Stochastic and Reduced Biophysical Models of Synaptic Transmission

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Abstract. Stochastic and reduced biophysical models of synaptic transmission are formulated and evaluated. The synaptic transmission involves presynaptic facilitation of neurotransmitter release, depletion and recovery of the presynaptic pool of readily releasable vesicles containing neurotransmitter molecules and saturation of postsynaptic receptors of both fast non-NMDA and slow NMDA types. The models are shown to display the principal dynamical characteristics experimentally observed of synaptic transmission. The two main types of neural coding, i.e. rate and temporal coding, can be distinguished by means of different dynamical properties of synaptic transmission determined by initial neurotransmitter release probability and presynaptic firing rate. From the temporal evolution of the postsynaptic membrane potential response to a train of presynaptic action potentials at a sustained firing rate, in particular the steady-state amplitude and steady-state average level of postsynaptic membrane potentials are determined as functions of both initial release probability and presynaptic firing rate. The models are applicable to studies of the primary stages of learning processes and can be extended to incorporate short-term and long-term potentiation in memory consolidation processes.

Key words: Depletion, facilitation, glutamate, intracellular calcium, neural coding, neurotransmitter release, NMDA, saturation, synaptic plasticity, synaptic transmission

1. Introduction

The computational processing in a system of interconnected neurons is controlled by the intrinsic dynamical properties of the neurons and by the dynamics of the synaptic interactions between neurons on both short and long timescales. On short timescales, the synaptic dynamics make the postsynaptic membrane potential response depend on the recent history of presynaptic activity. Various types of synaptic dynamics thus may allow multiple representations of the presynaptic information. The short-term synaptic processes include enhancement of transmission by facilitation, augmentation and short-term potentiation distinguished by successively longer timescales [1, 2] and also depletion and recovery of the presynaptic pool of readily releasable vesicles containing neurotransmitter molecules [3, 4], as well as saturation of postsynaptic receptors [5, 6]. On long timescales, learning in various memory systems is believed to be related to altered synaptic transmission by means of long-term potentiation [7, 8].

That calcium ions are involved in the neurotransmitter release processes was early recognized [9–11]. In particular, the short-term synaptic processes are associated with residual calcium in the presynaptic terminal [1, 2, 12–14]. Facilitation reflects a direct effect of calcium on the neurotransmitter release process, whereas augmentation and short-term potentiation may be indirect effects of calcium-reaction products that are generated and decay more slowly than the entry and decay, respectively, of calcium itself. Recently, the significance of short-term synaptic dynamics has attracted much attention and prompted numerous investigations [15–24]. Calcium imaging by means of a fluorescence technique has permitted simultaneous measurement of intracellular calcium at release sites and asynchronous transmitter release from the same synaptic terminal [25]. The recent results will be related to the present work in the discussion in Section 4.

The intrinsic dynamics of neurons also are governed by calcium ions. In particular, the firing-rate adaptation is based on the effect of intracellular calcium ions on the conductance of calcium-dependent potassium channels that regulate the slow afterhyperpolarization phase of action potentials and thereby the firing rate [26]. Low-dimensional model neurons incorporating pulsed calcium fluxes have recently been formulated and shown to display activation function and firing-rate adaptation in close agreement with the corresponding of detailed multicompartment conductance-based models [27–30]. In the present work, a biophysical model of synaptic transmission that is compatible with the low-dimensional model neurons is formulated and evaluated. Calcium dynamics in the synaptic terminal are described analogously to the calcium dynamics in the principal neuron compartment by means of pulsed calcium fluxes. From a stochastic version of the model, a reduced version is also derived. The combined simplicity and biological realism of this model permit insight into functional mechanisms and applicability to large-scale systems of interconnected neurons. It is shown that the reduced version displays the principal dynamical characteristics observed of synaptic transmission. In particular, the two main types of neural coding, i.e. rate and temporal coding, can be distinguished by means of different dynamical properties of synaptic transmission determined by initial neurotransmitter release probability and presynaptic firing rate.

The stochastic and reduced models of synaptic transmission are defined in Section 2 and applied to studies of synaptic dynamics in Section 3. The implications of the results obtained for neural coding are included in the discussion in Section 4.

