Information Processing with Frequency-Dependent Synaptic Connections

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The efficacy of synaptic transmission between two neurons changes as a function of the history of previous activations of the synaptic connection. This history dependence can be characterized by examining the dependence of transmission on the frequency of stimulation. In this framework synaptic plasticity can also be examined in terms of changes in the frequency dependence of transmission and not merely in terms of synaptic strength which constitutes only a linear scaling mechanism. Recent work shows that the frequency dependence of transmission determines the content of information transmitted between neurons and that synaptic modifications can change the content of information transmitted. Multipatch-clamp recordings revealed that the frequency dependence of transmission is potentially unique for each synaptic connection made by a single axon and that the class of pre–postsynaptic neuron determines the class of frequency dependence (activity independent), while the unique activity relationship between any two neurons could determine the precise values of the parameters within a specific class (activity dependent). The content of information transmitted between neurons is also formalized to provide synaptic transfer functions which can be used to determine the role of the synaptic connection within a network of neurons. It is proposed that deriving synaptic transfer functions is crucial in order to understand the link between synaptic transmission and information processing within networks of neurons and to understand the link between synaptic plasticity and learning and memory.
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INTRODUCTION

Hebb's formulation for the cellular substrates of learning and memory appears to have been largely influenced by the seemingly logical need for stimulus-driven neural activity patterns to "reverberate" within the nervous system even after the stimulus is over, since this could account for short-term memory (Hebb, 1949; Amit, 1996). The "growth of the assembly" by specific modifications of the efficiency of transmission between selected groups of neurons was then proposed to set up the conditions to reactivate these reverberations which could account for long-term memory storage. What Hebb and his followers did not consider were published data (Feng, 1941; Hutter, 1952; Liley & North, 1953; del Castillo and Katz, 1954; Liley, 1956; Takeuchi, 1958; Hubbard, 1963;

Thies, 1965; Betz, 1970; Zucker, 1989) showing that connections do not transmit all stimuli in an equal manner and hence did not consider how reverberations could occur if neurons were connected with frequency-dependent connections. To this day, this issue has not been addressed. In fact, Hebb's ideas not only initiated an enormous search for proofs, mechanisms, and algorithms for synaptic gain change (for reviews see Teyler & Fountain, 1987; Morris, Kandel, & Squire, 1988; Bliss & Collingridge, 1993; Jodar & Kaneto, 1995; Maren & Baudry, 1995; Cruikshank & Weinberger, 1996; McEachern & Shaw, 1996; Fregnac & Shulz, 1994), but also influenced profoundly the direction and interpretation of countless in vitro and in vivo experiments, experiments aimed at understanding neural information processing (see Hertz, Krogh, & Palmer, 1991; Churchland & Sejnowski, 1992; Arib, 1995), and, more recently, experiments aimed at linking synaptic gain change and learning and memory (Teyler & Fountain, 1987; Morris et al., 1988; Bliss & Collingridge, 1993; Jodar & Kaneto, 1995; Maren & Baudry, 1995; Cruikshank & Weinberger, 1996; McEachern & Shaw, 1996; Dudai, 1989). Our current concepts of neural information processing are therefore profoundly influenced by Hebb's view of the nervous system.

Frequency-dependent synaptic transmission seems to be a universal property of synapses in all animals (Feng, 1941; Liley & North, 1953; del Castillo & Katz, 1954; Parnas & Atwood, 1966; Pinsker, Kandel, Castellucci, & Kupfermann, 1970; Takeuchi, 1958; Zucker, 1989; Laurent & Sivaramakrishnan, 1992; Davis & Murphey, 1993; Katz, Kirk, & Govind, 1993) and has been observed at all types of synaptic connections in mammalian neocortex (Thomson & Deuchars, 1994). The rates of change in transmission are sufficiently rapid to be potentially relevant for most frequency ranges *in vivo,* and since the transmission is history dependent, linear approximations of the way in which synapses transfer information (referred to as "synaptic transfer functions") are correct only for restricted conditions of stimulation. Frequency-dependent synaptic transmission has been considered extensively in simple organisms where it has been central to perhaps the most thorough characterization of the cellular basis for learning and memory and simple behavior (Pinsker et al., 1970; Castellucci, Pinsker, Kupfermann, & Kandel, 1970; Byrne, 1978; Carew, Walters, & Kandel, 1981; Gingrich & Byrne, 1985; Buonomano, Baxter, & Byrne, 1990; Ciaccia, Maio, & Vacca, 1992). It is therefore surprising that the importance of frequency dependence has not been considered in information processing, learning, and memory in the mammalian cortex (but see Grossberg, 1969; McNaughton, 1989; Liaw & Berger, 1996).

In this paper we review recent work of ours that represents a "revival" of the study of frequency-dependent synaptic transmission with a new aim and new approach. Our aim is not only to examine frequency dependence from a biophysical perspective as has been done in the past, but to quantify its properties as they relate to its potential function. The studies reviewed are based on experimental recordings between identified synaptically coupled pairs, triples, and quadruples of neurons in neocortical slices and a phenomenological model of frequency-dependent synaptic transmission.

