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A model of activity-dependent formation of cerebellar microzones

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Abstract. According to modern views of the cerebellum in motor control, each cerebellar functional unit, or microzone, learns how to execute predictive and coordinative control, based on long-term depression of the granule cell-Purkinje cell synapses. In the present paper, in light of recent experimental and theoretical studies on synaptic elimination and cerebellar motor learning, a model of the formation of cerebellar microzones by climbing fiber synaptic elimination is proposed. It is shown that competition for an activity-dependent supply of neurotrophic factor can reproduce the spatio-temporal characteristics of climbing fiber synaptic elimination. It is further shown that when this elimination is accurate, motor coordination can be acquired in an arm reaching task. In view of the results of the present study, several predictions are proposed.

1 Introduction

The neural circuitry in the cerebellar cortex is very uniform and can be analyzed in terms of small structural and functional units, the microzones (Oscarsson 1980), inserted into various extracerebellar systems. In this paper, the formation of the microzones during development is studied.

A microzone is a narrow sagitally oriented band of cerebellar cortex (100–200 μm width).[1] A microzone receives two kinds of inputs (for simplification, other diffuse inputs are not considered): the mossy fibers and the axons of the inferior olive (IO) neurons – the climbing fibers (CFs). The set of mossy fiber inputs is relayed to the cerebellar cortex by the granule cells (GCs). The ascending branch of granule cell axons make several synaptic connections with the overlying Purkinje cells (PCs) before bifurcating into the parallel fiber (PF) portion of the axon and reaching PCs as far as several millimeters away (Pichitpornchai et al. 1994). As PCs have inhibitory action upon deep nuclear cells (while collaterals of some mossy fibers excite the nuclear cells), the signal flow from the nuclear cells is modulated by the microzone action. In contrast to the numerous GC inputs to a PC (up to 10^6 in man), there is only one CF per PC in the adult. This peculiar architecture led several researchers (Marr 1969; Albus 1971; Ito 1984) to propose that the PC acts as a simple perceptron: the GC input to a PC constitutes a 'context' for present sensorimotor actions, the CFs convey signals encoding error in the performance of the system in which the microzone is installed, and long-term depression (LTD) is induced in those GC-PC synapses which were activated with the CF.

According to modern views of the cerebellum in motor control (Ito 1984), each cerebellar microzone learns how to execute predictive and coordinative control, based on LTD. This is achieved by a precise one-to-one anatomical correspondence between each microzone, a small region of the IO, a small portion of the deep nucleus, and a motor cortical network (Kawato and Gomi 1992). Since connections in the central nervous system cannot be genetically specified at this level of detail, much of the neural wiring can only evolve after birth and requires sensory and motor experiences for proper maturation. It is now well established that during the early stages of nervous system development there are supernumerary connections between the IO and the PCs (Crepel et al. 1976). In the present study it is shown how a biologically plausible model of activity-dependent competitive processes can 'sculpt' each microzone by CF synaptic elimination so that proper CF error signals reach appropriate microzones.

Three different, but complementary, new types of research lines and their limitations motivate the present modeling study. Firstly, there is now a consequent body of data on the neurobiology of the development of the CF innervation (see below and, for a review, Lohof et al. 1996). However, while Crepel (1982) hypothesized that the mechanism underlying CF elimination results from

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[1] Please refer to Ito (1984) for all non-referenced data

competition for a limited supply of trophic factors, this mechanism is still unclear. Secondly, a new model of activity-dependent synaptic elimination based on competition for a limited amount of neurotrophic factor was proposed by Elliott and Shadbolt (1996). This model, unlike former models of synaptic competition (but see Elliott et al. 1996a,b), is much more biologically plausible since unrealistic weight normalization is not required. However, since only one cell was modeled it is not clear how this realistic model could accommodate the spatio-temporal characteristics of synaptic elimination in a network of neurons. Thirdly, a realistic cerebellar neural network for arm reaching movement control was recently proposed by Schweighofer et al. (1998a,b). This network could learn to compensate for the interaction forces arising during reaching movements (Bastian et al. 1996) in spite of the ultra-low firing rate of the IO cells. In this model, the one-to-one anatomical correspondence among each microzone, a small number of cells in the deep nucleus, a grouping of IO cells, and the motor network was fixed in an 'optimal' manner. Since the Schweighofer et al. model provided a detailed cerebellar neural network inserted in a complete motor-sensory system, the activity-dependent refinement of the neural connectivity of the developing cerebellum and the causal relationship between CF synaptic elimination and behavior can be potentially studied.

In the present paper, the model of Elliott and Shadbolt (1996) of synaptic elimination is extended to CF elimination. It is then shown how the elimination of the supernumerary CF processes can lead to formation of cerebellar microzones so that motor learning in an arm reaching task can occur with good performance. Several predictions are derived from the results of the present study.

2 The neurobiology of CF synaptic elimination

The experimental studies performed on CF elimination can be broadly classified in four categories. These are ordered, in decreasing level of current understanding, as follows: (i) the time course and required developmental stages of the elimination, (ii) the spatial aspect of elimination, (iii) the correlation between the lack of CF elimination and behavioral deficits, and (iv) the underlying neurochemical mechanisms. We now review these four points:

(i) Studies in the rodent (see review in Crepel 1982) have shown that at postnatal day 5 an average of 3.5 CF processes innervate a PC. Massive elimination of CF synapses occurs during the second and third postnatal weeks until a one-to-one relationship between the CF and PC is attained at postnatal day 15 (Mariani and Changeux 1981). This relationship is maintained throughout adult life. Multiple innervation persists if GCs do not develop normally (Crepel and Mariani 1976; Mariani et al. 1977) or if the GCs develop but fail to form synaptic contacts with the PCs (Crepel et al. 1980; Mariani and Changeux 1980). Thus, GC-PC synaptogenesis appears to be essential for the regression of multiple CF innervation of PCs. Moreover, it has been shown that functional maturation of the PC and its ability to respond to the GC input is required for elimination to occur (Rabacchi et al. 1992a).

