Neuroscience Vol. 48, No. 2, pp. 249–283, 1992
Printed in Great Britain

0306-4522/92 $5.00 + 0.00
Pergamon Press Ltd

COMMENTARY

WHY RUN PARALLEL FIBERS PARALLEL? TELEOSTEAN PURKINJE CELLS AS POSSIBLE COINCIDENCE DETECTORS, IN A TIMING DEVICE SUBSERVING SPATIAL CODING OF TEMPORAL DIFFERENCES

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Abstract—The present paper explores the possible functional significance of the parallel orientation of parallel fibers in teleostean cerebellar and cerebelloid molecular layers, taking advantage of the restricted width of these molecular layers compared with mammalian ones and several specific configurations of granule cells. These configurations include: (i) a unilateral location, i.e. at only one (lateral) side of the molecular layer, giving rise to parallel fibers without bifurcation in a unidirectional molecular layer, where all parallel fibers conduct signals in the same direction; (ii) a bilateral location at both sides of the molecular layer giving rise to a bidirectional molecular layer where parallel fibers conduct signals in two opposite directions originating from two discrete sources; and (iii) a basal (or sometimes apical) location underneath (or opposite to) the layer of Purkinje cells, giving rise to a bidirectional molecular layer where parallel fibers conduct signals in two opposite directions originating from a continuous range of sources.

It is argued that molecular layers with a bilateral location of granule cells, exemplified by the mormyrid lobus transitorius, represent an optimal configuration for the analysis of small temporal differences (up to 4 ms) between inputs to the right and left granule cell mass, by means of detection of the site of coincidence of parallel fiber activity running from left to right and vice versa. Morphological aspects that probably optimize such a function include not only the parallel course and bilateral origin of parallel fibers, but also their small diameter, large number and co-extensive location, as well as the sagittal orientation and the presence of many spines of Purkinje cell dendrites and the presence of stellate and other inhibitory interneurons. The only assumption underlying the present coincidence detection hypothesis is that Purkinje cells are supposed to be maximally stimulated by parallel fiber input when all spines are activated in such a way that their excitatory postsynaptic potentials reach the axon hillock simultaneously.

For molecular layers with a unilateral location of granule cells, exemplified by the teleostean torus longitudinalis-tectal marginal parallel fiber system, a similar coincidence detecting mechanism is proposed on the basis of the presence of two populations of parallel fibers with slightly different conduction velocities. Such a system might be suitable to adapt the location of coincidence peaks to topographic maps present in deeper layers of nervous tissue. Molecular layers with basally (or apically) located granule cells as encountered in the teleostean corpus cerebelli, are probably involved in the analysis of specific spatio-temporal input waves directed centripetally towards different Purkinje cells. Compared with mono- or bilateral locations of granule cells, a basal location of granule cells adds specificity at the expense of sensitivity to the coincidence detecting properties of the molecular layer, and requires a more precise topographic organization of mossy fiber input.

The possible functional significance of the configurations analysed is discussed on the basis of the literature available, while their specific advantages and constraints are evaluated using a model of the teleostean lateral line system. This system presents a nice example of different configurations of similar sensors at the same sensory interface working within the same space–time domain. Comparison of the teleostean cerebellar configurations analysed with the mammalian one suggests that the dramatically larger width of the latter does not only allow for the detection of a larger range of temporal differences and spatiotemporal input wave patterns, but might also reduce artefacts by juxtaposition of distinct zones with a similar input. The presence of basket cells and the discongruent extension of parallel fibers in the mammalian cerebellum might also optimize coincidence detection. Comparison with the acoustic and electrosensory communication system, where similar coincidence detection mechanisms have been demonstrated, suggests that these subserve fast analysis of phase differences of relatively simple, repetitive input of high frequency (an acoustic or electric tone), whereas cerebellar coincidence detection is probably involved in slower analysis of temporal differences of single or low-frequency repetitive inputs with a more complex and noisy shape and pattern. Finally, it is suggested that the specific palisade orientation of the dendrites of mormyrid Purkinje cells might well increase the tuning of Purkinje cells for specific input waves, not only in the transverse direction, but also in the apico-basal and rostro-caudal direction, and thus probably represents an ultimate optimization for cerebellar coincidence detection. In contrast, the mammalian Purkinje cell configuration seems optimal for integration of parallel fiber input with climbing fiber input, possibly involved in gain control of coincidence detection.

CONTENTS

1. INTRODUCTION

The cerebellum is one of the most investigated and best understood regions of the vertebrate brain, since many aspects of its structure, physiological properties and functions have been analysed and reviewed.[9,24,30,38,43,45,50,77,83,84,97] From these studies it appears that the pivot of cerebellar circuitry consists of the Purkinje cells with their sagittally oriented spiny dendritic trees and their dual input from climbing and parallel fibers. Remarkably, the climbing fibers, originating from the inferior olive, have a one-to-one relationship with Purkinje cells in most vertebrates, and thus establish one of the most specific and precise connections encountered in the central nervous system of vertebrates. In contrast, 100,000 or more different parallel fibers, originating from granule cells, synapse upon a single Purkinje cell, while each parallel fiber may terminate on 1000 or more different Purkinje cells, thus establishing one of the most aspecific, convergent as well as divergent connectivity patterns encountered in vertebrate brains. The cerebellar molecular layer, where parallel fibers interact with Purkinje dendritic spines, is the most regular part of the vertebrate brain since it has a strict orthogonal organization, with parallel fibers oriented in the transverse plane and Purkinje cell dendritic trees oriented in the sagittal plane.

In spite of the detailed knowledge of the morphological and physiological properties of parallel fibers,

Abbreviations used in the figures

cc	crista cerebellaris
eg	eminentia granularis
ega	anterior part of the eminentia granularis
egp	posterior part of the eminentia granularis
elll	electrosensory lateral-line lobe
lc	lobus caudalis cerebelli
lll	lobus lineae lateralis
lt	lobus transitorius cerebelli
pg	prominentia granularis
sm	stratum marginale tectale
sp	layer of Purkinje cells
tect	tectum mesencephali
tl	torus longitudinalis
ts	torus semicircularis
valv	valvula cerebelli
valvl	lateral part of valvula cerebelli
valvm	medial part of valvula cerebelli

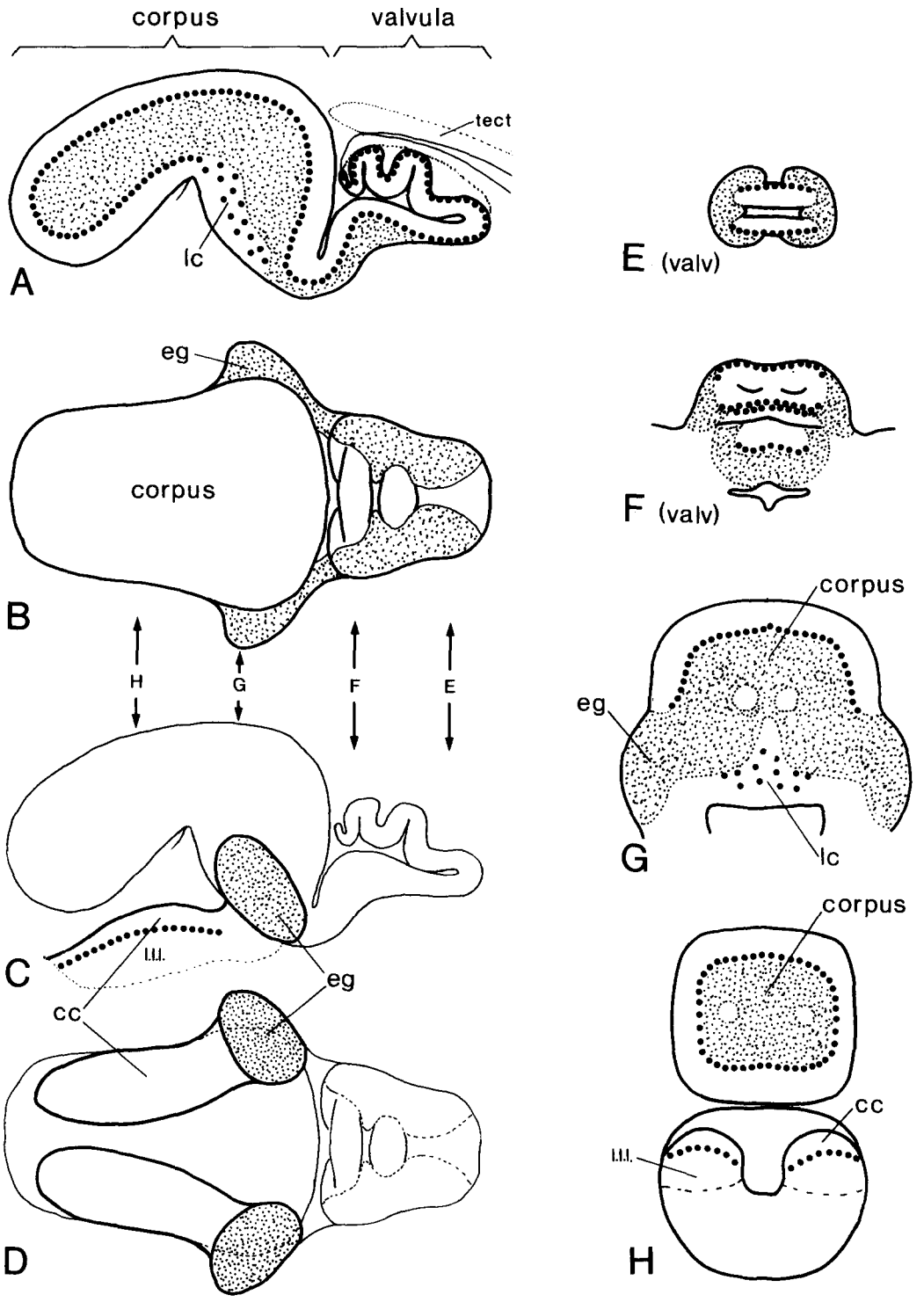

Fig. 1. The cerebellum of the trout, *Salmo gairdneri*, drawn at a magnification of × 10. (A) Midsagittal section, (B) dorsal view, (C) and (D) the granular eminence and cerebellar crest as present in a sagittal section (C) and a dorsal view (D) projected against the contours of A and B. (E–H) Transverse sections at the levels indicated on the left side through the rostral part of the valvula (E), the caudal part of the valvula (F), the rostral corpus and granular eminence (G) and the caudal corpus and cerebellar crest (H). The location of granule cells is indicated by small stipples and that of Purkinje cells and Purkinjoid crest cells by dots. The molecular layer is white. Notice the foliation and lateral location of granule cells in the valvula, which is located under the midbrain tectum; the tubular shape and caudal direction of the tip of the corpus, and the location of Purkinje cells within the molecular layer of the caudal lobe. In parts A–D, caudal is to the left and rostral to the right.

