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A theoretical network model to analyse neurogenesis and synaptogenesis in the dentate gyrus

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Abstract

We describe a strongly biologically motivated artificial neural network approach to model neurogenesis and synaptic turnover as it naturally occurs for example in the hippocampal dentate gyrus (DG) of the developing and adult mammalian and human brain. The results suggest that cell proliferation (CP) has not only a functional meaning for computational tasks and learning but is also relevant for maintaining homeostatic stability of the neural activity. Moderate rates of CP buffer disturbances in input activity more effectively than networks without or very high CP. Up to a critical mark an increase of CP enhances synaptogenesis which might be beneficial for learning. However, higher rates of CP are rather ineffective as they destabilize the network: high CP rates and a disturbing input activity effect a reduced cell survival. By these results the simulation model sheds light on the recurrent interdependence of structure and function in biological neural networks especially in hippocampal circuits and the interacting morphogenetic effects of neurogenesis and synaptogenesis.

Keywords: Hippocampus; Neurogenesis; Synaptogenesis; Cell proliferation; Apoptosis; Network model; Homoestatic plasticity; Rewiring

1. Introduction

Ongoing neurogenesis has been found in the CNS of completely different taxa of invertebrates and vertebrates (Altman and Das (1965), Harzsch, Miller, Benton, and Beltz (1999), Nottebohm (1981) and rev. in Cayre, Malaterre, Scotto-Lomassese, Strambi, and Strambi (2002)) and seems to be indispensable for certain cognitive functions in insects and mammals, including humans (Eriksson et al., 1998). Abolishing adult CP in crickets and rats, which occurs in mushroom bodies and in the subventricular zone/dentate gyrus (DG) respectively, impairs long-term memory function (Madsen et al., 2003; Scotto-Lomassese et al., 2003). However, it is not at all understood what kind of contribution new neurons add to an old network. Theoretical approaches — beside experimental investigations — offer an important insight in the complex functional and structural dynamics of biological networks with and without neurogenesis. For this purpose, a bottom-up approach is used: the proposed model is not directed at producing a particular, a priori defined behaviour, but is built to study the course of plastic reorganization in developing biological neural networks. This approach allows for the investigation of synaptic remodelling and cellular turnover in a combined manner. The main questions this work addresses are in which way and to what extent the embedding and survival of new neurons in an existing network is dependent on synaptic processes and on neuronal activity. The DG, which is the entrance region of the hippocampal formation, is a suitable example for the presented model as it does not only show adult CP but also is affected by a permanent strong sensory input. However, our formalization of those processes was as general as possible so as not to restrict the model to a particular brain region. Besides giving an insight to naturally occurring hippocampal neurogenesis, the model may also contribute to optimizing the survival of transplanted cells in neural tissues.

1.1. Modelling functional properties

In contrast to the bottom-up approach used here, current artificial neural network models are predominantly designed to

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mimic cognitive functions like pattern learning and recognition. Adding new cells to a multi-layer-perceptron, (Chambers et al., 2004) showed that CP is beneficial for memory capacities of the given network. However, it says little of the necessity for CP in biological neural networks. Learning algorithms that get closest to synaptic pattern formation in cortical networks are based on the well established biological concept of Hebbian learning. Accordingly, competition and reinforcement of the network's synapses generate an activity-dependent selectivity to sensory input patterns which is a powerful tool for many technical applications. However, this concept is a very restricted view of plasticity in biological neural networks and is itself not sufficient to maintain a functional organization of biological networks, as permanent reinforcement of synapses leads to a destabilization of postsynaptic firing rates (rev. in Turrigiano (1999)). Homeostasis is thus a fundamental precondition for learning in biological neural networks. More or less biologically plausible solutions for this problem like the BCM-model (Bienenstock, Cooper, & Munro, 1982) and synaptic scaling (Miller & MacKay, 1994) have been proposed. The latter could be found in vivo (Lissen et al., 1998; O'Brien et al., 1998; Turrigiano & Nelson, 1998) and shows remarkable computational properties (Abbott and Nelson (2000), cp. also Oja (1982)). Even though it can be assumed that the theoretically modelled mechanisms really exist on synapse level, biological neural networks are not as hard-wired as these computational models may suggest: adding and deleting synapses and even neurons lead to a more complex structural dynamic than changing connection strengths among neurons, only. Moreover, it has been shown that compensatory synaptic rewiring can be highly specific and even effects, under some biologically plausible preconditions, an input selectivity that is comparable to the Hebbian synapse plasticity (Dammasch, 1989).

1.2. Modelling structural processes

Neuronal networks in the brain are not only formed by scaling existing synapses but by persistent synaptogenesis, i.e. the separation of old and formation of new synapses: starting with a genetically given blueprint, ramification of axons and dendrites leads via transient states in ontogeny to a more or less stable connectivity pattern in adulthood (Abraham & Tate, 1997; Majewska, Newton, & Sur, 2006; Ruan et al., 2006; Ruthazer, 2005; Wolff, Leutgeb, Holzgraefe, & Teuchert, 1989). A model for synaptic pruning during development was proposed by Chechik et al. (2001). Even for the adult brain structural plasticity was reported (Benýtez-Temiño, de la Cruz, Tena, & Pastor, 2005; Cesa, Morando, & Strata, 2005; Wolff & Missler, 1992) and it has been shown to be ruled by hormonal influences in the avian brain (Nottebohm, 1981, 1991). A theoretical approach to simulate the process of the activity-dependent outgrowth of neurites was introduced by van Ooyen and co-workers (van Ooyen & van Pelt, 1994; van Ooyen, 1994; van Ooyen, van Pelt, & Corner, 1995; van Ooyen & van Pelt, 1996; van Ooyen, van Pelt, Corner, & Kater, 2003; van Oss & van Ooyen, 1997). This simulation model investigated the spatial development of the neuritic fields of excitatory and inhibitory neurons and their connectivity. Using the same underlying concept of a homeostatic neuronal regulation, Dammasch, Wagner, and Wolff (1986, 1988) simulated the reorganization of the connectivity pattern by an activity-dependent synaptic turnover. This requires the concept of pre- and postsynaptic elements being separately formed, disconnected and redistributed (Wolff, 1982). A highly dynamic connectivity pattern may arise from breaking and recombining existing synapses — a concept that has been largely neglected in the current computational neuroscience literature, but which is, however, fundamental for modelling the embedding of new neurons into mature neural networks.

Altogether, morphogenesis and homeostasis are two fundamental properties of biological neural networks. However, in a combined manner they are not discussed in current artificial network approaches. Thus, in this approach the neuron is seen as the central entity of plasticity, because the neuron differentiates and induces plastic adaptations while at the same time maintaining homeostatic balances. According to this, it is important to investigate the morphogenetic effect of new cells on the homeostasis of the pre-existing network. By the network approach used here we discuss the interfering effect of neurogenesis and synaptogenesis on network homeostasis as it can be observed in hippocampal circuits (Dawirs, Teuchert-Noodt, & Kacza, 1992; Dawirs, Teuchert-Noodt, Hildebrandt, & Fei, 2000).

2. Materials and methods

2.1. Definition of the network model

This work does not merely discuss the impact of the theoretical results for experimental research but also focuses on the description of the proposed algorithm. The artificial neural network used here is an extension of the McCulloch–Pitts network (McCulloch & Pitts, 1943) which was initially proposed by Dammasch et al. (1986, 1988) in order to simulate activity-dependent synaptic reorganization in cortical networks. For our recent studies, we upgraded this former algorithm so that it allowed us to deal with a changing number of neurons. Subsequently, rules for adding and deleting neurons were defined. Herein, the basic McCulloch–Pitts network and its dynamic was only used as a vehicle to model structural processes as synapse turnover, cell proliferation and apoptosis. According to the definition of McCulloch and Pitts, a network was defined by $\{N, NE, \mathbf{C}, \theta, \Phi, \beta\}$, where N is the number of logical neurons, $NE < N$ is the number of excitatory neurons, with the convention that the neurons are labelled such that neurons $\{1, \ldots, NE\}$ are excitatory and neurons $\{NE + 1, \ldots, N\}$ are inhibitory, $\mathbf{C}$ is the $(N \times N)$-matrix of connections between the neurons, θ is the common threshold of all neurons, Φ is the relative weight of inputs from inhibitory neurons, and β is the noise level in the threshold function. Neurons stay excitatory or inhibitory, respectively, for the entire simulation.

The state of a network at time t is a vector

$$\mathbf{z}^t = (z_1^t, \ldots, z_N^t) \tag{1}$$

where $z_i^t \in \{0, 1\}$, $1 \leq i \leq N$, $t = 0, 1, 2, \ldots$.