(ii) The cerebellar cortex is known for its 'patchy map' organization, which could be revealed either by neurochemical labeling techniques or by micromapping stimulation experiments (Mulle et al. 1987). These cerebellar maps are first organized by matching topographic chemical labels between incoming fibers and PCs (Sotelo and Wassef 1991). Piat et al. (1991) and Furhman et al. (1995) provide evidence that these chemically defined, broader bands (about 700 μm width) are then refined by CF synaptic elimination into the narrow adult-like 200-μm-wide microzones.

(iii) The behavioral deficits due to the non-elimination of supernumerary CF processes have been recently studied in mice by Chen et al. (1995). These authors showed that the primary cause of the observed motor discoordination in mutant PKCγ mice is the persistent multiple innervation of PCs by CFs. Interestingly, the PKCγ mutant mice can acquire the memory for elemental movements but cannot properly combine the elements temporally and spatially to achieve complex coordination.[2]

(iv) Crepel (1982), following an hypothesis for synaptic elimination at the neuro-muscular junction, suggested that the elimination of CF innervation results from the competitive interactions among CFs for a limiting factor such as a neurotrophic factor and that GC-PC activity fuels this competition. While recent results at the neuro-muscular junction (Parsadanian et al. 1997) tend to give credit to this hypothesis, such a mechanism has yet to be found in the cerebellum. Kano et al. (1995) showed that PKCγ is specifically involved in a signal cascade necessary for the elimination of surplus CF synapses. These authors suggest that the activity in the GC-PC pathway signals the elimination of the multiple CF innervation in an activity-dependent, hetero-synaptic fashion and that PKCγ transduces this signal. Rabbachi et al. (1992b) showed that the hyperexpression of the NMDA receptor in the cerebellum is a critical step in the regression of the CF-PC synapses during development. These authors pointed out that it is possible that the activation of NMDA receptors on the PCs by the GCs could lead to a cascade of biochemical events leading to a selective stabilization of co-active synapses.[3] This result suggests that CF synaptic elimination is an activity-dependent process.

[2] PKCγ being present all over the nervous system, it is also possible that at least some of the behavioral deficits due to the lack of PKCγ have their origins in other affected areas

[3] However, it is not yet known if the NMDA receptors are actually hyperexpressed on the PCs or on the GCs only

3 A model of synaptic elimination in the cerebellum

A new model of CF-PC synaptic elimination consistent with the above data is now proposed. Elliott and Shadbolt (1996) developed an elegant, biologically plausible algorithm for activity-dependent neural competition which does not impose the use of synaptic weight normalization, but uses competition for a limited amount of neurotrophic factor. Their model has the following characteristics: (1) neurotrophic factors are released at synapses and the release is dependent upon the activity of the presynaptic process; (2) the amount of neurotrophic factor released at each synapse is inversely proportional to the number of synapses of the target cell; (3) the release of neurotrophic factor by the target cell and its uptake by the neurotrophic factor receptors on the afferent process promotes the growth of the afferent process, and (4) afferent depolarization induces a regressive influence of the pre-synaptic processes. While the model of Elliott and Shadbolt (1996) accounts well for the temporal aspect of synaptic elimination, it cannot account for the spatial aspect of synaptic elimination because it contains only a single target cell. For spatial elimination to occur, a term akin to Hebbian synaptic plasticity is necessary, i.e. elimination should also depend upon some properties of the post-synaptic cell. Moreover, in the model of Elliott and Shadbolt (1996), two simplifications are made: the level of neurotrophic factors produced and released by the target cell is constant and the total number of neurotrophic factor receptors has a maximum upper value.

This algorithm is extended so that it takes into account known facts about CF elimination during development and it is applied to the relatively large cerebellar neural model for the control of visually guided reaching movements developed by Schweighofer et al. (1998a,b). This neural model was constrained as much as possible by known anatomical, neurochemical, and neurophysiological data and the number of neurons is scaled to provide a reasonable approximation. Notably, there are 81 mossy fibers, 2916 GCs, 36 PCs, 12 deep nuclear cells, and 12 IO cells. Because of the unidirectional functional change in PC weights due to LTD, the cerebellar system requires competition between agonist and antagonist microzone outputs. Since the simulated arm in the model has two degrees of freedom, four microzones were implemented – two controlling muscle synergies around the shoulder and two for the elbow. Thus, in the model, a microzone has nine PCs innervated by an IO cell group consisting of three IO cells.

The new model of elimination retains the four characteristics of the Elliott and Shadbolt model, but also includes the three following assumptions, derived from the data reviewed above. First, activities of the GCs impinging on a PC have a direct effect upon the level of activity of the PC, possibly via the transient hyperexpressed NMDA receptors in the developing cerebellum. Second, PC activation triggers a cascade of biochemical steps (which may include PKCγ), leading to a PC activity-dependent level of neurotrophic factors available at the level of the pre-synaptic terminals. Note that, at this stage, no assumptions are made regarding the mechanism of this activity-dependent process: it could be an activity-dependent regulation of the production of the neurotrophic factor, or an activity-dependent component of the release, or an activity-dependent regulation of the neurotrophic factor receptor expression, or a combination of any of the above (there is evidence for each of these activity-dependent mechanisms, as reviewed in Elliott and Shadbolt 1996). Third, in order to keep the number of neurotrophic receptors bounded for each IO cell, a penalty term is introduced, which avoids the unnatural cutting off by hand performed by Elliott and Shadbolt (1996). This pre-synaptic competitive mechanism prevents the IO axonal arbor from becoming too small or too large.