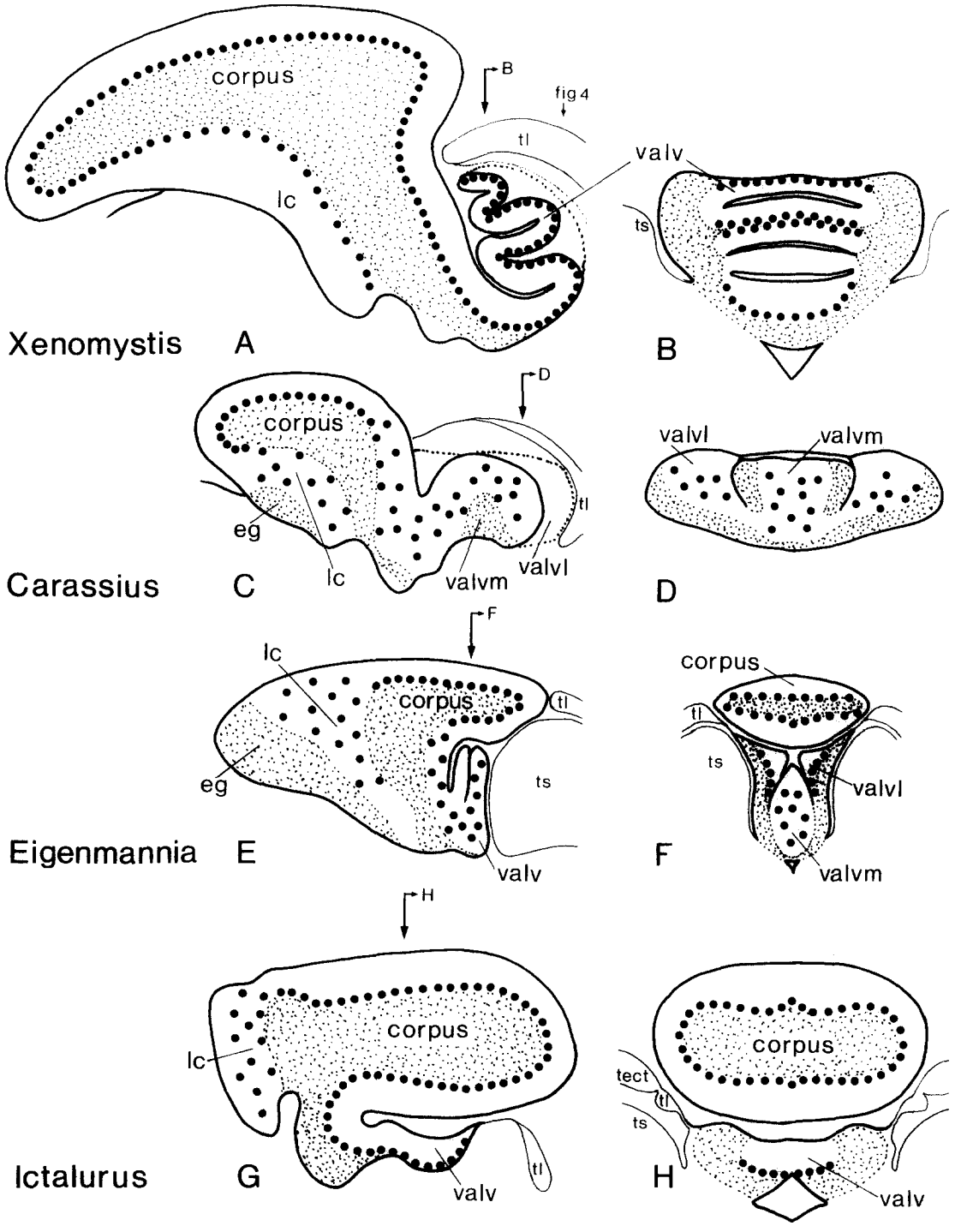

Fig. 2. Drawings of midsagittal sections (A, C, E, G) and transverse sections (B, D, F, H) of the cerebellum of four teleosts: (A, B) *Xenomystis nigri*; (C, D) *Carassius auratus*; (E, F) *Eigenmannia virescens*; (G, H) *Ictalurus nebulosus*, showing some aspects of the variability of the teleostean cerebellar organization. Just like in Fig. 1, small stipples indicate the locations of granule cells and large dots those of Purkinje cells, while the molecular layer is white. The magnification of this figure is $\times 20$. Variable aspects include the presence of a large valvula in *Xenomystis* (c.f. Fig. 1) and *Carassius*, but a small one in *Eigenmannia* and *Ictalurus*; the presence of a lateral valvula in *Carassius* and *Eigenmannia*, and the location of Purkinje cells in a monolayer in the valvula of *Xenomystis* (B), *Ictalurus* (H) and its lateral part in *Eigenmannia* but the location of Purkinje cells within the molecular valvular layer in *Carassius* and the medial valvula of *Eigenmannia*. Just like the corpus cerebelli of the trout (Fig. 1), that of *Xenomystis* (A) and *Carassius* (C) is directed caudally, but that of *Eigenmannia* (E) and *Ictalurus* (G) rostrally, which has its influence on the shape and position of the caudal cerebellar lobe. Notice that Purkinje cells in the corpus are always located in a ganglionic layer between the molecular and granule cell layer, whereas Purkinje cells in the caudal lobe are dispersed within the molecular layer, except for those in *Xenomystis* (A). The levels of sections B, D, F and H are indicated in figures A, C, E and G, respectively.

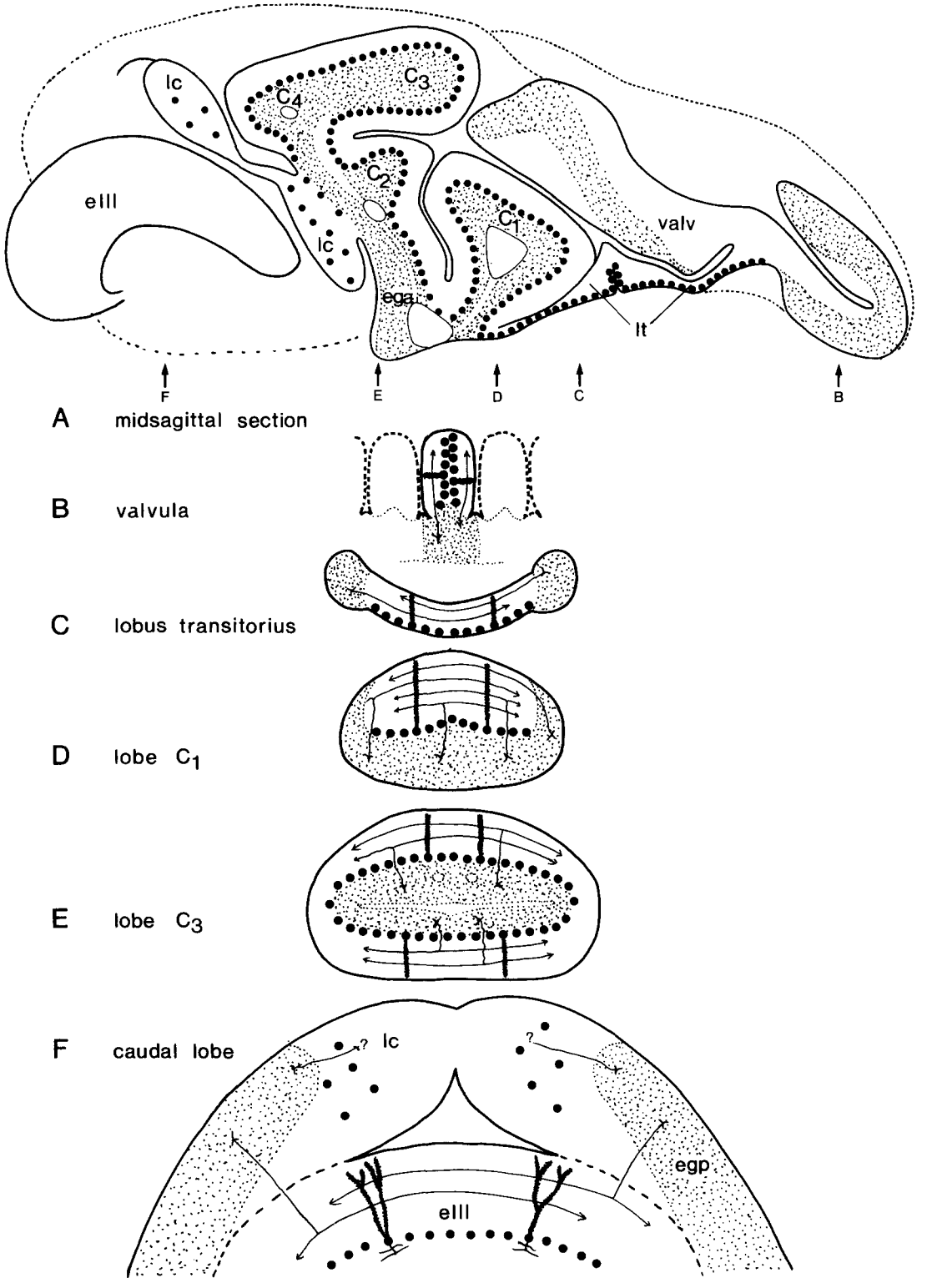

Fig. 3. The cerebellum of the mormyrid fish *Gnathonemus petersii*. (A) Midsagittal section (× 17.2). (B–F) Transverse sections (× 34.4) at the levels indicated in A through the valvula, lobus transitorius, lobe C_1, lobe C_3 and the caudal lobe, respectively. For further explanation, see section 2.2. Small stipples indicate the position of granule cells, and dots the position of Purkinje cells and Purkinjoid cells in the elll. The molecular layer is white. To show some aspects of the organization of the molecular layer as surveyed in section 2.2, the dendritic properties of some Purkinje or Purkinjoid cells and the axonal properties of some granule cells have been drawn schematically. C_{1-4} indicate the four cerebellar lobes distinguished.

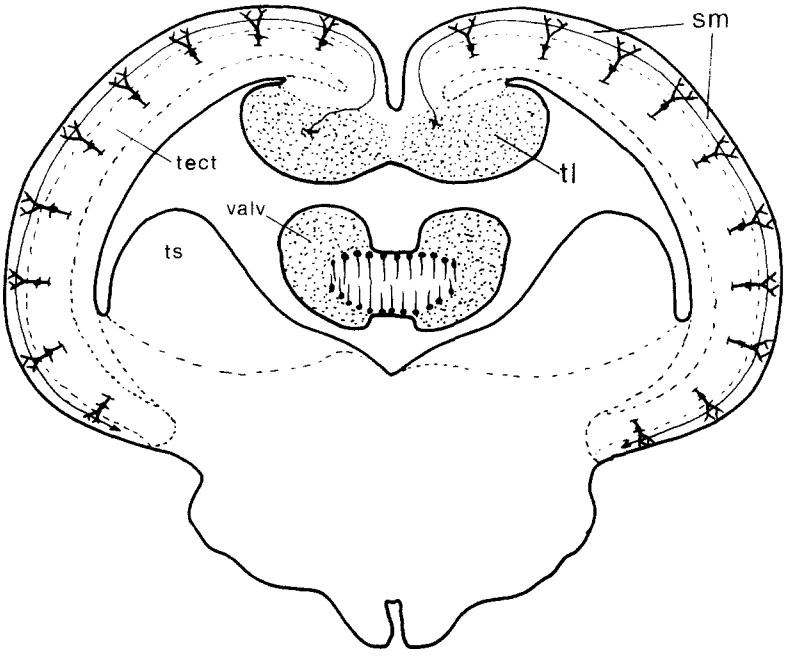

Fig. 4. The torus longitudinalis-tectal marginal parallel fiber system of *Xenomystis nigri* in a transverse section (×20) at a level indicated in Fig. 2A. To show some aspects of the organization of this system, the dendrites of some tectal cells and the axons of two granule cells in the torus longitudinalis have been drawn schematically. The location of granule cells is indicated by stipples. For further details, see Section 2.2.1.

climbing fibers and Purkinje cells, as well as of the inhibitory stellate, basket and Golgi interneurons and the deep cerebellar output neurons, the precise cerebellar functional mechanisms and their significance are still largely unknown.[24,38,84,97] Although several concepts have been proposed with respect to intracerebellar functional mechanisms,[2,38,58,87–90,98] none of these concepts explains why parallel fibers course parallel and why Purkinje cells are oriented perpendicular to the parallel fiber direction. All these concepts would also hold for locally distributed ('parallel fiber') input, without restriction to the transverse plane. The present paper is devoted to a conceptual analysis of the possible functional significance of this particular aspect of cerebellar organization, on the basis of cerebellar configurations encountered in teleostean fish. The starting points and configurations considered will be outlined in the Materials, Starting Points and Methods section, followed by a detailed theoretical analysis of the possible intracerebellar mechanisms and functional significance of several examples of teleostean cerebellar configurations, which will be compared with the mammalian case.

The general discussion is mainly devoted to a critical evaluation of the hypothesis proposed in the present paper and to the possible significance of the mormyrid palisade pattern in view of the present hypothesis. It concludes with a few comments on the possible influence of cerebellar climbing fiber input on coincidence detection of parallel fiber activity.

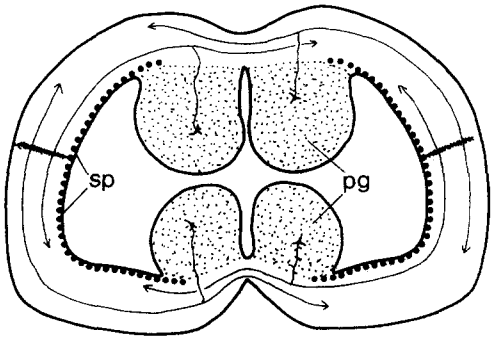

Fig. 5. Transverse section through the cerebellum of the elasmobranch fish *Squalus acanthias* (×8.6; c.f. Fig. 17 of Smeets *et al.*[95]). The position of granule cells is indicated by small stipples and that of Purkinje cells by dots, while the molecular layer is white. To show some aspects of the organization of the molecular layer, the dendritic properties of two Purkinje cells and the axonal properties of four granule cells have been drawn schematically according to the description of Nicholson *et al.*[76] For further details, see Section 2.2.2.

2. MATERIALS, STARTING POINTS AND METHODS

The present paper is an inductive exploration of the possible function of the orthogonal cerebellar parallel fiber–Purkinje cell configuration, based on observations concerning the cerebellar organization as described in the literature and visible in histological material from our own collection. The latter consists of 15-μm serial paraffin sections through the brains of a variety of vertebrates, including the teleostean fish *Salmo gairdneri* (Fig. 1), *Xenomystis nigri* (Figs 2, 4), *Carassius auratus*, *Eigenmannia virescens*, *Ictalurus*

nebulosus (Fig. 2) and *Gnathonemus petersii* (Fig. 3), as well as the elasmobranch fish *Squalus acanthias* (Fig. 5). These serial sections are alternatively stained according to Nissl, Bodian and Klüver–Barrera.