The network connectivity is given by

$$\mathbf{C} = \begin{pmatrix} c_{1,1} & \cdots & c_{1,NE} & c_{1,NE+1} & \cdots & c_{1,N} \\ \vdots & & \vdots & \vdots & & \vdots \\ c_{N,1} & \cdots & c_{N,NE} & c_{N,NE+1} & \cdots & c_{N,N} \end{pmatrix} \tag{2}$$

where $c_{i,j} \geq 0$ and $1 \leq i, j \leq N$ is the strength of the connection from neuron j onto neuron i. $\mathbf{C}$ is constructed by sharing $M \cdot N$ connection strength on $N \cdot N$ possible combination between all neurons that are initially in the network. The properties of different random connectivity matrices as starting conditions for the course of the compensation algorithm was extensively discussed by Dammasch and Wagner (1984). However, each synapse must be regarded rather as a value for the connectivity between two biological neurons and less as a single biological synapse. Anatomically it can be interpreted as the overlapping postsynaptic and presynaptic volume of two biological neurons which correlates with the probability for synaptogenesis between both cells (cp. van Ooyen et al. (2003)).

The membrane potential of neuron i at time t is

$$MP_i^t = \sum_{j=1}^{NE} c_{i,j} z_j^t - \Phi \sum_{j=NE+1}^{N} c_{i,j} z_j^t. \tag{3}$$

The probability of neuron i to be active in the next time instant is given by the threshold function

$$\text{prob}(z_i^{t+1}) = 1/(1 + \mathrm{e}^{(MP_i^t - \theta)/(-\beta)}). \tag{4}$$

If the noise level β approaches 0, the transition from network state $z(t)$ to its following state $z(t+1)$ is a deterministic function $z^{t+1} = f(z^t, \mathbf{C}, \theta, \Phi)$ with

$$z_i^{t+1} = \begin{cases} 1 & : \quad MP_i^t \geq \theta \\ 0 & : \quad \text{otherwise.} \end{cases} \tag{5}$$

For $\beta > 0$, the process is stochastic. It is assumed that the neuron can only change its state on a discrete time scale (Griffith, 1971).

In order to simulate external disturbances we add a percentage afference α to the network, shifting the firing probability of each neuron in each iteration step. This leads to a slightly altered probabilistic threshold function:

$$\text{prob}(z_i^{t+1}) = 1/(1 + \mathrm{e}^{(MP_i^t + \alpha - \theta)/(-\beta)}). \tag{6}$$

2.2. Modelling synaptogenesis in a recurrent network

In this section we summarize the underlying compensation algorithm for synaptogenesis (Dammasch et al., 1986). This algorithm is a formalization of the compensation theory of Wolff and Wagner (1983) that is derived from experimental findings (Spoerri & Wolff, 1981; Wolff, 1981) on synaptic reorganization. This concept later received support from other authors (cp. Dames, Joó, Fehér, Toldi, and Wolff (1985), Mattson (1988) and Lipton and Kater (1989)). According to the compensation theory (Fig. 1), high input activity leads to a decomposition of excitatory postsynaptic elements (cp. Mattson (1988)) and to an increased offer of inhibitory postsynaptic elements (Wolff & Wagner, 1983). Furthermore, highly activated cells begin to sprout free presynaptic offers (Jones, Rosser, & Bulloch, 1986). Inhibition, effecting low activity levels of a neuron, induces the opposite effects (Mattson & Kater, 1987). Even with respect to more recent work on structural plasticity and synaptic rewiring (Benýtez-Temiño et al., 2005; Cesa et al., 2005), the rather old experimental data, the compensation theory is based on, is still suitable to derive formal rules for activity-dependent morphogenesis of biological neural networks.

2.2.1. Morphogenetic states

Simulating synaptogenesis requires, besides a functional time scale modelling fast electro-physiological changes, a second, morphogenetic time scale for structural network reorganization. On a functional time scale the neuron's functional state — namely its membrane potential and its firing rate — varies over time but the structural state — namely the neuron's synaptic connectivity — stays constant. In each morphogenetic time step each neuron follows local rules (Palm, 1982) in order to compensate for long-term shifts of its input activity by structural adaptations. Consequently, each neuron's deviation from a desired medium average activity is called the neuron's morphogenetic state Δs_i which is computed for each cell i as follows:

$$\Delta s_i := s_i - 0.5, \quad \text{with } s_i := \frac{\sum_{t_0}^{t_0+\Delta t} \text{prob}(z_i^t)}{\Delta t} \text{ with } t_0, \Delta t \in \mathbb{N}, i = 1, \ldots, N. \tag{7}$$

2.2.2. Morphogenetic rules

In order to model synaptic reorganization, the excitatory and inhibitory pre- and postsynaptic offers (Table 1) must be represented separately. Synaptic offers also develop independently and must not necessarily be bound in synaptic junctions. According to the compensation algorithm, the sum of synaptic offers of the ith neuron is defined as σ_i and its change as $\Delta\sigma_i$. A label specifies the respective type of synaptic offers like σ_i^{bepo}, σ_i^{bipo}, σ_i^{fepo} or σ_i^{fipo}. Herein each letter indicates if synaptic offers are either bound (b) in synapses or free (f); further, either excitatory (e) or inhibitory (i); and finally, either postsynaptic (po) or presynaptic (pr). As all presynaptic offers of one cell are exclusively excitatory or inhibitory, sums over presynaptic free and bound elements are simply named σ_i^{fpr} and σ_i^{bpr}, respectively. Using these representations, the compensation algorithm offers a very detailed formalization of the observed synaptic processes by individual morphogenetic rules (Table 2). These rules depend on the morphogenetic state of a neuron Δs_i, the current structural state of the neuron

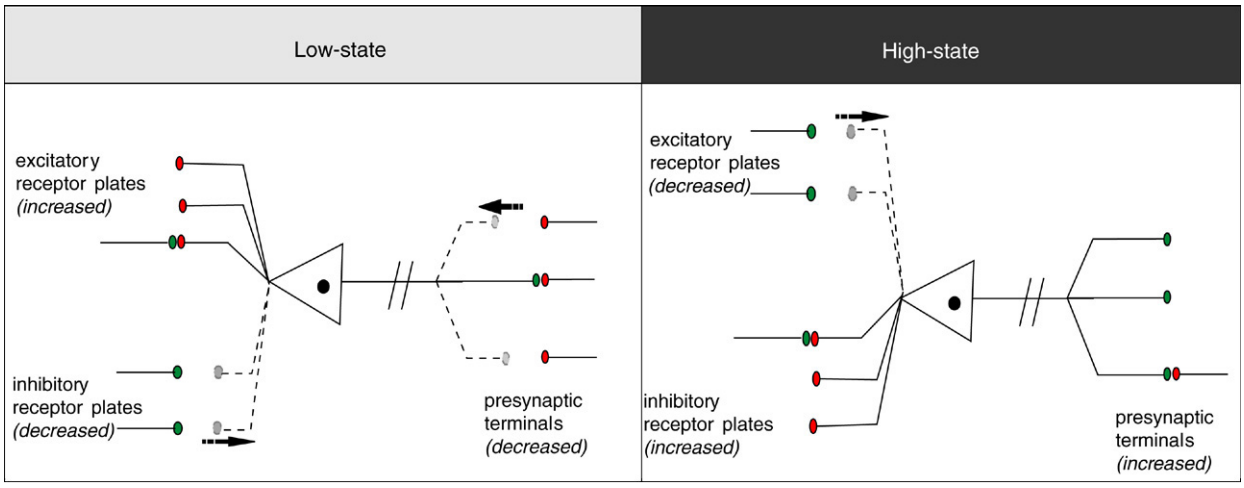

Fig. 1. Morphegenesis. The changes of the connectivity matrix are induced by adaptations of the pre- and postsynaptic connectivity pattern of each neuron. A shift of the neuronal mean activity leads to a tendency (morphogenetic state) to decrease or form different types of synaptic elements. The rules are different for cells with high mean activity (high-state cells) than for those with low mean activity (low-state cells).

Table 1
Synapse spectrum

	For all neurons $i = 1, \ldots, N$ we obtain:
$\sigma_i^{bepo} := \sum_{j=1}^{NE} c_{ij}$	Sum of excitatory synaptic input (bound excitatory postsynaptic elements)
$\sigma_i^{bipo} := \sum_{j=NE+1}^{N} c_{ij}$	Sum of inhibitory synaptic input (bound inhibitory postsynaptic elements)
$\sigma_j^{bpr} := \sum_{i=1}^{N} c_{ij}$	Sum of synaptic output (bound presynaptic elements). The effect of the entire output of a neuron is dependent on its type: either excitatory or inhibitory
σ_i^{fepo}	Sum of excitatory postsynaptic contact offers (free excitatory postsynaptic elements)
σ_i^{fipo}	Sum of inhibitory postsynaptic contact offers (free inhibitory postsynaptic elements)
σ_i^{fpr}	Sum of presynaptic contact offers (free presynaptic elements)
	The sums of free elements are initially set to zero.