The balance between neurotrophic factor-induced growth, depolarization-induced retraction, and competition at the pre-synaptic level determines the time course of the number of neurotrophic factor receptors on each CF afferent. Following the model of Elliott and Shadbolt, each pre-synaptic terminal is taken to possess a fixed number of neurotrophic receptors in its membrane. A change in the number of receptors is mediated by a change in the number of synapses (either by sprouting or retraction) of each CF process. Thus, the instantaneous change in number of receptors r_{ij} of the climbing fiber process CF_i contacting the cell PC_j can be modeled with the following three terms:

(i) $CF_i\left(r_{ij}/\sum_i r_{ij}\right)N_j$ is the instantaneous amount of neurotrophic factor available to the ith CF process and promoting its growth. N_j is the total amount of neurotrophic factor provided by the target cell as a function of the jth PC activity and time. A minimal model for the PC activity-dependent neurochemical cascade regulating the amount of trophic factor available is given by a cascade of two linear first-order differential equations with the same time constant; thus N_j is given by:

$$\tau^2 \frac{d^2 N_j}{dt^2} + 2\frac{\tau dN_j}{dt} + N_j = G \cdot PC_j \qquad (1)$$

where τ is the common time constant and G the input gain initially set to 1.0 (here CF_i and PC_j designate both the cell numbers and their activities). $\sum_i r_{ij}$ is the total number of receptors on all the processes CF_i contacting PC_j. Thus, $\left(r_{ij}/\sum_i r_{ij}\right)N_j$ expresses the assumption according to which the amount of neurotrophic factor uptake at each synapse is inversely proportional to the number of synapses of the target cell and proportional to the number of receptors r_{ij}.

(ii) $R \cdot CF_i$ is the activity-dependent regressive influence, where R is a constant (positive) regressive factor.

(iii) $\beta \sum_j r_{ij}$ is a 'penalty' term which limits the total number of receptors supported by a single IO cell (where β is a positive constant).

The evolution equation of the number of neurotrophic receptors r_{ij} of the climbing fiber process CF_i contacting the cell PC_j can now be given:

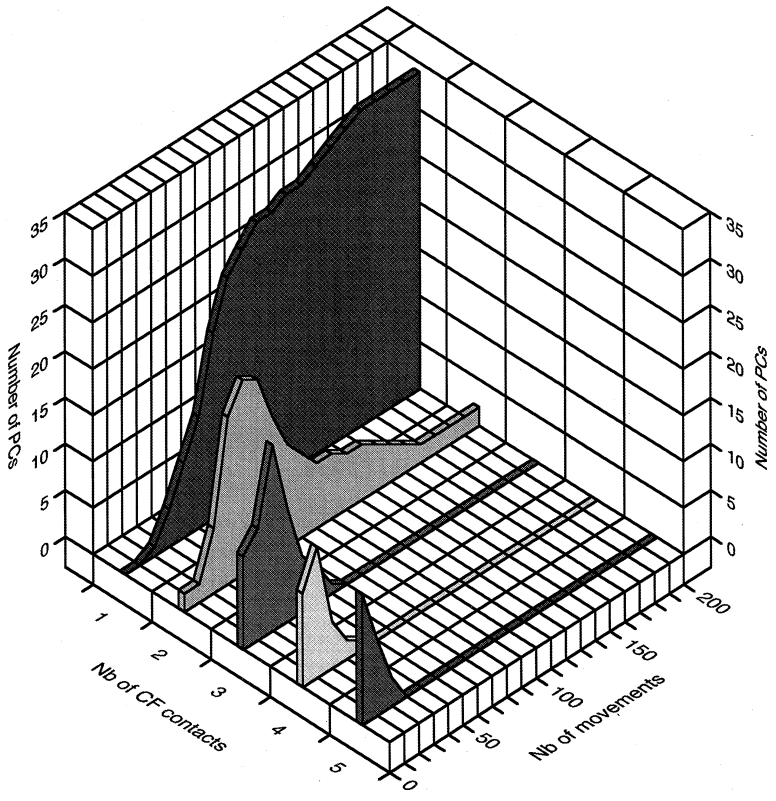

Fig. 1. Temporal evolution of the number of climbing fiber (*CF*) contacts per Purkinje cell (*PC*) during movement generation. Before the first movement, there is an average of about four CF processes per PC, with no PC receiving a single CF. Very rapidly (after about 70 reaching movements), no PC receives more than two contacts. When the stable state is attained, only two PCs receive two CF afferents; the other 34 receive a single CF process

$$\frac{dr_{ij}}{dt} = \alpha CF_i \left(\frac{r_{ij}}{\sum_i r_{ij}} N_j - R \right) - \beta \sum_j r_{ij} \qquad (2)$$

where $r_{ij} \geq 0$; if r_{ij} becomes zero, the connection is retracted and cannot grow again and α is the constant (positive) rate of elimination.

4 Results

4.1 Microzone formation

It is assumed that the cerebellar bands are initially defined with neurochemical labels corresponding to the two joints of the 2D arm. Thus, there are initially two bands, but four microzones are ultimately needed for proper cerebellar adaptive control. Reaching experiments to targets around a circle with a radius of 20 cm are simulated with a desired movement duration of 0.7 s. The target to the right of the start position was defined as the 0° direction and targets at successive counterclockwise positions were given in 45° increments. At $t = 0$ s, a movement is initiated toward a randomly chosen target. At $t = 1.0$ s (i.e. 0.3 s after the end of the desired movement), the target is again moved to the central position. At $t = 2.0$ s the movement is initiated toward a randomly chosen target and so on. The simulation time step is 5 ms, the program is written in C, and simulations were run on a DEC alpha workstation.