METHODS

The methods employed in the studies reviewed are described briefly. These involve the conditions for recording synaptically coupled neurons, the phenomenological model, and the neural network simulations.
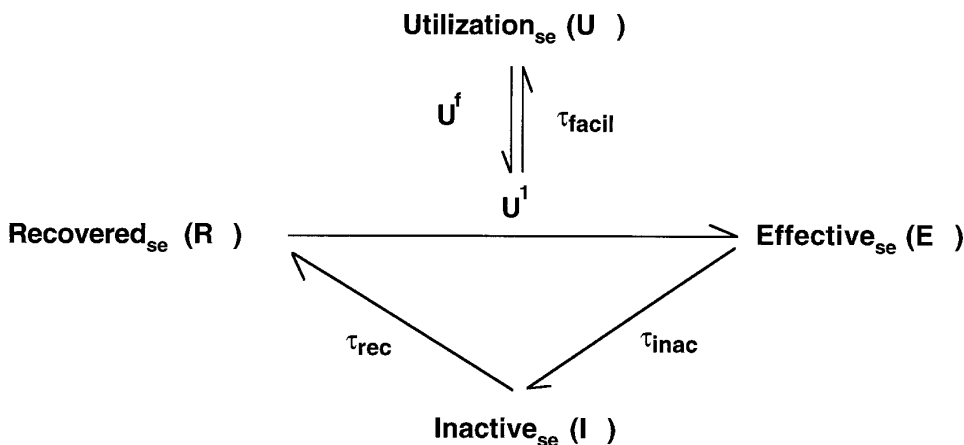
Utilization$_{se}$ (U)

U^f $\tau_{\textbf{facil}}$

U^1

Recovered$_{se}$ (R) $\longrightarrow$ Effective$_{se}$ (E)

$\tau_{\textbf{rec}}$ $\tau_{\textbf{inac}}$

Inactive$_{se}$ (I)

FIG. 1. Model of frequency-dependent synaptic transmission. Each AP uses (U) a fraction of the available/recovered synaptic efficacy (R). When an AP arrives, U is increased by an amplitude of U^f and becomes a variable, U^1. In the simulations, the value of U^f is the same as U. Depressing synapses can be simulated either by making U very large or by making t_{facil} very small. (Reprinted from *Neuropharmacology* **37,** Markram, Pikus, Gupta, and Tsodyks, Potential for multiple mechanisms, phenomena and algorithms for synaptic plasticity at single synapses, pp. 489–500, copyright 1998, with permission from Elsevier Science.)

Slice Preparation

Sagittal slices (300 μm) were cut from the somatosensory cortex of Wistar rats (13–15 days) (Markram, Lübke, Frotscher, Roth, & Sakmann, 1997a). Experiments were performed at 30–32°C with extracellular solution (in mM); 125 NaCl, 2.5 KCl, 25 glucose, 25 NaHCO$_3$, 1.25 NaH$_2$PO$_4$, 2 CaCl$_2$, and 1 MgCl$_2$. Neurons were preselected using infrared differential interference contrast video-microscopy on an upright microscope (Zeiss-Axioskop-FS, fitted with 40X-W/0.75NA objective) (Stuart, Dodt, & Sakmann, 1993; Markram et al., 1997a). Somatic whole-cell recordings (10–20 MΩ access resistances) were obtained and signals were amplified using Axoclamp-2B amplifiers (Axon Instruments), captured on computer using Pulse Control (by Dr. R. Bookman and colleagues, Miami University) and analyzed in programs written in Igor (Igor Wavemetrics, Lake Oswego, OR). Pipet solution contained (in mM): 100 K-gluconate, 20 KCl, 4 ATP-Mg, 10 phosphocreatine, 0.3 GTP, 10 Hepes, and 0.5% biocytin (pH 7.3, 310 mOsm). The resting membrane potential level for pyramidal neurons was -62 ± 2 mV, and for interneurons, below -74 mV. Input resistance for pyramidal neurons was 80–150 MΩ, and for interneurons, 600–1000 MΩ.

Phenomenological Model of Frequency-Dependent Synapses

Synaptic depression was formulated with three parameters as in Tsodyks and Markram (1997): absolute synaptic efficacy (A), utilization of synaptic efficacy (U), and recovery from depression (τ_{rec}). The model (Fig. 1) states that each presynaptic AP uses (U) a fraction of the absolute synaptic efficacy (A) available (fraction of recovered efficacy, R) at the time of its arrival (t_{AP}). The

postsynaptic response is given by the expression $A \cdot U \cdot R(t_{AP})$. Synaptic efficacy recovers between APs with a time constant τ_{rec}, and R therefore changes according to

$$\frac{dR}{dt} = \frac{(1 - R)}{\tau_{\text{rec}}} \, . \tag{1}$$

To model facilitation, U was changed from AP to AP, and this running value of U is referred to as U^1 (see Markram et al., 1998a). Biophysical models of facilitation (see Magleby & Zengel, 1982; Magleby, 1987; Zucker, 1989; Bertram, Sherman & Stanley, 1996) were simplified by incorporating a pulsed increase in U^1 with each AP by an amplitude of U^f. U^f was assigned the same value as U, and U refers to the first AP. U^1 decays according to a single relaxation time constant (τ_{facil}). The value of U^1 for any AP during a train is then

$$U^1(n + 1) = U^1(n)\exp\left(\frac{-\Delta t}{\tau_{\text{facil}}}\right) + U^f\left(1 - U^1(n)\exp\left(\frac{-\Delta t}{\tau_{\text{facil}}}\right)\right), \tag{2}$$

where Δt is the time interval between the nth and $(n + 1)$th APs.

