical methods provide some help. For example, it is possible to conduct phase-space analyses that give information about the topological dimension of attractors and about the number of dependent variables (embedding space) that may be involved in generating the attractors.[135,142] The evidence provides some justification supporting chaotic attractors and low-dimensional embedding space.

However, some of the calculated attractor dimensions were lower than two, posing some difficulties in interpretation of what the dynamics is. Continuous systems must have at least three Lyapunov exponents: there must be at least two non-negative ones, one being positive, as required for chaos, and one having zero value, as required by Haken's theorem (section IV.3.B). Given two non-negative exponents, calculations using the Kaplan-Yorke conjecture should be expected that the lowest attractor dimension for continuous chaotic systems be greater than two (examples are given in Andrade et al.[6]; Wolf[190]). One-variable discrete processes, such as the logistic equation, have dimensions less than 1. Two-variable discrete processes have dimensions between one and two: our own estimate of the Henn system gives dimension of about 1.36. Knowing the mathematical representation of a system allows one to place such numbers in appropriate context, but experimental data leaves numerical results ambiguous. Do we assume that attractor dimensions less then two are coupled discrete processes or is it a problem with the analytical methods? Of the latter possibility, the available tools, whether using time series of a single variable or all variables, calculation of attractor dimensions are difficult to obtain even for model systems. ~~For example, Andrade et al.[6] found that the Grassberger-Procaccia[89] method may significantly overestimate the attractor dimension of limit cycles and underestimate those for chaotic attractors.~~

Ed: delete last sentence, but retain reference "6"

Answers to questions as the one given above are necessary because they provide an indication about how information is processed and encoded. We are presently addressing them using numerical analyses of data from computer simulations of membrane patches and of responses of cells in networks where we have access to all parameters and variables of the system. Comparison of analyses on the data from measurements of continuous variables and from spike trains may yield some insight into implications relating to continuous and discrete processes.

2. RESPONSE OPTIMIZATION, ENERGY GRADIENTS, AND ATTRACTORS IN BIOLOGICAL NETWORKS

A. ATTRACTORS, FROM SEA SLUGS TO BEES Real[157] has shown recently that bees are able to adjust their behavior so as to optimize the use of food resources. Whether or not this involves gradients and attractors has not been addressed. The idea is consistent with the possibility that biological networks (and biological systems generally) may exhibit behavior that tends to minimize some gradient factor (as error or energy) through the ability of attractors to dissipate energy.[132,133] Attractors (see section IV.4) pull in any phase-space trajectory that falls within their basin of attraction. Thus, for example, in limit cycles, externally applied perturbations move the trajectory of the system away from the limit set, but if the state of the trajectory remains within the attractor's basin of insets, the trajectory will fall asymptotically back into the limit set. Chaotic attractors also attract nearby states but dissipate perturbations over their entire surface. We might say that attractors minimize energy or error.[133] Put differently, attractors optimize the match between their attracting set and activity that falls near it. In either case, the action may be consider a minimization process. On the behavioral level, bees are able to control their foraging techniques so as to optimize the use of food resources.[157] Whether this involves attractors and gradient-seeking is presently not known, but is potentially testable.

B. COMPARISON THROUGH ANALOGY IN PRINCIPLES, NOT IN IDENTITY OF MECHANISMS The potential consequences of the identity between attractors and optimization are rather interesting. Consider the following situations. In attempting to simplify computer simulations, it is often difficult to determine exactly where to limit the characterization of the biology. For example, the connectionist methods of error-backpropagation are usually faulted because of their obvious non-biological nature. But the answers that come from the use of such networks depends on the principles that are actually being simulated. The major driving element of error-backpropagation is that the system must follow a negative error gradient between a teacher function and the output of the system.[163] If the question being addressed has to do with the principle of error reduction, rather than, say, what second messengers might be involved in a cellular process, or how feedback actually occurs in a real nervous system, the backpropagation method might give some insight into how gradient-seeking systems store information in their distributed elements.

Response thresholds. Following this rationale, Mpitsos and Burton[134] obtained a number of results that might have relevance to biological systems. They found, for example, that the computational capabilities of networks are severely limited when only trainable synaptic strengths are used. Adding trainable thresholds significantly expands the computational power of the networks. In invertebrate learning studies, thresholds (as might be inferred from membrane changes in postsynaptic cells) have either not been observed at the cellular level or have not been generally attended to.[144] Studies on long-term potentiation (LTP) in rats have, however, provided evidence implicating response thresholds through changes in synaptically induced changes in the ratio of excitation and inhibition rather than changes in membrane impedance.[7,28] Heretofore, the methods used to test LTP have not focused on assessing the computational implications of threshold adjustments, nor the technical conditions to extend the findings, but it would be extremely interesting to determine whether adjustments in the ratio of excitation to inhibition were set differently for each cell, as might occur in gradient descent adjustments in thresholds during learning in neural networks.