The initial CF-PC contacts are generated from a Gaussian distribution centered on 3.5 contacts per PC with a standard deviation of 0.8. Once the existence of a contact has been determined, the initial values of the number of receptors per CF process r_{ij} are drawn from a uniform distribution from 0.04 to 0.06. In this first set of simulations there are 90% direct GC-PC connections, and thus there are 10% PF-PC synapses (see below).

For $\alpha = 5 \times 10^{-6}$, $\beta = 2.5 \times 10^{-5}$, $R = 20$, and $\tau = 30$ ms the distribution of CF-PC contacts as a function of the number of movements is shown in Fig. 1.[4] Initially, no PC receives a single CF afferent but progressively the number of cells receiving only one CF afferent increases. After convergence, 34 PCs receive one CF and two PCs receive two CFs. Thus, elimination occurs properly at the level of each PC. Similarly, the innervation is also well distributed among IO cells: three cells have two axonal branches, six cells three axonal branches and the last three cells four axonal branches.

Figure 2 shows that the elimination is also accurate spatially – the four microzones are properly formed with only a few mishaps. Note how the broadly defined chemical zones are narrowed down to bands occupying only a fourth of the cerebellar patch modeled. Figure 3 shows the percentage of incorrectly placed processes during elimination as a function of (1) the number of reaching movements and (2) the average number of CF contacts per PC. When the stable state is reached, i.e. after completion of about 200 movements, there is on

[4] The best elimination results are given by a particular set of initial conditions. Best results are obtained only if no necessary connections are missing when the initial random connections are generated

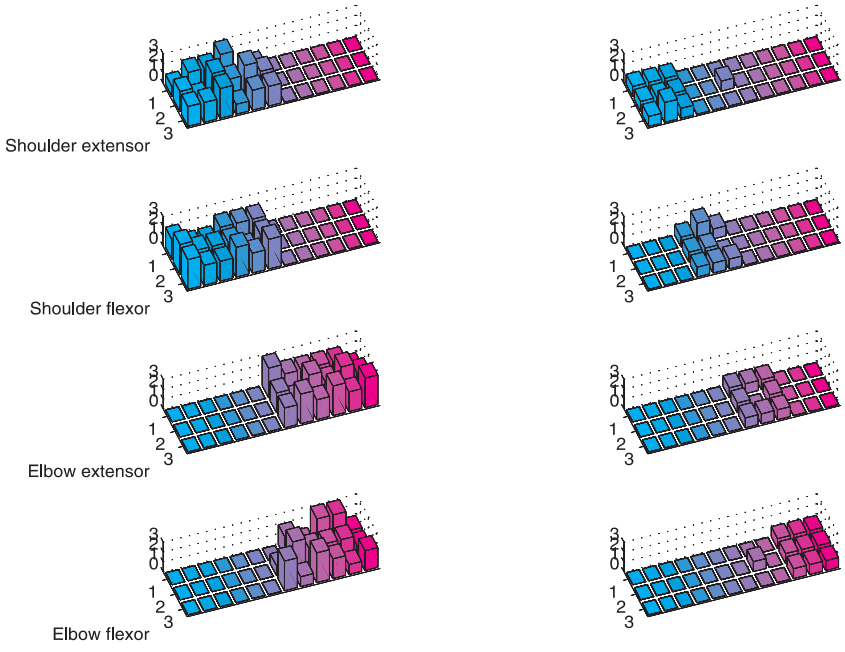

Fig. 2. Illustration of microzone formation. Each box represents a PC territory (there are a total of $3 \times 12 = 36$ PCs). The four figures on the *left side* are the projections maps of the four groups of inferior olive (IO) cells before elimination. The four maps on the *right side* show how the projections have clearly separated into four distinct microzones after the stable state is attained. As shown on the *left maps*, before the training session, each PC is innervated by up to three CF processes arising from the same IO group. On the *right maps*, it is clear that there is only one climbing fiber per PC (with the exception of two cells, which retain two processes)