RESULTS AND DISCUSSION

A Phenomenological Model of Frequency-Dependent Synaptic Transmission

Many different approaches have been employed to study frequency-dependent synaptic transmission, including experimental approaches, biophysical models, nonlinear systems analysis, and coefficient of variation analysis (Liley & North, 1953; del Castillo & Katz, 1954; Liley, 1956; Thies, 1965; Betz, 1970; Pinsker et al., 1970; Magleby & Zengel, 1976, 1982; Magleby, 1987; Zucker, 1989; Krausz & Friesen, 1977; Korn, Faber, Burnod, & Triller, 1984; Korn, Faber, & Triller, 1986; Gingrich & Byrne, 1985; Ciaccia et al., 1992; Destexhe, Mainen, & Sejnowski, 1994; Liaw & Berger, 1996; Bertram et al., 1996; Abbott, Varela, Sen, & Nelson, 1997). Our approach is to study frequency dependence using a phenomenological model (see Methods; Tsodyks & Markram, 1997; Markram et al., 1998a; Tsodyks, Pawelzik, & Markram, 1998). This approach is adopted to avoid debatable biophysical assumptions of the mechanism of release. This model describes frequency dependence in terms of four synaptic parameters. The absolute synaptic efficacy of a connection (A) is the maximal response that can be produced by a connection if the release probability were 1 at all possible release sites. The utilization of synaptic efficacy (U) describes the average fraction of the A that each AP uses and is analogous to the probability of neurotransmitter release (P_r) if the mechanism of frequency dependence is located purely presynaptically (see Jones & Westbrook, 1996). The parameter τ_{rec} defines the time constant for recovery from synaptic depression and τ_{facil} refers to the time constant of recovery from facilitation. Depending on the experimental data and the aim of the study, different amplitudes and time constants for potentially multiple components of depression and facilitation can be incorporated (see Magleby & Zengel, 1982; Zucker, 1989).

The synaptic parameters are derived iteratively to obtain the best fit of the experimentally derived postsynaptic potential (PSP) amplitudes. A major advantage of this approach is that only the averaged synaptic responses to high-frequency trains of presynaptic APs is required (see Tsodyks & Markram, 1997; Markram et al., 1998a; Markram, 1997). The analysis, therefore, does not depend on statistical analysis and overcomes the difficulty of measuring reliably very small PSPs that can result during high-frequency synaptic transmission. The synaptic parameters are used to simulate responses of the synaptic connection to arbitrary trains of APs.

Quantifying Frequency-Dependent Synaptic Transmission

In the simplest terms, frequency dependence means that synapses transmit presynaptic APs differently for different conditions of stimulation. As a first step to understanding the function of this synaptic property it is important to characterize this state-dependent behavior quantitatively. Two approaches are adopted. The first approach is experimental, where the synapses are driven at progressively higher presynaptic AP frequencies and the steady-state amplitudes of PSPs (PSP_{st}) for each frequency are measured. The second approach is theoretical, where the model formulations are explored. In each case the predictions or the results were tested experimentally and theoretically and found to be compatible. The frequency–PSP_{st} relationship is unique for a particular synapse depending on the precise values of the synaptic parameters.

When depressing synapses are driven at progressively higher frequencies, PSP_{st} decreases as the presynaptic frequency increases, and beyond a critical frequency, PSP_{st} begins to decrease inversely proportional to the frequency (Tsodyks & Markram, 1997; Abbott et al., 1997). This critical frequency is termed the limiting frequency (λ Hz) and depends inversely on the values of U_{se} and τ_{rec}. When facilitating-type synapses are stimulated at progressively higher frequencies, then a novel frequency–PSP_{st} relationship is revealed in which $PSP_{s\text{-}s}$ first increases and then decreases due to an interplay between facilitation and depression (see also Magleby & Zengel, 1976). λ Hz is reached only at very high frequencies (70–130 Hz), as apposed to 5–30 Hz for depressing synapses. The peak of the bell-shaped curve is referred to as the peak frequency (θ Hz). The peak frequency is a quantitative measure of the frequency at which the synapse responses reach the maximum. The value of θ Hz can be derived using the model and it depends inversely on the square root of the product of all three "kinetic parameters," U_{se}, τ_{rec}, and τ_{facil}. θ Hz typically varies between 3 and 30 Hz.

Transfer Functions of Frequency-Dependent Synapses

The values of the synaptic parameters, the characteristic frequency–PSP_{st} relationship, and the values of θ and λ provide a quantitative measure of frequency dependence, but the next level of complexity that is required is to formulate the transmission capacity of synapses. This is also achieved in a simple manner by determining the function that describes the relationship between the presynaptic AP activity and the postsynaptic response (Markram et al., 1998a). This function is referred to as the "synaptic transfer function." Because the transmission capacity of synapses changes in a frequency-dependent manner, the synaptic transfer function takes on different forms at differ-

ent frequencies. The frequencies at which these transitions in form occur are indicated by the values of λ Hz and θ Hz and therefore depend critically on the values of the synaptic parameters.