Details concerning the starting points and teleostean cerebellar configurations that underlie the subsequent theoretical analysis are provided. This will be supplemented by a short characterization of the teleostean lateral line system to evaluate specific advantages and constraints of the different cerebellar configurations considered.

2.1. *Starting points*

This paper will analyse a number of cerebellar configurations encountered in teleosts, by way of the assumption that Purkinje cells are maximally stimulated by parallel fibers when all contacts with parallel fibers are activated in such a way that the resulting membrane potentials reach the axon hillock simultaneously to generate spike activity of the axon. The precise implications and variations possible with respect to this assumption will be discussed later, when the hypothesis based on it has been elucidated.

An initial assessment of the conditions necessary to attain a maximal Purkinje cell stimulation is obtained by evaluating the conditions that would lead to approximately simultaneous stimulation of all parallel fiber contacts of a Purkinje cell. In mammals, such an analysis is hampered, if not made impossible, by the complex distribution of the T-shaped parallel fibers originating in ascending granule cell axons. This complex, unknown distribution, together with the unknown length-distributions of parallel fibers, intervenes with a reliable estimation of the populations of granule cells which project to individual Purkinje cells. However, in teleosts a number of simple granule-cell/parallel fiber configurations are present, which allow for a reliable estimation of the population of granule cells that will have to be excited (simultaneously or in a certain sequence) to result in simultaneous excitation of all spiny contacts of single Purkinje cells.

After exploration of the possible functional significance of some of the 'simple' teleostean cerebellar configurations, estimates of whether similar rules might also hold for the more complex, T-shaped granule-axon/parallel fiber configuration will be undertaken. For this purpose it is assumed that the most outstanding feature of a cerebellar cortex, i.e. a thick molecular layer with many thin parallel fibers terminating on spiny dendritic trees, reflects a similar mechanism with a similar functional significance in all the configurations encountered.

2.2. *Teleostean cerebellar configurations*

The cerebellum of teleosts consists of three main parts (Fig. 1), a valvula, a corpus and a caudal lobe.[31,45,77,86] The valvula cerebelli, only present in actinopterygian fishes and absent in all other vertebrate groups, is a rostral continuation of the corpus in the midbrain ventricle under the midbrain tectum (Figs 1, 2). The corpus cerebelli has a position in the dorsal roof of the rostral rhombencephalon (Figs 1, 2), just like the cerebellum of other vertebrate groups. The caudal lobe consists of a granular eminence and a cerebellar crest. The granular eminence is a paired cluster of granule cells located caudolateral with respect to the corpus (Fig. 1). It gives rise to parallel fibers that establish the so-called cerebellar crest, a molecular layer covering the laterodorsally located octavo-lateral line region of the teleostean rhombencephalon (Fig. 1). Similar configurations occur in other fishes, including Elasmobranchii, Holocephalii, Actinopterygii and Sarcopterygii.[45,77,95]

The largest and most differentiated teleostean cerebellum is encountered in mormyrids.[67,68,78,79,96] In these active electrosensory teleosts,[5,6] the valvula covers the entire dorsal surface of the brain, the corpus is differentiated into several lobes, and the large caudal lobe is differentiated into an anterior part, related with the mechanosensory lateral line lobe, and a posterior part, connected with the huge electrosensory lateral line lobe (Fig. 3).

A major difference between the teleostean cerebellum and the mammalian cerebellum is the width of these cerebella. In mammals, it may vary from, for example, about 40 mm in rats[66] to about 170 mm in humans.[12] Consequently, the length of the transversely oriented parallel fibers is not restricted by the dimensions of the molecular layer. However, in teleosts the width of the molecular layer is generally not larger than 2 mm, and frequently much smaller,[65,66] which means that the length of parallel fibers cannot be longer. Immunohistochemical investigations stress the significance of this difference, since a distinct sagittal zonation or compartmentalization of the cerebellar cortex, obviously present in mammals[14,36,103] is absent in teleosts.[14,66] Consequently, the teleostean cerebellum may be considered as a single cerebellar zone with restricted width that limits parallel fiber length. This also holds for the mormyrid 'gigantocerebellum'[78] since the lobulation of the corpus only reflects an increase in length and not in width, while the huge valvula consists of one highly folded ridge or zone of cerebellar cortex with a width of only 400 μm, and a length of approximately 1 m.[6,66,78]

In the present analysis, a detailed description of the different types of granule cell–parallel fiber configurations in teleostean cerebella or cerebellar-like structures is provided. We will start from the mormyrid cerebellum, where all kinds of configurations are present going from rostral to caudal (Fig. 3). Similar configurations observed elsewhere will be discussed in relation to this survey as depicted in Figs 2, 4 and 5.

2.2.1. *Unilaterally located granule cells.* In the rostralmost part of the mormyrid cerebellum, a unilateral location of the granule cells is observed, i.e. at only one side of the molecular layer in the valvular

ridges (Fig. 3B). Consequently, the granule cell axons have a straight course and give rise to parallel fibers without a T-bifurcation or any other branching pattern (Fig. 3B). This means that signal flow in the molecular layer is unidirectional, since all parallel fibers conduct signals in the same direction, from basal to apical in the valvular ridges. In this respect, the configuration deviates from the mammalian one, where molecular layer bidirectional signal transport can be encountered at any point by parallel fibers running from left to right and vice versa.

A similar unilateral location of granule cells with a unidirectional parallel fiber organization is encountered in a typical teleostean cerebelloid configuration in the marginal layer of the teleostean tectum (Fig. 4). The teleostean tectum has a peculiar superficial or marginal layer, like the valvula cerebelli only present in actinopterygians, which consists of numerous thin parallel fibers. These arise from a paired mass of medially located granule cells, termed torus longitudinalis[37,39] (Fig. 4). The teleostean tectal marginal parallel fibers terminate on the apical spiny dendrites of deeply located neurons[46,61,62,101] (Fig. 4), indicated as type I by Meek and Schellart.[69] Consequently, the teleostean tectal marginal layer resembles a cerebellar molecular layer, a similarity stressed by the physiological properties of this tectal layer.[102] Since all parallel fibers in the tectal marginal layer arise from the medially located torus longitudinalis, this system represents a second example of a unilateral location of granule cells and a unidirectional organization of parallel fibers. However, a major difference with the valvular organization just described concerns the parallel fiber length. In the valvular ridges this is restricted to about 400 μm but the parallel fibers covering the tectum are much longer, up to 5 mm or more, depending on the tectal size in different teleosts as well as on the individual size of the specimen under consideration. The ontogenetic as well as the phylogenetic origin of the actinopterygian torus longitudinalis–tectal marginal layer system is unknown. It might be suggested that it is a specialization derived from the valvula cerebelli, which is located just underneath the torus longitudinalis and in many teleosts is apposed to it, but there is no definite proof of this suggestion.

A third example of a unilateral location of granule cells is encountered in the caudal cerebellar lobe of all teleosts, including mormyrids. In this region, the granular eminences give rise to caudally directed parallel fibers covering the rhombencephalic lateral line structures in a so-called cerebellar crest[4,55,59] (Fig. 1). These parallel fibers thus have a unidirectional organization, although in this case not in the transverse but in the rostrocaudal direction. The parallel fibers in the cerebellar crest terminate on the spiny dendrites of Purkinjoid neurons underneath the cerebellar crest[15,70] (Fig. 1).

2.2.2. *Bilaterally located granule cells.* The large, ridged part of the mormyrid valvula cerebelli is connected with the corpus via the so-called lobus transitorius[78] (Fig. 3). This is an example of a bilateral location of granule cells, since these are restricted to two rows, located at the left and right side of the molecular layer. Basally located granule cells, with a position under the layer of Purkinje cells, are absent. Similarly to unilaterally located granule cells, the axons of bilaterally located granule cells give rise to parallel fibers that enter the molecular layer from a lateral location without any branching or T-bifurcation (Fig. 3C). However, in this case the molecular layer shows not a unidirectional, but a bidirectional parallel fiber organization, since at any place both fibers coursing from right to left and from left to right are present (Fig. 3C).

Additional examples of a bilateral granule cell location, although somewhat less strict or clear, can be encountered in the valvula cerebelli of other teleosts and in the cerebellum of elasmobranchs. In the valvula of, for example, trout, goldfish and *Xenomystis* (Figs 1, 2) the lateral location of granule cells dominates at several places. However a variable number of basally located granule cells (underneath the layer of Purkinje cells) may occur as well, yielding all kinds of transitions between the bilateral location encountered in the mormyrid lobus transitorius and the combined lateral–basal configuration in the mormyrid cerebellar lobe C_1 (Fig. 2).

The configuration of granule cells in elasmobranchs may also be considered as a bilateral location, since in these animals granule cells are restricted to two paired longitudinal ridges or prominentiae granulares[77,95] (Fig. 5). Thus, with respect to the largest, laterally located part of the elasmobranch cerebellar molecular layer, granule cells have a bilateral location as well, giving rise to parallel fibers either crossing the molecular layer from below to above or vice versa (Fig. 5).

2.2.3. *Basally located granule cells.* Continuing a rostro-caudal analysis of the mormyrid cerebellum, the lobus transitorius is followed by lobe C_1, which has been extensively analysed by light- and electron-microscopy.[65,67,80] Although previously considered as part of the corpus cerebelli, immunohistochemical data[66], as well as the granule cell location, suggest that it is most probably homologous to the medial part of the valvula of other teleosts.[66] In lobe C_1 a combined basal–lateral location of granule cells is encountered, with laterally located granule cells giving rise to unidirectional parallel fibers and with a majority of basally located granule cells (i.e. under the layer of Purkinje cells) giving rise to parallel fibers by way of a T-bifurcation. An interesting aspect of this configuration, as pointed out by Meek and Nieuwenhuys,[65] is that all parallel fibers, just as in uni- and bilateral locations, have the same length and extension in the left–right direction, but differ with respect to their site of origin. However, in contrast to the bilateral configuration described above, with only two possibilities, i.e. an origin from the left or the

right side, there is now a continuing range. This varies from medially located granule cells with a symmetrical T-bifurcation (i.e. with a left and right parallel fiber branch of equal length), via intermediate located granule cells with asymmetrical T-bifurcation (i.e. with a short ipsilateral and a long contralateral branch), to laterally located granule cells with similar unidirectional parallel fibers as present in uni- or bilaterally located populations of granule cells[65] (Fig. 3D). Similar configurations are encountered in the transition region between the corpus- and the valvula cerebelli of other teleosts (Figs 1, 2).

In lobes C_2–C_4 of mormyrids and in the corpus cerebelli of other teleosts, a basal location of granule cells predominates (Fig. 3E). Thus, similar to the organization of the mammalian cerebellum, granule cells are located underneath the layer of Purkinje cells and give rise to bidirectional parallel fibers via the well-known T-bifurcations in the molecular layer, although it cannot be excluded that the most laterally located granule cells still give rise to unidirectional parallel fibers, just as described for C_1. However, their contribution is relatively low. A major difference between the mammalian and teleostean situation is the width of the molecular layer. Although larger than in lobe C_1 and the lobus transitorius, where cerebellar width is about 700 μm, the width of the molecular layer of lobe C_2–C_4 hardly exceeds 2000 μm, and thus is substantially smaller and more restricted than that of mammals, e.g. in rats the width varies from about 10 to 50 mm in different parts,[66] while in cats and primates much larger values may occur.

Another difference between the mammalian and teleostean cerebellum is the tubular shape of the latter, which presents itself at several levels in transverse sections as a cylinder, with a central core of granule cells and a mantle of molecular layer (e.g. Figs 1H, 2F, 3E). We consider this configuration as a folded, double sheath of cerebellar cortex with a largely separate and independent dorsal and ventral part. Thus the configuration is not a true spheroid molecular layer with parallel fibers as long as the complete circumference which runs from dorsal to ventral for the following reasons. (1) We observed in Golgi preparations that most parallel fibers in lobe C_3 run horizontally, either in the dorsal or in the ventral part of the molecular layer, and that vertical orientations in the lateral part are scarce.[65] (2) We calculated that the average length of parallel fibers in lobe C_3 is equal to about half of the circumference.[65] (3) In the largest, caudal part of lobe C_3, as well as in most parts of the corpus of other vertebrates, the lateral parts of the molecular layer are very thin or even absent, suggesting only a small number or even an absence of fibers coursing from dorsal to ventral. (4) For lobe C_3 a true cylindrical transverse transection is only present in the most rostral part, where the lateral parts of the molecular layer are equally as thick as in the dorsal and ventral parts. However, the orientation of parallel fibers is different in this case occurring not from left to right but obliquely rostrocaudal. This suggests that the lateral part contains the lateral tips of the transversely running parallel fibers in the most rostral pole, and thus, is the result of strong dorsoventral folding of the cerebellar cortex at the tip of lobe C_3 (Fig. 3A), and not from any other, more complicated process with a specific functional significance. (5) The dorsal and ventral halves of lobe C_3 are connected with the brain with different fiber tracts, which contain different components.[68] (6) Comparison of the overall shape of the corpus cerebelli in many vertebrates shows a large variability. This is sometimes expressed as a lobe with a rostral pole, sometimes completely caudally directed, and sometimes both configurations are combined (Fig. 2). Most probably, this suggests a random folding or foliation, based on spatial constraints and the most efficient position in the skull, rather than on a specific functional significance of all variations encountered.

