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Neurocomputing 26–27 (1999) 633–639

NEUROCOMPUTING

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Neuronal regulation: A biologically plausible mechanism for efficient synaptic pruning in development

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Abstract

Neuronal regulation is a mechanism that was recently found to maintain the homeostasis of the neuron's membrane potential. We show that the operation of neuronal regulation changes the distribution of synaptic efficacies, pruning the weak synapses and strengthening the rest. Deriving optimal synaptic modification functions, we identify conditions under which neuronal regulation leads to near-optimal modification of synaptic efficacies, with considerable gain in memory performance. These results point to the possible important role of neuronal regulation as a biologically plausible mechanism that governs the fundamental process of synaptic pruning observed in mammalian brain development.

Keywords: Synaptic pruning; Brain development; Neuronal regulation; Weight normalization

1. Introduction

This paper studies one of the fundamental puzzles in brain development: the massive synaptic pruning observed in mammals during childhood, which removes more than half of the synapses [5] until puberty. In a previous work [1,2] we have shown that synaptic overgrowth followed by judicial synaptic pruning subject to synaptic constraints improves memory performance along development. This optimal pruning requires that synapses be deleted according to their efficacy, removing the weaker synapses first, and suggests a new computational explanation for synaptic pruning in early childhood.

Our previous work however, has left an important question unanswered: does there exist a biologically plausible mechanism that can actually implement the theoretically

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0925-2312/99/$ – see front matter
PII: S0925-2312(98)00161-1

derived optimal pruning? To answer this question, we focus here on studying the role of neuronal regulation (NR), a mechanism that operates to maintain the homeostasis of the membrane potential of the neuron [4]. The existence of NR has been proposed independently and identified experimentally by Turrigiano et al. [8]. They showed evidence that neurons both up-regulate and down-regulate the efficacy of their incoming synapses in a multiplicative manner, maintaining their membrane potential as required by NR. Both Horn et al. [4] and Turrigiano et al. [8] have independently hypothesized that NR, by reducing weak inputs while strengthening others, may lead to synaptic pruning.

In this paper we provide a computational support to this conjecture, showing that NR can serve as a mechanism that selectively prunes synapses depending on their efficacy. Our main results are twofold: First, the biologically plausible NR mechanism removes the weakest synapses in a manner that conserves the network's performance. Second, we identify a crucial parameter (degradation dimension) whose value determines if NR modifies the rest of the synapses in a near optimal manner. Since we propose that NR plays a prominent role in synaptic pruning during development, we predict that: (a) synapses are pruned in a weight-dependent manner and (b) degradation dimension has certain specific values in the brain during that period.

This article is organized as follows: We first study how NR modifies synaptic efficacies in an excitatory–inhibitory model. To this end, we identify the function of modified versus original synaptic values generated by the NR process. To obtain a yardstick for assessing the performance of the NR synaptic modification function, we derive optimal synaptic modification functions as in [2] but this time in the excitatory–inhibitory model (as required by NR). The NR modification function is then compared to these optimal modification functions.

2. Synaptic modification with neuronal regulation

We study NR in the general framework of associative memory networks. For specificity, we focus on an excitatory–inhibitory variation of a low-activity biologically-motivated model proposed by Tsodyks and Feigl'man [7]. In our model memories are stored in a network of inter-connected excitatory neurons via Hebbian learning. Neurons also receive an inhibitory input proportional to the activity of the excitatory network. The activity of the neuron i at time step $t+1$ is thus determined by

$$X_i^{t+1} = \theta(f_i), \qquad f_i = \sum_{j=1}^{N} W_{ij} X_j - I \sum_{j=1}^{N} X_j - T, \qquad \theta(x) = \frac{1 + \mathrm{sign}(x)}{2}, \tag{1}$$

where f_i is the neuronal input field, T is the neuronal threshold, and I is an inhibition coefficient. The excitatory–inhibitory segregation is needed so that a neuron can gauge its excitatory input field and modify its synaptic efficacies accordingly as required by NR. NR-driven synaptic modification results from two concomitant processes: *synaptic degradation*, which is an inevitable consequence of ongoing metabolic turnover [9], and neuronal regulation, operating to compensate for the

degradation. At each degradation/strengthening step, synaptic degradation stochastically reduces the synaptic strength W_t to W'_{t+1} by

$$\text{synaptic degredation:} \quad W'_{t+1} = W_t - (W_t)^{\alpha} * \eta_t \,, \tag{2}$$

where η is a normally distributed noise term and the power α is the degradation dimension parameter chosen in the range $[0,1]$. Then, the post-synaptic neuron multiplicatively strengthens all its synapses by a common factor, to retain its original post-synaptic potential (PSP)

$$\text{synaptic strengthening:} \quad W_{t+1} = W'_{t+1} * \frac{\text{baseline PSP}}{\text{current PSP}} \,. \tag{3}$$

The synaptic efficacies are assumed to have a soft upper bound (beyond which they are strongly degraded) reflecting the maximal synaptic efficacy, and a viability lower bound below which a synapse degenerates and vanishes. The degradation and strengthening processes described above are combined into a sequence of degradation/strengthening steps: at each step, synapses are first degraded according to Eq. (2). Then random patterns are presented to the network and each neuron employs NR, rescaling its synapses to maintain its input field in accordance with Eq. (3).

