Information Processing with Frequency-Dependent Synaptic Connections

Henry Markram, Anirudh Gupta, Asher Uziel, Yun Wang, and Misha Tsodyks

Department of Neurobiology, The Weizmann Institute for Science, Rehovot, 76100, Israel

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- and 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.

© 1998 Academic Press

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.
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 NaHCO₃, 1.25 NaH₂PO₄, 2 CaCl₂, and 1 MgCl₂. 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 (τ_{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 $\tau_{rec}$, and $R$ therefore changes according to

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

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 ($\tau_{facil}$). The value of $U^1$ for any AP during a train is then

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

where $\Delta t$ is the time interval between the $n$th 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 $\tau_{rec}$ defines the time constant for recovery from synaptic depression and $\tau_{facil}$ 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 (PSPst) 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–PSPst 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, PSPst decreases as the presynaptic frequency increases, and beyond a critical frequency, PSPst 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 Use and τrec. When facilitating-type synapses are stimulated at progressively higher frequencies, then a novel frequency–PSPst relationship is revealed in which PSPst 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 opposed 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,” Use, τrec, and τfacil. θ Hz typically varies between 3 and 30 Hz.

Transfer Functions of Frequency-Dependent Synapses

The values of the synaptic parameters, the characteristic frequency–PSPst 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 $\lambda$ Hz and $\theta$ Hz and therefore depend critically on
the values of the synaptic parameters.

Above $\lambda$ 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 $\lambda$ 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 $\lambda$ 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
$\theta$ Hz, and synapses transmit almost perfectly information about the absolute
discharge rates of the presynaptic neurons. For depressing synapses, the deriv-
ative 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 fre-
quency decreases from $\theta$ 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 dis-
charge rate during the time period of $\tau_{facil}$.

This formulation of transfer functions allows the derivation of the transmis-
sion capacity of frequency-dependent synapses and an understanding of the
potential functional relevance of the various synaptic parameters. For ex-
ample, 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 $\lambda$ 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 infor-
mation 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, 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 $t_{rec}$. 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 $A$, $U$, $t_{rec}$, and $t_{facil}$, 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, $\tau_{\text{rec}}$ was 60 ms, $\tau_{\text{facil}}$ 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, $\tau_{\text{rec}}$ was 150 ms, and $\tau_{\text{facil}}$ was 600 ms. (B2) Frequency dependence of the effect of changing $U$ from 0.01 to 0.05 in facilitating synapses. $A$ was 1, $\tau_{\text{rec}}$ was 60 ms, and $\tau_{\text{facil}}$ was 3000 ms. (C1) Synaptic responses of facilitating synapses when $\tau_{\text{rec}}$ was decreased from 150 to 75 ms. In this simulation, $U$ was 0.03 and $\tau_{\text{facil}}$ was 600 ms. (C2) Frequency dependence of the effect of decreasing $\tau_{\text{rec}}$ in depressing synapses. $A$ was 2, $U$ was 0.01, $\tau_{\text{facil}}$ was 3000 ms, and $\tau_{\text{rec}}$ was decreased from 600 to 60 ms. (D1) Synaptic response of facilitating synapses when $\tau_{\text{facil}}$ was increased from 200 to 600 ms. $A$ was 2, $U$ was 0.03, and $\tau_{\text{rec}}$ was 150 ms. (D2) Frequency dependence of the effect of increasing $\tau_{\text{facil}}$ (same parameters as in D1). Note that changing $\tau_{\text{facil}}$ 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 $U$, $\tau_{\text{rec}}$, and $\tau_{\text{facil}}$ 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 $\tau_{\text{rec}}$, on the other hand, serves as a mechanism to selectively modulate high-frequency synaptic transmission (Fig. 2C), and changing $\tau_{\text{facil}}$ 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 $\lambda$ and $\theta$ Hz. For example, Hebbian pairing increases $U$, which results in a decrease in $\lambda$ 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 $U$, $\tau_{\text{rec}}$, and $\tau_{\text{facil}}$ have a unique effect on $\theta$ 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 $\tau_{\text{rec}}$ may result in virtually no effect on transmission if $U_{\text{se}}$ 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