In conclusion, we consider the corpus cerebelli of teleosts, including lobe C_2–C_3 of mormyrids, as a folded plate of cerebellar cortex of restricted width, with a basal location of granule cells giving rise to parallel fibers by way of ascending granule cell axons with a characteristic T-bifurcation.

2.2.4. *Apically located granule cells.* A last configuration of granule cells encountered in mormyrids concerns the relation between the caudal lobe and the electrosensory, or posterior, lateral line lobe (Fig. 3F). The mormyrid mechanosensory, or anterior, lateral line lobe has a molecular layer, or cerebellar crest arising from anteriorly located granule cells similar to the unilateral location described above. The relationship between the posterior part of the granular eminence, or caudal lobe, and the electrosensory lateral line lobe are more complicated. Since the granule cells cover part of the molecular layer of the electrosensory lateral line lobe (Fig. 3F), they have attained an apical position, i.e. at the opposite side of the molecular layer to the Purkinjoid crest cells, which are differentiated into several subtypes in this lobe.[54] A similar configuration is present in gymnotiform fishes.[56] In most regions of the electrosensory lateral line lobe of both mormyrids and gymnotids we therefore encounter an apical position of granule cells, which gives rise to parallel fibers via a T-bifurcation, not arising from below, but from 'above'.

In the most medial part of the electrosensory lateral line lobe the situation is different, since this region is not covered with granule cells. Consequently, in this molecular layer, parallel fibers arise either from the left, or from the right cluster of granule cells, in a configuration resembling the bilateral location of granule cells as described above (Fig. 3F).

2.3. *The teleostean lateral line system*

For the evaluation of specific advantages and constraints of the cerebellar configurations just sur-

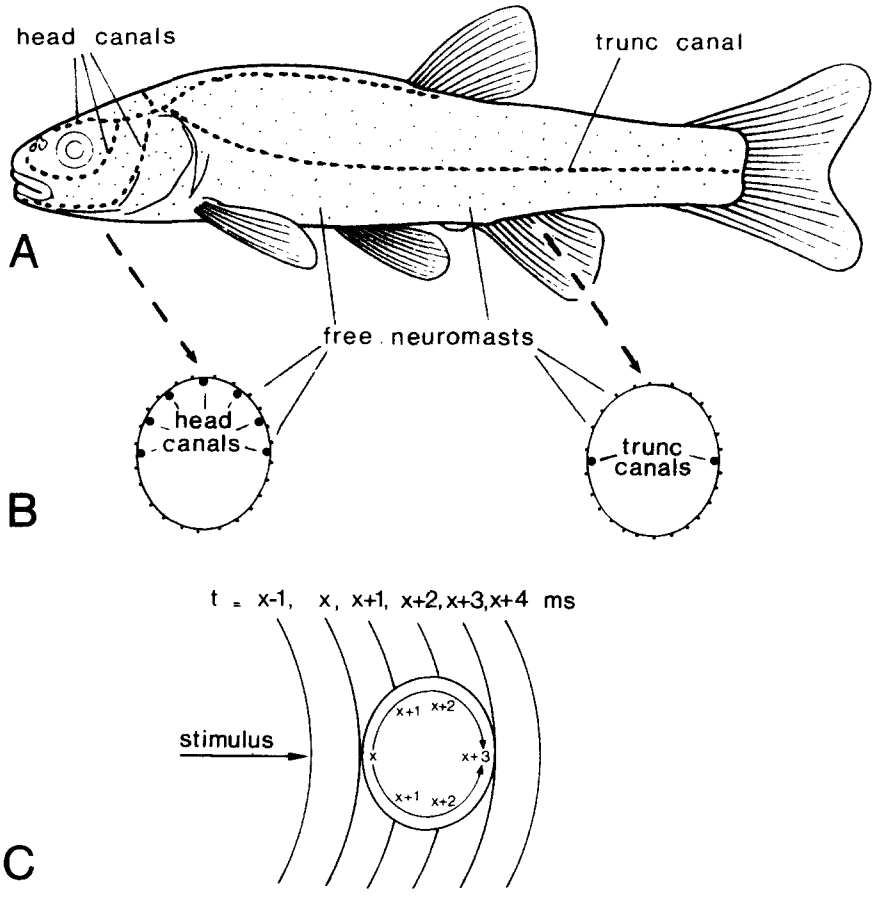

Fig. 6. Some aspects of the teleostean mechanosensory lateral line system, used as a conceptual model in the present study. (A) The approximate position of free neuromasts (small stipples) and lateral line canals (broken lines) in the head and trunc region of a teleost (after Dijkgraaf; see Ref. 22, Fig. 2.2). (B) The models used in the present paper, derived from modified and adapted transverse sections through the head and trunc region, with the presumed position of seven head canals and two trunc canals, and freely dispersed free neuromasts. (C) Approximate effect of a lateral line stimulus from a certain direction on the surface of a spheroid part of the body surface of a fish. Notice the time difference of three time units between stimulation of the left and right side of the body surface, and the presence of a stimulus wave on the dorsal and ventral surface of the body running from left to right. For further details, see Section 2.3.

veyed and the intracerebellar mechanisms to be proposed in the next sections, a conceptual framework based on several specializations and configurations of the well-developed teleostean lateral line system will be used as a model. Consequently, a short characterization of this system seems useful here. References will be largely confined to the reviews presented in the recent book on the mechanosensory lateral line, edited by Coombs, Görner and Münz.[22]

For our present purposes it is important to notice that the lateral line sensory system is involved in the detection of near field water movements[41,42] and consists of hair cells that are distributed over the surface of the animal (free neuromasts) or are concentrated in specialized groups in lateral line canals under the skin of the animal.[73,104,105] In general, there is one canal at each side in the trunk region, while in the head region canals with a more complex branching pattern occur[104,105] (Fig. 6). Lateral line sensory organs project via lateral line nerves to the rhombencephalic lateral line (or medial) nucleus, sometimes referred to as the mechanosensory lateral line lobe. This nucleus is covered with the cerebellar crest described above. The granular eminence, from which the parallel fibers in the crest occur, is the second major target of primary lateral line afferents. Some authors have reported additional projections to the corpus and valvula cerebelli.[60] The rhombencephalic lateral line nucleus projects massively, by way of the lateral lemniscus, to the midbrain torus semicircularis. Further projections from this torus terminate in the midbrain tectum, with which it is reciprocally connected,[64,94] and in the diencephalic nucleus preglomerulosus and the nucleus ventromedialias thalami.[74]

In mormyrids and gymnotids, the projections of the torus semicircularis are more widespread. In these teleosts, mechanosensory lateral line and electrosensory lateral line organs are present.[3] These project massively by way of an electrosensory rhomben-

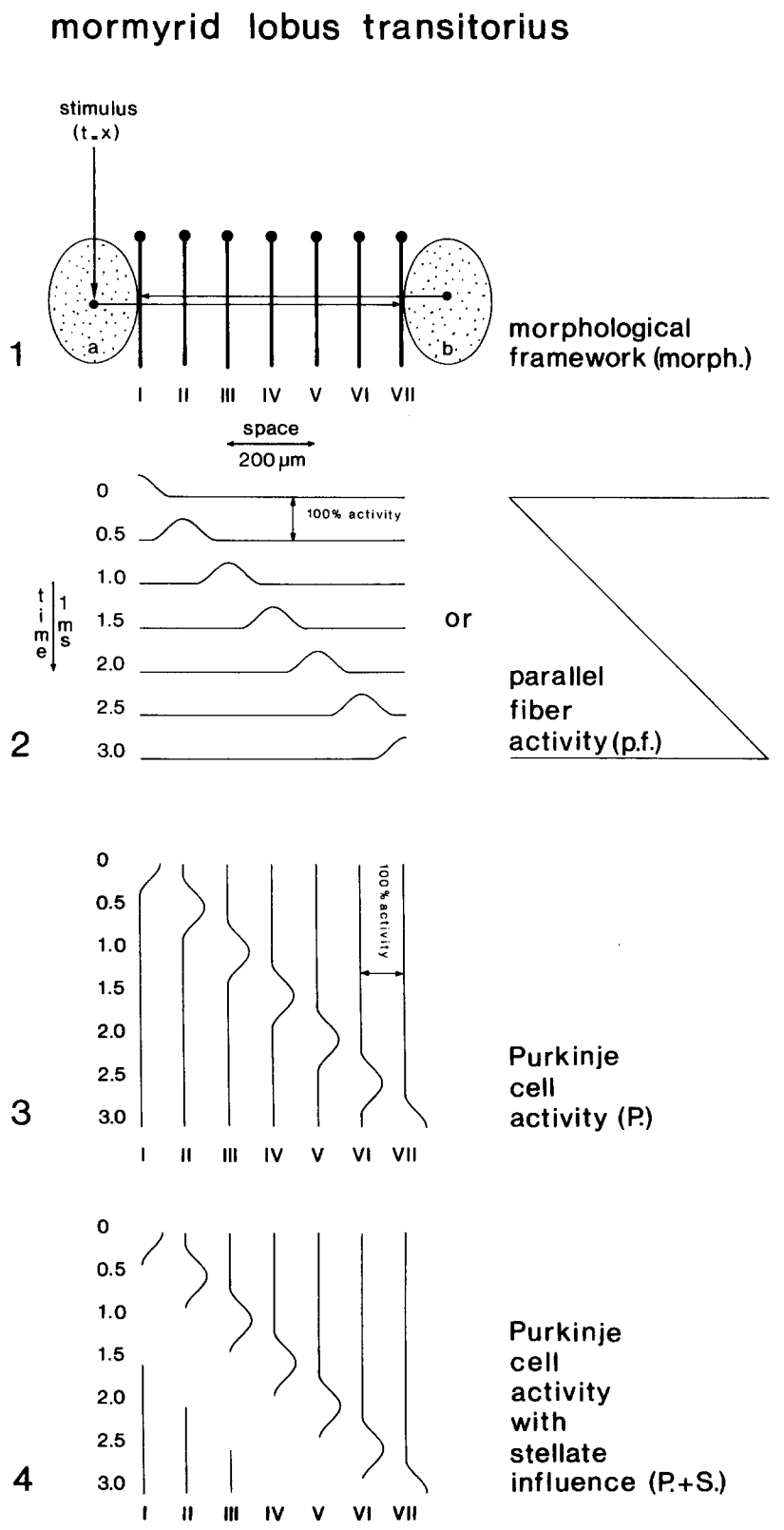

Fig. 7. Visualization of some aspects of the conceptual framework used to analyse intracerebellar mechanisms involved in signal processing of the mormyrid lobus transitorius. In this and subsequent figures, part 1 indicates the morphological framework (morph); part 2 parallel fiber activity (pf) in a space–time matrix; part 3 Purkinje cell activity (P) in a space–time matrix without consideration of effects of inhibitory stellate cells, and part 4 Purkinje cell activity with consideration of stellate cell effects (P + S). Part 5 (not present here but only in Figs 9–15) introduces the mechanosensory lateral line model (mllm) in the analyses of intracerebellar mechanisms. For further details, see Section 3.1.1.

cephalic lateral line lobe, into the midbrain torus semicircularis. The latter is very enlarged and specialized for electroreceptive purposes in these teleosts.[7,19] In gymnotids, the torus semicircularis projects, apart from to the tectum and diencephalic (electrosensory) nucleus, to a so-called nucleus prae-eminentialis and several other nuclei in the brainstem.[19,21] Remarkably, the electrosensory part of the mormyrid torus semicircularis also projects massively to the valvula cerebelli.[6,32]

Since a valvula cerebelli is only present in actinopterygians, including the most successful group of teleosts with more than 20,000 species,[75] several authors have correlated the presence of a valvula with the presence of a well-developed lateral line system, going on to indicate the valvula as a tertiary lateral line center.[77] In this analysis, the valvula would represent the interface between the lateral line system and motor control in a way similar to how the corpus cerebelli interfaces somatosensory input and motor control. However, apart from the involvement of the valvula of mormyrids in electroreception, the physiological evidence for this statement is rather weak. Although Lee and Bullock[47] found mechanosensory lateral line responses in the valvula of catfish, visual and somatosensory responses also appeared to be present.