Above λ Hz, synapses are not capable of transmitting information about the average discharge rate; they signal the change in presynaptic frequencies and hence signal phasic presynaptic events to the postsynaptic neuron. In other words the form of the transfer function above λ Hz is the derivative of the frequency and this signaling regime is referred to as a sublinear signaling regime. As the frequency of presynaptic discharge decreases below λ Hz the signal transmitted to the postsynaptic neuron begins to contain progressively more information about the absolute discharge rate. For facilitating synapses, virtually all information about the derivative of the discharge is absent near θ Hz, and synapses transmit almost perfectly information about the absolute discharge rates of the presynaptic neurons. For depressing synapses, the derivative component decreases as the frequency decreases and is virtually absent at frequencies less than $1/\tau_{rec}$. This signaling regime is referred to as a linear regime. At facilitating synapses another signaling regime emerges as the frequency decreases from θ to 0 Hz. The postsynaptic response now begins to reflect a facilitating component which carries with it information about the integral of the discharge rate. This is an intriguing property of facilitating synapses since they are now able to integrate or "count" the number of APs in an AP train. More specifically, the form of the transfer function for this frequency range is the discharge rate multiplied by the integral of the discharge rate during the time period of τ_{facil}.

This formulation of transfer functions allows the derivation of the transmission capacity of frequency-dependent synapses and an understanding of the potential functional relevance of the various synaptic parameters. For example, changing P_r is considered by many and hotly debated by others as a potential mechanism of increasing synaptic strength. This analysis clearly shows that changing P_r, would change U, which would change λ Hz and hence result in a shift in the transition frequency that demarcates the sublinear and linear signaling regimes. The effect is not simply a change in synaptic strength, but a complex change in the content of information that can be transmitted by a given AP train. A complete understanding of synaptic transmission and synaptic plasticity and particularly how synaptic transmission relates to information processing and how synaptic plasticity relates to learning and memory will have to involve moving away from such simplifications.

Heterogeneity in the Values of Synaptic Parameters at Single Synapses from the Same Axon

A single neuron may contact several thousand target neurons. The implications for neural information processing if each synapse on an axonal tree has a unique set of synaptic parameters, and hence a unique frequency-dependent behavior and a unique transfer function, has not been considered previously. Differential facilitation and depression of synaptic transmission via the same axon has been reported in several nonmammalian systems (Parnas & Atwood, 1966; Laurent & Sivaramakrishnan, 1992; Davis & Murphey, 1993; Katz et al., 1993; Cooper, Marin, & Atwood, 1995; Frost and Katz, 1996), and in the neocortex, paired recordings have shown that synaptic responses from pyrami-

dal neurons onto pyramidal neurons typically depress while responses onto interneurons usually facilitate (Thomson, Deuchars, & West, 1993a, 1993b; Thomson, 1997). In the hippocampus, P_r has also been shown to differ for synapses emerging from the same axon and contacting the same neuron (Murthy, Sejnowski, & Stevens, 1997), and in the hippocampus different metabotropic receptors can form on the synapses from the same axon depending on the nature of the target neuron (Shigemoto, Kulik, Roberts, Ohishi, Nusser, Kaneko, & Somogyi, 1996). Differential synaptic transmission could therefore be a prominent feature of neocortical information processing. We undertook a study aimed at quantifying the degree of heterogeneity of the values of the synaptic parameters emerging from the same axon or contacting the same neuron (Markram et al., 1998a).

Triple and quadruple neuron recordings revealed that the synaptic connections from a single pyramidal neuron onto two neighboring pyramidal neurons of the same morphological and electrophysiological class differed significantly in the number and dendritic location of synapses and in A, U, and τ_{rec}. When the postsynaptic neurons were a pyramidal neuron and an interneuron, then depression and facilitation were observed, respectively. Not all connections from pyramidal neurons to interneurons facilitated, and in one case the same axon was found to form a depressing connection onto one type of interneuron and a facilitating connection onto another. These results indicate that the postsynaptic target neuron dictates the type of synapse formed between the two neurons which is also a conclusion reached earlier from several studies in simpler organisms (see Gardner, 1991; Davis & Murphey, 1993; Laurent & Sivaramakrishnan, 1992). This heterogeneity, however, does not necessarily mean that there is large scope for synaptic modifications, since the power with which the postsynaptic neuron or even specific dendritic regions of the postsynaptic neuron dictate the synaptic properties are not known. The differences could therefore rather reflect the heterogeneity of neuronal types or dendritic innervation patterns rather than that of the synapses. We therefore recorded from two or three presynaptic pyramidal neurons of the same morphological class and a single postsynaptic interneuron and compared the values of the synaptic parameters. This analysis not only revealed large heterogeneity in the numbers of synaptic contacts making up the connection as well as A, U, τ_{rec}, and τ_{facil}, but also revealed that more than 65% of the putative contacts were located on the same dendritic branch. The conclusion of this study is therefore that the combination of the type of pre- and postsynaptic neurons determines the specific class of synapses (e.g., facilitating type or depressing type) while the unique interaction between the two neurons within the context of an active network determines the precise values of the synaptic parameters. Each synapse formed by an axon therefore has a potentially unique synaptic transfer function and there exists an enormous, and as yet unexplored, "plastic potential" at single synapses.

