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Continuum model of mnemonic and amnesic phenomena

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Abstract

Amnesia in its various forms is characterized by defects in one or more components of a complex system. Implantation of short-term memory occurs in the hippocampus, while long-term memory is essentially located in the neocortex; these regions are interconnected through complex synaptic structures. In the hippocampus, physiological data show that, as predicted by Hebb, excitatory synapses between nearby excitatory cells become strengthened by simultaneous activation. In contrast with this local process, the preponderance of clinical and experimental evidence indicates that cortical recall of a "memory" is the reconstruction of fragments stored in different synaptically distant brain regions. A mathematical model of memory must reconcile this apparent contradiction as well as explain how many different memories and "ideas" can be assembled within a given anatomical area. Continuum theory, which treats an *ensemble* of "cell assemblies" or neural networks, offers a step in this direction. Linear analysis using this approach shows that it is the nature of the neural continuum to generate activity waves of wavelength greater than synaptic connection ranges. These waves grow under certain circumstances, and their wavelength is controlled by the synaptic parameters. Both hippocampal and cortical tissue are subject to such wave growth. In the hippocampus, the local Hebbian strengthening controls the global wave growth, making the difference between wave decay and growth. The cortical wave structure can become very complex, so that reproducible memory recall as well as "creative thought" can be accommodated in the theory. Deficits in the functioning of the system may also be evaluated potentially by means of "goodness-of-fit" of the clinical and spatially resolved data with the model. (*JINS*, 2000, *6*, 593–607.)

Keywords: Memory, Hippocampus, Continuum theory, Neural networks, Cell assemblies

INTRODUCTION

To build a computational model of memory and its deficits we must first consider what is normally remembered. Bartlett (1932) made the point early that remembering cannot be regarded as the mere revival of previous experience; rather, it is a process of active reconstruction. In other words, events are not stored *in toto*; only certain critical elements are stored from which the event can be reconstructed. The more cues or elements provided contextually, the more exactly the event can be reconstructed and "remembered." If a trickle of water is poured on a hill (minimum sensory input), the water will trace only part of the route to the bottom, bypassing many of the small side channels. As more water (i.e., more contextual information) is added, it travels faster down the hill tracing more and more of the various channels originally followed (i.e., remembers the route more precisely).

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After a long delay, remembering may correctly identify the essential elements of sensory experience yet incorporate additional elements that, although compatible with the essential sensory experience, are erroneous. It is widely believed that this incorrect embellishment of the critical experience may account for the fallibility of eyewitness evidence in which plausible but erroneous details are "remembered."

Bartlett's proposition that remembering is reconstructing is particularly important in understanding the pathology of memory. An apparent defect of memory could result from a disorder, not only in the storage of sensory experience but possibly also in the later reconstruction of sensory experience from the critical features.

NEURONAL AND SYNAPTIC PROCESSES

Neurons in the brain are interconnected with many other neurons and, in turn, each neuron receives input from many synapses of its dendrites and cell body. The resulting neuronal loops according to Hebb (1972) contain neurons whose

output signal may be either excitatory or inhibitory. Although the neuronal loops are usually drawn as though they were in the cortex, many of the loops probably run from the cortex to the thalamus or other subcortical structures, such as the hippocampus, and back to the cortex. Because each neuron is believed to both send and receive thousands of outputs and inputs, the number of possible neuronal loops is truly immense.

In Hebb's (1949, 1972) theory, each psychologically important event, whether a sensation, percept, memory thought, or emotion is conceived to be the flow of activity in a given neuronal loop. Hebb proposed that the synapses in a particular path become functionally connected to form a cell assembly. In Hebb's view, the most probable way in which one cell could become more capable of firing another is that synaptic knobs grow or became more functional, increasing the area of contact between the afferent axon and efferent cell body and dendrites.

Hebb assumed that if two neurons are excited together, they become linked functionally. In Hebb's view, the cell assembly is a system that is initially organized by a particular sensory event but is capable of continuing its activity after the stimulation has ceased. Hebb proposed that, to produce functional changes in synaptic transmission, the cell assembly must be repeatedly activated. After the initial sensory input, the assembly would therefore reverberate. Repeated reverberations could then produce the structural changes. Clearly this conception of information storage could explain the phenomenon of short- and long-term memory: Short-term memory is reverberation of the closed loops of cell assemblies; long-term memory is more structural, a lasting change in synaptic connections.

In Hebb's theory, there is yet another factor in long-term memory. For the structural synaptic changes to occur there must be a period in which the cell assembly is left relatively undisturbed. Hebb referred to this process of structural change as consolidation, a period believed to require 15 min to 1 hr. Its existence was supported by observations that retention failed when brain function was disrupted soon after learning, as, for example, in the amnesia for events just before a concussion. The case of H.M. (Milner, 1968) invited a logical extrapolation of Hebb's theory: The hippocampus was assumed to be especially important to the process of consolidation, although just how it is involved could not be specified. New material is not remembered because it is not consolidated; old material is remembered because it was consolidated before the hippocampal damage.

Finally, Hebb assumed that any cell assembly could be excited by others. This idea provided the basis for thought or ideation. The essence of an idea is that it occurs in the absence of the original environmental event that it corresponds to.

In a thoughtful review in 1980, Goddard reviewed the cell assembly and found that, with few modifications, it was then a sound metaphor for psychological behavior. Goddard based his argument on the work of Eccles (cf. 1986) and others. Bliss and Gardner-Medwin (1973) demonstrated unequivocally that electrical stimulation of a neuron could produce either brief or long-lasting changes in synaptic transmission, according to the characteristics of brain stimulation. Brief pulses of current are delivered to an axon over a few seconds, and the magnitude of the response is recorded from areas known to receive projections from the stimulated axon. After a stable baseline of response to the stimulation has been established, the stimulation is changed to one of high frequency, driving the system very hard. This high frequency stimulation is then discontinued, and the brief test pulses are resumed.

The magnitude of the postsynaptic response can be compared with the original baseline, and the time course of the decay of changes in response magnitude can be measured as well. Two significant findings emerged from this study. First, response magnitude markedly increased immediately after the high-frequency stimulation. This increase declined over time and returned to baseline. The rate of decline depends on the details of stimulation. This short-term increase is called *post-tetanic potentiation*. Second, the changes in response magnitude may not decline to baseline but instead remain elevated, possibly for days or as long as is practical to measure it. This has been called *long-term potentiation (LTP)*. In some cases, LTP may be present after 2 months, and Barnes (1988) has shown that LTP is prolonged by occasional repetition of the high-frequency stimulation. The original studies of LTP were performed on the hippocampus, but these phenomena can be demonstrated elsewhere in the brain.

Goddard (1980) emphasized the similarity between the phenomena of short-term memory and post-tetanic potentiation and between long-term memory and LTP, supporting Hebb's (1949) original theory. As attractive as the physiological work is as a model for short- and long-term memory, it is still a substantial theoretical leap to understanding the effects of lesions on memory, such as the differential effects of temporal and parietal lobe lesions on short- and long-term memory respectively

The demonstration of LTP is important, but it still leaves open the question of what change in the brain allows such physiological phenomena and, presumably, memory. The nature of the changes that occur at the synapse in information storage is still uncertain. Greenough and Chang (1985) have shown that, when animals are trained in specific tasks or are exposed to specific environments, there are changes in the dendrites of neurons. If there is an increase in the number of dendrites of particular neurons, then it follows that there might be an increase in the number of synapses on these neurons. Greenough and his colleagues have shown this to be the case.

In addition, they have shown that there is a qualitative change in the synapses, presumably including not only new ones but also existing ones that have been changed by experience. These include changes in the size of various synaptic components, in vesicle numbers, in the size of postsynaptic thickenings, and in the size of the dendritic spines. (For a more complete review, see Greenough & Chang,

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1985.) Similar changes have also been found in neurons exhibiting LTP, thus adding evidence that LTP may be an analogue of normal learning.