The amount of pre- and postsynaptic elements of a neuron bound in a synapse is calculated by sums over columns and rows of the weight matrix C, respectively.

and also on the sensitivity of the cell to react with structural changes (named v as it defines the velocity of morphogenesis). The interplay of these rules has been intensively studied by Dammasch et al. (1988) and Cromme and Dammasch (1989).

2.2.3. Gradual changes

Gradual changes of the network connectivity are realized by reducing bound synaptic elements. A decay of presynaptic elements is distributed onto all contact partners proportionally to the strength of the existing connections:

$$c_{ij} := c_{ij} + \left(\Delta\sigma_j^{bpr} \cdot \frac{c_{ij}}{\sigma_j^{bpr}} \right) \quad \text{for all } c_{ij} \in \mathbf{C}. \tag{8}$$

Table 2
Morphogenetic rules

High-state neuron	Low-state neuron
$\Delta\sigma_i^{bpr} := 0$	$\Delta\sigma_i^{bpr} := -v \cdot \sigma_i^{bpr} \cdot \lvert\Delta s_i\rvert < 0$
$\Delta\sigma_i^{bepo} := -v \cdot \sigma_i^{bepo} \cdot \lvert\Delta s_i\rvert < 0$	$\Delta\sigma_i^{bepo} := 0$
$\Delta\sigma_i^{bipo} := 0$	$\Delta\sigma_i^{bipo} := -v \cdot \sigma_i^{bipo} \cdot \lvert\Delta s_i\rvert < 0$
$\Delta\sigma_i^{fpr} := v \cdot \lvert\Delta s_i\rvert > 0$	$\Delta\sigma_i^{fpr} := -v \cdot \sigma_i^{fpr} \cdot \lvert\Delta s_i\rvert \leq 0$
$\Delta\sigma_i^{fepo} := -v \cdot \sigma_i^{fepo} \cdot \lvert\Delta s_i\rvert \leq 0$	$\Delta\sigma_i^{fepo} := v \cdot \lvert\Delta s_i\rvert > 0$
$\Delta\sigma_i^{fipo} := v \cdot \lvert\Delta s_i\rvert > 0$	$\Delta\sigma_i^{fipo} := -v \cdot \sigma_i^{fipo} \cdot \lvert\Delta s_i\rvert \leq 0$

The changes of the synaptic spectrum $\Delta\sigma_i$ of each neuron are computed by the morphogenetic rules.

The loss of postsynaptic elements is computed for excitatory and inhibitory synapses individually according to the following equation:

$$c_{ij} := c_{ij} + \left\{ \begin{array}{ll} \Delta\sigma_i^{bepo} \cdot \dfrac{c_{ij}}{\sigma_i^{bepo}}, & j = 1, \ldots, NE \\ \underbrace{\Delta\sigma_i^{bipo} \cdot \dfrac{c_{ij}}{\sigma_i^{bipo}}}_{=:\delta_{ij}^{post} \leq 0}, & j = NE+1, \ldots, N \end{array} \right\}$$

$$\text{for all } c_{ij} \in \mathbf{C}. \tag{9}$$

The presynaptic element of a postsynaptically changed synapse is recombinable whereas the postsynaptic element vanishes. Therefore, previously bound presynaptic elements (equal to the amount of degraded postsynaptic counterparts $|\delta_{ij}^{post}|$) are transferred to the current amount of free presynaptic elements. The free synaptic elements are updated according to

$$\sigma_j^{fpr} := \sigma_j^{fpr} + \Delta\sigma_j^{fpr} + \sum_{i=1}^{N} |\delta_{ij}^{post}| \tag{10}$$

$$\sigma_i^{fepo} := \sigma_i^{fepo} + \Delta\sigma_i^{fepo} \tag{11}$$

Table 3
Overall offer of free contact elements in the network

$\Sigma^{fepo} := \sum_{i=1}^{N} \sigma_i^{fepo}$	Sum of free postsynaptic excitatory contact offers in the entire network.
$\Sigma^{fipo} := \sum_{i=1}^{N} \sigma_i^{fipo}$	Sum of free postsynaptic inhibitory contact offers in the entire network.
$\Sigma^{fepr} := \sum_{j=1}^{NE} \sigma_j^{fpr}$	Sum of free presynaptic excitatory contact offers in the entire network.
$\Sigma^{fipr} := \sum_{j=NE+1}^{N} \sigma_j^{fpr}$	Sum of free presynaptic inhibitory contact offers in the entire network.

The overall amount of free synaptic elements (Σ^{fepo}, Σ^{fipo}, Σ^{fepr}, Σ^{fipr}) is calculated for each type individually. We have to distinguish between excitatory and inhibitory pre- and postsynaptic offers when summing up over the entire net to ensure recombination between fitting synapse partners, only.

$$\sigma_i^{fipo} := \sigma_i^{fipo} + \Delta\sigma_i^{fipo} \tag{12}$$

for all pre- and postsynaptic cells $i, j = 1, \ldots, N$.

2.2.4. Recombination

New synaptic contacts as well as strengthening of existing synapses originate from a recombination of free synaptic contact offers. The more free contacts a neuron contributes to the network, the larger the amount of fitting contact partners it is allocated in one morphogenetic step. A minor offer of free synaptic elements was proportionally distributed to a larger demand of free possible contact partners. Therefore, the total sums of the different types of synaptic offers in the entire network were counted. According to Table 3, the total sums of free (f), excitatory (e) or inhibitory (i) elements that can either be postsynaptic (po) or presynaptic (pr) were labelled by Σ^{fepo}, Σ^{fipo}, Σ^{fepr} and Σ^{fipr}, respectively. The recombination was achieved by

$$c_{ij} := c_{ij} + \left\{ \begin{array}{ll} \dfrac{\sigma_j^{fpr} \cdot \sigma_i^{fepo}}{\max(\Sigma^{fepo}, \Sigma^{fepr})}, & j = 1, \ldots, NE \\ \underbrace{\dfrac{\sigma_j^{fpr} \cdot \sigma_i^{fipo}}{\max(\Sigma^{fipo}, \Sigma^{fipr})}}_{=:\gamma_{ij}^{free} \geq 0}, & j = NE+1, \ldots, N \end{array} \right\} \geq 0 \tag{13}$$

with $i = 1, \ldots, N$.

Subsequently, we have to update the amounts of free synaptic elements that are left over after recombination whereby γ_{ij}^{free} refers to those free synaptic elements that were recombined to synapses. Thus, this value has to be subtracted from current free synaptic offers as they are now regarded as bound synaptic elements. If there were fewer presynaptic than postsynaptic contact offers, we simply set the amount of free presynaptic elements to zero:

$$\sigma_j^{fpr} := 0 \quad \text{for} \quad \begin{cases} \Sigma^{fepr} \leq \Sigma^{fepo} & \text{if } j = 1, \ldots, NE \\ \Sigma^{fipr} \leq \Sigma^{fipo} & \text{if } j = NE+1, \ldots, N. \end{cases} \tag{14}$$

If the opposite is the case, the new amount of free presynaptic elements is computed by the following equation:

$$\sigma_j^{fpr} := \sigma_j^{fpr} - \sum_{i=1}^{N} \gamma_{ij}^{free}, \quad j = 1, \ldots, N. \tag{15}$$

The postsynaptic contact offers must be treated separately for excitatory and inhibitory elements:

$$\sigma_i^{fepo} := \begin{cases} 0 & \text{if } \Sigma^{fepo} \leq \Sigma^{fepr} \\ \sigma_i^{fepo} - \sum_{k=1}^{NE} \gamma_{kj}^{free} & \text{else.} \end{cases} \tag{16}$$

$$\sigma_i^{fipo} := \begin{cases} 0 & \text{if } \Sigma^{fipo} \leq \Sigma^{fipr} \\ \sigma_i^{fipo} - \sum_{k=NE+1}^{N} \gamma_{kj}^{free} & \text{else.} \end{cases} \tag{17}$$

2.3. Modelling CP and apoptosis in a network with synaptogenesis

In order to simulate neurogenesis, we have recently extended the compensation algorithm described in the previous section so that it now works on a growing cell number. Moreover, the rate for ingrowing neurons and a rule for apoptosis were defined. The simulation starts with an initial set of N' neurons of which NE' are excitatory. The network can hold a maximum number of N, respectively NE, excitatory neurons. N, the CP rate and the length of a simulation must be chosen so that this mark is not exceeded.