Multiple Mechanisms, Phenomena, and Algorithms of Synaptic Plasticity

Most approaches attempt to establish a single learning algorithm (see Fregnac & Shulz, 1994, for review). A recent theoretical analysis of the effect of changing the values of different synaptic parameters illustrates that distinct phenomena are generated (Markram, Pikus, Gupta, & Tsodyks, 1998b).
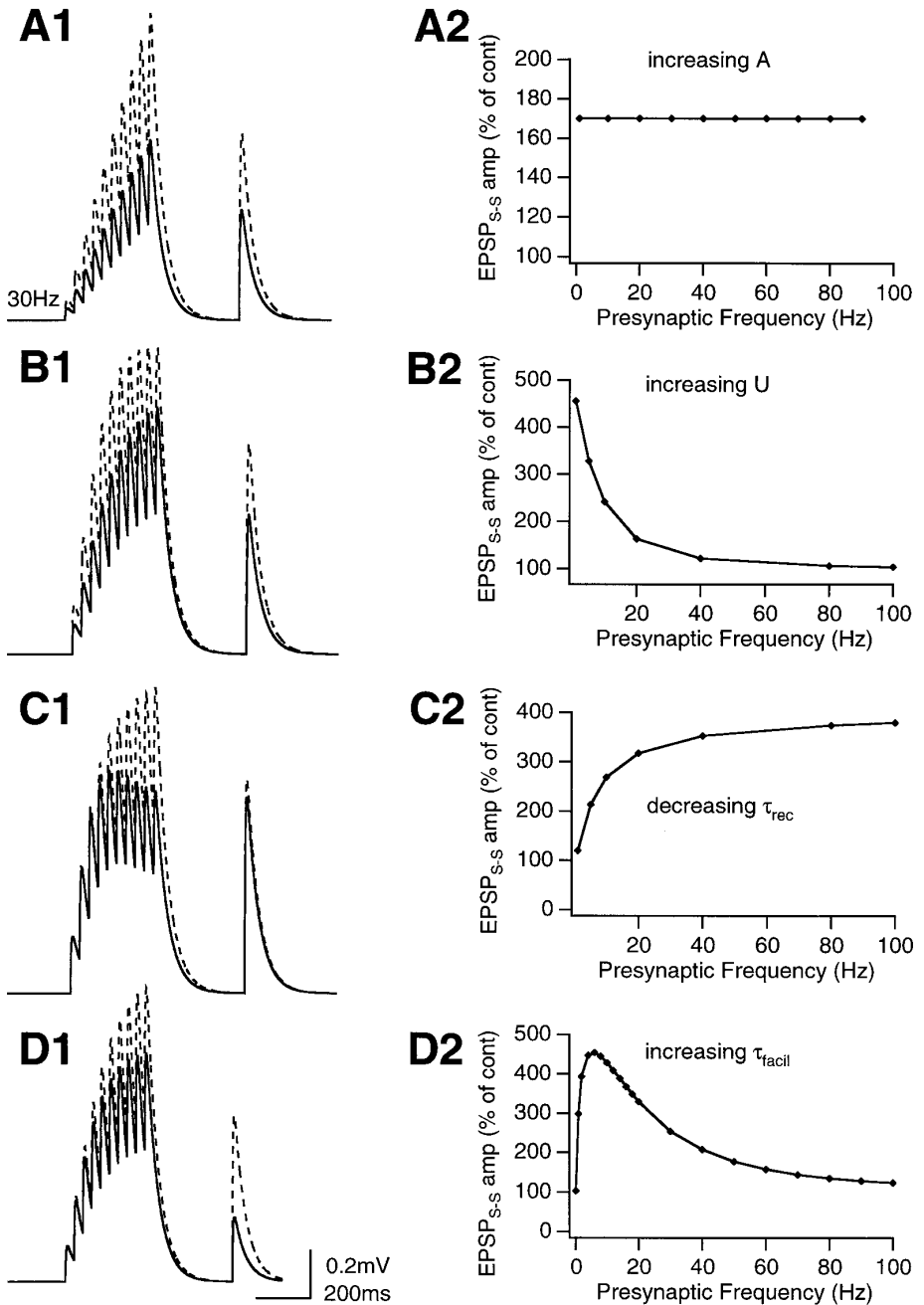
FIG. 2. Multiple mechanisms and phenomena of synaptic plasticity. (A1) Synaptic responses of facilitating synapses when A is increased 1.7-fold. In this simulation, U was 0.01, τ_{rec} was 60 ms, τ_{facil} was 3000 ms, and initial A was 2. (A2) The change is uniform for all frequencies. (B1) Synaptic responses of facilitating synapses when U was increased from 0.03 to 0.05. In this simulation, A was 1, τ_{rec} was 150 ms, and τ_{facil} was 600 ms. (B2) Frequency dependence of the effect of changing U from 0.01 to 0.05 in facilitating synapses. A was 1, τ_{rec} was 60 ms, and τ_{facil} was 3000 ms. (C1) Synaptic responses of facilitating synapses when τ_{rec} was decreased from 150 to 75 ms. In this simulation, U was 0.03 and τ_{facil} was 600 ms. (C2) Frequency dependence of the effect of decreasing τ_{rec} in depressing synapses. A was 2, U was 0.01, τ_{facil} was 3000 ms, and τ_{rec} was decreased from 600 to 60 ms. (D1) Synaptic response of facilitating synapses when τ_{facil} was increased from 200 to 600 ms. A was 2, U was 0.03, and τ_{rec} was 150 ms. (D2) Frequency dependence of the effect of increasing τ_{facil} (same parameters as in D1). Note that changing τ_{facil} exerts an effect only over an intermediate range of frequencies. In (A1) to (D1) the frequency of stimulation was 30 Hz. Adapted, with permission, from Markram et al. (1996).