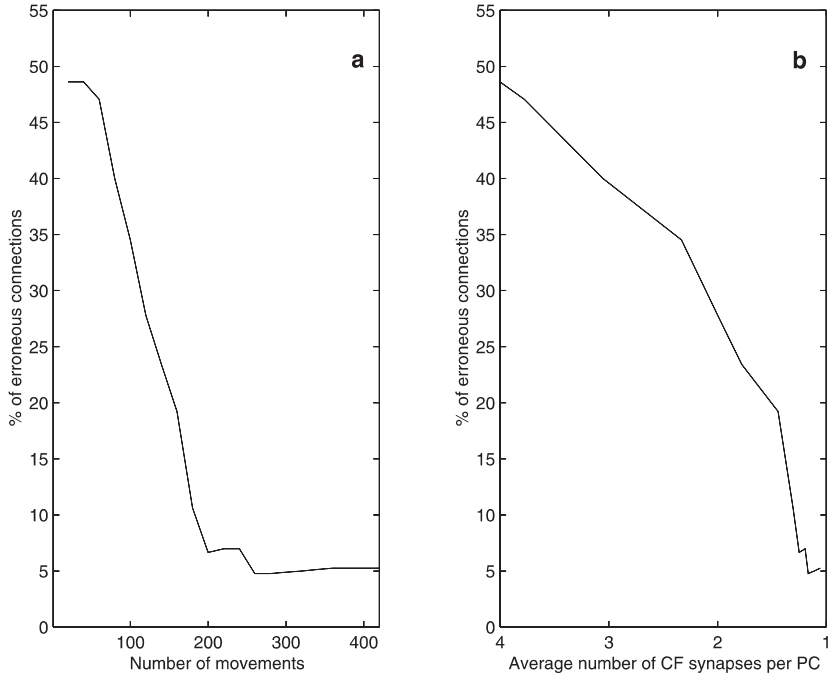

Fig. 3a, b. Spatial accuracy of microzone formation. The percentage of incorrectly placed synapses during elimination as a function of **a** the number of reaching movements and **b** the average number of CF synapses per PC. When the elimination is complete, after about 200 movements, only slightly more than 5% of the connections are erroneous

average almost only one CF process left per PC and only about 5% of the connections are erroneous.

In the original Elliott and Shadbolt model it was shown that excess neurotrophic factor prevents elimination, hence the competition of the afferents for a *limited* supply of neurotrophic factor. In order to simulate the available quantity of neurotrophic factor, the gain G of Eq. 1, initially set to unity, is now varied. Figure 4a shows that if $G > 2$, elimination does not occur properly, and for $G > 50$, no elimination occurs at all. Thus, the behavior of the Elliott and Shadbolt model, namely that excess neurotrophic factor prevents elimination, is maintained. However, in the present model, the spatial properties of the elimination are also crucial: in Fig. 4b the asymptotic percentage of incorrectly placed contacts as a function of the gain G is shown. Note that for small values of G, even if the number of synapses remaining after elimination is appropriate on average, their spatial distribution is not optimal.

As shown by Eqs. 1 and 2, τ controls the degree of temporal correlation between the activity-dependent availability of the neurotrophic factor and the CF activity . Figure 5 shows the asymptotic percentage of incorrectly placed contacts as a function of the time constant τ of Eq. 1 (with the same initial conditions as

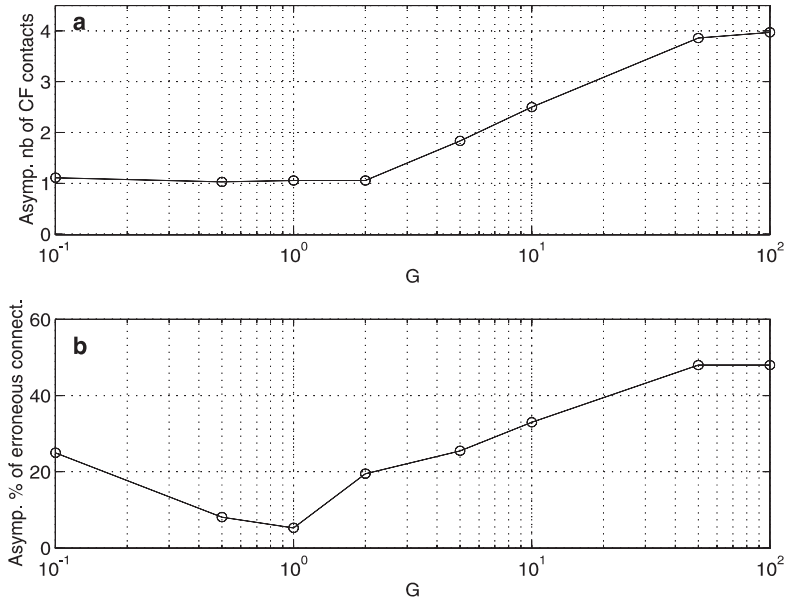

Fig. 4a, b. Influence of the average amount of the neurotrophic factor upon elimination (same initial conditions as above). **a** Asymptotic average number of CF contacts per PC. Note that when $G > 2$ (i.e. when the amount of neurotrophic factor becomes too large), elimination occurs poorly or not at all. **b** Asymptotic percentage of incorrectly placed synapse as a function of the gain G. Note the spatial accuracy of the elimination requires $0.5 < G < 1$

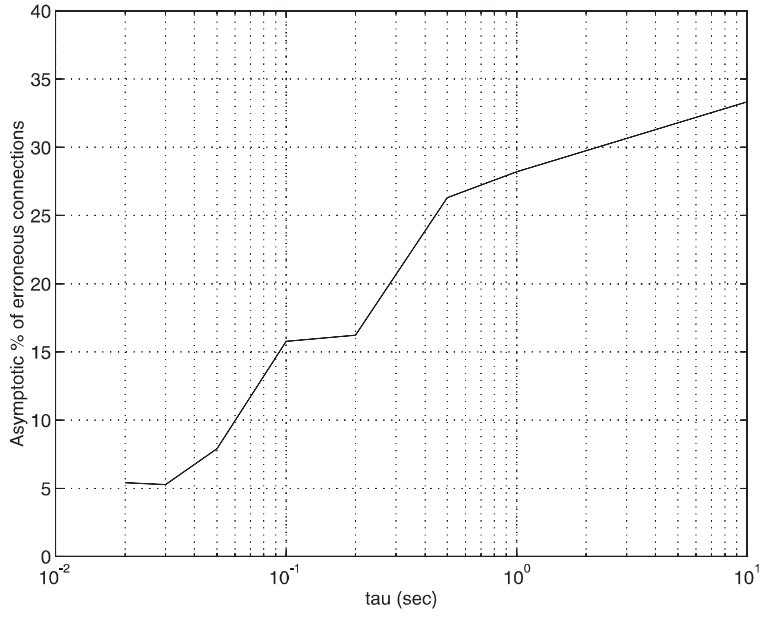

Fig. 5. Final percentage of incorrectly placed synapse as a function of the time constant τ of the neurotrophic factor availability (same initial conditions as above). This shows the sensitivity of the elimination to the time course of neurotrophic availability as a function of PC activity. This result shows that this time constant should be small (< 50 ms) in order to obtain proper elimination

above). The graph shows that this time constant should be small (< 50 ms) in order to obtain proper elimination.