2. Stochastic and Reduced Models of Synaptic Transmission

Consider the synaptic coupling of two neurons effected from a number of presynaptic release sites, at each of which resides a pool of readily releasable vesicles containing neurotransmitter molecules [31]. Different release sites behave independently, and within the pool of readily releasable vesicles at each site, different

vesicles act independently up to the first release which inhibits further releases for a given presynaptic action potential [17]. A release is associated with an action potential if it occurs within a certain time interval, after which a release is considered to be asynchronous [17]. Denoting the fusion probability within such a time interval of one vesicle by p_{fus} and the number of vesicles in the pool of readily releasable vesicles at one release site by n_v , the release probability is given by

$$p_{\text{rel}} = 1 - (1 - p_{\text{fus}})^{n_v}. \quad (1)$$

The fusion probability p_{fus} is observed to depend on calcium concentration in the synaptic terminal [1, 2, 12–14], as will be discussed below, and this is underlying the following formulation of the temporal evolution of the dynamical variables of two coupled neurons. Only those variables are included that are relevant in a situation where the coupling is studied by externally generating a given firing pattern of the presynaptic neuron.

$$\frac{d\tilde{c}_{t1}(t)}{dt} = \sum_{p1} \tilde{q}_{t1}(\tilde{c}_{t1}(t))\delta(t - \tilde{t}_{p1}) + (c_{t1}^o - \tilde{c}_{t1}(t))/\tau_{ct} \quad (2)$$

$$\begin{aligned} \frac{d\tilde{n}_{v1}^r(t)}{dt} = & \\ & - \sum_{p1} \tilde{p}_{\text{rel}}^r(\tilde{n}_{v1}^r(t), \tilde{c}_{t1}(t))\delta(t - \tilde{t}_{p1}) + \tilde{p}_{\text{rec}}^r(\tilde{n}_{v1}^r(t)) \\ & r = 1, \dots, N_{\text{rs}} \end{aligned} \quad (3)$$

$$\begin{aligned} c_m \frac{d\tilde{v}_2(t)}{dt} = & \\ & g_1(e_1 - \tilde{v}_2(t)) + g_{\text{K}(\text{Ca})}\tilde{c}_2(t)(e_{\text{K}} - \tilde{v}_2(t)) + \tilde{i}_{f2}(t) + \tilde{i}_{s2}(t) + \tilde{i}_{a2}(t) \end{aligned} \quad (4)$$

$$\frac{d\tilde{c}_2(t)}{dt} = \sum_{p2} \tilde{q}_2(\tilde{c}_2(t))\delta(t - \tilde{t}_{p2}) + (c_2^o - \tilde{c}_2(t))/\tau_c \quad (5)$$

$$\begin{aligned} \frac{d\tilde{i}_{f2}^r(t)}{dt} = & \\ & \sum_{p1} \tilde{p}_{\text{rel}}^r(\tilde{n}_{v1}^r(t), \tilde{c}_{t1}(t))(q_f - \tilde{i}_{f2}^r(t))\delta(t - t_{\text{df}} - \tilde{t}_{p1}) - \tilde{i}_{f2}^r(t)/\tau_f \\ & r = 1, \dots, N_{\text{rs}} \end{aligned} \quad (6)$$

$$\begin{aligned} \frac{d\tilde{i}_{s2}(t)}{dt} = & \\ & \sum_{p1} \tilde{p}_{\text{rel}}^r(\tilde{n}_{v1}^r(t), \tilde{c}_{t1}(t))(q_s - \tilde{i}_{s2}^r(t))\delta(t - t_{\text{ds}} - \tilde{t}_{p1}) - \tilde{i}_{s2}^r(t)/\tau_s \\ & r = 1, \dots, N_{\text{rs}} \end{aligned} \quad (7)$$

$$\tilde{n}_{v1}(t) = \sum_{r=1}^{N_{rs}} \tilde{n}_{v1}^r(t) \quad (8)$$

$$\tilde{i}_{f2}(t) = \sum_{r=1}^{N_{rs}} \tilde{i}_{f2}^r(t) \quad (9)$$

$$\tilde{i}_{s2}(t) = \sum_{r=1}^{N_{rs}} \tilde{i}_{s2}^r(t) \quad (10)$$

A neuron is considered to be composed of one principal compartment and one synaptic terminal compartment. The presynaptic and postsynaptic neuron are labelled 1 and 2, respectively. The release sites are labelled by r , and the total number of release sites is denoted N_{rs} . In the presynaptic neuron, $\tilde{c}_{t1}(t)$ and $\tilde{n}_{v1}^r(t)$ refer to intracellular calcium concentration in the synaptic terminal and the number of readily releasable vesicles at release site r , respectively. A tilde sign indicates stochastic character of a variable. The intracellular calcium concentration in the synaptic terminal is determined by a pulsed influx and a first order decay as described by the first and second term of the right-hand side of Equation (2), respectively. The influx takes place by an amount $\tilde{q}_{t1}(\tilde{c}_{t1}(t))$ at the times of action potentials arriving at the presynaptic terminal denoted $\tilde{t}_{p1}$, where $p1$ labels successive pulses. It is the intracellular calcium concentration prior to its jump that enters $\tilde{q}_{t1}(\tilde{c}_{t1}(t))$. The first order decay with a time constant τ_{ct} to the resting level c_{t1}^o corresponds to the effects of ionic pumps, internal buffering and diffusion. In Equation (3), $\tilde{p}_{rel}^r(\tilde{n}_{v1}^r(t), \tilde{c}_{t1}(t))$ and $\tilde{p}_{rec}^r(\tilde{n}_{v1}^r(t))$ are the stochastic release and recovery function, respectively. It was early observed that fusion probability as a function of calcium concentration can be expressed as a power law, this is discussed in more detail in Section 3. Denoting the exponent by v , the stochastic release function at release site r can be expressed