The cause of these changes in the synapse is unknown at present. Various hypotheses have been advanced to suggest that alterations in protein synthesis in neurons might be responsible, possibly because of some sort of change in gene expression in the neurons, which may be expressed through changes in RNA (Black et al., 1987). It follows that blocking protein synthesis ought to block both LTP and new learning, and this appears to be so. Another hypothesis is that the use of neurons leads to changes in presynaptic calcium permeability, which, in turn, leads to a series of biochemical changes (Lynch & Baudry, 1984). At present, although all of these hypotheses remain speculative, it seems highly likely that long-lasting behavioral change stems from a morphological change in neurons.

A QUESTION OF THE LOCATION OF MEMORY SYNAPSES

If a morphological change is the basis of memory, then we must ask which neurons in the brain are modified by experience. It is highly unlikely that every neuron would change with each experience, or, alternatively, that only one neuron would change with each experience. It seems reasonable to suppose that visual experiences would change neurons in the visual system, and auditory and somatosensory experiences would alter those in the respective sensory systems.

At least three problems arise, however. First, a sensory experience could not change every neuron in the relevant system or all subsequent experiences would be changed. That is, cells in the primary visual cortex cannot be allowed to change too much or the information sent to higher area would be radically different, which would lead to very different sensory experiences and perceptions over time. We know, however, that specific visual environments do change primary visual cortex (Blakemore, 1977; Blakemore & Mitchell, 1973), which leaves us with a puzzle! Nonetheless, it is logical to suppose that experiences will be more likely to affect higher level sensory areas than lower level ones. Second, if sensory experiences change sensory systems, thus permitting memories of the events, how do we remember ideas or thoughts? Presumably the mechanism is the same but the changes may be "elsewhere," although the location is still a mystery. Third, if experiences result in widespread changes in the synapses, how do we find specific memories? It would seem that if memories are widely distributed in large cell assemblies, then it would be a formidable task to locate the memories, especially if they are to be found quickly. Most of us have had the experience of being totally unable to recall some answer for an examination, then to remember one small fact that appears to allow us access to the entire memory. What mechanism could account for this?

We have assumed here that memories are likely to be stored in the cortex, but they need not be. Decorticated animals can learn many behavioral tasks (Bignall & Schramm, 1974; Oakley, 1979), and animals with a primitive nervous system (e.g., *Aplysia*) can learn and show evidence of "memory" (Kandel & Schwartz, 1981). It is reasonable, therefore, to suppose that memories will be stored in both cortical and subcortical structures. Furthermore, given that many memories are dependent on sensory processing and that sensory processing is carried out in multiple systems, it is reasonable to assume that memory may be a multiple-component system, with different types of information stored in different places in the brain. This would be especially true of short-term memory. Nearly any type of complex information processing requires a capacity for temporary storage, if only because it takes time to transmit the information, and thus one would expect to have specific short-term stores that are independent of one another. Indeed, we know that both frontal (Moscovitch, 1982) and parietal lobe lesions (Warrington & Weiskrantz, 1978; Weiskrantz, 1987) produce short-term memory deficits, but of a different nature. There may be separable long-term memory stores as well, but there are likely to be fewer of them, and possibly only one.

The neuropsychological literature is replete with studies attempting to locate a candidate brain region responsible for memory in all its forms. It has been reported that bilateral damage to either the hippocampus or the diencephalon produces global anterograde amnesia (Sanders & Warrington, 1971). Neocortical damage alone has not been shown to produce such an amnesia, although anterior temporal cortex lesions do produce impairments of memory. Unilateral damage does not produce amnesia, even for specific types of information, although there may be relative asymmetry in the effects of lesions.

Second, impairment is found only in tests that measure knowledge of facts and events or declarative memory, but patients are quite capable of normal performance on tests of procedural memory. H.M. (Milner, 1970, 1972) was able to perform mirror tracing, although he denied having knowledge of the test or the events surrounding the learning of it. Similarly, Schachter (1987) describes an amnesic Alzheimer's patient who denied playing golf before and then proceeded to play a respectable game. Dissociation of this type suggests that there are at least partially separable neural systems for declarative and procedural memory.

There are at least two ways to account for how declarative and procedural memory can be distinguished anatomically. One way is to postulate that amnesia results from a disconnection between the systems that are necessary for declarative memory and the motor systems that seem modified during procedural memory acquisition. Another type of explanation is to postulate that memory traces are laid down at least twice. One location would be in the system that executes the behavior. A second location would be in some sort of declarative-related memory store. The first memory trace would permit appropriate task execution, and the second would monitor the execution and would record relevant details of time, place, and success.

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The idea that there is such a dichotomy in the nervous system has a certain appeal. Indeed, there is overwhelming evidence that almost every level of the nervous system is capable of some sort of learning relevant to procedural memory, although only certain "high-level" structures appear capable of declarative memory. Squire (1982; 1987a) has made some interesting observations in this regard. He suggests that declarative memory may be a recent event in the evolution of the hippocampus and related cortical structures in mammals. He further suggests that declarative memory may develop late in ontogeny, in part because the hippocampus is slow to develop. This would lead to an alternative explanation for infantile amnesia.

Third, most amnesiacs have a period of retrograde as well as anterograde amnesia (Milner, 1970). Medial temporal lobe lesions produce a period of retrograde amnesia of at least 1 year, although the precise duration is difficult to measure. Diencephalic lesions produce a longer period of retrograde amnesia, head trauma, and ECT usually produce a shorter period of retrograde amnesia. Nonetheless, overall, amnesics show retrograde amnesia that is of limited duration and an anterograde amnesia that is total (see Markowitsch & Prtizel, 1985).

These facts suggest that the neural system that is damaged in amnesia must be involved in the memory of new facts as well as being involved in memory for a limited period after learning. Later, it is either not involved or certainly less involved in the storage of memories. In order to account for anterograde and retrograde results, it has been proposed by several authors (see Markowitsch & Prtizel, 1985) that at the time of learning the medial temporal region establishes some kind of functional relationship with memory storage sites. Perhaps the medial temporal region somehow binds together the various sites that have coded the specific data that define an event, that would include time, space, and content. Given that these data appear to be coded by diffuse regions (i.e., frontal cortex, posterior parietal cortex, and polymodal sensory cortex), it would seem that some structure or some system is indeed required for this purpose. The medial temporal region is the only structure in the forebrain that would appear to have the sensory anatomical connection for such a function. It is unclear, however, why this function would continue for 1 year or more after an event. It is also not clear what changes in the brain release the medial temporal lobe from its role in memory.

The study of nonhuman species has supported the general view that the medial-temporal region has a major role in memory. Historically, researchers who made hippocampal lesions in laboratory species were struck more by symptoms such as increased activity, a tendency to perseverate responses, and an inability to chain sequences of movements (Zola-Morgan et al., 1986) than they were by memory loss. O'Keefe and Nadel (1978) argued that the hippocampus functions to construct cognitive maps by which animals locate memories or ideas in the brain or spatial locations in the world. Olton et al. (1979) provided evidence that hippocampal lesions in rats produced deficits in a type of memory that they called working memory. This type of deficit was not expected based on the reports in the clinical literature. Both O'Keefe and Nadel and Olton et al. were not completely correct in their assessment. Hippocampal damage in rats affects long-term memory of spatial location, but it may also interfere with the manner in which the brain configures coincident sensory inputs, independent of spatial location (Sutherland & Rudy, 1989).

