Neuromodulatory Control of Neocortical Microcircuits with Activity-Dependent Short-Term Synaptic Depression

BO CARTLING

*Department of Physics, Division of Biological Physics, Royal Institute of Technology,
SE-106 91 Stockholm, Sweden
(e-mail: boc@theophys.kth.se)*

Abstract. A biophysical model of a neocortical microcircuit system is formulated and employed in studies of neuromodulatory control of dynamics and function. The model is based on recent observations of reciprocal connections between pyramidal cells and inhibitory interneurons and incorporates a new type of activity-dependent short-term depression of synaptic couplings recently observed. The model neurons are of a low-dimensional type also accounting for neuronal adaptation, i.e. the coupling between neuronal activity and excitability, which can be regulated by various neuromodulators in the brain. The results obtained demonstrate a capacity for neuromodulatory control of dynamical mode linked to functional mode. The functional aspects considered refer to the observed resolution of multiple objects in working memory as well as the binding of different features for the perception of an object. The effects of neuromodulators displayed by the model are in accordance with many observations on neuromodulatory influence on cognitive functions and brain disorders.

Key words: neocortical microcircuit dynamics, biophysical model neurons, neuronal adaptation, dynamic synapses, neuromodulation, working memory, cognitive functions

1. Introduction

Recent observations on connectivity [1–6] and a new type of activity dependence of synaptic couplings [4, 5] may provide clues to the function of neocortical microcircuitry. Reciprocal connections between pyramidal cells and various subtypes of inhibitory interneurons have been identified in cat [1, 2] and rat [3–5] neocortices. Interneurons constitute about 10% of the total number of neocortical neurons [7]. In particular, extensive reciprocal connections between a fast-spiking interneuron and surrounding pyramidal cells are observed [1–5]. Pyramidal cells may also be reciprocally connected to other pyramidal cells [6]. It has been recently demonstrated that back-propagating action potentials in interneuron dendrites in rat neocortex cause an activity-dependent release of GABA as a retrograde messenger depressing synaptic excitation of interneurons by pyramidal cells [4]. Similarly, it is shown

that activity-dependent dendritic release of glutamate as a retrograde messenger from pyramidal cells suppresses inhibitory transmission between interneurons and pyramidal cells [5].

Several types of process underlie activity-dependent modification of synaptic coupling strengths on different timescales [8–21]. On the shortest timescales, action-potential-driven accumulation of intracellular calcium ions in a presynaptic terminal causes facilitation of release of neurotransmitter-containing vesicles [8–9], and depletion of readily releasable vesicles is underlying depression of synaptic coupling [10]. Phenomenological models of these short-term processes for the analysis of neural information transmission and coding [15, 18–21] were recently complemented by stochastic and reduced biophysical models [22, 23]. The processes of facilitation and depletion act in opposite directions with respect to coupling strength, and the net effect varies between different cell types and is also a heterogeneous property, i.e. varies between different cells of a given type [16, 17]. For the purpose of identifying a possible function of the short-term depression due to dendritic release of retrograde messengers, a situation of an associative memory process and negligible net effect of facilitation and depletion is studied in the present work. On long timescales, processes of long-term potentiation and depression underlie memory consolidation and decay, respectively [13, 14], which are temporally well separated from the processes investigated in this work.

In the present work, the dynamics are studied and related to possible functions in systems incorporating the above findings on connectivity and short-term suppression of synaptic couplings. The model neurons employed are of a low-dimensional type also accounting for neuronal adaptation, i.e. the coupling between neuronal activity and excitability, and neuromodulation thereof [24–29]. The functional aspects considered refer to the observed resolution of multiple objects in working memory as well as the binding of different features for the perception of an object [28, 29]. A set of pyramidal cells reciprocally connected to a fast-spiking interneuron in a neocortical microcircuit is then considered representative of one type of object feature and can be divided into assemblies representing particular values of the feature. Several microcircuits of this type are interconnected via excitatory couplings between pyramidal cells to represent the different types of feature defining an object.

The model of a system of neocortical microcircuits is formulated in Section 2 and applied to studies of dynamics in Section 3. The results obtained and their implications for possible functions, as well as their relations to experimental observations, are discussed in Section 4.