$$\tilde{p}_{rel}^r(\tilde{n}_{v1}^r(t), \tilde{c}_{t1}(t)) = \begin{cases} 1 & \text{with probability } 1 - (1 - k_f \tilde{c}_{t1}^v(t))^{\tilde{n}_{v1}^r(t)} \\ 0 & \text{otherwise} \end{cases} \quad r = 1, \dots, N_{rs} \quad (11)$$

where k_f is a constant. The recovery of the number of readily releasable vesicles at the release site r to the resting value n_{v1}^{ro} is described as a first order process with time constant τ_{rec} by

$$\tilde{p}_{rec}^r(\tilde{n}_{v1}^r(t)) = \begin{cases} 1 & \text{with probability per unit time } (n_{v1}^{ro} - \tilde{n}_{v1}^r(t))/\tau_{rec} \\ 0 & \text{otherwise} \end{cases} \quad r = 1, \dots, N_{rs} \quad (12)$$

The subsequent equations, Equations (4)–(10), describe the development of variables relating to the principal compartment of the postsynaptic neuron. $\tilde{v}_2(t)$ is the membrane potential and $\tilde{c}_2(t)$ the intracellular calcium concentration in this

compartment. $\tilde{i}_{f2}^r(t)$ and $\tilde{i}_{s2}^r(t)$ denote the contributions from presynaptic release site r to the synaptic currents of fast and slow couplings involving non-NMDA and NMDA receptors [26], respectively. The contributions from different release sites sum up to $\tilde{i}_{f2}(t)$ and $\tilde{i}_{s2}(t)$, respectively. c_m is the cell membrane capacitance, which is charged by different currents as described by Equation (4). The first current is the leakage current determined by the leakage conductance, g_l , and reversal potential, e_l . The second current is the potassium current through calcium-dependent channels. $g_{K(Ca)}$ describes the strength of coupling between intracellular calcium concentration and conductance of the potassium channels. e_K is the electrochemical equilibrium potential of potassium ions. In addition to the synaptic currents, an externally applied current $\tilde{i}_{a2}(t)$ may also contribute to the charging of the membrane capacitance. The evolution of the intracellular calcium concentration $\tilde{c}_2(t)$ is described by Equation (5) analogously to that of the intracellular calcium concentration $\tilde{c}_{t1}(t)$ in the presynaptic terminal. $\tilde{q}_2(\tilde{c}_2(t))$ thus is the amount of calcium entering upon an action potential at time $\tilde{t}_{p2}$, where $p2$ denotes pulses in the postsynaptic neuron. c_2^o is the resting level of intracellular calcium concentration which is restored by a first order process with time constant τ_c . Equations (6) and (7) describe, respectively, the fast and slow synaptic current contributions from the presynaptic release sites as sequences of pulses triggered by the firing of the presynaptic neuron and with rise times negligible in comparison with the decay times τ_f and τ_s . At any time t , $\tilde{p}_{rel}^r(\tilde{n}_{v1}^r(t), \tilde{c}_{t1}(t))$ is evaluated only once for Equations (3), (6) and (7), and at the times of arrival of presynaptic action potentials it is the intracellular calcium concentration after its jump that is applicable for the evaluation. t_{df} and t_{ds} represent the delay times due to synaptic cleft traversal, receptor response and dendritic propagation for the fast and slow connections, respectively. The quantal amplitude of the postsynaptic membrane potential response to one released vesicle is denoted q_f and q_s for the fast and slow connections, respectively. Saturation of available postsynaptic receptors for neurotransmitter molecules limits the synaptic currents. Assuming that each presynaptic release site has an amount of postsynaptic receptors adapted to single vesicles [5, 6], the saturation condition can be expressed

$$\max(\tilde{i}_{x2}^r(t)) = q_x \quad x = f, s \quad r = 1, \dots, N_{rs} \quad (13)$$

Any dependence of synaptic currents on postsynaptic membrane potential, such as that of the Mg-block of NMDA-channels [26], is only included in an averaged way so that the quantal amplitudes resulting from integrated currents are reproduced, see Section 3. The condition for firing of the postsynaptic neuron is that the membrane potential $\tilde{v}_2(t)$ reaches a threshold value. In this work, the synaptic coupling is studied by means of subthreshold excitatory postsynaptic membrane potentials only.