Second, in the course of studying the manner in which the inferotemporal cortex processes visual information, Mishkin and his colleagues (Mishkin, 1978; Mishkin et al., 1984) looked carefully at the contribution of the anterior temporal cortex and medial temporal regions on visual processing, including visual memory, in monkeys. They found that bilateral lesions that included both the amygdala and hippocampus led to severe deficits in tests of recognition memory. Mishkin's work has especially used two behavioral tasks: delayed nonmatching to sample and discrimination learning. In the nonmatching task, a monkey is confronted with an unfamiliar object, which it displaces to find a reward. After a delay, the animal sees the same object paired with a new one. The task is to recognize the original object and to move the new one to gain the reward. In the discrimination learning test there are 20 pairs of objects, and one object of each pair consistently conceals the reward. The animal is shown each pair daily until it learns to choose the baited object in each pair consistently. A key difference between the tasks is that in the first task the animal sees the pair only once, while in the second task it sees the same objects repeatedly over a period of weeks until it learns. An analogy might be learning the face of a single person met on only one occasion as opposed to learning the names and faces of 50 individuals in a group to which one is exposed daily. Mishkin argues that the discrimination learning task, while appearing to be a more difficult task with greater mnemonic demands, is founded not on individual independent memories, but on "automatic connections" between stimulus and response, which he calls "habit." In contrast, he supposes that in the nonmatching test the solution cannot be done by a habit but rather only by a distinct memory of the stimuli.

Mishkin and his colleagues (Mishkin, 1978; Mishkin et al., 1984), selectively removing the prime candidate brain areas, found that combined damage of the amygdala and hippocampus prevented animals from learning the nonmatching test. Further work showed similar results (Mishkin et al., 1984), of varying severity, after lesions of the ventral prefrontal cortex, basal forebrain, or a combined lesion of the diencephalon and the mamillary body. Mishkin proposed that all of these structures form a circuit of structures that might interact to form a memory that he refers to as "recognition memory." This concept is similar to Squire's (1982, 1987a, 1987b) concept of declarative memory. Although the details of how this circuit operates are not specified, the model does fit the human clinical data. Two additional pieces of evidence are of interest here. First, Mishkin found that the young monkeys could learn the object discrimination task

long before they could learn the recognition memory task. This result is consistent with the idea that declarative memory and its neural circuitry develops more slowly than procedural memory and its circuitry. In addition, Parkinson et al. (1988) found that hippocampal lesions interfere with the ability of monkeys to remember the spatial location of objects.

It is not that Mishkin's model is without its difficulties. Mishkin assumes that the amygdala and hippocampus both play a key role in the formation of memories—a conclusion that is in accord with the findings in H.M. (Milner, 1972). Thus, when the amygdala and hippocampus are individually removed, there is little amnesia; it is only with their joint removal that severe memory disturbance exists. Unfortunately, the surgical approach used in Mishkin's studies necessarily included the entorhinal cortex in the joint removal but not in the independent removal of the hippocampus and amygdala. Squire and Zola-Morgan (1988) studied monkeys with lesions that included greater or lesser amounts of entorhinal damage. Their results emphasize the unique importance of the hippocampal and mediotemporal cortical regions, but sparing the amygdala. Their results produced an amnesic syndrome as severe as that with combined hippocampal and amygdala removal. This is in accord with the patient R.B., who had severe anterograde amnesia, an interruption in hippocampal processing, and an intact amygdala (Squire & Moore, 1979). A second problem with Mishkin's model is that it is vague on the question on retrograde amnesia. In an experiment by Sutherland and Arnold (1987), rats were trained to find a hidden location in the Morris Water Task (Morris et al., 1982). Sutherland and Arnold (1987) waited 1, 4, 8, or 12 weeks before producing hippocampal damage in different groups. All groups were tested again 2 weeks after the surgery. Their finding was that the longer the period between learning and hippocampal damage, the better the performance. In other words, the neural record of the training must have been changing over the period that the animals were simply living in their cages.

This experiment is consistent with the clinical observation of retrograde amnesia in medial temporal amnesics, and suggests that the hippocampus is transiently involved in the memory storage process and that other structures or systems maintain the permanent memories. Thus, a satisfactory anatomical model of memory would need to specify more precisely the role of the hippocampus in memory formation and its relation to other brain area and systems.

In summary, there is a body of evidence from the study of laboratory mammals that supports the view that the hippocampal formation is essential for normal declarative memory. Other structures may play a supporting role too, but their relative roles are yet unknown. We think that the focus on lesioning experiments and on the clinical evidence in patients with "circumscribed lesions" may hide the issue and hamper more global investigations of the nature of the memory process in its functioning and dysfunctional state. As the neocortex, for example, also plays a role in the formation of memories, the neural record underlying memories must surely be distributed widely in the cortex.

CONTINUUM ANALYSIS AND NEURAL ACTIVITY WAVES

Thus a computational methodology aimed at an explanation of memory function and by implication dysfunction must account for the following:

- The presumed organization into cell assemblies, which in actuality may be transient and/or figurative. For computational purposes, a cell assembly can be likened to a neural network; thus a theory capable of describing an ensemble of neural networks is the most pertinent.
- The distributed natures of both short and long term memory storage in hippocampus and neocortex, respectively. In particular a reconstructed memory must involve areas separated by distances much larger than typical synaptic connection ranges.
- The ability of the recall mechanism to discern among many different memories distributively stored in the same brain regions, and the capability to recombine these memories into ideas.
- The key role that must be played by Hebbian reinforcement in memory implantation. This local process, occurring at the synapses in a particular set of cells, has somehow to be related to the large-scale process of recall.

In addition, Traub et al. (1987, 1988, 1989) have extensively studied hippocampal structure and function at the cellular level. Any computational model must be consistent with their data.

The continuum theory of neural activity, first proposed by Wilson and Cowan (1973), is particularly appropriate for these requirements. The theory mathematically describes, through a nonlinear integrodifferential equation, the properties of a substance made of large assemblies of neurons, which can affect each other by excitatory and inhibitory connections. In simple terms, neural tissue is decomposed into excitatory and inhibitory "cells" that can be real or figurative according to the problem under consideration. Connections among the cell types have a probability that decreases with distance over a species-specific connection range.

Of prime importance to the present application of the theory is the fact that under the right circumstances the material thus described is "active"—capable of amplifying small disturbances. The amplified signal can be described as a superposition of waves (called *activity waves*), and those waves that preferentially grow are characterized by wavelengths considerably larger than typical synaptic connection ranges.

HIPPOCAMPAL MODEL

Within this framework we have constructed a model of the hippocampus (Koch & Leisman, in press), based on Traub's measurements of hippocampal tissue *in vitro*. Traub et al. (1987) identify three major species of cells, one excitatory and two inhibitory, the latter distinguished from each other

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only by the presence or absence of a synaptic time delay. In addition, they determined numerous synaptic parameters that were incorporated into our model. Of particular importance is the fact that the excitatory connection range was measured to be several times larger than the inhibitory range (Traub et al., 1989).

The significance of this finding lies in its implications for wave growth. Amplification requires an energy source, in this case the electrochemical energy represented by "*e–e*" connections (those among excitatory cells). If the strength of *e–e* connections decreases with distance more slowly than inhibitory connections, then only wavelengths longer than the *e–e* range will be amplified. In fact, maximum amplification, if it occurred, would be at an infinite wavelength.

We have previously surmised (Koch & Leisman, 1990) that such a situation would represent seizure activity, for instance, the "rhythmic population bursts" noted by Traub et al. (1989). Thus it is necessary to conclude that the *in vitro* hippocampus they studied could never support normal activity-wave growth.

Here is where Hebbian modification plays its role. Recent studies (Gould et al., 1998) have shown that hippocampal tissue is capable of regeneration. This suggests that there is a "life cycle," in which this tissue is "born" with the characteristics of the Traub hippocampus, is modified by experience through local Hebbian strengthening, and then, having fulfilled its role in the implantation of long-term memory, "dies," to be replaced in turn by new cells. The intermediate state, which is of most interest, can be treated as a heterogeneous medium, with many embedded highly localized regions of significantly increased *e–e* connection strength.