2. Model of a Neocortical Microcircuit System

2.1. MODEL NEURAL REPRESENTATION OF OBJECTS

A model of the neural representation of objects is formulated by means of a system of elementary neocortical microcircuits. An object is characterized by a set of features,

and a feature is represented by a neocortical microcircuit of a type experimentally observed [1–6]. In the model, the different values of a feature are represented by assemblies of pyramidal cells within the microcircuit. Excitatory interconnections within one such assembly synchronize the firing of the pyramidal cells and ensure robustness against single-cell failures. To reduce the number of independent variables in the model, the different pyramidal cells within a feature-value assembly are considered equivalent and represented by a single pyramidal cell. Figure 1 schematically illustrates a small-size example of a neocortical microcircuit referring to the

Figure 1. A schematic illustration of a small-size example of a model neocortical microcircuit. The triangular symbols denote excitatory pyramidal cells representing different values of one type of object feature. The diamond symbol at the center refers to a fast-spiking interneuron, the processes of which serve both axonal and dendritic functions. Small open circles denote excitatory synapses, and small filled circles refer to inhibitory synapses. Further details of the model are described in Section 2.

representation of one object feature type with four possible values. For the representation of an object, different microcircuits correspond to the different types of feature characterizing the object. Excitatory interconnections between pyramidal cells in different microcircuits underlie the binding of different features for the representation of an object and are schematically illustrated in Figure 2. To avoid

Figure 2. A schematic illustration of a small-size example of model inter-microcircuit connectivity. The rectangular boxes symbolize neocortical microcircuits of the type depicted in Figure 1. The different microcircuits represent different types of object feature, labelled by $j = 1, \dots, N$ ($N = 4$ in figure and $N = 5$ in simulations). Within each microcircuit, only the triangular symbols denoting pyramidal cells are shown. The different values of one type of object feature are labelled by $k = 1, \dots, M$ ($M = 4$ in figure and $M = 10$ in simulations). The connections between pyramidal cells are reciprocal and excitatory, as indicated by small open circles at both ends. Further details of the model are described in Section 2.

specification of particular objects that share the same value of certain feature types, the strongly simplifying assumption of characteristic feature values for each object is made. Such a non-overlapping, or orthogonal, neural representation of objects is more applicable at a high level of an hierarchically organized representation. An illustrative example of an object type is a person, and, on a high representational level, possible feature types include face, voice and other attributes of a person. A particular object, i.e. in the example a particular person, is associated with particular values of each of the object's defining feature types, i.e. in the example a particular face, voice, etc.

2.2. MODEL NEURONS AND SYNAPTIC COUPLINGS

The model neurons are of a low-dimensional type incorporating firing-rate adaptation [24, 25]. Two of the principal neuron types in the brain are selected as prototypes of the model neurons: the regularly spiking pyramidal cell and the fast-spiking interneuron [30, 31]. The firing rate of pyramidal cells is regulated via the slow afterhyperpolarization phase of action potentials, which is controlled via calcium-dependent potassium channels by the intracellular calcium concentration [32, 33]. Action potentials induce an influx of calcium ions, and in the reverse direction, ionic pumps, internal buffering and diffusion act to restore the resting level of the intracellular calcium concentration. The neuronal adaptivity, i.e. the degree to which previous activity affects the ability to fire action potentials, is given by the sensitivity of the conductance of calcium-dependent potassium channels to intracellular calcium concentration and can be controlled by various neuromodulators in the brain, as further discussed in Section 4. The fast-spiking interneurons do not display firing-rate adaptation. The excitatory couplings between pyramidal cells in the different microcircuits representing different features of an object are mediated by AMPA- and NMDA-receptors generating fast and slow responses, respectively [34–36]. The excitatory couplings from pyramidal cells to interneurons only engage AMPA-receptors [36, 37]. Backpropagating action potentials in interneuron dendrites induce an activity-dependent release of GABA as a retrograde messenger suppressing this type of excitatory coupling [4]. In the reverse direction, the inhibitory couplings from interneurons to pyramidal cells are accomplished by means of GABA_A-receptors [36]. These couplings are suppressed by an activity-dependent release of retrograde messenger glutamate from pyramidal cell dendrites [5].