The following simplified and adapted model of the lateral line sensory system will be used: receptors are concentrated in one canal on each side in the trunk region, in seven dorsally and laterally located canals in the head region, and dispersed freely over the animal surface (Fig. 6B). The canal organs project to the rhombencephalic lateral line nucleus in a way that maintains their rostro-caudal topographic organization (trunk canal) as well as their medio-lateral location (head canals). The same reasoning holds for free neuromasts. We presume in addition that the order is roughly maintained in further central connections. Finally, we should mention that the lateral line system is able to determine its stimulus source (or target) angle at the water surface on the basis of time differences between different canal organs as shown by behavioural experiments[8,93] (e.g. Fig. 6C). Conduction velocities of water movements involved in this detection vary from 23 cm/s to 50 cm/s on the water surface.[8,93] Underwater, conduction velocities rapidly increase to much higher values.[41,42,93]

The lateral line system will be used as a conceptual framework to discuss the possible functional significance, and especially the constraints, of the different cerebellar configurations to be considered and the intracerebellar mechanisms proposed. The mechanosensory lateral line system is particularly useful for this purpose since there are indications that the teleostean cerebellum might indeed in part be involved in lateral line input processing, and since it has three different types of configurations that represent examples of three different ways of receiving a similar peripheral (physical) input, i.e. working in the same sensory interface and space–time domain (Fig. 6B, C). It should be stressed that it is not the intention to exclude any other possibility with respect to teleostean cerebellar functions. These will be discussed more fully when physiological or other pertinent data become available.

3. RESULTS AND DISCUSSIONS

3.1. *Example 1: the mormyrid lobus transitorius*

3.1.1. *Conceptual framework* 1. In the next section, the possible functional mechanisms present in the lobus transitorius of the mormyrid cerebellum will be explored. The lobus transitorius is presented above as a clear example of a molecular layer with bilaterally located granule cells (Fig. 3C). We will now consider how spiny contacts with parallel fibers from a specific Purkinje cell can be simultaneously activated (see Starting points). For this purpose we will consider seven Purkinje cells at a similar rostrocaudal level, but with a different position in the transverse plane (Fig. 7.1). These are all contacted by the same population of parallel fibers, 50% arising from the left and 50% arising from the right side, and all traversing the complete molecular layer, which has a width of about 600 μm (Fig. 7.1). The seven Purkinje cells under consideration have an equidistant distribution with mutual distances of about 100 μm. The conduction velocity of parallel fibers is set at 0.2 m/s, a value frequently reported for thin, unmyelinated parallel fibers in lower vertebrates.[38,76,85,102] It should be noted, however, that the precise real value is unknown, but also unimportant for our model.

Within the conceptual framework just presented, simultaneous stimulation of all granule cells at the left side of the lobus transitorius would result in excitation of 50% of all parallel fibers in the molecular layer in an activity wave of unknown shape, running from left to right in 3 ms, as visualized in Fig. 7.2; excitation of 50% of the parallel fibers is encoded by the height of the activity peak in this figure. The time at which the peak of parallel fiber activity reaches Purkinje cell I is set at $t = 0$; the time of mossy fiber stimulation precedes $t = 0$ with an unknown but fixed number of ms (x); and the shape of the parallel fiber activity wave has been chosen arbitrarily, since the precise spatio-temporal distribution pattern of mossy fiber input as well as the precise response characteristics of granule cells are unknown. (The shape chosen in Fig. 7.2 would mean a population spike of 0.75 ms, occupying 150 μm parallel fiber length at a conduction velocity of 0.2 m/s). For our model, only the peak activity is important and all kinds of shapes are acceptable, although the sharper the better. When only the peak activity is considered, parallel fiber excitation in the lobus transitorius can be visualized as a simple oblique line in a time–space matrix (Fig. 7.2, right side).

The presumed Purkinje cell activity that results is indicated in Fig. 7.3. Each Purkinje cell gives a similar

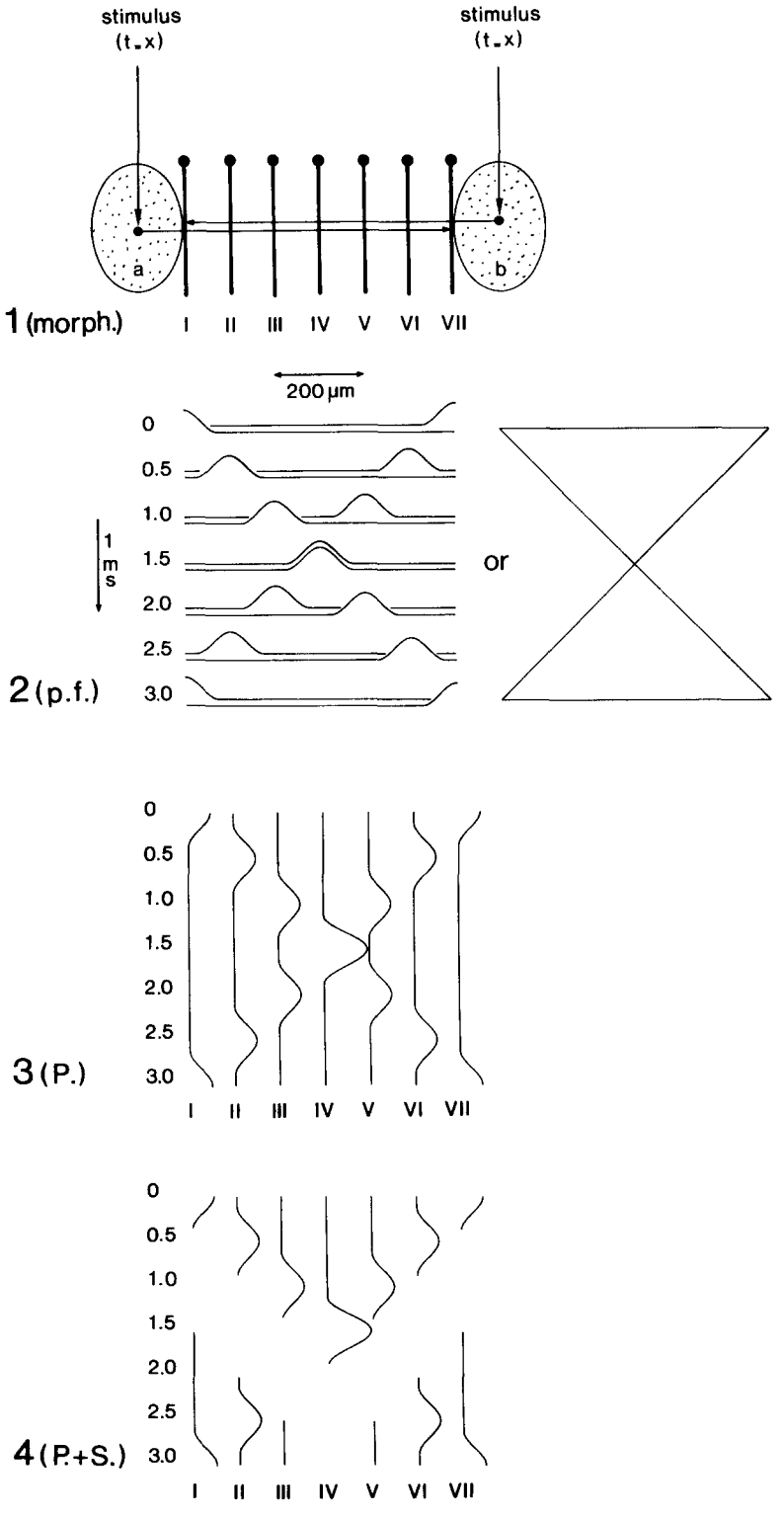

Fig. 8. Visualization of the intracerebellar mechanism presumed to be involved in coincidence detection in the mormyrid lobus transitorius. For further details, see legend of Fig. 7 and Section 3.1.2.

response, the shape of which is again chosen arbitrarily and the height of which is 50% of the maximal activity possible, in line with our starting point. The only difference between the activity of the seven Purkinje cells under consideration is the time of their activity. Each of them has its peak activity 0.5 ms later than the previous one. For the sake of simplicity, the fixed and constant time delay between parallel fiber activity and Purkinje cell activity has not been addressed.

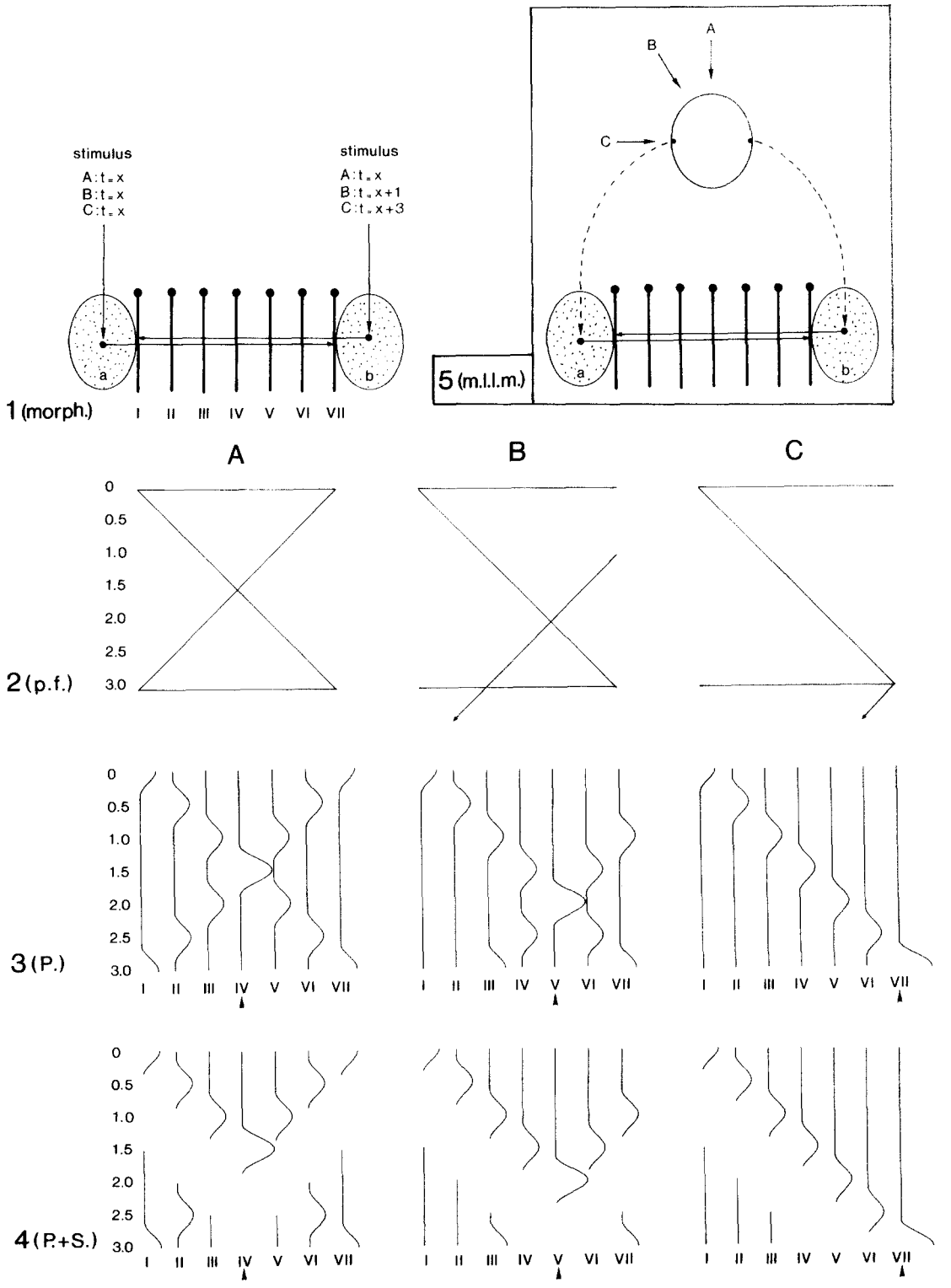

Fig. 9. Visualization of some further aspects of intracerebellar mechanisms presumed to be involved in coincidence detection in the mormyrid lobus transitorius. A, B and C indicate situations with different time delays between left and right cerebellar input, as indicated left above. This might be related with different stimulus sources as indicated right above in part 5. For further details, see legend of Fig. 7 and Section 3.1.2.