The aforementioned interplay between wave amplification and connection range is only one way in which the complementary relationship between spatial location and wavelength enters into this study, a relationship akin to the uncertainty principle in quantum mechanics. Paradoxically, it is the very local nature of the strengthened synapses that makes possible the growth of waves with long but finite wavelength. Within a reasonable set of assumptions, the net effect of Hebbian modification on *e–e* connections in the entire medium can be expressed as a slowly increasing parameter, which we call *H*. In effect, this introduces very strong *e–e* connections with a connection range of zero, the weighted *e–e* connection range becomes less than the inhibitory range, and finite wavelength activity waves can grow.

SYNAPTIC PARAMETERS

In particular there is a wave, called the *most-favored mode*, that grows fastest (or decays at the slowest rate) among all possible waves. This wave has a definite wavelength, determined from solution of an equation called a *dispersion relation*. Among the necessary conditions for the validity of this decomposition into waves is that the wave amplitudes remain small (linear approximation). Thus the analysis can determine which waves preferentially grow, but it is not valid after growth has taken place. (Activity is most conveniently expressed in terms of the fraction of a given species firing at a given time and place. The active fraction is the deviation from a norm, the species "excitation threshold" (Wilson & Cowan, 1973), and thus can be either positive or negative; the theory is valid until the absolute value of this fraction, initially small, is of order unity.)

The dispersion relation results from a change of variables in the linearized Wilson–Cowan (1973) equation from real space–time to "wave space," where it is transformed into an algebraic equation. Here the spatial (independent) variable is the wave number *k*, the number of wave maxima per unit length, equal to 2π divided by the wavelength. The temporal (dependent) variable is a complex variable p, with imaginary part ω equal to the angular temporal frequency (2π times the temporal frequency). Its real part γ, if positive, is the growth rate (reciprocal exponentiation time), or if negative, the decay rate. For any set of parameters the most-favored mode is that value of k (hence the wavelength) that gives rise to the maximum value of γ.

There are several parameters in the dispersion relation, which must be properly estimated for solutions to be plausible. These can be classified as described in the following sections.

Constants

The theory assumes neural activity to have a universal decay time; it is taken to be unity, so that times are measured in decay periods. The other significant time is the delay time T in some of the inhibitory neurons. Traub's (Traub et al., 1988) measurements show this to be about three to four decay times. It is of great interest that the theory explicitly determines that this time is related to the hippocampal "gamma rhythm" (Traub et al., 1990) by $fT \approx 0.5$, where f is the gamma frequency.

There are several other parameters that are fixed in the unmodified hippocampal structure:

1. The ratio between inhibitory and excitatory cell densities, which is measured to be about 0.1.

2. The fraction δ of delayed inhibitory cells, compared with the total number of inhibitory cells. Because of the outward similarity between the two types, Traub et al. (1987) cannot give a morphologically based estimate. The theory shows that the upper limit for δ is 1/3. This is equivalent to $\xi = 1/2$, where ξ is the ratio of delayed to "fast" inhibitory cells, related to δ by $(1 + \xi)(1 - \delta) = 1$.

3. The ratio S between the inhibitory and excitatory connection ranges: $S = \sigma_i/\sigma_e$, where σ_s, $s = e, i$ is the connection range for species s in the unmodified hippocampus. Thus ratio is measured to be 1/4 to 1/3 (Traub et al., 1989). In the computations σ_e is taken to be unity, so that $\sigma_i = S$. Thus all lengths are measured in terms of σ_e.

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4. The species connection probabilities P_{us}, $u, s = e, i$ (the probability that a cell of afferent species u is connected to a cell of efferent species s in the unmodified hippocampus). According to Traub et al. (1987) $P_{ee} = .015$, $P_{ei} = .05$, $P_{ie} = .45$, and $P_{ii} = .25$, approximately.

Connection coefficients and chemical state parameters

The coefficients $C_{us}(k)$ that occur in the dispersion relation represent the effect of activity in species u upon the activity of species s, when participating in an activity wave of wave number k. Because of the decrease in connectivity with distance, C_{us} is a decreasing function of k (increases with increasing wavelength). The approximation used here is

$$C_{us}(k) = \frac{D_{us}}{1 + (\sigma_u k)^2},$$

where D is independent of wavelength.

According to Wilson and Cowan (1973), $D_{us} = \nu_s \sigma_u \rho_u P_{us}$, where ρ_s is the density of species s (cells per unit length in the present filamentary geometry) and ν_s is an electrochemical parameter representing the sensitivity of efferent species s to stimuli. Thus the connection parameters, and hence the dispersion-relation results, are strongly dependent on the chemical state, as is also reflected in the extensive experiments and simulations of Traub et al. (1987, 1988).

Because of the constraints of Traub's measurements, there are two independent state parameters related to the unmodified hippocampus, which can be taken to be D_{ee}, and D_{ei}. To avoid growth of infinite-wavelength modes in our computation, the state parameters for the unmodified hippocampus have been chosen so that there is no growth (γ is always less than zero).

The Hebbian synaptic strengthening parameter

The Hebbian parameter H reflects a gradual increase with time in the e–e influence coefficient, due to increased sensitivity ν_e and/or proliferation P_{ee}, in one or more localized areas (Greenough & Chang, 1985). In its most general definition it is a complicated function of the space–time history of the hippocampal activity. There are some simple configurations, however, in which it can be approximated by a slowly increasing function of time only and hence as a constant in the dispersion relation. This approximation is used in our computation in order to provide a relatively simple example of the qualitative effect of synaptic strengthening.

One requirement for this is the assumption that the connection range of the enhanced e–e connections is strictly zero. Because of the real space–wave-space duality, this has the paradoxical result of providing the equivalent of a decrease in the decay rate for excitatory activity only, for all wavelengths, everywhere in the medium. If a succession of "snapshots" of the dispersion relation $[p + 1 - H - C_{ee}][p + 1 + C_{ii}(1 - \xi + \xi e^{-pT})] + C_{ie}C_{ei}(1 - \xi + \xi e^{-pT}) = 0$ are taken at successive times, with increasing values of H, eventually a situation is reached where waves begin to grow.

NUMERICAL RESULTS

Figure 1 shows the solution of the dispersion relation as a function of wave number k and Hebbian parameter H for parameter values $S = \delta = .3$, $T = 4$, $D_{ee} = 3$, and $D_{ei} = 12$. The parameters have been chosen so that there is no growth ($\gamma < 0$) in the absence of conditioning ($H = 0$). As H increases, growth becomes possible ($\gamma > 0$) and the wave num-

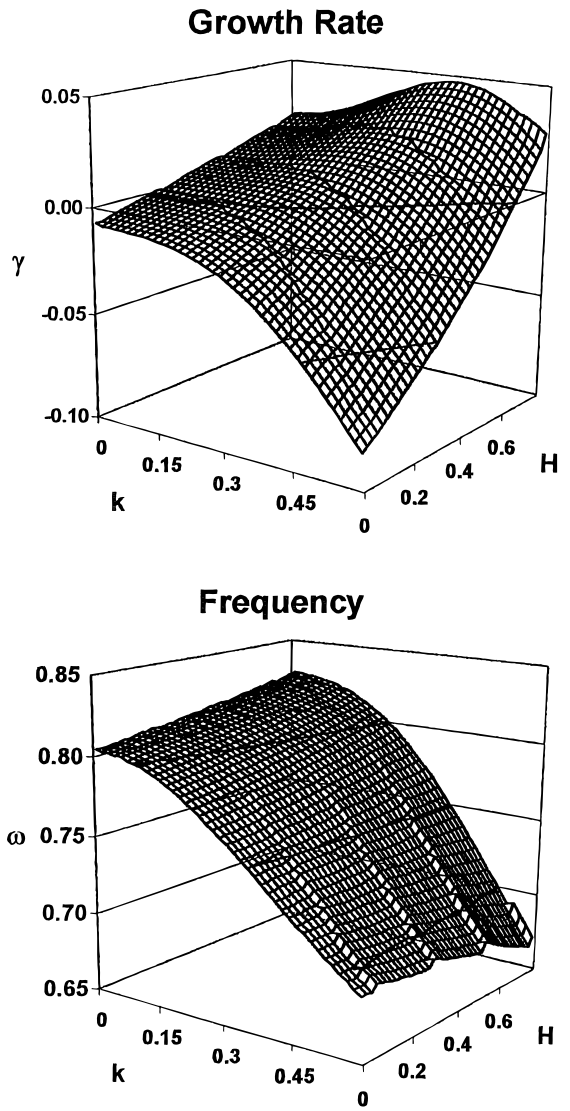

Fig. 1. Solution to the dispersion relation for the hippocampal model. The real part γ (growth rate) and imaginary part ω (angular temporal frequency) of the complex frequency variable are plotted as functions of the wave number k (angular spatial frequency) of an activity wave and the Hebbian conditioning parameter H. Times are measured in terms of the neural activity decay time and distances in terms of the excitatory connection range. The parameters are given in the text.