A reduced version of the above stochastic model of synaptic transmission can be formulated by ensemble-averaging over the different presynaptic release sites and replacing the stochastic variables by their corresponding deterministic averages.

Since the probability for the stochastic release function $\tilde{p}_{\text{rel}}(\tilde{n}_{v1}(t), \tilde{c}_{t1}(t))$ to be 1, according to Equation (11), is a non-linear function of $\tilde{n}_{v1}(t)$ and $\tilde{c}_{t1}(t)$, the reduced version represents an approximation of the stochastic version obtained by neglecting higher moments of $\tilde{n}_{v1}(t)$ and $\tilde{c}_{t1}(t)$ in the evaluation of the ensemble-average of $\tilde{p}_{\text{rel}}(\tilde{n}_{v1}(t), \tilde{c}_{t1}(t))$.

$$\frac{dc_{t1}(t)}{dt} = \sum_{p1} q_{t1}(c_{t1}(t))\delta(t - t_{p1}) + (c_{t1}^0 - c_{t1}(t))/\tau_{ct} \quad (14)$$

$$\begin{aligned} \frac{dn_{v1}(t)}{dt} = & \\ & - \sum_{p1} p_{\text{rel}}(n_{v1}(t), c_{t1}(t))\min(1, n_{v1}(t))\delta(t - t_{p1}) + \\ & (n_{v1}^o - n_{v1}(t))/\tau_{\text{rec}} \end{aligned} \quad (15)$$

$$c_m \frac{dv_2(t)}{dt} = g_1(e_1 - v_2(t)) + g_{K(\text{Ca})}c_2(t)(e_K - v_2(t)) + i_{f2}(t) + i_{s2}(t) + i_{a2}(t) \quad (16)$$

$$\frac{dc_2(t)}{dt} = \sum_{p2} q_2(c_2(t))\delta(t - t_{p2}) + (c_2^o - c_2(t))/\tau_c \quad (17)$$

$$\begin{aligned} \frac{di_{f2}(t)}{dt} = & \\ & \sum_{p1} p_{\text{rel}}(n_{v1}(t), c_{t1}(t))(q_{af} - i_{f2}(t))\delta(t - t_{df} - t_{p1}) - i_{f2}(t)/\tau_f \end{aligned} \quad (18)$$

$$\begin{aligned} \frac{di_{s2}(t)}{dt} = & \\ & \sum_{p1} p_{\text{rel}}(n_{v1}(t), c_{t1}(t))(q_{as} - i_{s2}(t))\delta(t - t_{ds} - t_{p1}) - i_{s2}(t)/\tau_s \end{aligned} \quad (19)$$

$$p_{\text{rel}}(n_{v1}(t), c_{t1}(t)) = 1 - (1 - k_f c_{t1}^v(t))^{n_{v1}(t)} \quad (20)$$

The saturation of synaptic currents is expressed by

$$\max(i_{x2}(t)) = q_x \quad x = f, s \quad (21)$$

3. Dynamics of Synaptic Transmission

In this section, the stochastic and reduced models of synaptic transmission defined in Section 2 are applied to studies of the dynamics of the synaptic interaction

between two neurons. The prototype of the model neurons is the neocortical pyramidal cell [32, 33], which is the principal excitatory neuron in the brain. The primary excitatory neurotransmitter is glutamate. The evolution of the postsynaptic membrane potential is determined as a function of initial neurotransmitter release probability and presynaptic firing rate. In particular, the steady-state amplitude and steady-state average level of postsynaptic membrane potentials for a sustained presynaptic firing rate are analyzed. It is shown that the dynamics of synaptic transmission can control the character of neural coding.

The parameters of the low-dimensional model neuron that do not refer to the synaptic interaction have recently been determined by means of comparisons with a detailed multicompartment conductance-based model [27–30]. The conductance-based model [34, 35] is fitted to experimental data of a regularly spiking neocortical pyramidal cell [32, 33] and is composed of six compartments corresponding to the soma, axon initial segment, basal dendrite and three sections of the apical dendrite. The soma compartment in addition to sodium, potassium and calcium channels also include calcium-dependent potassium channels. The axon initial segment contains sodium and potassium channels, whereas the dendritic compartments are purely passive. It was shown that the low-dimensional model neuron closely reproduces the activation function and firing-rate adaptation of the conductance-based model for the following parameters: $c_m = 0.139 \cdot 10^{-9}$ F, $g_l = 0.702 \cdot 10^{-8}$ S, $e_l = -65$ mV, $e_K = -80$ mV and $g_{K(Ca)} = 0.330 \cdot 10^{-7}$ S per the arbitrary unit used for intracellular calcium concentration in the principal compartment. For the situation studied, where the presynaptic neuron is externally driven at a certain firing rate, the dynamical variables of the principal compartment are only of interest for the postsynaptic neuron. The amplitude of calcium pulses in the principal compartment of the postsynaptic neuron, $\tilde{q}_2(\tilde{c}_2(t))$ in Equation (5), is well fitted by $\tilde{q}_2(\tilde{c}_2(t)) = a/(b + \tilde{c}_2(t))$ with $a = 0.11$ and $b = 0.90$. The time constant of the first order decay of intracellular calcium concentration in the principal compartment is $\tau_c = 111$ ms. The resting level of calcium concentration c_2^o is very low [36] and is neglected. The parameters specifying the integrate-and-fire type of operation of the model neuron are the threshold potential -50 mV, reset potential -60 mV and absolute refractory period 3.0 ms.