Changes in A cause a frequency-independent amplification of synaptic transmission (Fig. 2), while changes in U, τ_{rec}, and τ_{facil} result in changes in the frequency dependence of transmission, also referred to as "redistribution of synaptic efficacy" (Markram & Tsodyks, 1996). Specifically, changing U results in a selective change in low-frequency synaptic transmission, leaving high-frequency transmission unaffected (Fig. 2B). Changing τ_{rec}, on the other hand, serves as a mechanism to selectively modulate high-frequency synaptic transmission (Fig. 2C), and changing τ_{facil} selectively modulates transmission of intermediate frequencies (Fig. 2D). There are therefore four basic classes of potential mechanisms and phenomena of synaptic plasticity.

Synaptic modifications can also be quantified in terms of changes in λ and θ Hz. For example, Hebbian pairing increases U, which results in a decrease in λ Hz, and hence the transfer function is altered such that the synapse begins to transmit the derivatives of presynaptic discharge rates at lower frequencies. Changes in U, τ_{rec}, and τ_{facil} have a unique effect on θ Hz, which indicates the limit of the frequency range for transmission of information about integrated presynaptic activity.

A theoretical analysis also revealed that the importance of one synaptic parameter in determining synaptic responses also depends on the values of the other parameters (in preparation; Markram et al., 1998b). For example, large changes in τ_{rec} may result in virtually no effect on transmission if U_{se} is very small. This complex interdependence of synaptic parameters in determining the synaptic response predicts that algorithms that govern the modification of different synaptic parameters would be different, but interrelated to maintain coherency between the parameters. Synaptic modifications may therefore be governed by a universal algorithm for synaptic plasticity consisting of multiple interrelated algorithms.

Multiple mechanisms, phenomena, and algorithms for synaptic plasticity as well as a universal "synaptic plasticity code" are suggested by this formulation of frequency-dependent synaptic transmission and the heterogeneity of synaptic properties. For example, two recent studies demonstrate that the same stimulation conditions lead to different phenomena of synaptic plasticity depending on whether a metabotropic-type receptor is activated or not. Activity when neurotrophins are co-applied has been shown to result in structural changes of dendrites (McAllister, Lo, & Katz, 1995) and two different forms of LTD can be produced with the same stimulation protocol depending on whether a metabotropic receptor is activated or not (Kemp & Bashir, 1997). The potential for multiple gating mechanisms directing multiple phenomena of synaptic plasticity is enormous, but has been virtually unexplored, largely because of the limited view of synaptic plasticity involving only "gain changes in synaptic transmission."

CONCLUSIONS

The studies reviewed in this paper introduce a new approach to the study of synaptic transmission, synaptic plasticity, information processing, and learning and memory. Most of the findings that actually support this approach date back to the beginning of studies on synaptic transmission about 50 years ago. Our primary claim is that an understanding of the functional implications of synaptic transmission and the phenomenologies of synaptic plasticity is

essential to linking synaptic transmission to information processing and hence to linking synaptic plasticity to learning and memory.

REFERENCES

Abbott, L. F., Varela, J. A., Sen, K., & Nelson, S. B. (1997). Synaptic depression and cortical gain control. *Science,* **275,** 220–224.

Amit, D. J. (1996). The Hebbian paradigm reintegrated: Local reverberations as internal representations. *Behavioural Brain Research (Amsterdam),* **18.**

Arib, M. A. (1995). *The handbook of brain theory and neural networks.* London: MIT Press.

Bertram, R., Sherman, A., & Stanley, E. F. (1996). Single-domain/bound calcium hypothesis of transmitter release and facilitation. *Journal of Neurophysiology,* **75,** 1919–1931.

Betz, W. J. (1970). Depression of transmitter release at the neuromuscular junction. *Journal of Physiology (London),* **206,** 626–644.

Bliss, T. V. P., & Collingridge, G. L. (1993). A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature,* **361,** 31–39.

Buonomano, D. V., Baxter, D. A., & Byrne, J. H. (1990). Small networks of empirically derived adaptive elements simulate some high-order features of classical conditioning. *Neural Networks,* **3,** 507–523.

Byrne, J. (1978). Analysis of the synaptic depression contribution to habituation of gill-withdrawal reflex in *Aplysia californica. Journal of Neurophysiology,* **48,** 431–438.

Carew, T. J., Walters, E. T., & Kandel, E. R. (1981). Classical conditioning in a simple withdrawal reflex in *Aplysia californica. Journal of Neuroscience,* **1,** 1426–1437.

Castellucci, V., Pinsker, H., Kupfermann, I., & Kandel, E. R. (1970). Neuronal mechanisms of habituation and dishabituation of the gill-withdrawal reflex in *Aplysia. Science,* **167,** 1745–1748.

Churchland, P. S., & Sejnowski, T. J. (1992). *The computational brain.* Cambridge, MA: MIT Press.

Ciaccia, P., Maio, D., & Vacca, G. P. (1992). An analytical short- and long-term memory model of presynaptic plasticity. *Biological Cybernetics,* **67,** 335–345.

Cooper, R. L., Marin, L., & Atwood, H. L. (1995). Synaptic differentiation of a single motor neuron: Conjoint definition of transmitter release, presynaptic calcium signals, and ultrastructure. *Journal of Neuroscience,* **15,** 4209–4222.

Crick, F., & Koch, C. (1995). Are we aware of neural activity in primary visual cortex? *Nature,* **375,** 121–123.