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ber for which γ is maximum (favored wave number) becomes greater than zero, indicating that the response to an infinitesimal disturbance is a growing wave of finite wavelength. The most favored mode, for which γ is a maximum, is a function of H.

Figure 2 shows the variation of the wave number, growth rate, and temporal frequency of this preferred mode as functions of the connection parameters D_{ee} and D_{ei}, which change with the chemical state, for various values of H, which is a slowly increasing function of time. The constant parameters of the model, S, δ, and T, are the same as for Figure 1.

It is clear from these figures that the temporal frequency varies within a small range, satisfying approximately $\omega T = \pi$. This result can be explained by the exponential term in the equation, which has a maximum negative value when $\omega T = \pi$, contributing maximally to the growth. It translates to $fT = 0.5$, where f is the externally measured temporal frequency of hippocampal activity. Setting $f = 20$ Hz, typical of the gamma rhythm (Traub et al., 1990), leads to $T = 25$ ms, which is close to the measured value (Traub et al., 1988). Furthermore, if this relationship is assumed to be exactly true (and the product γT is assumed to be much less than unity), the dispersion relation becomes $[p + 1 - H - C_{ee}][p + 1 + C_{ii}(1 - 2\xi)] + C_{ie}C_{ei}(1 - 2\xi) = 0$, which shows a singularity as $\xi \to 1/2$ ($\delta \to 1/3$). When $\delta = 1/3$ the inhibition has no effect and above $\delta = 1/3$ all waves grow as the effect of inhibition is reversed. This indicates that the proportion of delayed inhibitory cells is absolutely constrained to be less than 1/3 for normal function.

Another significant result is the dependence of the favored wavelength upon the chemical state while H remains constant. The connection parameters are capable of change

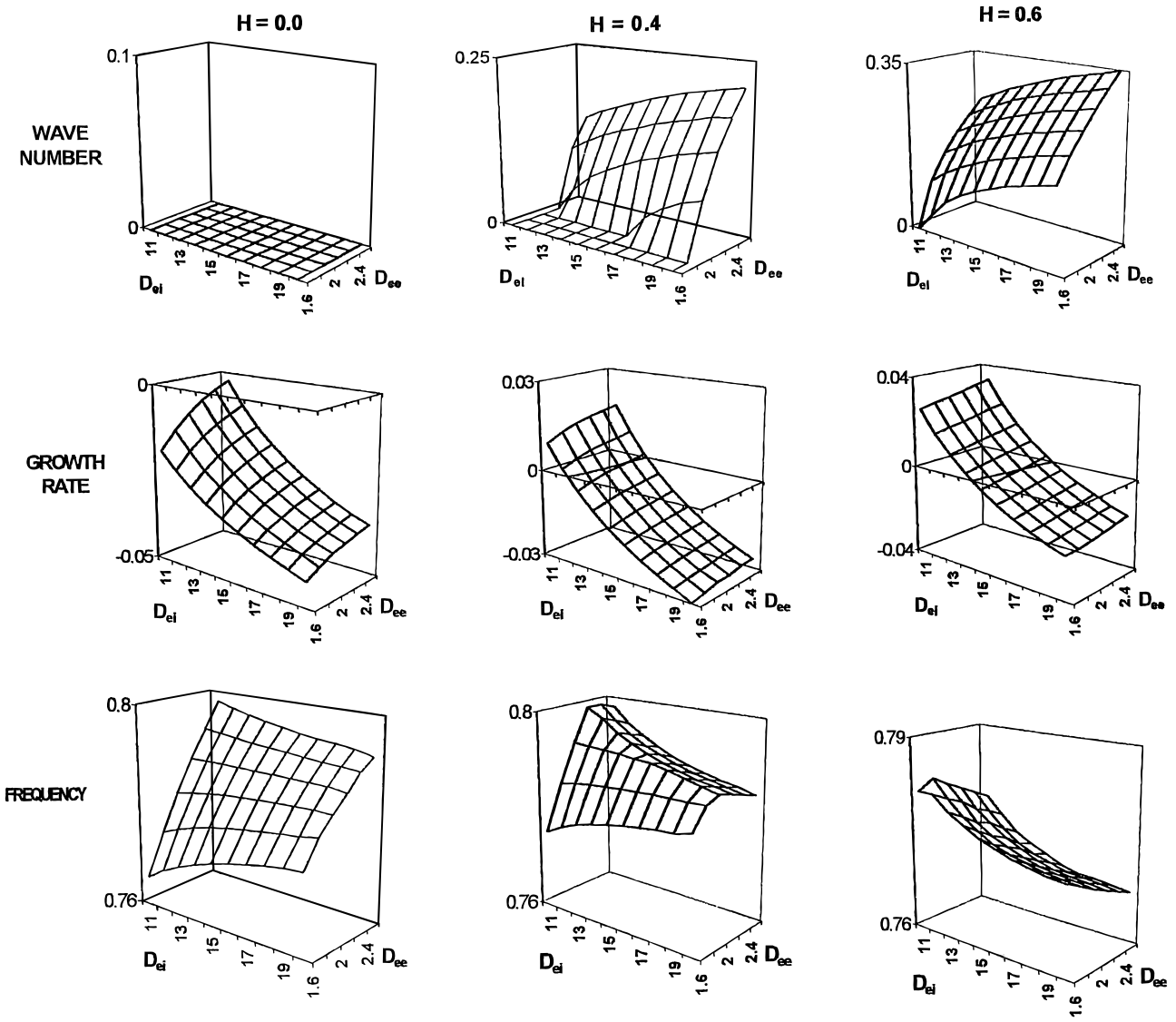

Fig. 2. Characteristics of the fastest-growing (or slowest-decaying) wave mode for the hippocampal model. The favored wave number, growth rate, and temporal frequency are plotted against the chemical state connection parameters D_{ei} and D_{ee} (defined in the text) for increasing values of the conditioning parameter H. Other parameters are given in the text.

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on a time scale considerably faster than the presumed adiabatic increase in H (Eccles, 1986). Thus they can act as a wavelength tuning mechanism for the amplified waves at any stage of the conditioning history.

Note, however, that at $H = 0.4$, while the growth rate for some values of the connection parameters has become positive, there is a region of the parameter space (approximately $D_{ei} < 12$ and $D_{ee} < 2.2$) within which this occurs while the favored wave number is still zero. For reasons discussed above, this region must be forbidden for normal hippocampal function. At $H = 0.6$, all favored wavelengths within the range displayed are finite.