The remaining parameters to be specified refer to the synaptic interaction between the neurons. A synaptic coupling between two neurons may involve a number of presynaptic release sites which is denoted N_{rs} . From studies of the anatomy of synaptic connections between pyramidal cells in layer 5 of the rat somatosensory cortex [37], the number of synaptic contacts formed by a presynaptic neuron on a target neuron was found to have a value of 5.5 ± 1.1 . We put $N_{rs} = 5$. At release site r there is a pool of $n_{v1}^r(t)$ readily releasable vesicles containing neurotransmitter molecules. The number of vesicles in such a pool has been determined in synapses between rat hippocampal CA3 and CA1 cells to be 5.0 ± 3.0 [17]. We assign the initial value $n_{v1}^o = 5$ independent of r . For the time constant τ_{rec} of vesicle recovery we select the typical value 1 s [20, 21]. By investigations in [17], it was

shown that the decrease in response size during trains of fast stimuli is not due to desensitization of postsynaptic receptors. Also inhibitory feedback of released glutamate through presynaptic metabotropic glutamate receptors and postsynaptic inhibition through GABA_A or GABA_B receptors were excluded as primary causes. It was concluded that the decreased response is due to depletion of the pool of readily releasable vesicles at a release site.

A cooperative action of calcium ions on the neurotransmitter release process, manifested in an exponent of 4 in the dependence of excitatory postsynaptic potentials on the external calcium concentration in a neuromuscular junction, was early observed [10]. It has been argued that this may underestimate the dependence on intracellular calcium, for which an exponent of 5 has been proposed [2, 38]. However, recent simultaneous measurements of intracellular calcium and asynchronous transmitter release from the same synaptic terminal, resulted in a Hill coefficient of 3–4 [25]. This coefficient is equivalent to an exponent in the range of normal firing rates. In this work, we use an exponent $\nu = 4$ in Equation (11). In the investigation [17] of the synaptic interaction between rat hippocampal CA3 and CA1 cells mentioned above, a strong heterogeneity was observed with respect to facilitation. Single synapses displayed from no facilitation to a six-fold increase of the postsynaptic response in relation to that of the first stimulus. The average increase for multiple synapses was about two-fold, and this value may be somewhat affected by beginning depletion (see below). We select a maximal facilitation of 3. The arbitrary scale of calcium concentration in the presynaptic terminal is chosen such that the maximal steady-state value for a presynaptic firing rate of 100 Hz is equal to 1. Absolute concentration values are typically in the micromolar range [25]. The amplitude of calcium pulses in the presynaptic terminal at the times of presynaptic action potentials is described analogously to that of the corresponding in the principal compartment by $\tilde{q}_{t1}(\tilde{c}_{t1}(t)) = a_t/(b_t + \tilde{c}_{t1}(t))$. A value $b_t = 1$ is close to the analogous b -value in the principal compartment and corresponds to a halving of the amplitude as $\tilde{c}_{t1}(t)$ goes from 0 to 1. The value of a_t can be determined from the maximal facilitation and the time constant τ_{ct} of the decay towards the resting level of calcium concentration. Two phases of facilitation have been distinguished with time constants 50 ms and 300 ms [39] or 60 ms and 500 ms [40] in neuromuscular junctions. More recent studies of central synapses display heterogeneous behaviour and facilitation may be obscured by depression [15–24]. A range 50–150 ms was observed for the rapid facilitation phase of excitatory synapses in the rat primary visual cortex [22–24]. In this work, we select a value of $\tau_{ct} = 100$ ms. Together with the maximal facilitation, this determines the value $a_t = 0.051$. The constant k_f in the expression for the neurotransmitter release probability in Equation (11) is treated as a variable parameter in the study of different cases. For a given initial number of readily releasable vesicles n_{v1}^o and the resting level of calcium concentration in the presynaptic terminal c_{t1}^o determined from the maximal facilitation, the k_f -value determines the initial neurotransmitter release probability. It varies between 0.031 and 0.826 when the initial release probability

is in the range investigated from 0.05 to 0.8. A typical initial release probability is 0.35 [17].