Since the inhibitory influence of stellate cells on Purkinje cell activation by parallel fiber input is a general and constant feature in cerebellar molecular layers, it is incorporated into our framework (see Fig. 7.4). After the time delay necessary for stellate cell–Purkinje cell signal transduction, Purkinje cells

will be inhibited by the stellate activity evoked by parallel fiber activity. This is indicated by an interruption of arbitrary length in the Purkinje cell activity line (see Fig. 7.4). Such a visualization removes the unknown strength of the stellate inhibition from the frame of reference. Also out of consideration is whether or not the inhibition would lead to a reduction or abolishment of spontaneous activity or to a reduced excitability in normally non-spontaneously active cells. The duration of stellate inhibition was set arbitrarily to 1.5 ms to remain within the boundaries of the space–time matrix used in Fig. 7, but it should be noted that longer lasting stellate inhibitions have been reported.[38,76]

3.1.2. *Purkinje cells as coincidence coders* 1. The hypothesis that Purkinje cells act as coincidence coders for parallel fiber activity in a cerebellar timing device is shown in Figs 8 and 9. Within the conceptual framework presented above, the following interactions between left–right and right–left running parallel fiber activity waves may be expected. When mossy fiber activity simultaneously stimulates the left and right populations of granule cells at $t = x$ (Fig. 8.1), it not only evokes the activity wave running from left to right as shown in Fig. 7.1, but also a similar one running from right to left (Fig. 8.2). Both waves meet each other at $t = 1.5$ at the location of the most medial Purkinje cell (IV in Fig. 8), with the result that this Purkinje cell is once excited 100% instead of twice for 50%, as is the case for the other cells shown in Fig. 8.3. The inhibitory activity of stellate cells greatly enhances the spatio-temporal activity differences of Purkinje cells, since they not only inhibit the activity of the maximally stimulated Purkinje cell (IV) after its maximal stimulation, but also the activity of neighbouring Purkinje cells during and after maximal stimulation of this Purkinje cell (Fig. 8.4). This increases both spatial and temporal 'contrast' in Purkinje cell activity.

The fact that the mechanism just described is a suitable timing device for decoding temporal differences in different places is shown in Fig. 9. When the left and right populations of granule cells are not stimulated simultaneously (Fig. 9A), but with a difference of 1 ms (Fig. 9B) to 3 ms (Fig. 9C), the 100% Purkinje cell activity peak shifts to more laterally located Purkinje cells, the position of which is directly related to certain left–right temporal differences. Both the sagittal orientation of Purkinje cell dendritic trees, i.e. perpendicular to the course of parallel fibers, as well as the inhibitory activity of stellate cells, greatly enhance the coincidence detecting possibilities of Purkinje cells as proposed. This is because they greatly sharpen, both in space and time, the intracerebellar activity peak of Purkinje cell activity resulting from stimulation of the left and right populations of granule cells in the mormyrid lobus transitorius (Fig. 9.4).

3.1.3. *Possible functional significance* 1. With respect to the functional significance of the coincidence detection proposed above, no definite statements can be made, since the afferent and efferent connections of the lobus transitorius are unknown and physiological data are lacking. In general, the cerebellum is thought to be involved in motor control, and in such a system the timing mechanism proposed could be involved in evaluation and correction of planned movements that require fixed time differences between the left and right part of the body or between certain groups of muscles. These time differences should be within the range of 3–4 ms, since the restricted width of the lobus transitorius does not allow for the analysis of larger differences in our model.

When one considers the possible functional significance of time-difference analysis in the lobus transitorius for the analyses of input on the basis of the conceptual lateral line model depicted in Fig. 6B, C, the trunk canals are of particular interest. Aquatic motions from a certain source will reach each canal with a certain time delay which is related to their origin from the left, the right or intermediate sides of the body (Fig. 6C). When these differences lie within the range of 3 ms, the lobus transitorius could calculate the original position of the source of lateral line canal input on the basis of temporal differences, provided that the left and right canal organs are connected in a regular way with the left and right (or vice versa) granule cell ridge of the lobus transitorius. More generally stated, the lobus transitorius seems well organized for the detection of time differences within the range of 0–3 ms, and this might be used to localize the direction of a stimulus source received by a paired set of sensors. The situations indicated at A, B and C in Fig. 9.2–4 would then correspond with A, B and C of Fig. 9.5. It should be noted that the conduction velocity of aquatic movement signals for the canal organs should be in the range of 100 m/s to yield a left–right difference of approximately 3 ms, a value which in reality does not seem to be involved in stimulus source detection on the basis of lateral line input.[8,93]

3.1.4. *Discussion* 1. The hypothesis proposed above, which states that Purkinje cells in the lobus transitorius, a cerebellar cortex with a bilateral location of granule cells, are coincidence detectors in a timing device, is based on a theoretical analysis of the possible functional significance of the morphological specializations observed, and should be further investigated with electrophysiological techniques. The lobus transitorius seems very suitable for this purpose, since it does not seem too complicated to stimulate the left and right population of granule cells with electrodes and to investigate whether medially and laterally located Purkinje cells are indeed tuned to different left–right temporal differences.

Awaiting further electrophysiological validation or rejection of the hypothesis proposed, the following arguments in favor of this hypothesis might be put forward. When one considers the optimal configur-

ation of a timing device in the central nervous system, a number of requirements are met by the organization of the lobus transitorius. Firstly, the afferent (parallel) fibers interacting with each other from two opposite sides should be as small as possible to decrease conduction velocity and to increase spatial segregation of temporal differences. Secondly, the number of these small fibers should be as large as possible in order to optimize the signal–noise ratio of their interactions. Thirdly, the dendritic fields of the postsynaptic elements to these numerous fibers (i.e. the Purkinje cells) should be oriented perpendicularly to the fiber stream without overlap, to be as sharply as possible tuned to the time differences and interactions of left–right and right–left populations of parallel fibers. Fourthly, the effect of each small parallel fiber should be very small, to prevent a situation where postsynaptic cells give maximal responses when only a subpopulation of their afferents are active. This would require an attenuating device that can determine and reduce the weight of individual inputs in relation to the total input on a neuron, a function which is frequently proposed for cerebellar spines (e.g. see Ref. 65 for review). Fifthly, inhibitory interneurons which inhibit the primary postsynaptic elements (Purkinje cells) immediately after their peak activity, would greatly enhance the contrast in activity levels of different Purkinje cells, and would thus act as a spatio-temporal filter optimizing the tuning of individual Purkinje cells for specific time differences. Finally, these inhibitory interneurons should not have attenuating spines, but should be strongly excited by parallel fiber input, to inhibit the Purkinje cells as soon and as strongly as possible after their balanced peak activity. Consequently, the structural organization of the lobus transitorius seems, at first hand, optimally specialized for a timing device, and less optimal for any other function that may be proposed.

The intracerebellar mechanism proposed for the mormyrid lobus transitorius resembles, in several aspects, the coincidence detecting mechanism present in the acoustic nucleus laminaris.[16,18] In this nucleus, the degree of coincidence of input entering from opposite sides is used to calculate the position of acoustic stimuli on the basis of interaural temporal differences. However, the nucleus laminaris receives input from a very precise and fast-conducting fiber system, while cerebellar input seems much less precise, since it is not directly connected with sensory and/or corollary motor input, but is connected via several relays, each introducing delays and noise. The general implications of such input compared with the precise acoustic input for coincidence-detecting mechanisms will be considered in the general discussion.

In the introduction, the lobus transitorius was presented as an example of a cerebellar molecular layer with a bilateral location of granule cells. We suggest that similar mechanisms may be proposed for other cerebellar parts with a comparable location of granule cells. Special attention in this area should be given to the elasmobranch cerebellum since the granule cells in these aquatic vertebrates are concentrated into ridges, two at the right side and two at the left side (Fig. 5). A similar coincidence-detection mechanism is proposed as for the lobus transitorius, not across the midline but in a dorso-ventral direction at the right and at the left side. Similarly to the teleostean valvula, part of the cerebellar input in elasmobranchs, although certainly not all, originates in lateral line centers.[95]

3.2. *Example 2: the torus longitudinalis–tectal marginal layer system*

In the present section, an analysis will be made of possible coincidence-detecting mechanisms in some examples of molecular layers with a unilateral location of granule cells. Most attention will center on the cerebelloid marginal layer of the midbrain tectum and the unilateral location of its granule cells in the torus longitudinalis (Fig. 4), since this is the best-investigated teleostean cerebelloid circuit.[35,81,82,101,102]

3.2.1. *Conceptual framework* 2. The present analysis starts from marginal tectal parallel fibers of 3 mm in length, a value within the range of tectal dimensions encountered in teleosts,[63,101] although it should be noted that smaller as well as much longer marginal fibers may occur. Just as in the previous example, we will consider seven postsynaptic Purkinjoid neurons, indicated as type I in the tectum,[63,64,69] located from medial to lateral with mutual distances of 500 μm. Similar to Purkinje cells, they make spiny contacts with parallel fibers, but unlike Purkinje cells, their dendrites are not restricted to the sagittal, or any other, plane (Fig. 10.1). It is otherwise similar to Example 1 (Fig. 7), except for the conduction velocity of the parallel fibers.

The crucial base of the present example is the observation of Vanegas *et al.*[102] that the tectal marginal parallel fibers are composed of two populations, one with a conduction velocity of about 0.16 m/s and one with a conduction velocity of about 0.20 m/s. In Fig. 10.1 these are indicated by a thin and a thicker line, originating accordingly from a small and a somewhat larger granule cell. This means that in our model signals conducted by the slowly conducting fibers (0.16 m/s) traverse their parallel fiber trajectory of 3000 μm in about 18 ms, while those conducted by the faster fibers (0.20 m/s) reach the lateral margin of the tectum in 15 ms.

3.2.2. *Coincidence detection* 2. On the basis of the framework presented above, it is easy to postulate a useful coincidence detecting mechanism for the torus longitudinalis–tectal marginal layer parallel fiber system. In this system, when the 'thick' and 'thin' fiber populations were stimulated with a time delay of 1.5 ms, the 'fast' fiber response would pass the 'slow' fiber response at the site of cell IV (Fig. 10) which would thus be excited once for 100% instead of twice

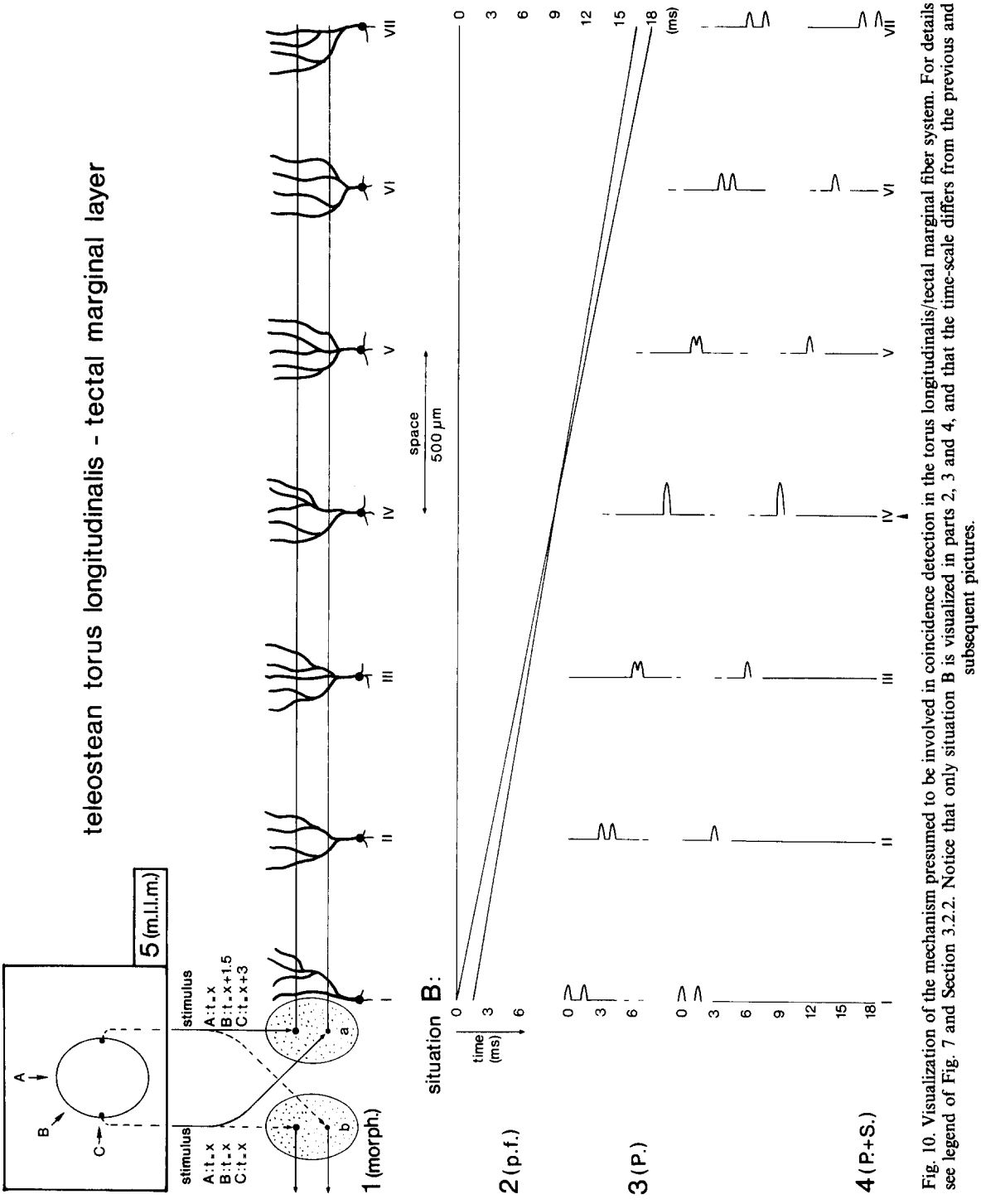

Fig. 10. Visualization of the mechanism presumed to be involved in coincidence detection in the torus longitudinalis/tectal marginal fiber system. For details see legend of Fig. 7 and Section 3.2.2. Notice that only situation B is visualized in parts 2, 3 and 4, and that the time-scale differs from the previous and subsequent pictures.

for only 50%, similar to the situation described in Example 1. Other time delays, varying from 0 to 3 ms would stimulate other cells for 100%, whose location is consequently correlated with particular time differences, varying from 0 ms for the medialmost cell (I in Fig. 10) to 3 ms for the most lateral cell in our model (VII in Fig. 10). The influence of inhibitory interneurons would, as described in Example 1, greatly enhance the spatial 'contrast' of activity in type I cells, since in the neighbourhood of the interaction peak the excitation of the fast fibers falls within the inhibition of the slow fibers or vice versa (Fig. 10.4).