Through inverse transformation, the solutions to the dispersion relation can be used to show the wave behavior in real space–time. Figure 3 shows the spatiotemporal response of the hippocampal model to impulsive stimuli (ratio A of wave amplitude to initial excitation amplitude): (a) a single stimulus at $x = 0$, $t = 0$; (b) two stimuli, one at $x = 0$, $t = 0$ and the second at $x = 240$ and $t = 5$. (Distances are measured in terms of excitatory connection lengths and times in activity decay times.) The parameters are $H = 0.8$, $S = \delta = .3$, $T = 4$, $D_{ee} = 3$, and $D_{ei} = 14$. The results are presented, in ascending order, for longer and longer elapsed times, to show the growth and propagation of the wave responses.

With an isolated signal, the response is a relatively tight wave packet that propagates through the medium. The two interfering signals lead to a considerably broader, more persistent, wave structure. In either case the response remains coherent, with constant wavelength. A persistent growing coherent signal of constant wavelength as well as the existence as of a hippocampal wavelength tuning mechanism dependent on the chemical state strongly suggest the beginnings of a theory of memory implantation—and, by implication, recall—through activity waves.

MODEL OF NEOCORTICAL RECALL

In previous work (Koch & Leisman, 1996), we have postulated that the cortical mechanism of memory recall depends primarily upon amplified waves whose wavelength changes sporadically over time; this is reminiscent of Pribram's (1971) metaphor of "holographic" memory. The waves provide simultaneous activity in mutually remote regions separated by an integral multiple of the current favored wavelength. These elements of the continuum, which can variously be likened to "cell assemblies" (Hebb, 1949) or neural networks or "groups" (Edelman, 1978), could be or contain fragments that can be reconstructed into a memory, in accordance with Bartlett's (1932) concept.

Variations in the preferentially amplified wavelength could be brought about by changes in the chemical state, as in the hippocampus. However, the layered geometry of the neocortex suggests the possible importance of a delay in synaptic signal transmission between the layers. The delay could be variable as in the synaptic "tapped delay line" postulated by Desmond and Moore (1988), and changes in delay can result in changes in the favored wavelength.

This applies to the response to small stimuli of a model we constructed that we believe is relevant to the neocortex. Our model is the simplest realization of a layered geometry, namely two layers each containing excitatory and inhibitory cells with a variable interlayer delay, the same for all types of connection. More speculatively, we assume that the connection coefficients are constant and favorable to wave growth (in particular, the inhibitory range is assumed larger than the excitatory range). The delay is thus the sole tuning mechanism.

Basically, the solution of the dispersion relation for this system consists of two coupled amplified waves, each of which may have more than one relative maximum in growth rate. The complexity of the structure depends on the interlayer delay, as shown in Figure 4. Here the situation has been simplified by assuming the layers to be identical; in that case the waves uncouple and can be characterized as *plus* (+) and *minus* (−), depending on the relative phases in the activity of like cells in opposite layers (Koch & Leisman, 1996).

Figures 4a and 4b show the respective growth rates as a function of wave number k and delay time T (distances are measured in terms of the excitatory connection range and times in terms of the activity decay time). Each wave type in itself undergoes an increase in complexity (number of maxima in k) as T increases. Figure 4c displays the growth rate of the + or − wave, whichever is greater, for each value of k or T; this would be the dominant wave under those conditions. It should be noted that for larger values of T there could be as many as three or four different values of k at which a relative maximum in growth occurs.

By reverse transformation the solutions of the dispersion relation can be converted into the activity-wave structure in real space–time. Figures 5 and 6 show the response of the model to small disturbances, in this case a single impulse (delta function) at $x = 0$, $t = 0$, for several values of delay T and the same connection parameters as in Figure 4. To enhance clarity the display is divided into two time periods; early times and later times are shown in Figures 5 and 6, respectively. (Infinities connected with the delta function are avoided by starting at $t = 0.5$ decay periods.)

In addition, the response has been spectrally analyzed via fast Fourier transforms, and the resulting spatial spectra are also shown in the figures. As delay increases, the number of growing spectral lines increases from one to three, and the wavelength maxima themselves move towards increasing k. The line that is near $k = 0.5$ at $T = 0.75$ migrates to k near 0.75 at $T = 1.25$, but a new line has been excited, near $k = 0.25$ at this value of T, with slightly higher growth rate.

When $T = 1.75$, the original line has almost negligible growth, at a high value of k, the second line dominates at k near 0.5, and a third line at low k also competes.

The response at $T = 0.75$ (Figures 5a and 6a) is a coherent propagating wave with no wake, which looks very much like the hippocampal response to a similar stimulus (Fig-

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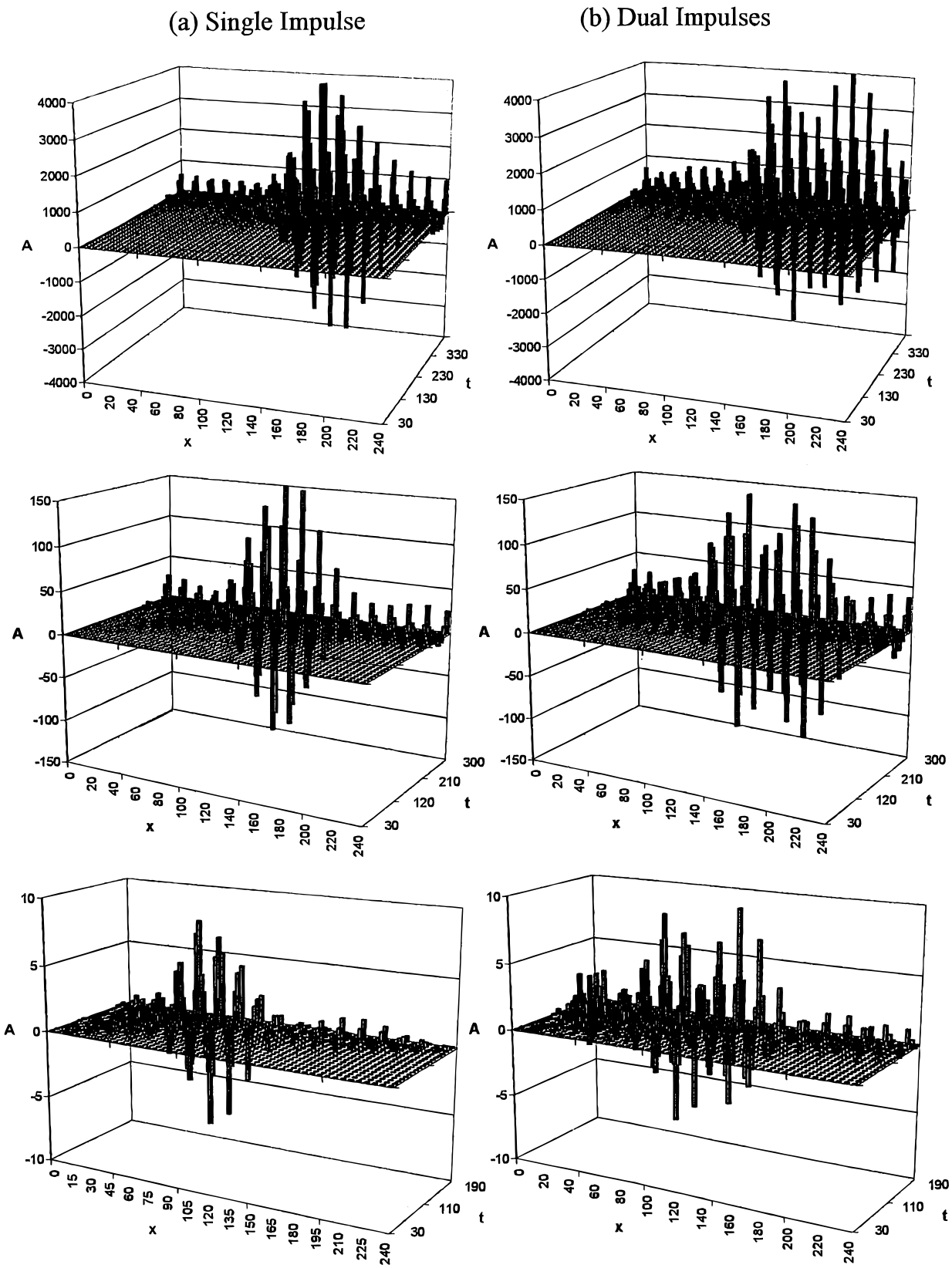

Fig. 3. Spatiotemporal wave response of the hippocampal model to (a) a single unit impulsive input at $x = 0$ and $t = 0\,[\delta(x, t)]$; (b) two unit impulses, separated in space and time. The wave amplitude A (in multiples of the unit input) is presented in three different time frames, progressing from early times (bottom) to appreciably later times (top). The parameters are the same as in Figure 1, with $H = 0.8$.