The postsynaptic membrane potential response to presynaptically released vesicles of neurotransmitter molecules is composed of fast and slow components involving non-NMDA and NMDA receptors [26], respectively. The synaptic decay and delay times are assigned the typical values $\tau_f = 10$ ms and $t_{df} = 1$ ms for the fast component and $\tau_s = 150$ ms and $t_{ds} = 5$ ms for the slow component [35]. A typical amplitude ratio between the fast and slow components of 0.25 [41, 42] is selected. The quantal amplitude of the postsynaptic potential response to one released vesicle is typically in the range 0.2–1.0 mV [37] and we select 0.4 mV which corresponds to $q_f = 0.982 \cdot 10^{-11}$ A and $q_s = 0.836 \cdot 10^{-12}$ A.

The evolution of the dynamical variables of the stochastic and reduced models of synaptic transmission is determined as function of initial neurotransmitter release probability and presynaptic firing rate by means of the equation systems defined in Section 2 and the parameters defined above. Figures 1 and 2 show examples obtained by means of the stochastic and reduced models, respectively, for an initial release probability of 0.4 and a sustained presynaptic firing rate of 30 Hz. The dependence of postsynaptic membrane potential curves on both initial neurotransmitter release probability and presynaptic firing rate is visualized in Figures 3–5. From these curves, the steady-state amplitude and steady-state average level of postsynaptic membrane potentials are extracted and displayed in Figures 6 and 7, respectively. The amplitude of a postsynaptic membrane potential response to a given presynaptic action potential is determined from the difference of membrane potential curves obtained with and without the presynaptic action potential. For reference, Figure 6 also includes a curve illustrating an inverse dependence of the steady-state response amplitude on the firing rate. The implications of the results obtained with respect to neural coding are included in the discussion in Section 4.

4. Discussion

The temporal signal processing performed by synapses influences the postsynaptic representation of complex patterns of presynaptic activity. It thus may play a fundamental role in the brain in determining the response to e.g. sensory information. Early studies of the temporal transfer characteristics of synapses were performed on the neuromuscular junction and revealed various forms of short-term enhancement and depression [1–4]. To the former belong facilitation, augmentation and short-term potentiation and to the latter depletion of the pool of readily releasable vesicles containing neurotransmitter molecules. These synaptic processes have later also been identified in central synapses which, however, display a large degree of heterogeneity linked to variation of neurotransmitter release probability [15–24]. At a strong release probability depletion may dominate over facilitation. In this section, the control of neural coding by means of the dynamical character-

Figure 1. An example of the time development of the dynamical variables of two synaptically coupled pyramidal cells according to the stochastic model defined in Sections 2 and 3. The presynaptic neuron is externally driven to fire action potentials at a constant rate. In the upper panel, n_v is the total number of readily releasable vesicles summed over all release sites ($n_v = \sum_{r=1}^{N_{rs}} n_v^r$, step curve) and c_t is the intracellular calcium concentration (unit arbitrary) in the presynaptic terminal (sawtooth curve). In the remaining panels, v is the postsynaptic membrane potential (unit mV), i_f and i_s are the fast and slow synaptic currents (units 10^{-11} and 10^{-12} A, respectively) mediated by non-NMDA and NMDA postsynaptic receptors, respectively. The unit of time t is s. The presynaptic firing rate is 30 Hz, the initial neurotransmitter release probability is 0.4 and other parameters are specified in Section 3.

istics of synaptic transmission are discussed with reference to the results obtained in Section 3.

The present models of synaptic transmission are based on the central role played by calcium ions in short-term enhancements of neurotransmitter release [1, 2, 9–14]. Presynaptic action potentials open voltage-gated calcium channels in the

membrane of the synaptic terminal. The calcium ions entering trigger the fusion of vesicles underlying neurotransmitter release, and residual calcium from preceding activity may account for facilitation. The slower forms of short-term enhancements, augmentation and short-term potentiation, may require products of rapid biochemical reactions of calcium that affect the probability of neurotransmitter release and account for the longer formation and decay times of these phases. Recently, calcium imaging by means of fura-2 fluorescence, permitted simultaneous measurement of intracellular calcium at the release sites and asynchronous transmitter release from the same synaptic terminal [25]. Such a measurement is difficult to perform for evoked release due to insufficient spatial and temporal resolution of this imaging technique. A Hill-coefficient between 3 and 4 was obtained for the relationship between the rate of asynchronous release and intracellular calcium.