Cruikshank, S. J., & Weinberger, N. M. (1996). Evidence for the Hebbian hypothesis in experience-dependent physiological plasticity of neocortex: A critical review. *Brain Research Reviews,* **22,** 191–228.

Davis, G. W., & Murphey, R. K. (1993). A role for postsynaptic neurons in determining presynaptic release properties in the cricket CNS: Evidence for retrograde control of facilitation. *Journal of Neuroscience,* **13,** 3827–3838.

Del Castillo, J., & Katz, B. (1954). Statistical factors involved in the neuromuscular facilitation and depression. *Journal of Physiology (London),* **124,** 574–585.

Destexhe, A., Mainen, Z. F., & Sejnowski, T. J. (1994). *Journal of Computational Neuroscience,* **1,** 195–230.

Dudai, Y. (1989). *The neurobiology of memory.* New York: Oxford Univ. Press.

Feng, T. P. (1941). Studies on the neuromuscular junction. XXVI. The changes of the end-plate potential during and after prolonged stimulation. *Chinese Journal of Physiology,* **16,** 341–372.

Fregnac, Y., & Shulz, D. (1994). Models of synaptic plasticity and cellular analogs of learning in developing and adult visual cortex. *In* V. A. Casagrande & P. G. Shinkman (Eds.), *Advances in Neuronal and Behavioral Development* (Vol. 4, pp. 149–235) Ablex, NJ.

Frost, W. N., & Katz, P. S. (1996). Single neuron control over a complex motor program. *Proceedings of the National Academy of Sciences of the United States of America,* **93,** 422–426.

Gardner, D. (1991). Presynaptic transmitter release is specified by postsynaptic neurons of *Aplysia* buccal ganglia. *Journal of Neurophysiology,* **66,** 2150–2154.

Gingrich, K. J., & Byrne, J. (1985). Simulation of synaptic depression, posttetanic potentiation, and presynaptic facilitation of synaptic potentials from sensory neurons mediating gill-withdrawal reflex in *Aplysia. Journal of Neurophysiology,* **53,** 652–669.

Gluck, M. A., & Myers, C. E. (1997). Psychobiological models of hippocampal function in learning and memory. *Annual Reviews of Psychology,* **48,** 481–514.

Grossberg, S. (1969). On the production and release of chemical transmitters and related topics in cellular control. *Journal of Theoretical Biology,* **22,** 325–364.

Hebb, D. O. (1949). *The organization of behavior.* New York: Wiley.

Hertz, J., Krogh, A., & Palmer, R. G. (1991). *Introduction to the theory of neural computation.* New York: Addison–Wesley.

Hubbard, J. I. (1963). Repetitive stimulation at the neuromuscular junction, and the mobilization of transmitter. *Journal of Physiology (London),* **169,** 641–662.

Hutter, O. F. (1952). Post-tetanic restoration of neuromuscular transmission blocked by *d*-tubocurarine. *Journal of Physiology (London),* **118,** 216–227.

Jodar, L., & Kaneto, H. (1995). Synaptic plasticity: Stairway to memory. *Japanese Journal of Pharmacology,* **68,** 359–387.

Jones, M. V., & Westbrook, G. L. (1996). The impact of receptor desensitization on fast synaptic transmission. *Trends in Neuroscience,* **19,** 96–101.

Katz, P. S., Kirk, M. D., & Govind, C. K. (1993). Facilitation and depression at different branches of the same motor axon: Evidence for presynaptic differences in release. *Journal of Neuroscience,* **13,** 3075–3089.

Kemp, N., & Bashir, Z. I. (1997). LTD induced by paired pulse low-frequency stimulation in the CA1 region of the adult rat hippocampus in vitro. *Society for Neuroscience Abstracts,* **679,** 14.

Korn, H., Faber, D. S., Burnod, Y., & Triller, A. (1984). Regulation of efficacy at central synapses. *Journal of Neuroscience,* **4,** 125–130.

Korn, H., Faber, D. S., & Triller, A. (1986). Probabilistic determination of synaptic strength. *Journal of Neurophysiology,* **55,** 402–421.

Krausz, H. I., & Friesen, O. (1977). The analysis of nonlinear synaptic transmission. *Journal of General Physiology,* **70,** 244–265.

Laurent, G., & Sivaramakrishnan, A. (1992). Single local interneurons in the locust make central synapses with different properties of transmitter release on distinct postsynaptic neurons. *Journal of Neuroscience,* **12,** 2370–2380.

Liaw, J. S., & Berger, T. W. (1996). Dynamic synapse: A new concept of neural representation and computation. *Hippocampus,* **6,** 591–600.

Liley, A. W. (1956). The quantal components of the mammalian end-plate potential. *Journal of Physiology (London),* **133,** 571–587.

Liley, A. W., & North, K. A. K. (1953). An electrical investigation of the effects of repetitive stimulation on mammalian neuromuscular junction. *Journal of Neurophysiology,* **16,** 509–527.

Magleby, K. L. (1987). Short-term changes in synaptic efficacy. *In* G. M. Edelman, W. E. Gall, & Cowman (Eds.), *Synaptic Function* (pp. 21–56). New York: Wiley.

Magleby, K. L., & Zengel, J. E. (1976). Long term changes in augmentation, potentiation, and depression of transmitter release as a function of repeated synaptic activity at the frog neuromuscular junction. *Journal of Physiology (London),* **257,** 471–494.