2.3. MODEL EQUATIONS OF DYNAMICS

A system of neocortical microcircuits for the representation of objects, as outlined in Section 2.1, is built from the model neurons and synaptic couplings defined in Section 2.2. The time development of the dynamical variables of the microcircuit system can be determined by a set of equations successively introduced and explained below. The principal dynamical variables are the input currents to the

various neurons that are described by Eqs. (1)–(4):

$$\tau^{\text{eer}} \frac{di_{jk}^{\text{eer}}(t)}{dt} = -i_{jk}^{\text{eer}}(t) + s^{\text{er}} \left\{ \sum_{n=1}^N \sum_{l=1}^M \omega_{jk,nl}^{\text{ee}} g_{nl}^{\text{e}}(i_{nl}^{\text{e}}(t), c_{nl}^{\text{e}}(t)) + i_{jk}^{\text{eb}}(t) \right\} \quad (1)$$

$r = \text{a,n}; \quad j = 1, \dots, N; \quad k = 1, \dots, M$

$$\tau^{\text{ei}} \frac{di_{jk}^{\text{ei}}(t)}{dt} = -i_{jk}^{\text{ei}}(t) + w_{jk,j}^{\text{ei}}(t) g_j^{\text{i}}(i_j^{\text{ie}}(t)) \quad (2)$$

$j = 1, \dots, N; \quad k = 1, \dots, M$

$$\tau^{\text{ie}} \frac{di_j^{\text{ie}}(t)}{dt} = -i_j^{\text{ie}}(t) + \sum_{l=1}^M w_{j,l}^{\text{ie}}(t) g_{jl}^{\text{e}}(i_{jl}^{\text{e}}(t), c_{jl}^{\text{e}}(t)) \quad j = 1, \dots, N \quad (3)$$

$$i_{jk}^{\text{e}}(t) = i_{jk}^{\text{eea}}(t) + i_{jk}^{\text{een}}(t) - i_{jk}^{\text{ei}}(t) \quad j = 1, \dots, N; \quad k = 1, \dots, M \quad (4)$$

The model system applies to the representation of one type of object characterized by N features, each represented by an elementary neocortical microcircuit. Within one microcircuit, M assemblies of pyramidal cells represent different values of the feature. In the model, each feature-value assembly is represented by a single pyramidal cell, as justified in Section 2.1. Eqs. (1)–(3) describe the development of the different contributions to the input currents to the neurons in the system. The current contribution to a pyramidal cell labelled by k in a microcircuit labelled by j is denoted by i_{jk}^{xyr} , where x and y specify the type of post- and pre-synaptic neuron, respectively, and r denotes type of post-synaptic receptor. The possible values of x and y are e and i for excitatory pyramidal cell and inhibitory interneuron, respectively. In couplings between pyramidal cells, the two receptor types AMPA and NMDA are denoted by r equal to a and n , respectively. For couplings between pyramidal cells and interneurons, only one type of receptor is engaged in each direction, as described above, and the superscript r is left out. The superscripts of the synaptic time constants τ^{xyr} are defined analogously to those of the current contributions. The activity of a neuron is given by the firing rate normalized to the range 0–1. The activation function of input current $i_{nl}^{\text{e}}(t)$ to, and intracellular calcium concentration $c_{nl}^{\text{e}}(t)$ in, a pyramidal cell l in microcircuit n , is denoted $g_{nl}^{\text{e}}(i_{nl}^{\text{e}}(t), c_{nl}^{\text{e}}(t))$. For the non-adapting interneuron in microcircuit j , the analogous notation is simplified to $g_j^{\text{i}}(i_j^{\text{ie}}(t))$. Two types of synaptic coupling strengths are distinguished, fixed and time-dependent. The fixed synaptic coupling strengths $\omega_{jk,nl}^{\text{xy}}$ are labelled by x and y for type of post- and pre-synaptic neuron, respectively. In the subscript, jk and nl refer to post- and pre-synaptic neuron, respectively, by the notation in terms of microcircuit and pyramidal cell indices defined above. The labelling of pyramidal cells is ordered such that the feature-value subscripts for different feature types are equal for one object, as is illustrated in Figure 2. The time-dependent synaptic couplings are denoted by $w_{jk,j}^{\text{ei}}(t)$ for the coupling from the interneuron in microcircuit j to pyramidal cell k in the same microcircuit and $w_{j,jl}^{\text{ie}}(t)$ for the coupling from pyramidal cell l in microcircuit j to the interneuron

in the same microcircuit. The relative amounts of AMPA- and NMDA-receptors in the couplings between pyramidal cells are denoted by s^r , where r is a or n, as defined above, and $s^a + s^n = 1$. An externally applied stimulus current $i_{jk}^{eb}(t)$ is included in Eq. (1). The total input current to a pyramidal cell k in microcircuit j , denoted by $i_{jk}^e(t)$, is given by the different contributions described above according to Eq. (4).