3.2.3. *Possible functional significance* 2. The teleostean tectum is a frequently investigated part of the brain, involved in the processing of visual as well as non-visual sensory input and in the generation of goal directed movements (for review, see e.g. Refs. 35, 63, 64, 101). An important aspect of its organization is the topographic representation of visual as well as several non-visual afferents, which constitute tectal maps of the space around the animal. The way in which the medio-laterally running beams of marginal parallel fiber activity could fit into such a topographically organized system has been unclear until now. One of the most attractive aspects of the coincidence detecting hypothesis we propose is that it presents a straightforward mechanism by which the marginal fibers can provide a topographically organized input on the basis of coincidence coding of temporal differences carried by parallel fibers with a similar direction but with a different conduction velocity.

With respect to the possible sensory input of the torus longitudinalis, it is very attractive to consider, as a model, a similar lateral line input as introduced for the lobus transitorius, originating from the left and right trunk lateral line canal. By means of a simple, although indirect, connectivity between the left and right canal organs, the ipsilateral fast marginal fiber system and the contralateral slow fiber system one could obtain a precise match between the source position indicated by the marginal fiber system on the basis of temporal differences in lateral line input, and the visuotopic map in the tectum (Fig. 10.5). The functional significance of the torus longitudinalis–marginal fiber-type I cerebelloid system could then be indicated as integration of topographical aspects of lateral line and visual input for the generation of goal directed movements.

The evidence in favor of such a functional significance of the torus longitudinalis–marginal fiber system is largely circumstantial. Kishida[44] has shown that a well-developed torus-longitudinalis-marginal tectal layer system is correlated with a habitat in streaming water or with the ability to traverse large depth differences and, therefore, with the dependence of the animal on its lateral line system. Since the main input to the torus longitudinalis comes from the valvula cerebelli,[39] the uncertainties discussed with regard to the involvement of the valvula in lateral line input processing also hold for the torus longitudinalis. The main point until now is that the configurations encountered in the lobus transitorius, with a bilateral location of granule cells, and in the torus longitudinalis, with its unilateral location of granule cells, seem to represent a very effective mechanism for determining temporal differences between two inputs, and, thus could be used for calculation of the position of a stimulus in space on the basis of time differences in the activation of a paired set of sensors along the body of the animal, or along any other cylindrical part of the body (e.g. a muscle).

Physiological experiments point to an alternative functional significance of the torus, i.e. providing the tectum with a corollary eye movement signal.[81,82] Northmore *et al.*[82] found two populations of neurons in each torus longitudinalis, a dorsal one bursting after light dimming in the contralateral visual field, and a ventral one responsive in relation with active, but not passive eye movements. The photic response is probably generated by tectal input, and the corollary input by the valvula.[81] Thus, these results suggest a function in comparing expected movements of the visual environment with the actual observed input, or, alternatively in relating body movements to eye movements.[35] It is presently not clear how the coincidence-detecting mechanism proposed would be of significance to such a function. However, it is equally obscure how the unilateral location of granule cells might in another way be of advantage to such a function, since differentiation of signals is only possible in the rostrocaudal direction, but not in the medio-lateral direction, without coincidence detection. In addition, it is unexplained why in particular teleosts, with their restricted eye movement repertoire, should have developed such a peculiar and specialized valvula cerebelli-torus longitudinalis–tectal marginal layer system to relate visual input with active eye movements, where similar functions in animals with much more complicated eye and head movements are met by other, apparently less specialized centers. More physiological data are necessary to more fully evaluate the functional involvement of the teleostean torus longitudinalis–tectal marginal fiber system in detail.

3.2.4. *Discussion* 2. In addition to the functional aspects, the following points deserve some discussion.

Example 2 shows that for molecular layers with a unilateral location of granule cells, a similar coincidence-detecting mechanism is possible as proposed for molecular layers with a bilateral location of granule cells. This is on the basis of parallel fibers coursing in the same direction with a different conduction velocity instead of parallel fibers running in opposite directions with a similar conduction velocity. Two marked differences in the organization of the molecular layers involved were noticed. Firstly, the parallel fibers in the unilateral system are much longer, and have to be about five times as long as in a bilateral system to be able to detect a similar range of time differences (in our example 3000 μm instead

of 600 μm for 3 ms). This implies that the spatial sharpness of parallel fiber activity interference peaks is much lower.

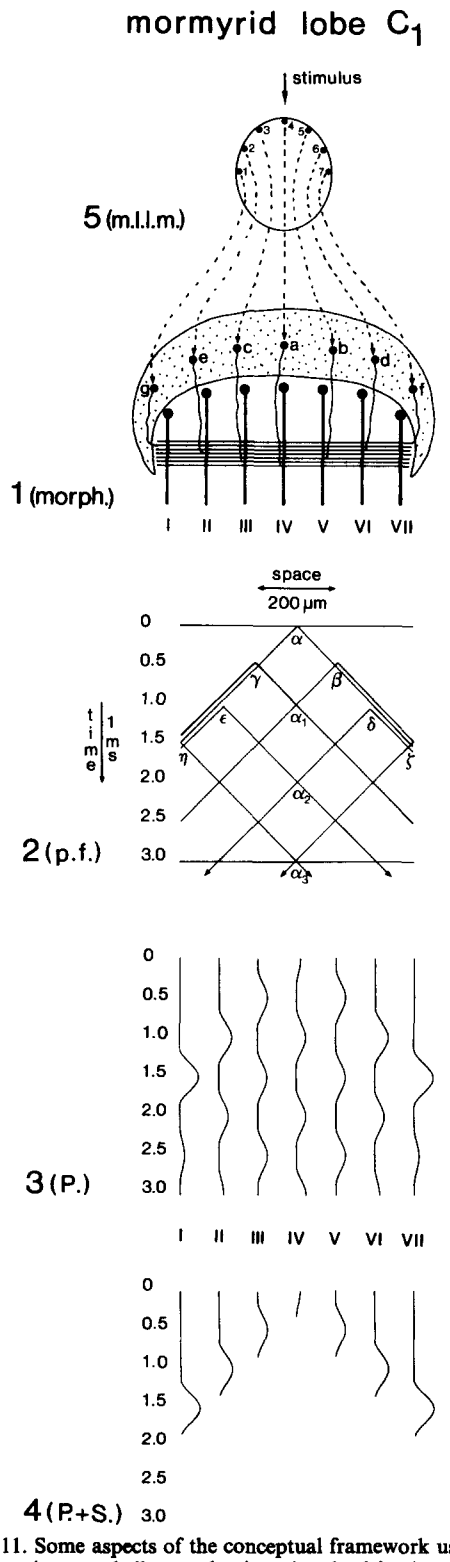

Fig. 11. Some aspects of the conceptual framework used to analyse intracerebellar mechanisms involved in signal processing of the mormyrid cerebellar lobe C_1. For details see legend of Fig. 7 and Section 3.3.1.

Related to the first difference is the absence of a sagittal orientation of the postsynaptic, coincidence-detecting dendritic trees. Conceivably, a more sagittal orientation of dendrites in the marginal tectal layer would not substantially enhance spatial differentiation of time differences because of the broad interference waves of the unidirectional parallel fiber activity. Consequently, we can say that for coincidence detection a bilateral location of granule cells with a bidirectional organization of parallel fibers needs less tissue but a more precise organization of postsynaptic cells, whereas a unidirectional organization of parallel fibers needs more tissue (longer parallel fibers) but less precision in the organization of the postsynaptic elements to reach a similar precision in the capacity to detect time differences. It should be noted that similar characteristics are present in the cerebellar crest, a second example of a molecular layer with a unilateral location of granule cells (Fig. 1), i.e. long parallel fibers and postsynaptic dendritic trees not precisely oriented perpendicular to the parallel fibers. It is unknown whether parallel fibers in the cerebellar crest can be subdivided into populations with different conduction velocities.

A major advantage of unidirectional molecular layers might be their plasticity or adaptability to other systems. In the marginal tectal layer, the location of coincidence peaks should fit with other maps present in deeper tectal layers (e.g. the visuotopic map). It has been shown that the eye as well as the tectum of teleosts may grow continuously throughout life, and that the visual map shifts accordingly within the tectum.[25,26,99] The unidirectional marginal fiber layer with the unilaterally located torus longitudinalis could easily adapt to this shifting map by a lengthening of parallel fibers equal to the tectal enlargement and by small changes in the conduction velocity of the slow and/or 'fast' fibers. The same might hold for the cerebellar crest, where possible coincidence peaks should be in register with the deep lateral line input.

Apart from the tectal marginal layer and the cerebellar crest, a third example of a unilateral location of granule cells is the organization of the mormyrid valvular ridges (Fig. 3B). This specialization is more difficult to fit into our hypothesis, because of the short length of the parallel fibers in the molecular layer (about 400 μm), which does not seem to be enough for any detectable differentiation of coincidence peaks in a unidirectional slow-conducting parallel fiber system. Consequently, it seems most appropriate at present to presume that coincidence detection is absent in this system, and only place detection is important to this extremely long ridge of 1 m.[6] The fact that several output cells do not have their dendrites restricted to a single plane but rather spread throughout the entire extent of a ridge is in line with such a suggestion,[79] although Purkinje cell dendrites have a rather strict orientation perpendicular to the parallel fiber direction in the valvular ridges.

The functional significance of the structural organization of the mormyrid valvular ridges cannot be explained by the present hypothesis of coincidence detection. Evaluation of the significance of this remarkable mormyrid cerebellar specialization awaits further physiological studies.[5,91]

3.3. *Example 3: mormyrid lobe* C_1

3.3.1. *Conceptual framework* 3. Lobe C_1 is a sheet of cerebellar tissue with a restricted width of about 700 μm with laterally as well as basally located granule cells that give rise to co-extensive parallel fibers of equal length[65] (Fig. 3D). In the present section we will consider as an example seven Purkinje cells, equidistantly dispersed in the transverse plane, interacting with parallel fibers of 600 μm in length with equal conduction velocities, originating from granule cells differing only in position, i.e. more laterally or more medially in the granule cell layer (Fig. 11.1). Maximal stimulation of Purkinje cells is again supposed to be achieved when all contacts with parallel fibers are activated simultaneously. In our example there are seven parallel fibers, and thus each individual parallel fiber leads to only 14% stimulation of Purkinje cells as indicated by peak heights (see previous examples).

In contrast to the previous examples, we will directly include an orderly connection between this cerebellar configuration and our conceptual lateral line framework, i.e. with seven head canals as introduced in Fig. 6B. It should be stressed that this connection is only meant as a conceptual framework for the evaluation of possible intracerebellar mechanisms and their functional significance, and not as an *a priori* suggestion of the real involvement of lobe C_1 in lateral line input processing. As in the previous examples, we presume a good fit between stimulus conduction velocity around the animal and intracerebellar parallel fiber conduction velocity.