Magleby, K. L., & Zengel, J. E. (1982). A quantitative description of stimulation-induced changes in transmitter release at the frog neuromuscular junction. *Journal of General Physiology,* **80,** 613–638.

Maren, S., & Baudry, M. (1995). Properties and mechanisms of long-term synaptic plasticity in the mammalian brain: Relationships to learning and memory. *Neurobiology of Learning and Memory,* **63,** 1–18.

Markram, H. (1997). A network of tufted layer 5 pyramidal neurons. *Cerebral Cortex,* **7,** 523–533.

Markram, H., Lübke, J., Frotscher, M., Roth, A., & Sakmann, B. (1997a). Physiology and anatomy of synaptically coupled connections between thick tufted pyramidal neurons in the developing rat neocortex. *Journal of Physiology (London),* **500,** 409–440.

Markram, H., Lübke, J., Frotscher, M., Roth, A., & Sakmann, B. (1997b). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science,* **275,** 213–215.

Markram, H., & Tsodyks, M. (1996). Redistribution of synaptic efficacy between neocortical pyramidal neurons. *Nature,* **382,** 807–810.

Markram, H., Wang, Y., & Tsodyks, M. (1998a). Differential synaptic signaling via the same axon of neocortical pyramidal neurons. *Proceedings of the National Academy of Sciences of the United States of America,* in press.

Markram, H., Pikus, D., Gupta, A., & Tsodyks, H. (1998b). Potential for multiple mechanisms, phenomena and algorithms for synaptic plasticity at single synapses. *Neuropharmacology* **37,** 489–500.

McAllister, A. K., Lo, D. C., & Katz, L. C. (1995). Neurotrophins regulate dendritic growth in developing visual cortex. *Neuron,* **15,** 791–803.

McEachern, J. C., & Shaw, C. A. (1996). An alternative to the LTP orthodoxy: A plasticity–pathology continuum model. *Brain Research Reviews,* **22,** 51–92.

McNaughton, B. L. (1989). Neural mechanisms for spatial computation and information storage. *In* L. Nadel, L. A. Cooper, P. Culicover, & R. M. Harnish (Eds.), *Neural connections, mental computations.* London: MIT Press.

Morris, R. G. M., Kandel, E. R., & Squire, L. (1988). The neuroscience of learning and memory: Cells, neural circuits and behavior. *Trends in Neuroscience,* **11,** 125–127.

Murthy, V. N., Sejnowski, T. J., & Stevens, C. F. (1997). Heterogeneous release properties of visualized individual hippocampal synapses. *Neuron,* **18,** 599–612.

Parnas, I., & Atwood, H. L. (1966). Phasic and tonic neuromuscular systems in the abdominal extensor muscles of the crayfish and rock lobster. *Computational Biochemistry and Physiology,* **18,** 701–723.

Pinsker, H., Kandel, E. R., Castellucci, V., & Kupfermann, I. (1970). An analysis of habituation and dishabituation in *Aplysia. Advances in Biochemical Psychopharmacology,* **2,** 351–373.

Stuart, G. J., Dodt, H.-U., & Sakmann, B. (1993). Patch-clamp recordings from the soma and dendrites of neurons in brain slices. *Pflueger's Archiv,* **490,** 511–518.

Shigemoto, R., Kulik, A., Roberts, J. D., Ohishi, H., Nusser, Z., Kaneko, T., & Somogyi, P. (1996). Target-cell-specific concentration of a metabotropic glutamate receptor in the presynaptic active zone. *Nature,* **381,** 523–525.

Takeuchi, A. (1958). The long lasting depression in neuromuscular transmission of frog. *Japanese Journal of Physiology,* **8,** 102–113.

Teyler, T. J., & Fountain, S. B. (1987). Neuronal plasticity in the mammalian brain: Relevance to behavioral learning and memory. *Child Development,* **58,** 698–712.

Thies, R. E. (1965). Neuromuscular depression and the apparent depletion of transmitter in mammalian muscle. *Journal of Neurophysiology,* **212,** 431–446.

Thomson, A. M. (1997). Activity-dependent properties of synaptic transmission at two classes of connections made by rat neocortical pyramidal axons in vitro. *Journal of Physiology (London),* **502,** 131–147.

Thomson, A. M., & Deuchars, J. (1994). Temporal and spatial properties of local circuits in neocortex. *Trends in Neuroscience,* **17,** 119–126.

Thomson, A. M., Deuchars, J., & West, D. C. (1993a). Large, deep layer pyramid–pyramid single axon EPSPs in slices of rat motor cortex display paired pulse and frequency-dependent depression, mediated presynaptically, and self-facilitation, mediated postsynaptically. *Journal of Neurophysiology,* **70,** 2354–2369.

Thomson, A. M., Deuchars, J., & West, D. C. (1993b). Single axon excitatory postsynaptic potentials in neocortical interneurons exhibit pronounced paired pulse facilitation. *Neuroscience,* **54,** 347–360.

Tsodyks, M., & Markram, H. (1997). The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability. *Proceedings of the National Academy of Sciences of the United States of America,* **94,** 719–723.

Tsodyks, M., Pawelzik, K., & Markram, H. (1998). Neural network computation with dynamic synapses. *Neural Computation,* in press.

Zucker, R. S. (1989). Short-term synaptic plasticity. *Annual Reviews of Neuroscience,* **12,** 13–31.