The intracellular calcium concentration in a pyramidal cell $c_{jk}^e(t)$ develops by influx and decay processes as described by Eq. (5):

$$\frac{dc_{jk}^e(t)}{dt} = q^e(c_{jk}^e(t))g_{jk}^e(i_{jk}^e(t), c_{jk}^e(t)) - c_{jk}^e(t)/\tau^{ec}$$

$$j = 1, \dots, N; \quad k = 1, \dots, M \quad (5)$$

The inflow of calcium ions is represented by the first term, where $q^e(c_{jk}^e(t))$ is proportional to the amount of calcium ions that enters per action potential [38]. The influx is counteracted by ionic pumps, internal buffering and diffusion, all acting to restore the resting level of intracellular calcium concentration, as described by the second term of Eq. (5) in terms of a first-order process with time constant τ^{ec} . The resting level of intracellular calcium concentration is very low and is neglected [39].

The synaptic couplings between pyramidal cells and interneurons display an activity-dependent suppression due to retrograde messengers as discussed above and described by Eqs. (6) and (7):

$$\tau^{wei} \frac{dw_{jk,j}^{ei}(t)}{dt} = -w_{jk,j}^{ei}(t) + \omega_{jk,j}^{ei} \{1 - \varsigma^e g_{jk}^e(i_{jk}^e(t), c_{jk}^e(t))\}$$

$$j = 1, \dots, N, \quad k = 1, \dots, M \quad (6)$$

$$\tau^{wie} \frac{dw_{j,jl}^{ie}(t)}{dt} = -w_{j,jl}^{ie}(t) + \omega_{j,jl}^{ie} \{1 - \varsigma^i g_j^i(i_j^{ie}(t))\}$$

$$j = 1, \dots, N; \quad l = 1, \dots, M \quad (7)$$

The degree of suppression of the inhibitory coupling $\omega_{jk,j}^{ei}$ from an interneuron in the microcircuit j to a pyramidal cell k in the same microcircuit is expressed by means of a suppression parameter ς^e and the level of activity of the pyramidal cell $g_{jk}^e(i_{jk}^e(t), c_{jk}^e(t))$. The proposed mechanism underlying the suppression involves metabotropic glutamate receptors and G-proteins inhibiting voltage-gated calcium channels so that GABA release from the presynaptic terminal is reduced [5]. This indirect mechanism is assigned a time constant τ^{wei} in Eq. (6). The suppression of the reciprocal excitatory coupling from a pyramidal cell to an interneuron, involving metabotropic GABA_B-receptors and reduced glutamate release [4], is described analogously by means of a suppression parameter ς^i and a time constant τ^{wie} in Eq. (7).

The normalized firing rate of a neuron is determined from the total input current, and for pyramidal cells also from the intracellular calcium concentration, by means of generalized activation functions [24, 25] defined in Eqs. (8) and (9) for pyramidal cells and interneurons, respectively:

$$g_{jk}^e(i_{jk}^e(t), c_{jk}^e(t)) = \max(\tanh(\beta^e i_{jk}^e(t) - \eta^e c_{jk}^e(t) - \theta^e), 0) \quad j = 1, \dots, N; \quad k = 1, \dots, M \quad (8)$$

$$g_j^i(i_j^i(t)) = \max(\tanh(\beta^i i_j^i(t) - \theta^i), 0) \quad j = 1, \dots, N. \quad (9)$$

The parameters β^e and β^i correspond to the gain, i.e. the slope of the activation function with respect to input current, for pyramidal cells and interneurons, respectively. The adaptivity is determined by the sensitivity of the conductance of calcium-dependent potassium channels to intracellular calcium concentration and is described by the parameter η^e . The threshold parameters θ^e and θ^i account for a bias due to background activity that ensures a rapid response of a neuron [40].

2.4. MODEL PARAMETER VALUES

In this section, the values of model parameters employed in the dynamics studies are defined. The number N of neocortical microcircuits, corresponding to different types of object feature, is put equal to five. The number M of pyramidal cells representing assemblies, that in turn represent different values of a feature type, is selected to be 10 in approximate accordance with the observed ratio of the numbers of interneurons and pyramidal cells in the neocortex [7].