The rate of elimination depends upon the structure of the cerebellum. The average number of synapses on the vertical branch of the GC axon is varied from 0 (100% of PF-PC synapses) to 9 (10% of PF-PC synapses). Figure 6 shows the final percentage of incorrectly placed CF contacts as a function of the average percentage of PF-PC inputs (with the same initial conditions as above). The result indicates that the synapses from the ascending branch of the GC are not only necessary, but also that a fair number of them are required to obtain good CF synaptic elimination.

4.2 LTD learning

In order to test the quality of synaptic elimination, LTD learning experiments are run in different conditions. In the simulations, training sets of 100 movements (duration of each desired movement is 0.7 s) to random targets (as described above) are alternated with testing sets of 15 movements (same duration). In the test set, the hand position is initially on the target farthest from the body and then target positions are switched by 45° increments until the hand is back on the initial target.

First, the model is trained with LTD after elimination of the supernumerary synapses; for best LTD learning, 50% of PF–PC connections are re-installed (instead of

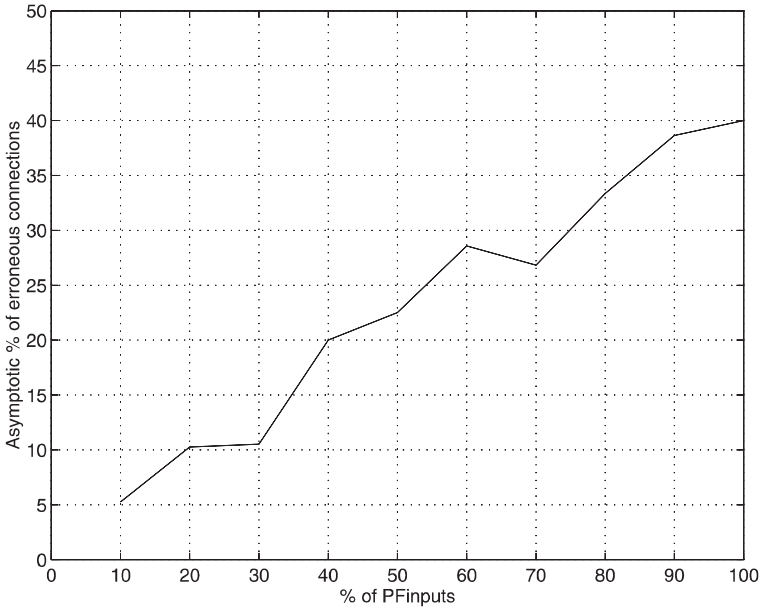

Fig. 6. Final percentage of incorrectly placed synapses as a function of the percentage of parallel fiber (PF) inputs on PCs (same initial conditions as above)

10% as above) as in Schweighofer et al. (1998b). [5] The trajectories before and after training can be seen in Fig. 7a and b. Note that, after training, the trajectories are almost straight since the interaction torques have been compensated for by the cerebellum. The learning curve can be shown in Fig. 8 (plain curve), where the mean square error (MSE) is plotted as a function of the number of training movements (the MSE is computed with the difference between the desired trajectory delayed by 30 ms, which corresponded to the spinal cord delay, and the real trajectory. In order to compare this result with the 'optimal' model, i.e. the model in which the CF-PC connections are fixed in a ad hoc manner, the cerebellar neural network described in Schweighofer et al. (1998a,b) is trained. The learning curve is shown in Fig. 8 (dash and dot curve). As expected, the performance is better than that of the self-organized model, but only slightly. Indeed, the trajectories after learning (not shown) barely differ from those shown in Fig. 7b. Finally, the learning capabilities in a 'mutant' model, in which the CF elimination has not occurred, are tested. Trajectories after learning are shown in Fig. 7c and the learning curve is shown in Fig. 8 (dot curve). Note that some learning proceeds but that motor coordination is not achieved, as evidenced by large deviations from the desired trajectories.

Finally, the effect of the pre-synaptic mechanism (last term of Eq. 2) upon both the elimination and the overall performance of the system is studied. Figure 9a shows how for $\beta < 2 \times 10^{-5}$ the number of CF contacts is on average more than one per PC (up to two when no pre-synaptic mechanism is present). In Fig. 9b the asymptotic MSE is plotted as a function of β. Best learning occurs for $0.2 \times 10^{-5} < \beta < 0.5 \times 10^{-5}$. For lower values, elimination is incomplete and IO cells contact several Purkinje cells belonging to different microzones, resulting in poor learning. For higher values, even though a single CF process innervated each PC on average, the process can arise from an IO cell belonging to an inappropriate olivary cell group. Consequently, the appropriate error signals are not directed to the proper PCs, which in turn degrade LTD learning performance.