2.3.1. Modifications of the compensation algorithm

To realize varying cell numbers in a McCulloch–Pitts network, we simply extended the connectivity matrix by lines and columns of zeros according to Fig. 2 as placeholders for synapses of neurons which have not been embedded yet. In order to avoid changes of zero-weights among nonexistent neurons, a vector of N binary elements is defined:

$$\textbf{Cells} := (cells_1, \ldots, cells_N) \quad \text{with } cells_i \in \{0, 1\} \tag{18}$$

where

$$cells_i := \begin{cases} 1 & \text{if the cell exists} \\ 0 & \text{if the cell does not exist.} \end{cases} \tag{19}$$

All morphogenetic values are simply multiplied with this binary value of the existence of a cell whereby a zero product (in the case of a non-existing or apoptotic cell) does not induce any morphogenetic change.

2.3.2. Modelling CP by adding new cells

Inside the hippocampal DG, a wealth of influencing factors have a direct or indirect impact on CP, thereby varying the number of ingrowing cells as we have reviewed in another paper (rev. in Lehmann, Butz, and Teuchert-Noodt (2005)). However, systemic factors changing CP rates do not necessarily depend on the current stimuli flow. Thus, it is legitimate to choose the rate of CP as a constant even though the

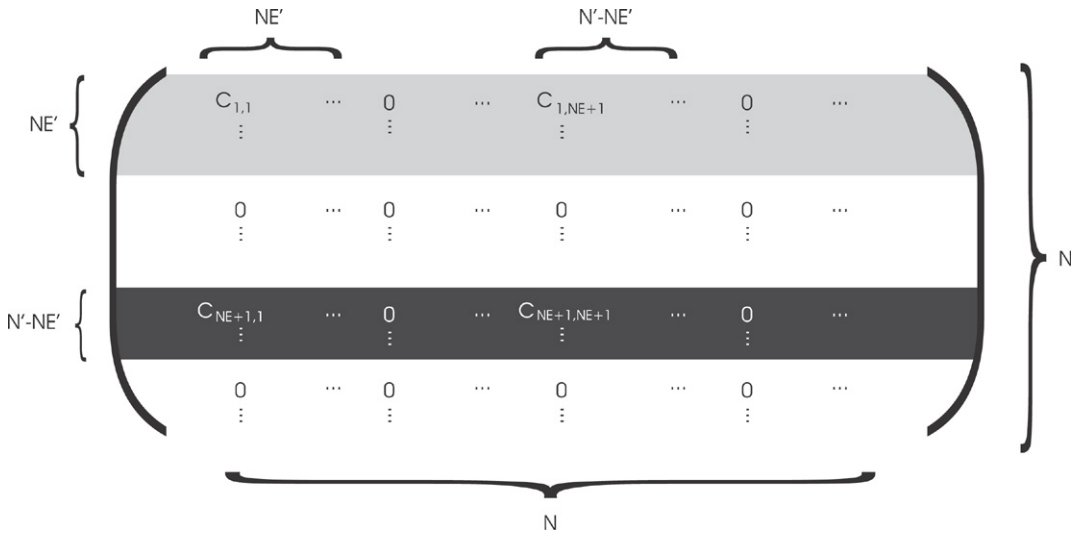

Fig. 2. Extended connectivity matrix. The initial connectivity matrix is shaped according to this scheme. The network initially contains N' neurons of which NE' are excitatory. The maximum number of neurons in the network is given by N and NE for all and just the excitatory neurons, respectively. Each line holds the strengths of the neuron's postsynaptic inputs. The columns hold the presynaptic outputs. The zero rows and columns are placeholders for new neurons' synaptic contacts to be formed during a simulation.

interdependences of CP in the biological network are rather complex. A set of simulations are made to study the effects of different CP rates. To add a new cell at the ith position, the ith entry of the **Cells**-vector is set to 1. A new cell is endowed with a set of free postsynaptic offers as follows:

$$\sigma_i^{fepo} = M \cdot \frac{NE'}{N'} \tag{20}$$

$$\sigma_i^{fipo} = M \cdot \frac{N' - NE'}{N'}. \tag{21}$$

M is the initially expected number of connections of one of the first N' neurons which can be derived from the initial connectivity matrix $\mathbf{C}$ (cp. Sections 2.1 and 2.4). The available postsynapses on a new neuron are divided into excitatory σ_i^{fepo} and inhibitory offers σ_i^{fipo} with the same proportion as there are excitatory (NE') and inhibitory neurons ($N' - NE'$) in the network at the beginning of the simulation. Presynaptic offers develop according to the morphogenetic rules (Table 2). However, the number of realized connections with this neuron depends on the amount of fitting contact partners and the ongoing synaptic reorganization. In order to develop their synapse strengths according to their needs, ingrowing neurons are prevented from apoptosis for 30 morphogenetic steps.

2.3.3. Modelling apoptosis by deleting cells

Modelling apoptosis is a novelty compared to the compensation algorithm by Dammasch et al. (1986) in so far as the simulation does not only drive neurons to a medium activity level by synaptic processes but also defines a corridor of activity which is relevant for the cells' survival. The apoptosis criteria are based on the calcium set-point hypothesis (Franklin & Johnson, 1992). According to this, cells undergo apoptosis if their intracellular calcium concentration is substantially below resting levels or severely increased. The calcium concentration inside a cell is, in turn, directly correlated to the membrane potential and the neuronal activity level, respectively. Asymmetrical borders for the desired range of activity of s_i with $0.25 < s_i < 0.85$ are most suitable to keep the network stable. These borders are biologically plausible with respect to the calcium set-point hypothesis. A firing probability of $s_i = 0.25$ is only reached if the cell is inhibited and, thus, below its resting potential and its resting level of intracellular calcium, respectively. A value of s_i beyond 0.85 corresponds to an extremely high level of synaptic input and an expected high level of calcium in the cell. Neurons which fail to stabilize their activity level undergo apoptosis. For established neurons, it is checked in every morphogenetic time step (after 30 steps for ingrowing neurons) whether its average activity is in a given interval.

In each of these cases, the neuron is deleted by switching one position of the **cells**' vector, bitwise, marking the existence of each neuron:

$$cells_i := \begin{cases} 1 & \text{if } 0.25 < s_i < 0.85 \\ 0 & \text{else.} \end{cases} \tag{22}$$

By deleting the ith cell, the involved synapses are also deleted. According to the compensation algorithm, the presynaptic cells keep their free elements and can recombine them, whereas disconnected postsynaptic elements are lost:

$$\sigma_j^{fpr} := \sigma_j^{fpr} + \sum_{j=1}^{NE} c_{ij} \quad \text{for all } i \text{ with } cells_i = 0. \tag{23}$$

The role of nerve growth factors for cell survival goes beyond the scope of this work as the model focusses on homeostatic plasticity rather than molecular processes. However, possible extensions of this model are the ingrowth of inhibitory neurons and different apoptosis criteria which may lead to a more complex structural dynamic.

2.4. Simulation runs

A common network configuration was chosen for all simulation runs. By two simulation approaches we analysed the dependence of synaptogenesis as well as cell survival on both CP and afferent activity.

2.4.1. Common network configuration

An initial number of $N = 30$ cells was chosen of which $NE = 27$ are excitatory and the rest inhibitory. The implementation allows networks that are able to hold a maximum number of 400 cells. Initially, 600 weights were distributed onto 900 possible positions of the weight matrix, which corresponds to an expected number of $M = 20$ synaptic connections per neuron. The initial synaptic strength is a normal distributed random value around one (cp. Dammasch and Wagner (1984)). Further parameters were set to $\theta = 1$, $\Phi = 8$ and $\beta = 2$. The influence of the chosen parameters on the network dynamic and on the course of morphogenetic changes was extensively studied by Dammasch et al. (1988) and Cromme and Dammasch (1989). The compensatory effect is a generic property of the compensation algorithm which is rather robust against changes in the parameter set. However, the right parameter configuration ensures keeping the network stable and allows for a smooth run of morphogenetic changes.

2.4.2. Simulation approach for estimating synaptogenesis

In order to quantify synaptogenesis in networks with CP, the average amount of synthesized synapses on one neuron in each time step was quantified within an appropriate time frame (300, 1000 or 3000 simulation steps) depending on the proliferation rate. In the first set of simulations (with no afferent activity) $CP = \{1{:}50; 1{:}30; 1{:}20; 1{:}10; 1{:}5; 1{:}3; 1{:}2; 1{:}1\}$ and in a second set $\alpha = \{-0.2; -0.15; -0.1; 0; 0.1; 0.2; 0.3; 0.4; 0.5\}$ hold as independent variables. Values for α stronger than 0.5 totally determine the effect of a functional network dynamic and make the cell's morphogenetic changes independent of its current excitation level. Furthermore, the compensation algorithm is not symmetric concerning the toleration of an external afference *(unpublished results)*. Excitatory afferences are compensated up to 50% whereas an external inhibition of more than 15% leads to morphogenetic effects destroying the network.