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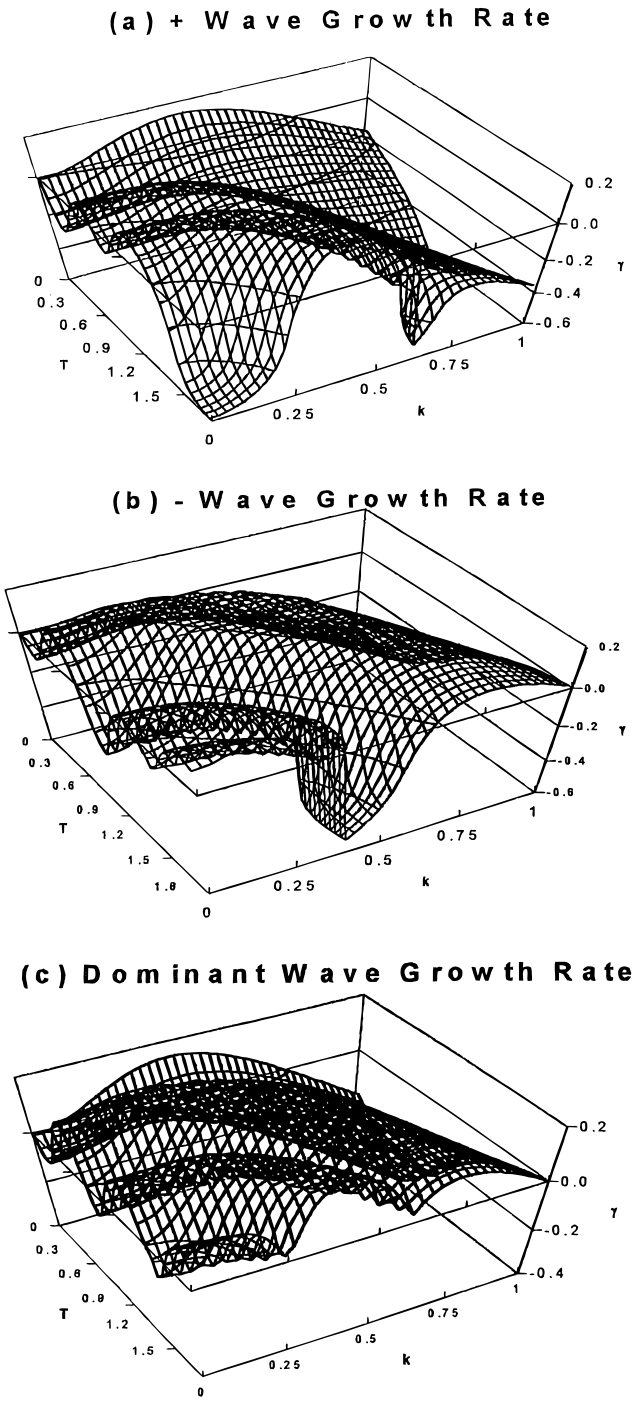

Fig. 4. Growth rate for activity waves in the cortical model. The response of two identical layers with interlayer synaptic delay T can be expressed as the sum of two uncoupled waves (+ and −), described in the text. The growth rates of these waves are shown respectively in (a) and (b), as functions of T and wave number k. In (c) the greater growth rate between the two waves is shown. This is the dominant growth rate for the given value of k and T. The parameters for this figure, and for Figures 5 and 6, are described in detail in Koch and Leisman (1996).

ure 3a). At the higher values of T, the activity-wave structure is significantly more complex, although it is relatively simple when spectrally analyzed. Especially at early times (Figures 5b and 5c), there is a low-frequency oscillatory spectral signal of constant relatively high amplitude at k near zero; this reflects the significant wakes left by the propagating activity waves. The mutual interference of the competing spectral lines results in an incoherent appearance in the response, again especially at early times.

At later times, the spectrum for $T = 1.75$ is very close to monochromatic, as the central line increasingly dominates. Because of its earlier history, however, the response has a more complex structure than the literally monochromatic wave for $T = 0.75$; this structure is reproduced in successive wave maxima. For $T = 1.25$, the spectral lines remain at near equal amplitudes, so that the wave continues to grow as a pattern of interfering wave fronts, leading to a structure that appears stochastic throughout.

Although the maximum growth rates are about equal for the delay times presented (Figure 4c), the maximum amplitudes attained at equal elapsed time are significantly less for the more complex spectral structures. For the latter, however, the amplified activity involves many more continuum elements at any given time.

INTERPRETATION OF THE CORTICAL RESPONSE

To understand these results it is necessary to recall that each element (each spike in Figures 5 and 6) is several connection ranges in diameter and contains some thousands of neurons (Wilson & Cowan, 1973). This number is sufficient to perform many complex tasks in artificial neural network configurations (Grossberg, 1989); although the exact mode of functioning is almost certainly different in this case it is reasonable to assume that the present "modules" are capable of similar tasks.

Thus the wave patterns illustrate the activation patterns of large complex cell assemblies; when several of these assemblies are simultaneously active, they can be thought of as constituting a "mental state." A succession of such states, for example the waves illustrated in Figures 5 and 6, involving perhaps 10^7 cells (Koch & Leisman, 1996), can be considered a "memory" or "thought."

Within this framework, the pattern at $T = 0.75$ (Figures 5a and 6a) illustrates a pure memory recollection, perhaps of that implanted by the hippocampal wave of Figure 3a. A standing wave pattern caused by two or more stimuli such as in Figure 3b would have a similar monochromatic cortical equivalent. As the waves grow, they recruit more and more cells, in analogy to the cascade effect noted by Bartlett (1932). Growth might eventually be limited by the nonlinear effects that the Wilson and Cowan (1973) equation takes into account. Alternatively, the conditions for growth at the wavelength in question could cease to exist; specifically a change in delay time will favor a different wavelength. This is analogous to an attention shift (Koch & Leisman, 1996).

The simultaneous activation states at longer delays have both regularities and random features. The spectra, espe-