Numerical simulation of the dynamics described above, show that the system quickly reaches a metastable state in which some of the synapses are pruned and the other lie close to the upper bound, as shown in Fig. 1.

Plotting the final synaptic values as a function of the initial synaptic values reveals that the above process modifies synaptic values in a sigmoidal manner, removing the weaker synapses. The sigmoid's slope strongly depends on the degradation dimension α, as plotted in Fig. 2.

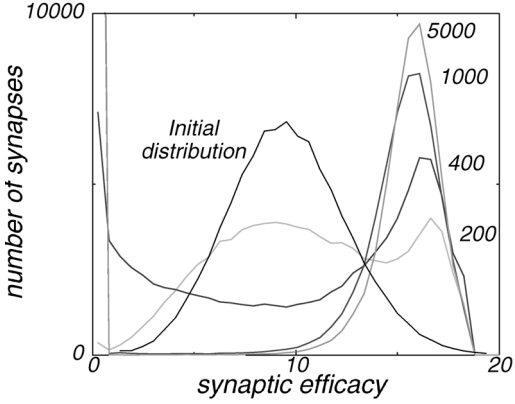

Fig. 1. Distribution of synaptic values following a degradation/strengthening process, after 0,200,400,1000 and 5000 degradation/strengthening steps. Initial synaptic efficacies were normally distributed, reflecting a typical associative memory matrix. Simulation parameters: $\alpha = 0.8$, $N = 400$, $M = 1000$, $B^- = 10^{-5}$, $B^+ = 18$. Qualitatively similar results are obtained for a wide range of simulation parameters.

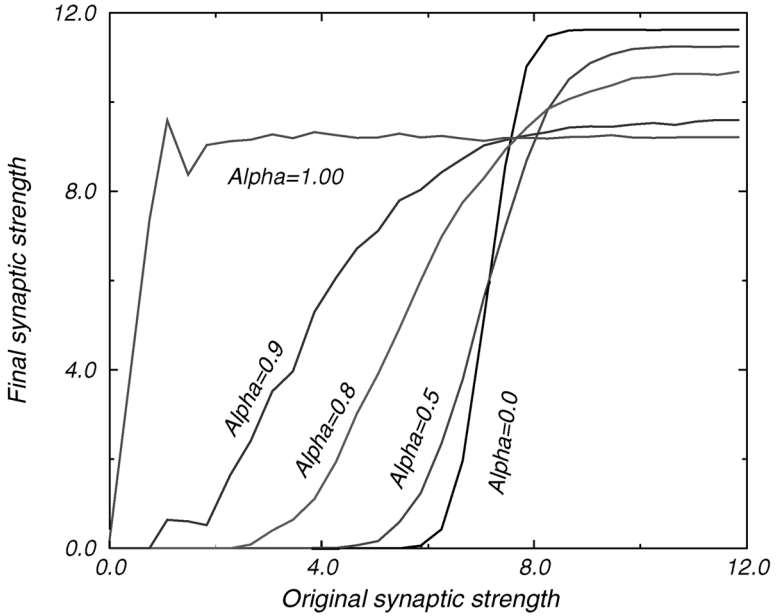

Fig. 2. Synaptic modification functions at the metastable state for different α values ($\alpha = 0.0,0.5,0.8,0.9$ and 1.00). The slope of the sigmoid strongly depends on the degradation dimension: in the two extreme cases, $\alpha = 0$ results in a step function, and $\alpha = 1$ results in a memory-less state. Simulation parameters are as in Fig. 1, except $B^+ = 12$.

3. Synaptic pruning in excitatory–inhibitory networks

We have shown that NR implements a selective pruning mechanism, which removes the weakest synapses and modifies the rest in a sigmoidal manner. But is such a pruning strategy effective? And what is its effect on network performance? To answer these questions, we have analytically studied optimal modification functions under various synaptic constraints and calculated the resulting network performance.

Our analysis extends the well-known method of signal-to-noise analysis of neuronal input fields used in [1], and applies it to the excitatory–inhibitory model described in the previous section. We investigate the effect of a general modification function $g(w)$ over the excitatory synapses, which (a) prunes some of the synapses, and (b) possibly modifies the rest. As synaptic resources are believed to be costly [6], we look for optimal g functions under constraints of limited number of synapses and limited total synaptic efficacies. Our results are described below omitting the derivations.