For the latter simulation set we subsequently used networks with low ($CP = 1{:}30$), moderate ($CP = 1{:}10$) and high ($CP = 1{:}1$) CP rates. This approach was also used to estimate the dependence of synaptic regression on CP and afferent activity.

2.4.3. Simulation approach for estimating cell survival

In order to study the effect of CP and afferent activity on the cell survival, two independent variables, namely, $CP = \{1\ cell{:}50\ steps; 1{:}30; 1{:}20; 1{:}10; 1{:}5; 1{:}3; 1{:}2, ; 1{:}1\}$ and afferent activity $\alpha = \{-0.2; -0.15; -0.1; 0; 0.1; 0.2; 0.3; 0.4; 0.5\}$ were chosen so that each combination of CP and α was one single trial. To estimate the dependence of cell survival on CP and afferent activity, the percentage of surviving cells was measured at the end of each simulation.

3. Results

First of all, the simulation results confirm the former work of Dammasch et al. (1986) as the compensation algorithm balances the neuronal activity of each cell (Fig. 3(a), (b)). This generic effect is also obtained in a network with proliferating cells (Fig. 3(c), (d)). Even a disturbing afference is compensated (Fig. 3(e), (f)) so that the firing probability of old and new neurons develop towards a medium value. This functional effect is achieved by an ongoing synaptogenesis among pre-existing and proliferating cells and also by apoptosis. For analysing the obtained results, we have to precisely differentiate between pre- and postsynaptic effects causing particular morphogenetic network properties.

3.1. Synaptogenesis depending on CP

The question is to what extent CP influences synaptogenesis in the simulation model as ingrowing neurons compete with other unbalanced neurons for synaptic contact partners. According to Fig. 4, new cells amplify the synthesis of synapses in an existing network; each time a new cell occurs, there is a peak in synaptogenesis. However, synaptogenesis decreases during the course of morphogenesis, i.e. that the amplitude of peaks indicating high synaptogenesis in one morphogenetic step are higher in the beginning of a simulation run than those which appear at later stages of the simulation. Comparing Fig. 4(a) with (b) shows a ten times steeper decay in synaptogenesis for a high CP rate (one cell per one morphogenetic time step) than for a medium proliferation rate (one cell per ten time steps). The rate of synaptogenesis reaches a stable level above zero within a larger time frame.

3.1.1. Development of postsynapses

This morphogenetic development implies a decreasing offer for new (excitatory) neurons of fitting postsynaptic contact partners in the pre-existing network. The amount of free excitatory postsynapses, in turn, depends on the number of neurons currently on a low state needing more activating input. In other words, the decay in synaptogenesis is also caused by the fact that the model network gets balanced over time. After several hundred morphogenetic time steps, stabilized neurons offer fewer free postsynaptic elements than in the beginning of the simulation when homeostasis is not yet achieved. By occupying free (excitatory) postsynaptic elements, moderate rates of ingrowing neurons are sufficient to stabilize the membrane potential of other cells in the network. Thus, up to a certain degree, CP accelerates structural compensation of the network's neural activity. On the other hand, a certain imbalance of neuronal activities is a precondition for a new cell to be well embedded.

3.1.2. Development of presynapses

The afferent support that new cells can get is dependent on the overall amount of free presynaptic terminals available in the old network and provided by new neurons. In the model in general, free terminals result either from an activity-dependent synaptic growth or from a turnover. However,

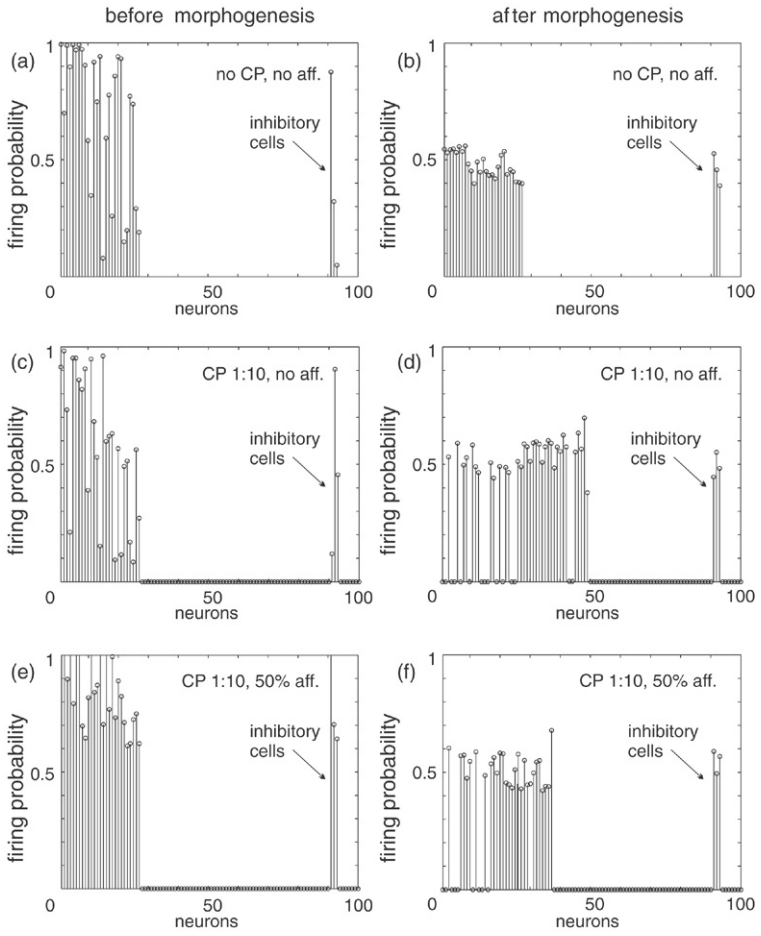

Fig. 3. Firing probabilities. The diagrams show the average firing probability s_i of each neuron being currently in the model network before and after morphogenesis. Three different settings are displayed. (a), (b) A network without CP and without any external afference develops over 300 morphogenetic time steps into a homoeostatic state where all neurons have a medium firing probability of 50%. (c), (d) The algorithm used has the same compensatory effect on a network with a variable number of neurons (CP rate: 1:10). Cells that have recently grown in show a certain degree of disbalance that has still to be compensated. Empty positions can be occupied or re-occupied, respectively, by ingrowing excitatory neurons. (e), (f) The firing probability of neurons facing a high, 50% excitatory afference is shown. The CP rate is the same as in the simulation (c) and (d) but more cells became apoptotic. Consequently, the resulting number of neurons in the network is lower than in (c) and (d).

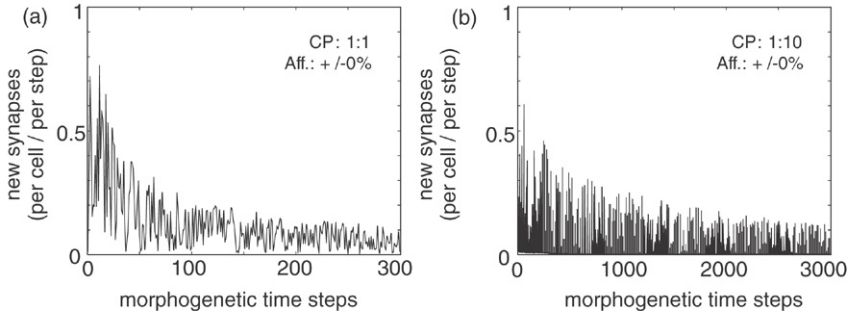

Fig. 4. Synaptogenesis. The figure shows the average amount of new formed synapses per cell in each morphogenetic step. Obviously, these are no countable volumes of synaptic contacts but rather a measure for additional connectivity a cell has gained. Compared to the initial connectivity of each neuron that follows a Gaussian distribution around one, the diagrammed synaptogenesis results can be regarded as a percentage value of the cell's initial connectivity. (a) Simulation run with a high rate of CP (1:1) and no external afference. (b) Simulation run with a moderate CP rate (1:10) and no afference. Two different time scales on the abscissa have been used for both diagrams to show a comparable course of different CP rates in respective time frames.

excitatory presynapses increase with proliferating excitatory neurons, whereas the number of inhibitory neurons providing presynaptic offers is fixed. Of course, the more cells are sharing the current amount of available presynapses, the more quickly this offer is exhausted.