The dynamics of the model system are determined by means of the equation system formulated in Section 2.3. The synaptic time constants denoted τ^{ea} , τ^{en} , τ^{ei} and τ^{ie} corresponding to AMPA-, NMDA-, GABA_A- and AMPA-receptors, respectively, are assigned the values 10, 150, 10 and 10 ms, respectively, based on experimental observations on excitatory and inhibitory postsynaptic currents in neocortical [41] and hippocampal [42] systems. The relative amounts of AMPA- and NMDA-receptors in synaptic couplings between pyramidal cells have been estimated to be $s^a = 0.8$ and $s^b = 0.2$ [34, 35]. The development of the intracellular calcium concentration is described by Eq. (5), in which $q^e(c_{jk}^e(t))$ relates the inflow of calcium to the normalized activity and can be fitted by the expression $q^e(c_{jk}^e(t)) = a^e / (b^e + c_{jk}^e(t))$ [24, 25]. The calcium concentration is measured on an arbitrary scale which is fixed by selecting $b^e = 1.0$. Absolute values of the intracellular concentration of calcium ions are typically in the micromolar range [38]. Experimental observations of the slow afterhyperpolarization [31, 43, 44], which is governed by the intracellular calcium concentration, yield an estimate of $a^e = 50$. The decay time constant of the intracellular calcium concentration due to the restoration of the resting level by ionic pumps, internal buffering and diffusion is assigned the typical value $\tau^{\text{ec}} = 100$ ms [31, 43, 44].

The activity in terms of a normalized firing rate of pyramidal cells and interneurons is given by the generalized activation function in Eqs. (8) and (9), respectively.

The gain parameters are determined so that most of the activity range is spanned by an input interval of one unit, $\beta^e = \beta^i = 2.0$. The adaptivity parameter of the pyramidal cell activation function, η^e , is varied between the different cases studied as described in Section 3. Finally, the activation functions include a threshold parameter corresponding to the background activity. In pyramidal cells, there is a dynamical threshold contribution from the adaptation as described by the adaptivity parameter and intracellular calcium concentration, and $\theta^e = -0.8$ is used. For non-adapting interneurons, which lack the dynamical threshold, $\theta^i = -0.04$.

The connectivity of the system of neocortical microcircuits is described in Sections 2.2 and 2.3. The fixed synaptic couplings $\omega_{jk,nl}^{ee}$ and the non-suppressed values $\omega_{jk,j}^{ei}$ and $\omega_{j,jl}^{ie}$ of the activity-dependent couplings $w_{jk,j}^{ei}(t)$ and $w_{j,jl}^{ie}(t)$, respectively, are sampled from normal distributions. The average value of $\omega_{jk,nl}^{ee}$ is 0.5 for non-diagonal elements and 1.0 for diagonal elements, corresponding to the stronger reciprocal couplings within an assembly represented by one pyramidal cell [45]. The inhibitory couplings from interneurons to pyramidal cells are stronger than excitatory couplings due to the different sites and number of synaptic contacts involved [46, 47]. The average non-suppressed value of inhibitory couplings $\omega_{jk,j}^{ei}$ of 6.0 provides a proper balance between excitation and inhibition in the system. The excitatory couplings from pyramidal cells to interneurons are assigned the average non-suppressed value $\omega_{j,jl}^{ie} = 0.5$. In the normal distributions of synaptic coupling strengths, the standard deviation relative to the average value is set to 3%. The activity-dependent synaptic couplings are also described by the suppression parameters $\zeta^e = \zeta^i = 0.5$. For a typical variation of the neuronal activity by 0.2, this implies a 10% change of coupling strength asymptotically. The suppression mechanisms are of an indirect character, as described in Section 2.3, and are assigned the time constants $\tau^{wei} = \tau^{wie} = 150$ ms, comparable with the time constant of the slow NMDA-receptors.

3. Results

The dynamics of the model system of neocortical microcircuits are studied by means of the equation system formulated in Section 2.3 with parameter values defined in Section 2.4. The adaptation of pyramidal cells is an important determinant of the dynamics. It can be regulated by means of various neuromodulators in the brain affecting the sensitivity of the conductance of calcium-dependent potassium channels to intracellular calcium concentration, as discussed further in Section 4. The adaptivity is described by the parameter η^e in the generalized activation function of pyramidal cells in Eq. (8) and is used as a variable parameter to study different cases. An initial state is defined by stimulating one particular object, i.e. the five pyramidal cells representing the applicable values of the five features defining an object in the model system. An external input current $i_{jk}^{eb}(t) = 0.1$ is applied during 1 s to the pyramidal cells labelled $k = 1$ in the microcircuits labelled $j = 1-5$.