5 Discussion

A model of synaptic elimination based on competition for a limited amount of neurotrophic factor was successfully applied to self-organization of a cerebellar neural network for reaching movements. It was shown that accurate spatial CF synaptic elimination occurs, if the amount of neurotrophic factor available was activity-dependent. Moreover, proper weighting between (1) the overall average level of neurotrophic factor, (2) the regressive influence, and (3) the pre-synaptic mechanism controlling the growth of the IO axonal arbor are required for accurate spatial elimination. As suggested by Chen et al. (1995), it was shown that proper CF elimination is required for ultimate refinement of motor programs and motor coordination. By removing the undesired supernumerary synapses from the PC by a process which amounts to a correlation between CF and (filtered) PC activity in the early stages of life, each PC is well positioned to receive an 'optimal' CF error signal. Each cerebellar microzone can thus learn how to execute predictive and coordinative control, based on LTD. In contrast, if multiple CF processes remain on each PC, the microzones do not specialize in the control of specific motor synergies. Thus, interaction torques arising during reaching are not compensated for properly,

[5] This might seem somewhat artificial. However, since the exact cerebellar architecture is not modeled here, the results shown here should be interpreted more on a qualitative rather than quantitative basis

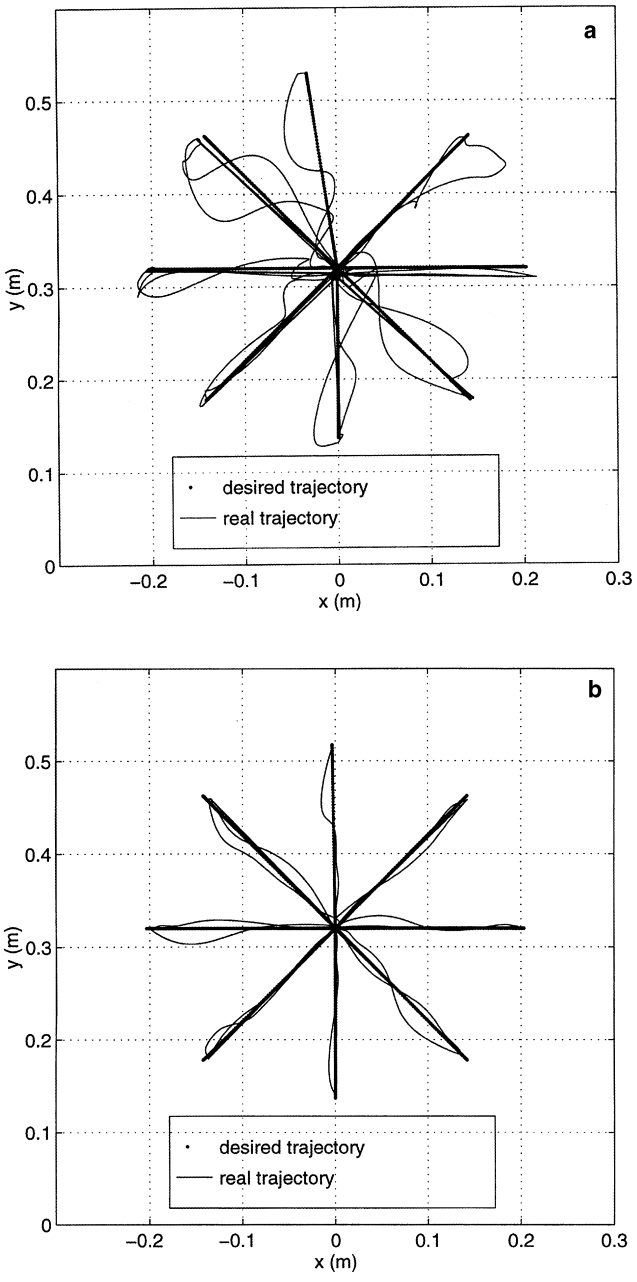

Fig. 7a–c. Reaching to eight targets arrayed at 45° intervals around a circle with a radius of 20 cm. Duration of individual desired movement = 0.7 s. The target to the right of the start position is defined as the 0° direction and targets at successive counter-clockwise positions are given in 45° increments. Reaching movements **a** before LTD learning, **b** after learning, for complete CF elimination, and **c** for no CF elimination

which results in poor coordination between the two joints and therefore poor reaching movements.

5.1 Limitations of the present study

The present model has two major limitations. Firstly, since the CF elimination occurs only after electrical maturation of the GC-PC system, the establishment of the mossy fiber input map is crucial for the microzone formation. In the model, the mossy fiber map was pre-established in an ad hoc manner (see Schweighofer et al. 1998a,b). However, it is known that this map is first grossly defined by chemical markers (Ji and Hawkes 1995), and that activity-dependent processes play a role in refining this input map (Ji and Hawkes 1996). Secondly, the PC-deep nuclear cells and the deep nuclear cells-motor cortical cells connections were also pre-determined. Since a precise mapping of these connections is also required for good coordinative and predictive control, as discussed above, they are also presumably refined by activity-dependent processes. It is conceivable that synaptic elimination of these connections could also be ruled by the same algorithm as above.

5.2 Comparison with previous models

No previous model directly deals with CF-PC synaptic elimination or even cerebellar self-organization. However, several studies are relevant to the present one.

First, activity-dependent segregation had been successfully modeled earlier by von der Malsburg (1973). This model, and most other models since then, make use of synapse-specific Hebbian learning rules that require synaptic normalization in order to induce competition. However, there is little or no experimental evidence for synaptic normalization.

Second, Elliott et al. (1996a,b) recently presented two related models of nervous system plasticity in terms of sprouting and retraction of axonal processes rather than changes in synaptic strength implied by synapse-specific Hebbian models. They employed statistical mechanics to simulate changes in the pattern of network connectivity and their formalism uses the concept of an energy function. However, Elliott et al. related the energy function to the levels of target-generated neurotrophins for which afferents compete, but no detailed modeling of the neurotrophic factor influence was included.