3.1.3. A bottle-neck for inhibition

It is the current opinion in neuroscience that proliferating cells in the dentate gyrus (DG) predominantly develop into excitatory neurons. Thus, it is also an interesting theoretical question to what extent a fixed number of inhibitory neurons

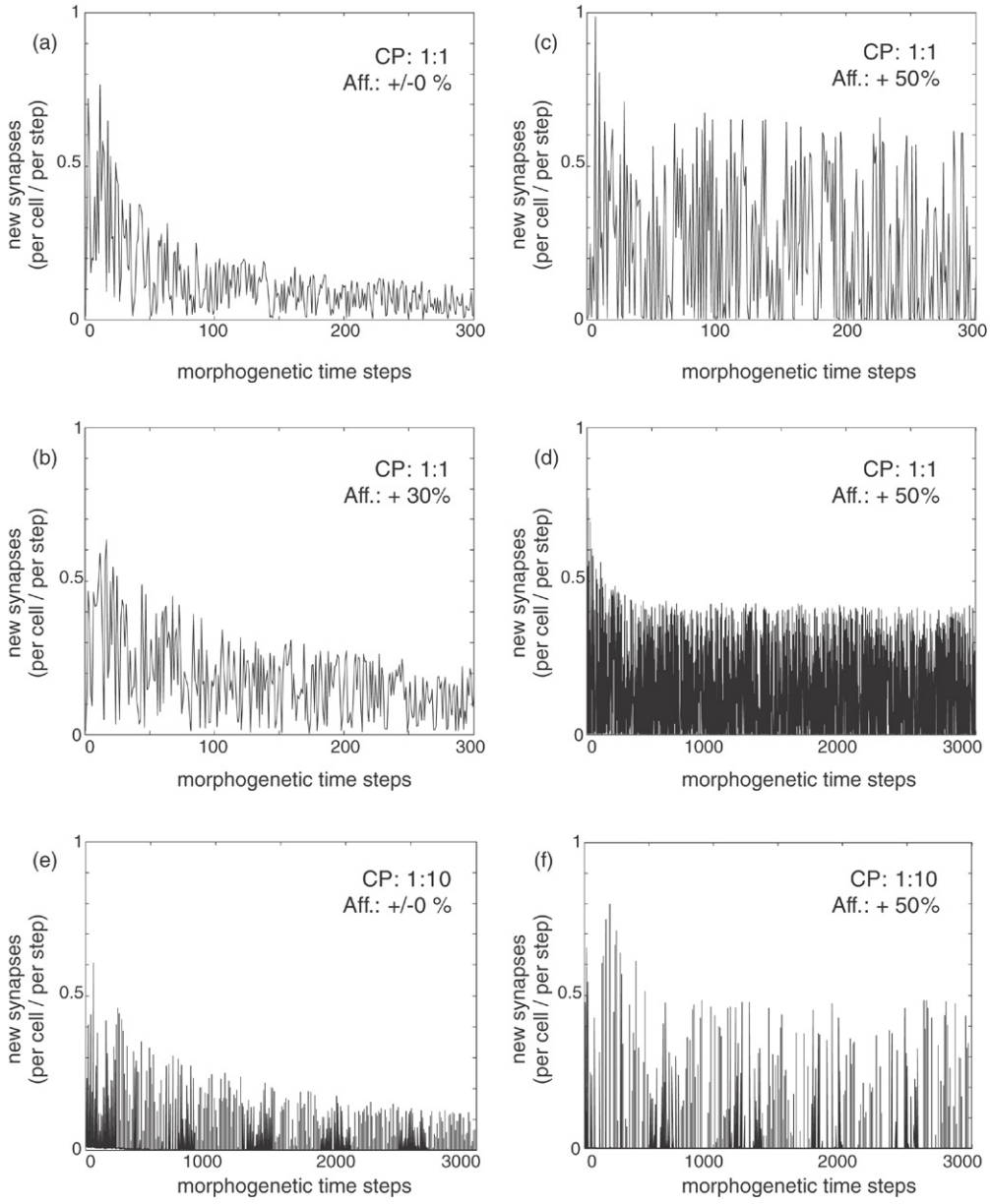

Fig. 5. Synaptogenesis under an external afference. Comparable to Fig. 4, synaptogenesis has been plotted over time under different conditions. (a)–(c) A set of increasingly strong afferences (±0, +30, +50) impinges on a network with a CP rate (1:1). A rather short time frame (up to 300 steps) allows us to focus on initial effects. (d) The results of the same setting as (c) but in a ten times larger time frame which reveals a strongly increased stable level of synaptogenesis. (e)–(f) Simulation runs with a moderate CP rate (1:10) plus zero and 50% external afference, respectively.

with their contact offers is sufficient to stabilize a growing number of excitatory cells. The model is based on local rules only, so that an increasing demand of inhibition will not directly increase the offer. However, a rising network activity due to an increasing number of excitatory cells induces sprouting also of inhibitory presynaptic elements (cp. Section 3.2) though this process might not be fast enough to cope with the ongoing CP. Fig. 6, in fact, reveals a dramatic breakdown in forming new inhibitory synapses in the course of simulation which affects not only ingrowing neurons but all neurons in the entire network. According to this, the beneficial effect of an increasing activity leading to a surplus in presynaptic offers is quickly swept off by the growing cell number. Consequently, in the simulation the available inhibitory offers are a decisive factor for the survival of unbalanced neurons (cp. Section 3.4).

3.2. Synaptogenesis depending on afferent activity and CP

A recurrent network without any external afferences — as used in the previous section — is a rather non-physiological situation as neural networks are always affected by afferent activities caused by sensory stimuli or afferent projections from other parts of the brain. Thus, in the model an excitatory afference is defined that shifts the neuronal firing probability by a constant value. Studying the course of synaptogenesis (Fig. 5), for high rates of CP (a)–(d) and medium rates (e) and (f) reveals that a disturbing afference keeps synaptogenesis

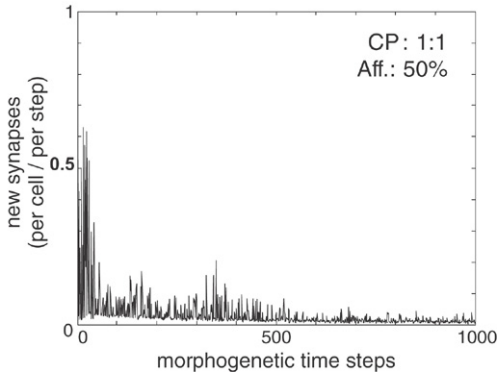

Fig. 6. Synaptogenesis of inhibitory contacts. Comparable to Figs. 4 and 5, synaptogenesis has been plotted over time but for inhibitory synapses, only. A time frame of 1000 morphogenetic steps is sufficient to demonstrate the rapid decay in synaptogenesis of inhibitory contacts.

on a high level. The enhanced synaptogenesis is carried by two factors. First, according to the morphogenetic rules, an increased excitatory afferent activity leads to a surplus of presynaptic offers that are available for ingrowing neurons. Second, increasing apoptosis is accompanied by a breaking of synapses which is a source for further free synaptic elements available for recombination. According to Fig. 5(d), (f) the simulation even preserves this situation for high and medium proliferation rates over a larger time frame. A high turnover caused by apoptosis is also the reason for slightly increased synaptogenesis in networks affected by a slight inhibition. However, stronger inhibitory afferences effect the regression of presynaptic elements which lowers synaptogenesis considerably.

3.3. Synaptic regression depending on afferent activity and CP

Regressive events (Cowan, Fawcett, O'Leary, & Stanfield, 1984) play an important role in selectively modifying neural network functions. Thus, the relationship between CP/apoptoses and synaptic regression was addressed by these recent simulations. Networks without CP respond with an increased synaptic decay on severe excitatory disturbances (Fig. 7(a), (b)) which is a consequence of the morphogenetic rules (cp. Section 2.2.2). In contrast, simulations with CP and apoptosis do not show a compensatory increased loss of synapses (Fig. 7(c)) — apart from apoptotic neurons losing their synaptic contacts — because neurons that are far outside medium activity levels are deleted. Obviously, a replacement of inadequately connected and thereby hypo- or hyperexcited neurons is an additional and in simulations a quicker way to bring the network in balance. Thereby, the network efficiently safes itself against far over-excited neurons that may also disturb already stabilized cells and prevents them from a compensatory synaptic regression. As the simulation reveals, this compensation process in fact converges towards a medium activity level of all cells. In contrast, afferent inhibition increases synaptic regression also in networks with CP.