Network size may be self-limiting. An unexpected finding in the studies of Mpitsos and Burton[134] was that increasing the number of neurons in a hidden layer or interneuronal layer beyond a certain point slows and eventually causes the system to cease learning; i.e., group size may be self-limiting. Limitation of group size has been enforced algorithmically in simulations of mammalian cortex through synaptic competition and inhibitory synapses.[52,153] It is also conceivable, however, that group size may be additionally limited by the gradient tendencies of attractors. If the findings of Mpitsos and Burton hold biologically, the slower organizational times of large networks may be superseded by smaller subsets of neurons as they form attractors. Once sufficiently formed, the attractors themselves may restrict group size, partly by their gradient processes, and partly by learning-related synaptic competition. To our knowledge, the network-forming aspects of synaptic competition have been viewed only at the level of neuronal trophic factors and whether or not activity occurs. What we are attempting to point out here is that the network not only generates activity, but that the dynamics of this activity may affect the characteristics of the network architecture.

A similar distinction between activity and dynamics may be raised in studies of motor pattern switching. In a traditional sense, switching between patterns of activity require some network change or the introduction of activity in a controlling neuron.[39] We do not deny this possibility, but add that the notion of bifurcation raises the discussion from the level of activity alone to a level involving dynamical processes. Using John's terminology,[81] the former is a "switchboard" effect relating to particular neuron(s), whereas the latter is an abstraction of the self-organizing activity in neurons, and quite likely may not be identifiable in network structure,[137] although some identifiable structural indices may be obtainable as discussed for the studies of Figure 4.

Metaknowledge and lazy synapses. Metaknowledge represents that ability of networks to store different forms of information.[23] We discussed it above in dealing with reductionism (section VII.3.D), and we believe that it may be a consequence of

gradient tendencies. Our computational studies also found that although networks set their synaptic weights and thresholds at optimum levels, many of the synaptic weights produce little effect when removed from the network; i.e., they are "lazy." Mpitsos and Burton[134] discuss a number of uses for such synapses. One of the most interesting possibilities comes from somewhat different studies by Warren[184] who showed that certain synapses may be deleted after training without significantly affecting network performance on a previously learned task, but networks were unable to learn the task if they started with the reduced number of synapses in the first place. This poses interesting problems to biologists since weak connections are often observed between the interactive components of their experimental systems. The tendency in the past has been to dismiss such connections, or to presume that they would be "pruned" away if not used. Our findings along with Warren's indicate that these synapses may be crucial for learning new tasks. By analogy to computers, they might be considered as temporary registers that permit gradient descent, but once gradient descent has been reached, they are no longer needed for that task.

3. LOCAL ERROR MINIMA IN BIOLOGICAL ADAPTATION

The idea that a system tends to optimize its behavior has a somewhat different expression in biological systems than it might have in computer simulations of connectionist neural networks. With enough time and stable environmental conditions, we can envision that evolutionary competition between organisms will produce changes that best adapt the species to the environment. One might think of the process as reaching an absolute error minimum between the response of the organism and the best possible response under the imposed conditions. Any response that is not optimal represents a local minimum. In neural networks, methods have been developed (see section IV.5.C) to avoid local minima using, for example, simulated annealing[92] and time-invariant noise algorithms (TINA).[23] Simulated annealing usually involves exponential decay of noise over time. TINA adjusts noise as a function of the amount of error that is produced when a system responds to its input stimuli. This method, however, was chosen only as a vehicle to demonstrate the idea of TINA. Other methods, not necessarily directly related to error feedback, may also be used that retain time invariance. For example, our present attempts to implement TINA in networks consisting of neurons having biologically realistic characteristics is to adjust the probabilistic release of transmitter[97] or to use short-term activity-dependent learning rules such as sensitization[144] to maintain the flow in a given part of the network. Our goal is to assign certain facilitatory responses to classes of neurons, and then to allow the actual pathway to emerge dynamically. Low-error would be represented by activity recurring through a particular part of the network. As error increases, diffusely distributed feedback onto the network would disrupt such preferentially frequented pathways, permitting others to emerge. If these new pathways lead to low error, feedback decreases, allowing the flow through the pathway to continue. If attractors self-organize, the preferential

pathways would then be further entrenched, because, as discussed above, the basin of insets to the attractor itself may represent an energy or error-minimizing process.

This process does not require that the tendency to follow a gradient actually reach an optimal minimum, or, equivalently, that the attractor be spatio-temporally a robust, stable structure. Biologically, in both the daily behavior of organisms and in their evolutionary succession, local minima are extremely important in generating adaptive responses. Whatever works is sufficient, whether the response is optimal or not. Thus, our notion of an adaptive system is one that can generate different minima that can be addressed rapidly, and exited rapidly if they do not meet the need. Indeed, we believe that it is from the ability to generate many local minima that multi-behavioral networks may have evolved.

Part of the understanding about the generation of local minima will be to see how multibehavioral networks generate different attractors in computer simulations. Transitions between different attractors may yield labile intermediate forms that only partially resemble more stable ones. The most difficult problem that we face here is to determine how best to visualize temporal activity graphically for spike trains.[135,142] Continuous non-spiking processes pose less of a problem.[6] Part of the answer may also come from an understanding of spatio-temporal dynamics.