The analysis yields that in the excitatory–inhibitory model, optimal synaptic modification is obtained by *mean synaptic pruning*, a strategy that prunes intermediate value synapses and linearly modifies the non-pruned synapses. However, if the

excitatory–inhibitory segregation must be preserved then *weak synapses pruning*, a modification strategy that removes the weakest synapses and linearly modifies the remaining synapses is optimal. Fig. 3A shows the marked advantage of these two modification functions over random (non-weight dependent) pruning. The close similarity between the modification function generated by NR and the weak-synapses pruning strategy is shown in Fig. 3B. Near optimality is obtained when the degradation parameter α is about 0.9, generating the favorable dependency of synaptic degradation on the synaptic weights. In principle, this dependency is an experimentally observable variable.

The theoretical advantages of the optimal modification strategies, displayed in Fig. 3, imply similar advantages of NR-driven modification, that are verified in network simulations. Fig. 4 traces the average retrieval acuity of a network throughout the operation of NR, compared with a network subject to random deletion at the same pruning levels. While the retrieval of the randomly pruned network collapses already at low pruning levels, a network undergoing NR performs well even in high deletion levels.

In summary, neuronal regulation, a mechanism experimentally found to maintain neuronal firing rates during early development, leads to weight dependent synaptic pruning removing the weak synapses. Interestingly, recent studies in the neuromuscular junction have shown that synapses are either strengthened or pruned during early development, depending on their efficacies [3]. Our analysis shows that in addition to its role in maintaining membrane potential, neuronal regulation results in near optimal synaptic modification maximizing memory performance.

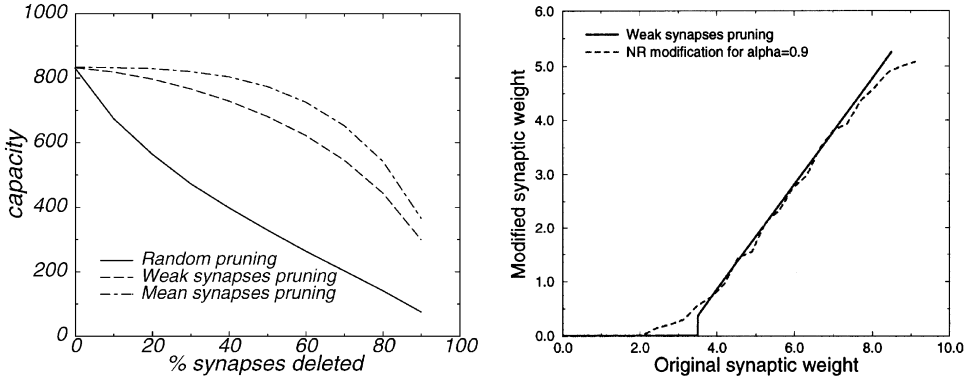

Fig. 3. (A) Comparison between performance of different modification strategies as a function of the deletion level (percentage of synapses pruned). Results were obtained analytically for a network of 800 neurons. Capacity is measured as the number of patterns that can be stored in the network and be recalled almost correctly from a degraded pattern. (B) NR modification function (with $\alpha = 0.9$) and weak synapses pruning derived to modify synapses optimally when 50% of the synapses are pruned (following the pruning levels observed in the human brain).

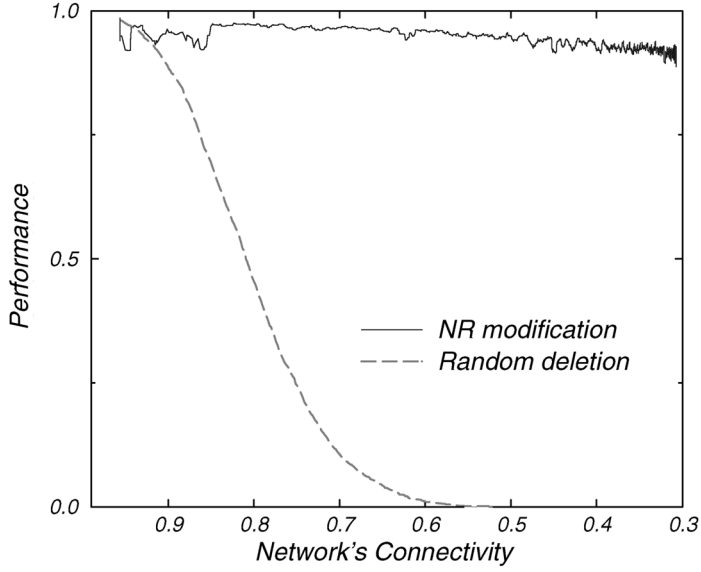

Fig. 4. Performance of networks undergoing NR modification and random deletion. The retrieval acuity of 200 memories stored in a network of 800 neurons is portrayed as a function of network connectivity $\alpha = 0, B^{+} = 7.5$, the rest of parameters are as in Fig. 2.

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