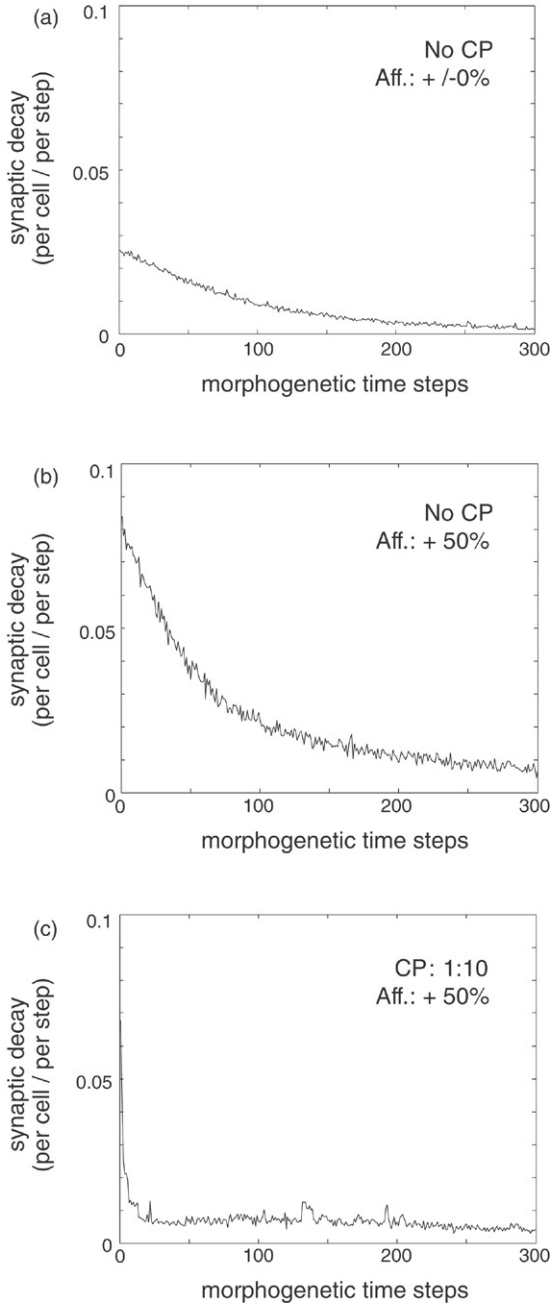

Fig. 7. Synaptic decay. The diagrams show the compensatory degradation of established synapses, on average for one neuron, over time. (a) Simulation without cell turnover (=constant number of neurons) and no external afference. (b) As (a) but with a strong external afference (+50%). (c) Simulation with a moderate CP and a strong afference (+50%). A loss of synapses caused by apoptosis is not taken into consideration.

3.4. Cell survival as a function of CP and activity

Basically, an increased CP does not necessarily mean a greater number of neurons in the network model. Fig. 8 shows neurogenesis as a function of CP and afferent activity. Without any external afference, the survival rate of all cells in the network averages between 60% for low proliferation (one new cell in every 50th step) and 70% for a high proliferation (one new cell in each step). With a difference of only 10%, survival

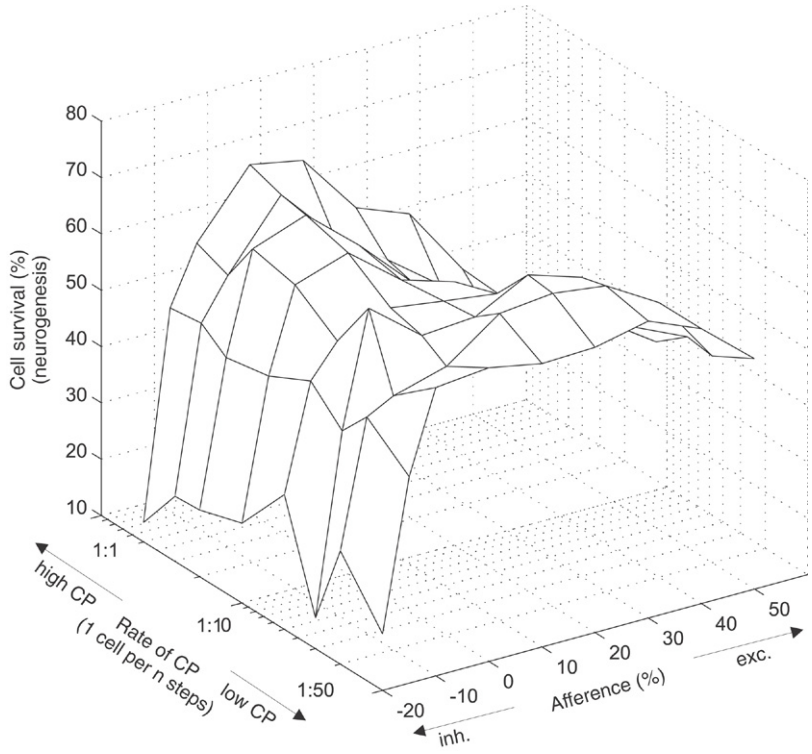

Fig. 8. Cell survival. Notated are the values of a percentage afference on the $x1$-axis and the rate of cell proliferation (measured in one cell per n morphogenetic steps) on the logarithmic $x2$-axis. The $x3$-axis shows the percentage value of the amount of survived cells after a run with 300 morphogenetic steps. In a first approximation to a certainly more complex interdependence, the rate of survived cells (neurogenesis) can be modelled as a function of cell proliferation and afferent activity. Moderate afferences are well compensated by a low cell proliferation, whereas the same afferences lead to a significantly decreased rate of surviving cells if the rate of cell proliferation is high.

rates stay remarkably stable under a changing CP rate from 1:50 to 1:1. An external afference interferes with the network in two different ways depending on the rate of CP. If CP is rather low (CP rate up to 1:20), afferent activity shows only little effects on neurogenesis: in this case, still more than 60% of all cells survive permanent shifts of their activity between -10% and $+40\%$. A moderate excitatory afference can even increase cell survival, as the gently inclined plateau of the three-dimensional landscape for low CP rates indicates. For higher rates of CP the landscape turns into a narrow ridge with a maximum line along zero afference. As these simulations reveal, an overreaching CP leads to network disturbances that impair the network's ability to compensate for interfering external afferences. In the case of high CP rates (above 1:10), even a moderate afference leads to a significantly decreased cell survival.

The statistical analysis performed with a two-way analysis-of-variance test (two-way ANOVA, Matlab, version 6.5) revealed that the curves in both dimensions (CP and activity) differ from each other with high significance (columns of CP: $p < 0.0001$; rows of activity: $p = 0.0001$; interaction between rows and columns: $p < 0.0001$).

3.4.1. Network instability due to increased excitation

What causes these disturbing effects of high CP rates in the theoretical model? There are basically two sources of disturbances associated with an increased CP — a functional and a structural one. First, with a rising proportion of excitatory to inhibitory neurons, the overall network activity enhances. This proportion shifts the faster, the more neurons grow in. Second, according to the previous subsections, there is a competitive situation among ingrowing neurons that is generally reached by sharing a minor amount of contact offers onto appropriate contact partners proportionally. However, if the CP rate is moderate, the morphogenetic effect is rather low but rises dramatically when the ingrowth of new cells exceeds a critical mark. This mark is reached when the offer of free synaptic elements of new cells is larger than the amount of counterparts in the whole network. In this case, the ingrowing neurons quickly exhaust the entire amount, in particular, of available inhibitory synaptic elements. As a consequence of an increasing activity and a limited amount of inhibitory support, the network turns to be instable. As synaptic reorganization in this network situation is not sufficient to compensate also for an additional excitatory afference, rates of apoptosis strongly increase.

3.4.2. Network instability due to increased inhibition

Attention should be paid to the aspect that the three-dimensional curve is not symmetric; an inhibitory afference of -20% leads to a cell survival of less than 30% for all rates of CP, whereas positive afferences up to 20% do not lead to comparable loss in cell survival. Thus, afferent inhibition is a critical influence for this type of model network as low-state cells reduce their presynaptic contacts. Then, there is no intrinsic activity enhancer that could compete with the external inhibition.

4. Discussion

The investigated network model features an ongoing remodelling of its connectivity pattern by CP, apoptosis and synaptogenesis. Neurogenesis, in terms of the percentage of surviving cells, depends on the rate of CP and also on the current network activity. The role of CP is twofold. On the one hand, CP helps to compensate disturbing input and enhances the synaptogenesis in the network up to certain levels. On the other hand proliferating cells themselves have a disturbing effect on the network, dramatically perturbing the whole network if the number of ingrowing cells exceeds a critical value. In this case, the model network fails to buffer an external afference and, as a consequence thereof, a severely increased number of cells undergo apoptosis. The simulation reveals that neurogenesis must not only be seen in a computational context, i.e. the benefits for memory capacities of a neural network, but also has an important homeostatic aspect. The theoretical results are now discussed in an experimental context.