Figures 3–6 display the development of pyramidal cell activity, as given by the activation function $g_{jk}^e(t)$, in the four cases defined by the adaptivity parameter $\eta^e = 2.0, 1.0, 0.7$ and 0.52 , respectively. The duration of an associative process of the type studied can vary considerably. The immediate response to an input stimulus is of a transient character, and here a period of 0.5 s starting at 9.5 s after the onset of the stimulus current is selected for display. The microcircuit referred to, representing one type of object feature, is $j = 1$, and the different values of the features, corresponding to different objects, are labelled by $k = 1, \dots, 10$ and visualized in separate subpanels of each figure. It should be remarked that the background activity, represented by the threshold parameters in the activity functions, is low enough to keep pyramidal cells not continuously firing but sufficient to allow disinhibited pyramidal cells to fire. This describes a situation permitting associations between objects of the same type, even without common feature values. The results demonstrate that the dynamics undergo bifurcations, i.e. transitions between different modes, with the neuronal adaptivity of the pyramidal cells as a control parameter. At strong adaptivity, the order of successively activated pyramidal cells representing different objects is irregular. An example at adaptivity $\eta = 2.0$ is shown in Figure 3. The frequency of successive activations is higher compared to that at weaker adaptivity. More objects are activated and coactivations of multiple objects are also more frequently occurring at strong adaptivity than at weak adaptivity. The intensity level of activations is low, presumably implying a reduced degree of conscious awareness. As the adaptivity is reduced, regularly ordered reactivations of the pyramidal cells representing different objects develop, i.e. the dynamics assume limit-cycle character. Examples at adaptivity $\eta = 1.0$ and 0.7 are shown in Figures 4 and 5, respectively. The frequency of reactivations is successively lowered as adaptivity is decreased and is in the range of theta oscillations observed in the brain [48]. At adaptivity $\eta = 1.0$, this frequency is about 3.8 Hz and at $\eta = 0.7$, it is about 3.2 Hz. The intensity level of pyramidal cell activations successively increases, corresponding to a higher degree of conscious awareness of the objects represented. In contrast to the strong-adaptivity behaviour, serially resolved and consciously perceived object representations can be activated at intermediate adaptivity. The number of objects consecutively activated is reduced as the adaptivity is decreased. In the neural representation space, this corresponds to a reduced dimension of the activated subspace. At sufficiently weak adaptivity, the long-time dynamics display a fixed-point character in the neural representation space corresponding to the activation of a single object. Figure 6 shows an example at adaptivity $\eta = 0.52$. The high intensity level of activation corresponds to focused attention on this object. Throughout this sequence of decreased adaptivity values, there is faster oscillatory activity superimposed. The frequency of these oscillations is in the range of gamma oscillations observed in the brain [49] and is successively reduced with the neuronal adaptivity. In the four cases represented by Figures 3–6, the frequencies are estimated from averages over the time interval displayed to be about $62, 46, 40$ and 32 Hz for adaptivity $\eta = 2.0, 1.0, 0.7$ and 0.52 , respectively.

Figure 3. The time development of the activity $g_{jk}^e(t)$ of pyramidal cells representing different values, labelled $k = 1-10$, of one type of object feature, labelled $j = 1$, corresponding to different objects of one type. The neuronal adaptivity of pyramidal cells is $\eta^e = 2.0$. The activity scale marked at the top subpanel applies to all subpanels. The unit of time t is s.

Figure 4. Same as Figure 3, but the neuronal adaptivity of pyramidal cells is $\eta^e = 1.0$.

Figure 5. Same as Figure 3, but the neuronal adaptivity of pyramidal cells is $\eta^e = 0.7$.

Figure 6. Same as Figure 3, but the neuronal adaptivity of pyramidal cells is $\eta^e = 0.52$.

As discussed further in Section 4, synchronization of the gamma frequency oscillations of the activities of pyramidal cells representing different features of an object has been linked to the feature binding underlying perception of an object. Such synchronization is illustrated by a comparison of the pyramidal cell activity $g_{jk}^e(t)$ of a given object, i.e. a given value of k , and different microcircuits labelled by j . Figure 7 shows $g_{jk}^e(t)$ for $j = 2$, $k = 1, \dots, 10$ and $\eta^e = 1.0$ and is to be compared with Figure 4 for $j = 1$, $k = 1, \dots, 10$ and the same adaptivity value. The two figures of the pyramidal cell activities representing two types of feature demonstrate the synchronization between activities related to the same object, i.e. the correlated value of each type of feature. Figure 8 shows the corresponding activity $g_j^i(t)$ of the interneuron of microcircuit $j = 1$ and demonstrates a variation in synchrony with the gamma oscillations of pyramidal cell activities.