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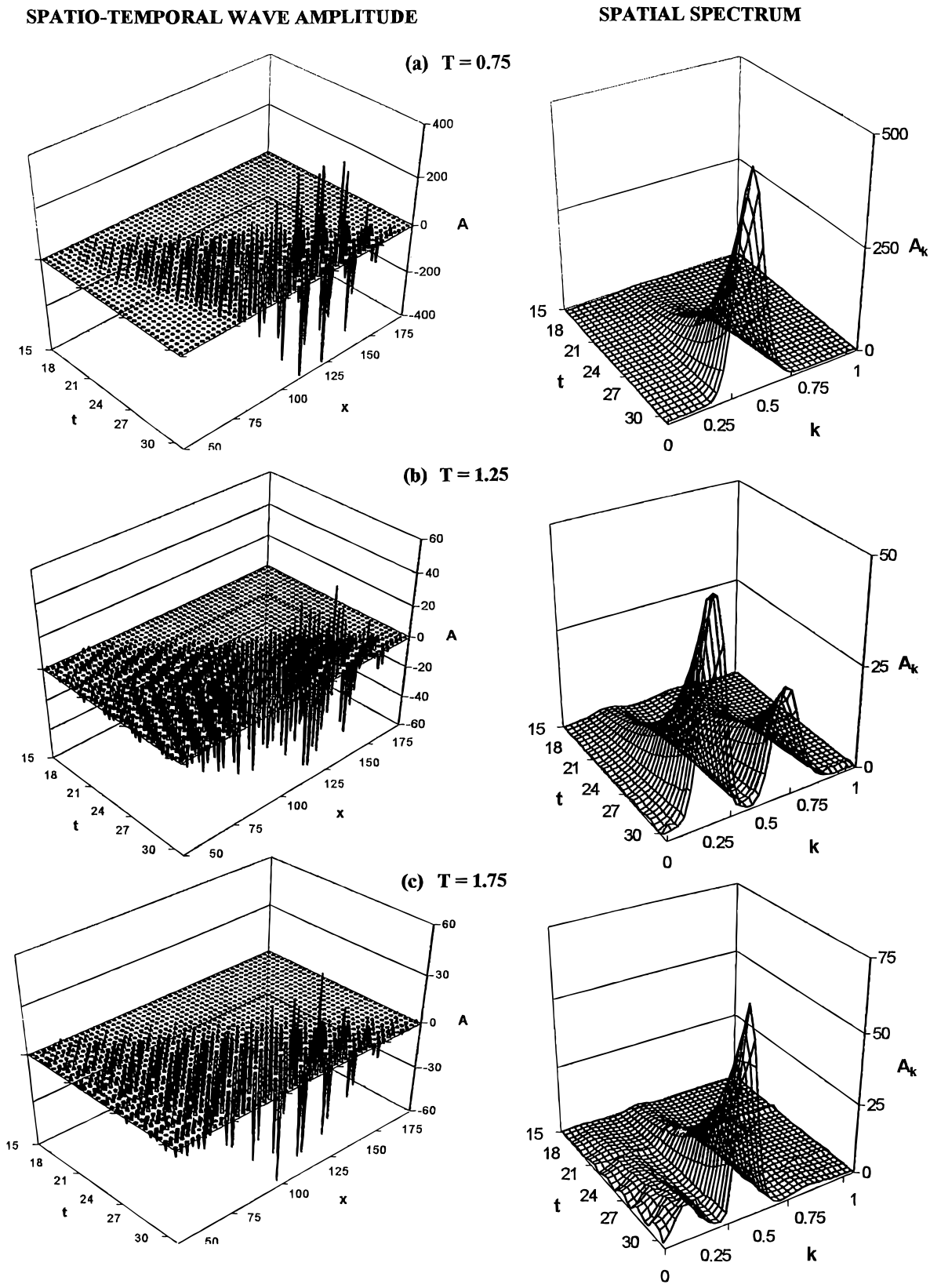

Fig. 5. Spatiotemporal response, at early times, of the cortical model to a unit impulse at $x = 0$ and $t = 0$. The amplitude A (relative to the impulse amplitude) of the response and the amplitude of its spatial spectral density A_k are plotted for different values of the interlayer delay time T. To avoid infinities connected with the delta function, the earliest time shown is $t = 0.5$.

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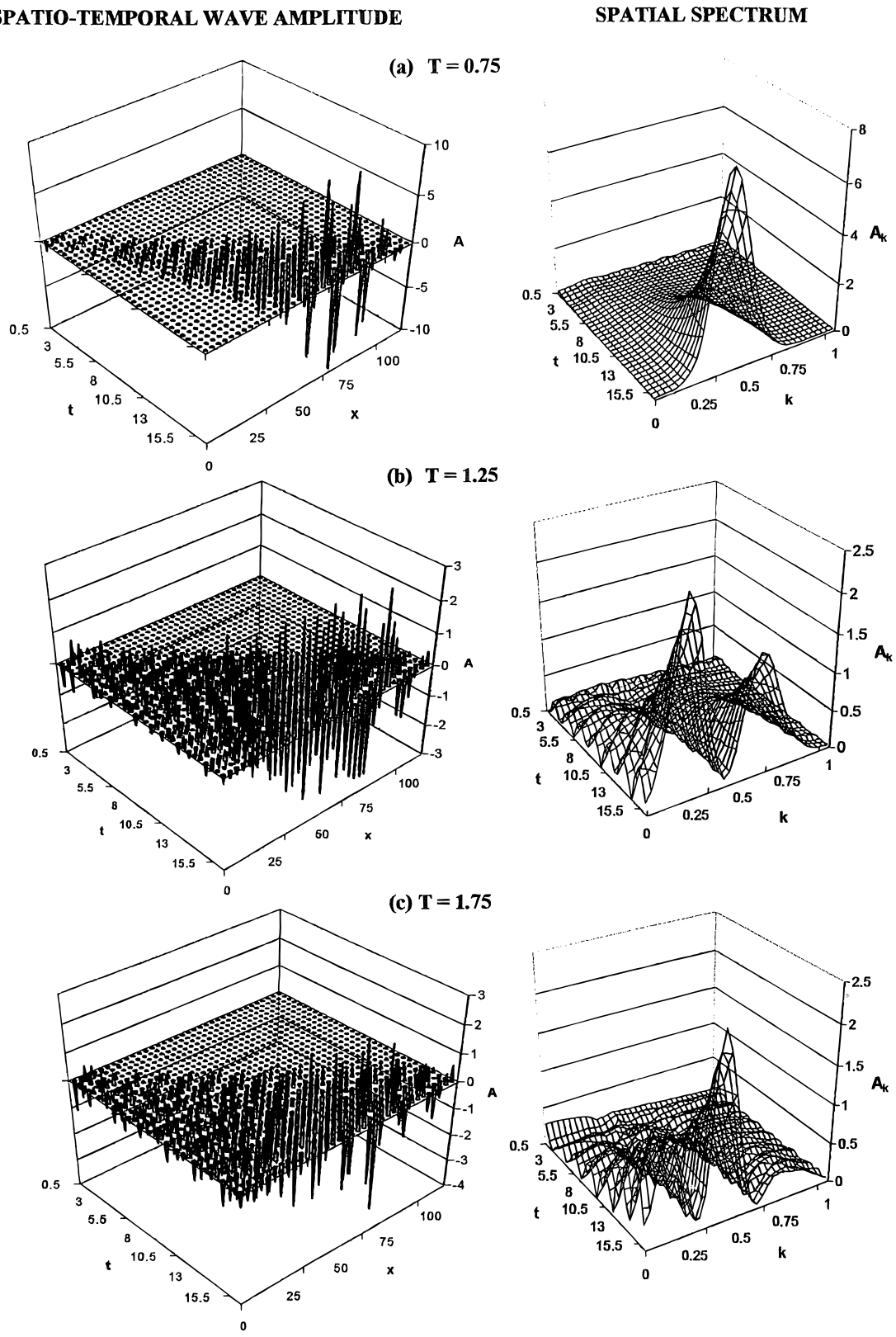

Fig. 6. Spatiotemporal response of the cortical model at later times.

cially at late times as in Figures 6b and 6c, are simple and reproducible, but the interference effects cause irregular patterns in activity. In some instances this effect manifests itself as large amounts of simultaneous activity in adjacent elements. Since the underlying system is deterministic, the locations of these regions of high activity are fixed with re-

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spect to the position of the initial impulse. However, that impulse itself results from noise and therefore its location is random in both space and time.

Thus the response of the simple two-layer cortical model begins to exhibit features characteristic of the mental phenomena of both creative thought and reproducible memory. In both the hippocampal and cortical models, which, we believe, have a strong relation to reality, amplified activity waves of variable wavelength provide a means by which synaptically distant elements can be meaningfully connected. With the ability to measure accurately spatially resolved activity in the brain as exemplified by Mayevsky et al. (1996), we predict that the instant model will support an evaluation of the adequacy of memory function and dysfunction.

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