4.1. Homeostatic plasticity as a key to cell survival

Synaptic reorganization never ceases in the adult nervous system, raising the question whether it might be a key mechanism to both challenge and enable homeostasis by adding further degrees of freedom to neural plasticity. Experimental work has recently confirmed in vivo that spines and synaptic junctions are indeed constantly rebuilt even in the mature brain (Grutzendler et al., 2002; Trachtenberg et al., 2002). Although this synaptic remodelling decreases with age in the cortex (Grutzendler et al., 2002), ongoing synaptogenesis and even neurogenesis of an early ontogenetic development is conserved in the DG (Dawirs et al., 1992, 2000) throughout life. Synaptogenesis and CP interact in the DG as cells need afferent supply to rule their level of activity in order to prevent apoptosis (Linden, 1994). The simulation reveals that a sufficient presynaptic offer, which can be enhanced by an external afference, activates new neurons and increases their chances for survive. In good accordance with the presented theoretical results, it has been shown that depolarization enhances the survival of several neuronal populations in vitro (Bennett & White, 1981; Gallo et al., 1987; Larmet et al., 1992). However, the molecular signal cascades underlying the calcium set-point hypothesis (Franklin & Johnson, 1992) which draws a link between activity and apoptosis have still to be uncovered in detail. So far, calcium as well as an "activity-dependent neurotrophic factor" have been reported to be important players in this regulation.

4.2. Stabilizing effect of CP

CP in a neural network enhances learning (Chambers et al., 2004), seems to be a prerequisite for hippocampal learning (Hodges et al., 1998; Madsen et al., 2003; Shors, Miesegaes, Beylin, Zhao, & Gould, 2001; Shors, Townsend, Zhao, Kozorovitskiy, & Gould, 2002) and correlates with certain learning abilities (Drapeau et al. (2003), but see also Merrill, Karim, Darraq, Chiba, and Tuszynski (2003)). But from a biological point of view, increasing CP only makes sense if it allows more neurons to acquire a position in the network. Thus, we have measured the quality of morphogenesis in terms of cell survival (neurogenesis). Our results imply, for biological networks, that there are two divergent paths leading to higher survival rates compared to baseline conditions: either CP rates are kept low with increasing excitatory afferences, or they may be raised when the afferences remain at baseline level. The two strategies exert opposing effects onto the network, for which reason we dub them *stabilizing* vs. *destabilizing CP*.

According to a *stabilizing CP*, low CP rates leads to an effective bounding of new neurons even under disturbing afferences. The explanation for the compensatory effect of new neurons under such conditions must be seen in the extra-offer of synaptic elements they add to the existing network. This is in accordance with experimental findings in proliferating hippocampal cells (sprouting axons: Stanfield and Trice (1988) and Hastings, Seth, Tanapat, Rydel, and Gould (2002); postsynaptic elements: Carlén et al. (2002) and Lu, Jones, Snyder, and Tuszynski (2003)). The additional offer of presynaptic contacts can be used by old cells to satisfy their demand of binding partners and may prevent them from cell death (Cunningham et al., 1979). This prevents the network from a loss of established synapses and a pathologic reconstruction of the connectivity pattern as can be seen, for instance, in the prefrontal cortex (Butz & Teuchert-Noodt, 2006). Thus, it can be assumed that the organism lowers CP rates during high perforant path activity to achieve a stabilizing CP. This prediction is supported by many classical studies (Bernabeu & Sharp, 2000; Cameron, McEwen, & Gould, 1995; Gould, McEwen, Tanapat, Galea, & Fuchs, 1997; Nacher et al., 2001). Furthermore, different experimental results (Cameron, Tanapat, & Gould, 1998; Reymann & Ott, 1983; West & Deadwyler, 1980) point to an increased perforant path activity during stress. Consequently, stress also attenuates the mitotic activity in the DG (Coe et al. (2003), Galea, Kavaliers, and Ossenkopp (1996), Gould et al. (1997) and Tanapat, Galea, and Gould (1998), rev. in McEwen (1999)). Beyond mere network stabilization, even an increase in cell survival can be achieved under conditions when CP rates are kept low and new information to be learnt provides the DG with an excitatory input. This is the case in the paradigms of enriched rearing and housing, spatial learning tests and mossy fibre stimulation (Brown et al. (2003), Derrick, York, and Martinez (2000), Gould, Tanapat, Hastings, and Shors (1999), Keller, Bagorda, Hildebrandt, and Teuchert-Noodt (2000), Kempermann, Kuhn, and Gage (1997), Nilsson, Perfilieva, Johansson, Orwar, and Eriksson (1999) and rev. in Lehmann et al. (2005)).

4.3. Destabilizing effect of CP

Whereas a moderate appearance of new cells shows a compensatory effect, an overreaching CP induces disturbances in the hippocampal network (cp. Teuchert-Noodt (2000)). This leads to destabilizing structural as well as functional effects

— i.e. to a *destabilizing CP*. Even before cells form synapses they exert a morphogenetic influence on the other neurons. Like in ontogeny, young cells in the adult DG compete for possible targets (Wolff, 1982). Guided by neurotrophins, their outgrowing axons try to occupy a limited number (O'Leary & Cowan, 1984) of free postsynaptic receptor sites (Davies et al., 1987). The neuron population is pruned as an outcome of competitive interactions among developing axons and dendrites on the level of their targets and afferent support (rev. in Linden (1994)). External activity interferes with this intrinsic competitive network development by inducing compensatory structural compensations and even apoptosis. The worst case appears when the whole network degenerates, which can be seen as a model for epilepsy: a massive over-excitation of the hippocampus enforces a dramatically increased cell loss in the DG (Parent et al., 1997) while destroying virtually the whole ammon's horn (Magloczky et al., 2000). The simulation model is not merely sensitive to overstimulation but also degenerates under a strongly depressive afference even with rather low CP rates. This correlates well to the results of post-mortem studies of depressive patients, where a long-term reduction of excitatory input via the perforant path, combined with a reduced CP rate, causes lower cell numbers in the DG (Jacobs, 2002; Sheline, Gado, & Kraemer, 2003).

4.4. Efficiency of CP

The survival of neurons is possibly not the only criterion for a successful CP. The offer of new synapses that proliferating cells contribute to the network can be seen as a second measure for the efficiency of CP. In fact, the model implies also for biological neural networks that an increase in CP enhances synaptogenesis up to a critical value and thereby facilitates synaptic plasticity being relevant for learning processes. Thus, a medium proliferation rate seems to be the preferable choice for dentate networks as the compensatory effects are sufficient and their disturbing influences are negligible. However, the CP rate is dependent on systemic factors that are not directly linked to the actual functional stimuli processing (Lehmann et al., 2005). In fact, the neural system has to predict the stimuli flow for a specific latency period of one to two weeks until new neurons are integrated synaptically (Hastings & Gould, 1999; van Praag et al., 2002). Firstly then, changes in CP rates become effective. This is particularly important for neural networks that have a multimodal sensory interface like the DG and thus need permanently a massive compensatory reorganization (cp. Cecchi, Petreanu, Alvarez-Buylla, and Magnasco (2001)). From this point of view, our theoretical data imply that cell turnover combined with synaptic turnover should be an effective strategy for compensating neuronal activity disbalances and to maintain a synaptic continuity among established and well balanced neurons. Thereby, cell turnover is, at least in simulations, a faster compensation mechanism than synaptic reorganization, which may become necessary when a neural network is affected by especially strong or complex afferences. Our hypothesis is that downstream networks, i.e. in the hippocampal CA1-region, show no need for such a material-consuming compensation mechanism like cell turnover in the DG. On the one hand, they already receive a filtered input and on the other hand, simulations suggest that new neurons are hard to embed into stabilized networks.

5. Conclusions and future perspective

There is a conflict between enhancing plasticity for openness to novelty on the one side, and maintaining network stability on the other. A stable structural dynamic is the basis for all computational processes in biological neural networks. Thus, biological learning in contrast to artificial intelligence depends on developmental and structural properties of the neural system. Simulating biological learning requires respecting not only the functional and cognitive efficiency but also the structural constraints of biological networks. Thus, maintaining homeostatic balance of neuronal activity and further metabolic parameters is a decisive driving force in developing and adult brains and, consequently, a key feature in the proposed simulation model. CP must be regarded as a fast but material-consuming mechanism that contributes to the homeostasis of the system and leads to a stabilized connectivity among established neurons. Even though the CP rate in the DG leading to a current number of ingrowing cells certainly depends on rather systemic factors (Lehmann et al., 2005), the imbedding and survival of new neurons rely on the local situation of the network.

The model presented here is, of course, a first approximation to a certainly vastly more complex system of interdependent checks and balances in the alive hippocampus. CP rates are not independent variables but most likely are influenced themselves by activity of the DG and its information processes as well as physical activity of the whole animal (Fabel et al., 2003; van Praag, Kempermann, & Gage, 1999). However, the model addresses the problem of neurogenesis from a different point of view than other current approaches do (cp. Kempermann, Wiskott, and Gage (2004)) by focusing on structural and systemic effects of CP rather than on computational properties of networks with growing cell numbers. As every computational performance of a biological neural network arises from its plastic developing structure, this approach adds a new aspect to the discussion what new neurons in the brain might be essential for.

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