4. Discussion

The interplay of the cellular and synaptic dynamical processes in the system of neocortical microcircuits generates complex spatio-temporal activity patterns. As described in the account of the results obtained in Section 3, three types of dynamical phenomena can be distinguished, viz. reactivations of the neural representatives of one object, transfer of activity between the neural representatives of different objects and, superimposed on these processes, faster oscillatory neural activity. The results also demonstrate that the dynamics undergo bifurcations, i.e. transitions between different modes, with the neuronal adaptivity of the pyramidal cells as a control parameter. The adaptivity is given by the sensitivity of the conductance of calcium-dependent potassium channels to the intracellular calcium concentration and can be regulated by several neuromodulators in the brain, as further discussed below. The different dynamical modes are related to functional modes referring to the temporal resolution of different objects in working memory and to the binding of different features for the perception of an object. Working memory is a short-term memory of limited capacity engaged in both consolidation and retrieval of information in long-term memory [50, 51]. The neural basis of working memory is believed to be maintained neural activity in the same widely distributed and interconnected neocortical substrate as that of long-term memory [51–54].

The resolution of separate objects in working memory has been linked to a temporal multiplexing of the activities of the neural representatives of the objects [55–58]. Activity is then successively transferred from the pyramidal cells that are representative of the features of one object to the pyramidal cells representing the features of another object. As possible underlying mechanisms of such activity transfer, the firing-rate adaptation of the pyramidal cells most active before the activity transfer and the disinhibition of the pyramidal cells to become activated have been proposed and investigated [28, 29]. The timescale of reactivation of the pyramidal cells representing different features of one object is determined by both

Figure 7. Same as Figure 3, but for type of object feature labelled $j = 2$ and neuronal adaptivity of pyramidal cells is $\eta_j^e = 1.0$.

Figure 8. The time course of the activity $g_1^i(t)$ of the fast-spiking interneuron in the microcircuit representing one type of object feature labelled $j = 1$. The neuronal adaptivity of pyramidal cells is $\eta^e = 1.0$. The unit of time t is s.

the firing-rate adaptation upon high activity and the restoration of excitability during low activity. The firing-rate adaptation of a pyramidal cell is also assisted by the less suppressed inhibitory coupling from the coupled interneuron as the pyramidal cell activity is lowered. The period of reactivations is dominated by the restoration of excitability, which is linked to the return of the intracellular calcium concentration towards its resting level during low activity. The influence of the adaptation of the pyramidal cells on the reactivation process makes this process cyclic for adaptivity values within a certain intermediate range, as described in Section 3. The results obtained in Section 3 also show that cyclic reactivations occur with a frequency in the range of theta oscillations observed in the brain [48].

The transfer of activation between sets of pyramidal cells representing the features of different objects takes place on a shorter timescale than the reactivation dynamics described above. The activation transfer relies on the reciprocal connections between pyramidal cells and the interneuron within a microcircuit. The timescale is given by the firing-rate adaptation of the pyramidal cells and the time-constants of the different synaptic couplings. As the activity level of a pyramidal cell is reduced by firing-rate adaptation, the activity of the coupled interneuron is not as strongly reduced due to the developing activity in other pyramidal cells coupled to the interneuron and due to the activity-dependence of the couplings from pyramidal cells to an interneuron. These excitatory couplings are less suppressed as the interneuron activity is reduced, and this affects the driving of the interneuron from both the formerly most active pyramidal cell and the disinhibited pyramidal cells. An example of limited amplitude of interneuron activity is shown in Figure 8. The disinhibition

of the pyramidal cells becoming activated derives from both the reduced activity of the interneuron and the more strongly suppressed inhibitory couplings from the interneuron to these pyramidal cells as their activity develops. In analogy with the situation for reactivation of one pyramidal cell, the firing-rate adaptation of the formerly most active pyramidal cell is also assisted by the less suppressed inhibitory coupling from the interneuron as pyramidal cell activity is lowered. The dependence of activity transfer on pyramidal cell adaptivity is described in Section 3.

Superimposed on the two types of long-time dynamics are faster oscillatory dynamics primarily determined by the fast synaptic couplings in the negative feedback loops of the reciprocal connections between pyramidal cells and interneurons. The corresponding frequency is in the range of gamma oscillations observed in the brain [49], and it decreases with reduced adaptivity of the pyramidal cells, as described in Section 3. Synchronization of gamma oscillations between neurons representing different features of an object has been suggested to bind the features as required for perception of an object [59–66]. Such synchronization has been observed e.g. in the visual cortex of cat [61, 62]. Cognitive temporal binding of auditory stimuli have been related to gamma oscillations in the auditory area of the right hemisphere of the human brain [63]. In cat visual cortex, synchronization of gamma oscillations have been shown to correlate with perception in interocular rivalry [65]. Desynchronization of odour-encoding neural assemblies in the locust antennal lobe has been correlated with impaired odour discrimination [66].