In the present formulation of synaptic transmission, the principal stochastic influence is on the neurotransmitter release process, specifically on the dynamical variable representing the number of readily releasable vesicles at a release site. Other dynamical variables derive their stochastic variation indirectly from the release process. Figure 1 displays an example of the evolution of dynamical variables involved in an excitatory synaptic coupling between two pyramidal cells. The upper panel of Figure 1 shows the calcium concentration in the presynaptic terminal. The pulsed build-up of calcium occurs at the times of presynaptic action potentials and the first-order decay towards the resting level takes place in the interspike intervals. The same panel of Figure 1 also includes the total number of readily releasable vesicles summed over all release sites. At the times of presynaptic action potentials this number may decrease according to the stochastic release processes at the different release sites. The recovery of the number of readily releasable vesicles is described as a stochastic version of a continuous first-order process. Equations (11) and (12) are formulated to ensure that changes of this number take place by one unit for any release site. Directly linked to the neurotransmitter release events is the development of the fast and slow synaptic current variables. These currents involve postsynaptic receptors of non-NMDA and NMDA type [26], respectively, and are distinguished by different quantal amplitudes and different decay and delay time constants. At each release site, the amount of postsynaptic receptors of both types are saturated by the neurotransmitters contained in a single vesicle [5, 6]. The postsynaptic membrane potential is determined by the current pulses charging the membrane capacitance and the leakage process characterized by a time constant given by the leakage conductance and membrane capacitance. For a sustained presynaptic firing at a certain rate, all dynamical variables will eventually fluctuate around steady-state levels.

For the purpose of simulations of large-scale systems of interacting neurons, the individual behaviour of different release sites is suppressed in a reduced version of the model of synaptic transmission. Figure 2 refers to the same situation as Figure 1 but is obtained by ensemble-averaging over the different presynaptic release sites and replacing the stochastic variables by their corresponding deter-

Figure 2. As Figure 1 but for the reduced model of synaptic transmission defined in Sections 2 and 3. In this model, the dynamical variables represent averages of the corresponding variables in the stochastic model. The number of readily releasable vesicles n_v refers to one release site.

inistic averages. The development of the calcium concentration in the presynaptic terminal, and thus the facilitation of neurotransmitter release, remain the same as in the stochastic model. The smoother behaviour of other dynamical variables, as compared with the corresponding in the stochastic model, makes the approach to steady-state levels for a given presynaptic firing rate more evident in the reduced model. It is by means of the reduced model that the dynamical characteristics of synaptic transmission influencing the information processing in a system of coupled neurons are next discussed.

From the results obtained in Section 3 and visualized in Figures 3 - 7, two limiting behaviours are evident which may be related to the principal types of neural coding, i.e. rate and temporal coding. The temporal evolution of the post-

Figure 3. The time course of the postsynaptic membrane potential v (unit mV) in response to a train of presynaptic action potentials according to the reduced model of the same system as in Figure 1. Each curve corresponds to a constant presynaptic firing rate ($f = 5, 10, 20, 40, 60, 80, 100$ Hz, respectively). The unit of time t is s. The initial neurotransmitter release probability is 0.1 and other parameters are specified in Section 3.

Figure 4. As Figure 3 but for initial neurotransmitter release probability 0.4.

synaptic membrane potential response to a train of presynaptic action potentials at a sustained firing rate is shown as a function of both initial neurotransmitter release probability and presynaptic firing rate in Figures 3–5. Figures 6 and 7 display the steady-state amplitude and steady-state average level, respectively, of postsynaptic membrane potentials as functions of initial release probability and presynaptic firing rate. The two cases of rate and temporal coding are discussed in the following two paragraphs.

A rate coding is based on the variation of the steady-state average level of postsynaptic membrane potential with presynaptic firing rate. It can be accomplished at a low initial neurotransmitter release probability as most clearly seen in Figure 7.

Figure 5. As Figure 3 but for initial neurotransmitter release probability 0.8.

Figure 6. The steady-state amplitude of the postsynaptic membrane potential v (unit mV) responses to presynaptic action potentials as a function of the presynaptic firing rate f (unit Hz) for the same system as in Figure 1. The amplitude of the response to a presynaptic action potential is determined from the difference of membrane potential curves obtained with and without the presynaptic action potential. The different curves in the figure are labelled by the initial neurotransmitter release probability. Other parameters are specified in Section 3. The dashed curve illustrates an inverse dependence of steady-state response amplitude on firing rate by means of the function C/f , where the constant C is determined by the steady-state response amplitude at $f = 100$ Hz for an initial release probability 0.8.

Figure 7. The steady-state average postsynaptic membrane potential v (unit mV) in response to presynaptic action potentials as a function of the presynaptic firing rate f (unit Hz) for the same system as in Figure 1. The average refers to an action potential cycle. The different solid curves are labelled by the initial neurotransmitter release probability. Other parameters are specified in Section 3.