4. VISUALIZATION OF SPATIO-TEMPORAL DYNAMICS

~~At this point, we are, in a sense, back to the Introduction.~~ The more we study ~~the~~ biology, the more it seems that we must somehow leave it to gain a feel for what may be happening there. Put simply, biological systems are too complex and uncontrollable even to perform experiments as those represented by Figure 4. We must imbue these simulation networks with as much biological information as needed to obtain activity that somehow resembles the activity of the biological system. But complete state-space parameterization of the biological system is beyond hope, as one glimpse of the complexity in Figures 2 and 3 will show. At the level at which we can attribute realistic biological characteristics to a network, the system becomes intractable even for simple analyses of steady states (see example analysis of a simple model system in Andrade et al.[6]).

Given the growing power of computer graphics and the increasingly easier access to supercomputers, the recourse for biologists interested in the emergence of group dynamics is to conduct the type of experiments shown in Figure 4, and, especially, to visualize the spatio-temporal flow of activity in large-scale simulations involving many interacting units. An understanding of such spatio-temporal flows is, we believe, one of the central questions facing neuroscience. Walter Freeman and coworkers were perhaps the first to begin a detailed account of spatially distributed recordings in their studies of rabbit olfactory bulb (e.g., see review in Skarda and Freeman[170]). But even in these studies, the analysis of the temporal flow is of the time series of single recording sites. Perhaps the major lesson in dynamical systems work over the decade has been the fact that much can be learned about the activity of a system by the analysis of its phase-space geometry. Up to four variables

can be analyzed simultaneously using time series analysis (e.g., see Figures 8-11 in Andrade et al.,[6] and Figure 13 in Mpitsos and Burton[134]). We need to do the same for many variables, both spatially and temporally.

By such methods it may be possible to examine the possibility of limit cycles, chaotic attractors, SOCs and turbulence, the coexistence of multiple attractors, movement of these attractors spatially, and possibly even their blending into one another. From such studies it may also be possible to determine how particular circuit structures emerge, how variability appears controlled by particular circuit characteristics. In the long term it will be important to ask how such structures are affected by system-wide factors. If we are to believe our neurochemical findings, it is quite likely that bifurcation parameters may be more accurately defined as being distributed over a large number of cells rather than, for example, in the conductance modification of a single cell. The first possibility may explain the fact that some systems are relatively insensitive to changes in only a few of their components.

X. CONCLUSION

In answer to the title of this paper, we have actually said little about what sea slugs can tell us explicitly about the neurointegration of specific human movement. But we believe that the findings tell us considerably about what must be addressed in order to gain a unified perspective of biological integration that might eventually affect how we view human movement. We understand that much has been said appropriately by others about coordination of limbs in invertebrates and vertebrates, the rightful importance of FAPs, and selective control of individual neurotransmitters on pattern generation and in the formation of network structure, and that such findings may be applicable to human motor behavior. Perhaps most of the time all of these studies provide the best answers, as most of the time Newtonian physics provides the right answers in daily engineering problems. Perhaps also, the neurointegrative processes in *Pleurobranchaea* and *Aplysia* follow the same predictabilities most of the time.

The instances that are not explainable by traditional neurocircuit perspectives might be dismissed as biological aberrance. Alternatively, owing to the fact that the animal seems to function well enough with them, they may be pursued as being of adaptive significance. We have followed the latter route, and have been forced into a perspective that is more statistical mechanical and dynamical than classically "switchboard." Lorenz[111] voiced the long-held view that all biological information is stored in structure. We hardly disagree with that. But the question is, how do we read that information, and is much of it redundant and even of nonsense or accidental value? The latter possibilities may actually provide certain adaptive value adventitiously in ever changing and unpredictable environments. In reaching a new theoretical perspective that addresses these issues, our view is that there are two levels of solution: the special case, relating to the switchboard neurocircuit,

and the general solution, that must be reducible to the special case but must also provide a general theoretical foundation that is extensible to many other cases.

The shift to dynamics, or at least away from answering all questions by using reflexes, marks a shift away from mechanism to organization. Although each biological level of organization may express the dynamics in its own processes, the dynamical principles may be applicable to all levels of organization. The central question in all of these systems is "*How does the individual influence the group, and, in turn, how does the group influence the actions of the individual?*" We have tried as much as possible to couch our ideas on biological findings, though much more data needs to be gathered (and re-gathered) before we feel more comfortable. If we are wrong, we have already hedged our bets because our view holds that error is an advantage in adaptive systems. Is it too extreme to assert that the practice of science itself is as much an indication of the biology of the human brain as the more academic notion of organized activity among neurons, or are we to presume that science is the practice of absolutes? There is too much evidence showing error in long-held dogmas to answer naught but "No," and "No," respectively, to the two parts of the question. If what we have discussed is accurate, then, as Barbara McClintock envisioned, "We are going to have a new realization of the relationship of things to each other."[87]

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