Considering both the processes of reactivation of the neural representatives of one object and of activity transfer between pyramidal cells representing different objects, the resolution of perceived objects is limited by the number of activity transfers that can be contained within a period of reactivation. The number of objects, $M = 10$, in the present studies is large enough to reveal the limited capacity of short-term working memory, i.e. that not all objects get activated. Of the cases studied, the one represented in Figure 2 corresponds to the largest number of objects activated, and the number is between five and eight depending on selected threshold level of activity. This is in good agreement with the “magical number seven, plus or minus two,” an observed limit on our capacity for processing information [67]. The gamma frequency represents a limiting frequency for the process of activity transfer, corresponding to single gamma-period activity of each object. It is well established that memory processes are accompanied by oscillatory brain activity in both theta [68–71] and gamma [49, 63, 65, 72] frequency ranges. Supporting evidence of the present mechanism are the observations that the phase of the theta cycle varies between different place cells in the hippocampus [73, 74]. The timescale of successive activations is also in accordance with psychophysical measurements of the temporal separation of serially activated items in the Sternberg task [75]. A different mechanism for storage of short-term memories in oscillatory subcycles has also been proposed on the basis of fast NMDA-channels [56, 58]. Alternative mechanisms of the generation of theta rhythms include the medial septum acting as a pacemaker [76]. The observed influence of acetylcholine on the

amplitude of theta oscillations in the hippocampus [77] is in accordance with the present adaptation-based mechanism together with the effect of acetylcholine on the adaptivity of excitatory neurons discussed below. An important conclusion of the present results on neuromodulatory control of neocortical microcircuit dynamics is that they confirm previous findings for models with more individual inhibitory control of pyramidal cells [26–29]. This is due to the activity-dependent depression, discussed above, of the inhibitory coupling to an active pyramidal cell, which provides the required distinction between different pyramidal cells.

In the brain, the neuronal adaptivity of excitatory neurons, as given by the sensitivity of the conductance of calcium-dependent potassium channels to intracellular calcium ions, can be influenced by several neuromodulators [33, 78–84]. This sensitivity can be decreased or increased by phosphorylation or dephosphorylation, respectively, of the calcium-dependent potassium channels through neuromodulator-receptor-mediated indirect activation of kinases or phosphatases, respectively. Metabotropic receptors of glutamate [82] and muscarinic receptors of acetylcholine [80] are examples of receptors mediating a reduction of neuronal adaptivity. The D1-type of dopamine receptor exemplifies the reverse, i.e. a receptor engaged in an increase of neuronal adaptivity [83, 84]. The cholinergic neuromodulatory system is well established to be involved in cognitive processes [85–87]. According to the present model, the stronger adaptivity at low levels of acetylcholine causes an irregular network activity at low intensity. This is in accordance with the reduced cognitive capacity in Alzheimer's disease, in which cholinergic neurons in the basal forebrain degenerate [88, 89]. Acetylcholinesterase inhibitors, such as physostigmine, can enhance the performance of learning and recall [90–92], whereas muscarinic agonists, such as scopolamine and atropine, act in the opposite direction [93–96]. Intrusions from previous information during recall under the influence of scopolamine [97] and impaired learning in conditions of damaged cholinergic septal nuclei in the basal forebrain, e.g. caused by artery aneurysms or lesions [98, 99], are also consistent with the cholinergic influence according to the present model. As mentioned above, the reverse dependence of neuronal adaptivity on neuromodulator concentration compared to the cholinergic system is represented by the D1-receptor-dopaminergic system. In prefrontal cortex, the dominant type of dopamine receptor is D1 [100]. Schizophrenics, which are suffering from a hyperactive dopaminergic system, show working memory deficits and correlated prefrontal dysfunction [101–103]. These observations are in accordance with the influence of increased neuronal adaptivity at raised levels of dopamine on the behaviour of the present model. Neuromodulators in addition to its influence on neuronal adaptivity may have other effects, e.g. on synaptic transmission [87].

In conclusion, the present model of neocortical microcircuit systems, based on recently established connectivity and activity dependence of synaptic couplings, demonstrates a capacity for neuromodulatory control of dynamical mode linked to functional mode that is consistent with many observations on neuromodulatory influence on cognitive functions and brain disorders.

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