A near linear increase of the steady-state average postsynaptic membrane potential with increased presynaptic firing rate over an interval of typical firing rates is obtained at a low initial release probability and is experimentally observed [19–24]. This can be contrasted with the distinctly different behaviour at a high initial release probability, to be discussed below. The firing-rate dependence of the steady-state average postsynaptic membrane potential can be traced to the behaviour of the steady-state amplitude of postsynaptic membrane potentials shown in Figure 6. At a low initial release probability, this amplitude is nearly constant for varying presynaptic firing rate, which accounts for the nearly linear increase of the steady-state average postsynaptic membrane potential with increasing presynaptic firing rate.

A temporal coding is based on detecting synchrony of changes of firing in a population of presynaptic neurons. A coincidence detection is enabled by a pronounced phasic response, and it is seen in Figures 3–5 that such a response is promoted by a large initial neurotransmitter release probability and a high presynaptic firing rate. The initial enhancement of neurotransmitter release is due to facilitation caused by rapidly accumulating intracellular calcium. The transient response is then rapidly terminated due to depletion because of the large neurotransmitter release. The high presynaptic firing rate leaves little time for intracellular calcium

to be restored towards its resting level and for vesicles to recover during interspike intervals. The generation of a postsynaptic action potential requires the concerted effects of a population of presynaptic neurons, whereas the contribution from any individual connection is subthreshold. Conditions generating transient postsynaptic membrane potential responses should be viewed as a prerequisite for coincidence detection. If present, strong variations of dendritic propagation times as well as strong noise reduce the possibility for coincidence detection. In the steady-state, the amplitude of the postsynaptic membrane potential decreases with increasing presynaptic firing rate for a high initial release probability, as seen in Figure 6. For a given initial release probability, there exists a limiting rate above which the steady-state amplitude is nearly inversely proportional to the firing rate, cf. the reference curve in Figure 6. The resulting steady-state average level of the postsynaptic membrane potential then remains nearly constant for varying presynaptic firing rate, as seen in the curve for a high initial release probability in Figure 7. At a high initial release probability, it is thus not possible to transfer information on the presynaptic firing rate to the postsynaptic neuron in the form of an averaged postsynaptic membrane potential, cf. the discussion of rate coding above. An inverse dependence of the steady-state amplitude on presynaptic firing rate is experimentally observed [19–24] and used in a qualitative estimate of the transient response of the postsynaptic membrane potential to a change of presynaptic firing rate [20, 22]. Assuming that the transient response is proportional to the product of the change of firing rate and the amplitude before this change, an inverse relationship between the amplitude and the firing rate makes the transient response reflect the relative change of firing rate rather than the absolute firing rate. Such a gain control mechanism ensures that changes of weak, i.e. low-rate, signals are not concealed by fluctuations of strong, i.e. high-rate, signals. That this estimate of the transient response is qualitative is seen in Figures 3–5, which show that depletion may reduce pulse amplitudes before the maximum of a transient response is attained.

The presynaptic facilitation of synaptic transmission, as well as the effects of the slow NMDA receptors, may constitute primary stages in learning processes. The present models are also suited to describe neuromodulatory effects on synaptic transmission [24, 43, 44]. The effects of neuromodulators on adaptation of the firing rate were recently studied by means of low-dimensional model neurons [30, 45–47]. Neuromodulators influence the sensitivity to calcium of the conductance of calcium-dependent potassium channels which regulates the slow afterhyperpolarization phase of action potentials and thereby the firing-rate adaptation. It was shown that neuromodulators control the complexity of network dynamics, e.g. between exploratory and retrieval modes in associative processes, via their influence on the firing-rate adaptation. Analogously, the sensitivity of the vesicle fusion probability to calcium can be influenced by neuromodulators. The effect of depletion of the presynaptic pool of readily releasable vesicles containing neurotransmitter molecules, which seem to be dominant in many pyramidal cells [19–24], is analogous

to the effect of firing-rate adaptation in that the postsynaptic response to a sustained presynaptic firing successively diminishes. In their present forms, the biophysical models of synaptic transmission accounting for facilitation, depletion, saturation and neuromodulatory effects are directly applicable to studies of the early stages of learning processes in various memory systems. In particular, the reduced model combines simplicity and biological realism in a way to make it useful for analyzing large-scale systems. In this model, only one calcium variable is introduced for all terminals of a given presynaptic neuron. The only variable that is specific to one connection is the number of remaining vesicles in the pools of readily releasable vesicles at the associated release sites. By inclusion of equations describing biochemical reactions of calcium the products of which affect presynaptic vesicle fusion probability or postsynaptic quantal amplitude, the models may be extended to incorporate short-term and long-term potentiation in memory consolidation processes.

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