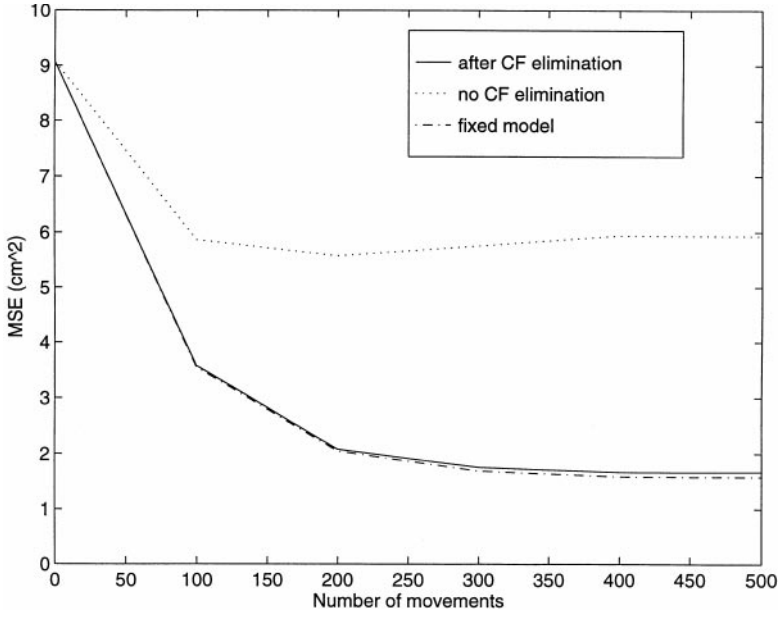

Fig. 8. LTD learning curves where the mean square error (*MSE*) is plotted as a function of the number of training movements. *Plain curve*: performance of the model after elimination has occurred. *Dash-dot curve*: performance of the fixed, 'optimal' model described in Schweighofer et al. (1998a,b). *Dot curve*: case in which the CF elimination has not occurred

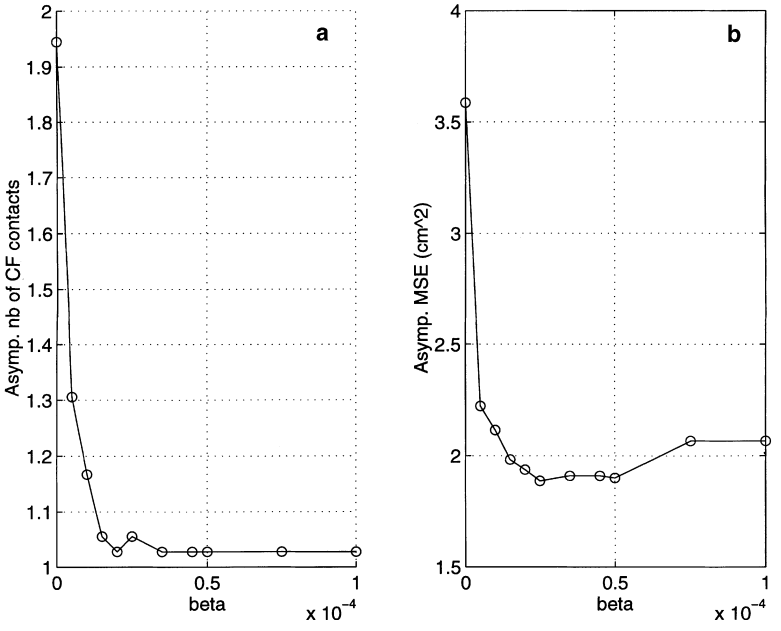

Fig. 9. Effect of the weight β of pre-synaptic mechanism upon **a** asymptotic CF elimination and **b** asymptotic MSE. See text

Finally, Eddi et al. (1996) presented a topological model of the CF synaptic redundancy in the neonate. These authors notably showed that a model of random stacking of non-penetrating hard spheres can remarkably well describe the synaptic redundancy of 3.5 CF processes on average per PC seen in the neonate. However, this model does not deal directly with the process of synaptic elimination.

5.3 Predictions

In order to provide generalized significance, computer models have to be experimentally validated. Several testable predictions are now proposed that may lead to future progress in the empirical studies of cerebellar synaptic elimination.

Prediction 1: synaptic elimination in the cerebellum climbing fiber results from activity-dependent competition for an activity-dependent supply of neurotrophic factor.

Prediction 2: Evidence from the hippocampus (Blöchl and Thoenen 1995) suggests that activity-independent release of neurotrophic factor occurs at or near the cell body, while activity-dependent release occurs on dendrites. However, CF elimination occurs when the PCs are morphologically immature, and at this stage the dendrites are only partially developed (see Lohof et al. 1996 for instance). As a consequence, many of the CF synapses are eliminated at or near the PC bodies. Thus, it is predicted that activity-dependent release

of neurotrophic factor is spatially dissimilar in the developing PC and in the mature hippocampal cell.

Prediction 3: Elimination does not occur when the average level of neurotrophic factor is too large. Thus, it is predicted that infusion of excess neurotrophic factor into the developing cerebellum prevents CF elimination.

Prediction 4: Activity-dependent regulation of production, release, or regulation of neurotrophic factor expression has a small time window, i.e. it correlates well temporally with the activity of the target cell. Since it is doubtful that the time constant of regulation of production and regulation of expression of the neurotrophic factor receptor is in the range required (a few tens of milliseconds), a prediction of the model is that a fast activity-dependent regulation of the release is crucial for proper formation of microzones.

Prediction 5: The synapses of the ascending branch of the GCs (Bower and Woolston 1983; Pichitpornchai et al., 1994) are crucial for proper spatial elimination of the CF supernumerary synapses.

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