The fact that the remaining aspects of conceptual framework 3 are similar to Examples 1 and 2 is shown in Fig. 11. Lateral line stimulation from a certain direction first indirectly stimulates a specific granule cell population, which gives rise to parallel fiber activity waves directed from the center to both the left and right periphery in the molecular layer (Fig. 11.2). After a short time, more laterally located granule cell populations are stimulated (b, c in Fig. 11.1) and giving rise to similar parallel fiber activity waves (β and γ in Fig. 11.2, etc.; d,e and f,g respectively). The response of Purkinje cells is related to the activity of the parallel fibers that traverse their dendritic trees (Fig. 11.3). Under the conditions shown in Fig. 11.5, i.e. with the stimulus at the side of the receptor location, it is, however, nowhere near 100%, and is always highest in the lateral boundary region of the molecular layer. The latter will be indicated as an 'undesired boundary effect', since this coincidence peak in the boundary region of the molecular layer is not related to particular input conditions and is thus not seen to be significant. In more medial cerebellar regions, only rather noisy Purkinje cell activity is present under the conditions shown in Fig. 11.

Figure 11.4 shows that stellate cells are very effective in eliminating noisy activity of Purkinje cells. Each time new waves of parallel fiber input reach a Purkinje cell (e.g. α_1, α_2, α_3 for cell IV in Fig. 11.2), their effects on Purkinje cell output are inhibited by stellate cell inhibition resulting from the previous stimulation, while stellate cells are activated in each case in order to inhibit Purkinje cell activity (c.f. Figs 11.3 and 11.4). Consequently, noisy activity of parallel fibers can be seen to lead to prolonged inhibition of Purkinje cell activity by stellate cells, which thus seem to constitute an effective d.c. filter for Purkinje cell output by allowing for rapid transient changes in parallel fiber input. In our examples, we assume (arbitrarily) that stellate inhibition is about twice as strong as the Purkinje cell excitation produced by the same volley of parallel fiber signals. This means that parallel fiber activity which follows a previous parallel fiber stimulus, within the 1.5 ms of stellate inhibition assumed in our model (see above), will only lead to increased Purkinje cell activity when it is more than twice as strong as the previous parallel fiber activity. These Purkinje cell activity peaks (falling within the domain of stellate inhibition but more than twice as high as the foregoing parallel fiber activity) are indicated by stipples in the following figures (e.g. Fig. 12.4).

3.3.2. *Coincidence detection* 3. Figure 12 shows how the configuration encountered in lobe C_1 can subserve coincidence coding within the same space–time domain as used in the previous examples, 1 and 2, provided that the stimulus comes from the side opposite to the supposed receptor location. On the basis of our conceptual framework, stimulus A in Fig. 12.5 will reach receptors 1 and 7 first, which will lead to stimulation of the most lateral granule cells in lobe C_1. Next, receptors 2 and 6, 3 and 5, and 4 will be stimulated, followed by stimulation of granule cell populations in lobe C_1 with an increasing medial location. Accordingly, Purkinje cell IV will be stimulated maximally in Figs 12.3 and 12.4 after stimulus direction A, with other cells being maximally stimulated by other stimulus directions (V by B, VI by C and VII by D in the example shown in Fig. 12).

With respect to intracerebellar mechanisms, Example 3 shows that Purkinje cells in a molecular layer with basally located granule cells and with parallel fibers originating from T-bifurcations, may also function in the detection of coincidence parallel fiber activity at their specific location as suggested above for the more simple configurations with only bi- or unilaterally located granule cells. The major difference with these configurations (Examples 1 and 2) is that maximal Purkinje cell stimulation (by way of maximal coincidence of parallel fiber input) does not so much encode a temporal difference between two stimuli, but rather a more complex, specific

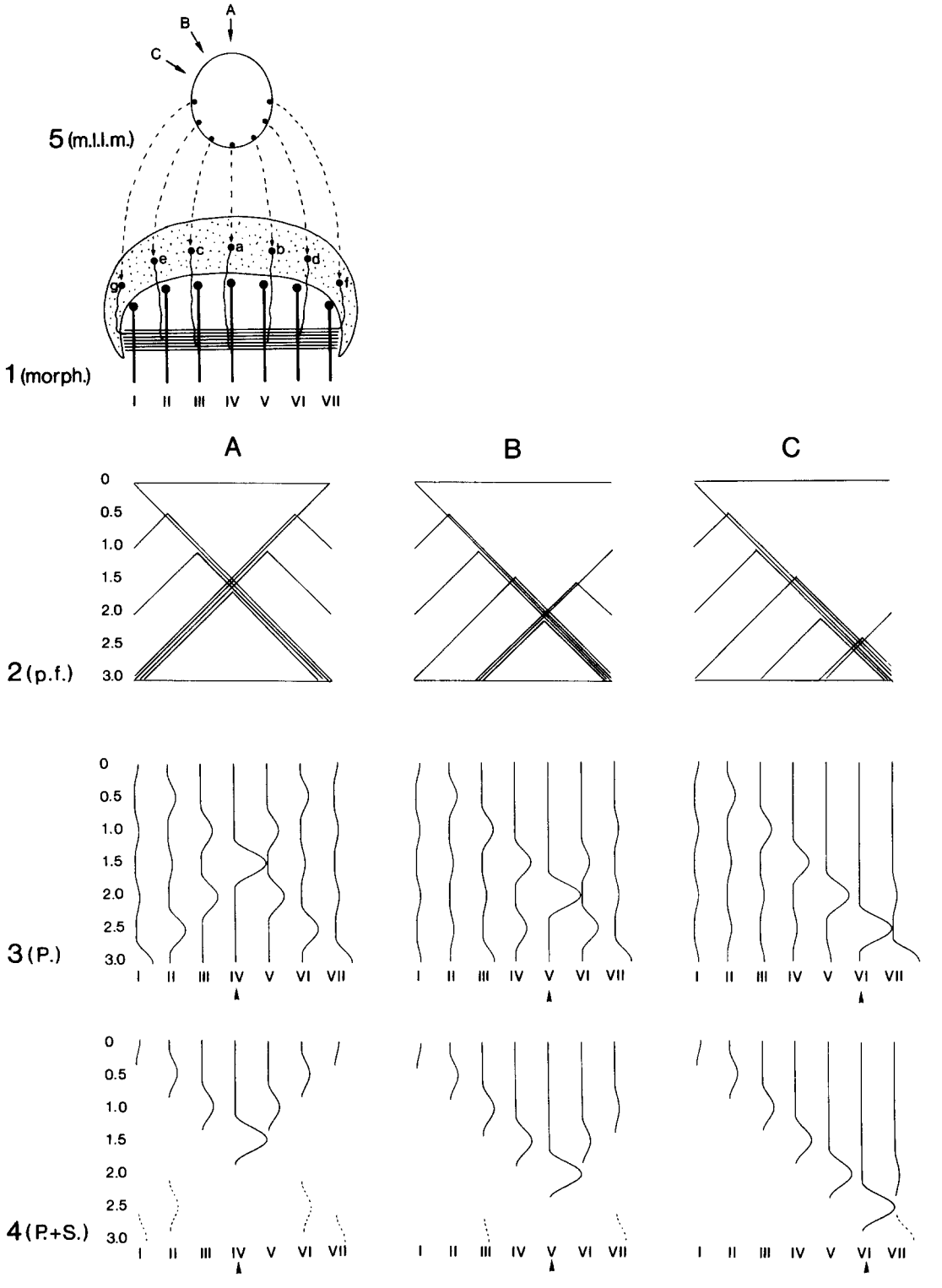

Fig. 12. Visualization of the intracerebellar mechanisms presumed to be involved in coincidence detection in the mormyrid cerebellar lobe C_1. For details see legends of Figs 7 and 9 and Section 3.3.2.

spatio-temporal pattern of mossy fiber activity, in this case a wave going from both the left and the right side of the granule cell layer towards the location of any Purkinje cell under consideration, with a conduction velocity equal to that of the parallel fibers in the molecular layer. Only spatio-temporal patterns of mossy fiber activity which fulfil these criteria will lead to maximal coincidences, i.e. simultaneous stimulation of all parallel fiber contacts of a certain Purkinje cell. All other mossy fiber activity patterns

seem to be less effective. Stellate cells (and other inhibitory interneurons which are possibly involved) are, in the present example, equally effective in optimizing the spatial resolution of the system as shown and discussed for Example 1 where there is a molecular layer with bilaterally located granule cells (c.f. Figs 12.4 and 9.4).

3.3.3. *Possible functional significance* 3. Although we assumed lateral line input to be a conceptual basis for an analysis of the possible significance of the cerebellar configuration encountered in lobe C_1, its actual involvement in the lateral line information process is uncertain. We considered lobe C_1 as part of the valvula (see above) and thus assumed that similar circumstantial evidence, as previously presented with regard to other valvular parts, hold for lobe C_1. Further validation of its possible involvement in lateral line input processing has to be evidenced by the functional significance of input provided by various specialized parts of nucleus lateralis valvulae, which projects massively on lobe C_1.[67]

Apart from nucleus lateralis valvulae, lobe C_1 is particularly connected with the trigeminal system[67] which suggests involvement in somatosensory processes. Without any further physiological data dealing with lobe C_1, all suggestions remain speculative. Meek and Nieuwenhuys[65] have shown that Purkinje cells in lobe C_1 have a regular, dendritic palisade pattern, the functional significance of which will be dealt with in the General Discussion.

3.3.4. *Discussion* 3. Lobe C_1 is of particular importance in the present analysis, because it combines several aspects of the organization of Examples 1 and 2 with the more generally encountered, mammalian-like cerebellar configuration. It has an equally restricted width of about 700 μm to the lobus transitorius (Example 1) and thus may detect time differences of an equally restricted range, between 0 and about 4 ms, as in Examples 1 and 2, but still it combines these constraints with not only a lateral, but also, even predominantly, a basal mammalian-like location of granule cells. Compared with Examples 1 and 2, this seems to increase specificity at the expense of sensitivity. The specificity of signal detection is larger, since coincidence of parallel fiber activity at a certain location does not only encode a specific time difference, but also a peculiar spatiotemporal pattern of mossy fiber input. In our example of possible lateral line input analysis, this means that the system now may discriminate between input coming from above or below, which was not the case in Examples 1 and 2. However, sensitivity seems to be lower since the spatial resolution in coincidence peaks becomes lower (c.f. Fig. 12.3 with Fig. 9.3).

Only by means of well-adjusted stellate inhibition properties can a sufficiently large difference between significant and non-significant coincidence peaks be reached, as in Example 3 (c.f. Figs 12.3 with 12.4), which suggests that, in systems with a basal location of granule cells, the role of stellate (and other) inhibitory interneurons, is of more crucial importance than in molecular layers with a (uni- or bi-) lateral location of granule cells. This might well be the reason that in higher vertebrates a specialized type of stellate cells is present, i.e. the basket cell with its powerful inhibitory properties, which are not seen in teleosts. Other inhibitory feedback loops, including those established by Golgi cells in the granular layer and by Purkinje axon terminals in the ganglionic (or Purkinje cell) layer, may have similar roles.

The present example of lobe C_1 shows that coincidence coding and detection might be equally as important in molecular layers with a basal location of granule cells as it is in cerebellar specializations with a uni- or bilateral location of granule cells. For this purpose, a more precise topographic organization of the granule cell layer is necessary. It can be seen that whereas in bi- or monolaterally located granule cell populations only two sets of mossy fibers need to be distributed over two sets of granule cells (Examples 1 and 2), basally located granule cells require a topographic (either continuous or patchy) distribution of mossy fiber input for useful cerebellar coincidence detection. In the present example (Fig. 12), this implies that the head lateral line canals should be connected in a regular way with the granule cells, but for other possible cerebellar mossy fiber input (either exteroceptive or proprioceptive) the same requirements hold.

With respect to the topographic distribution of mossy fiber input to basally located granule cells (as found in a granule cell layer), two aspects are particularly important, namely the scale and the precision of this projection. The generation of coincidence peaks in the molecular layer depends on a fixed relationship between time and (parallel fiber delay) length, as set by the conduction velocity of parallel fibers. On the other hand, our example assumes fixed time differences between distinct sets of mossy fiber input, as determined by the physical properties of the sensory interface (Fig. 12). Both fixed relations should be brought in register by the scale of the mossy fiber–granule cell projection map, which should match the time differences or spatiotemporal wave patterns to be analysed with the fixed spatiotemporal parallel fiber properties. This implies that multiple projections with different scales are necessary when the time differences in mossy fiber input are not fixed but variable (see Discussion 4).

A greater precision of the topographic organization of mossy fiber input (i.e. a lower degree of overlap between the projections of different sets) would lead to sharper parallel fiber coincidence peaks and better coincidence detection. However, it is plausible that the requirements for precision are less strict than for the scale of mossy fiber projections, since a number of enhancing mechanisms already discussed, as well as the stochastic character of cerebellar coincidence detection, might still lead to useful discrimination between different spatiotem-

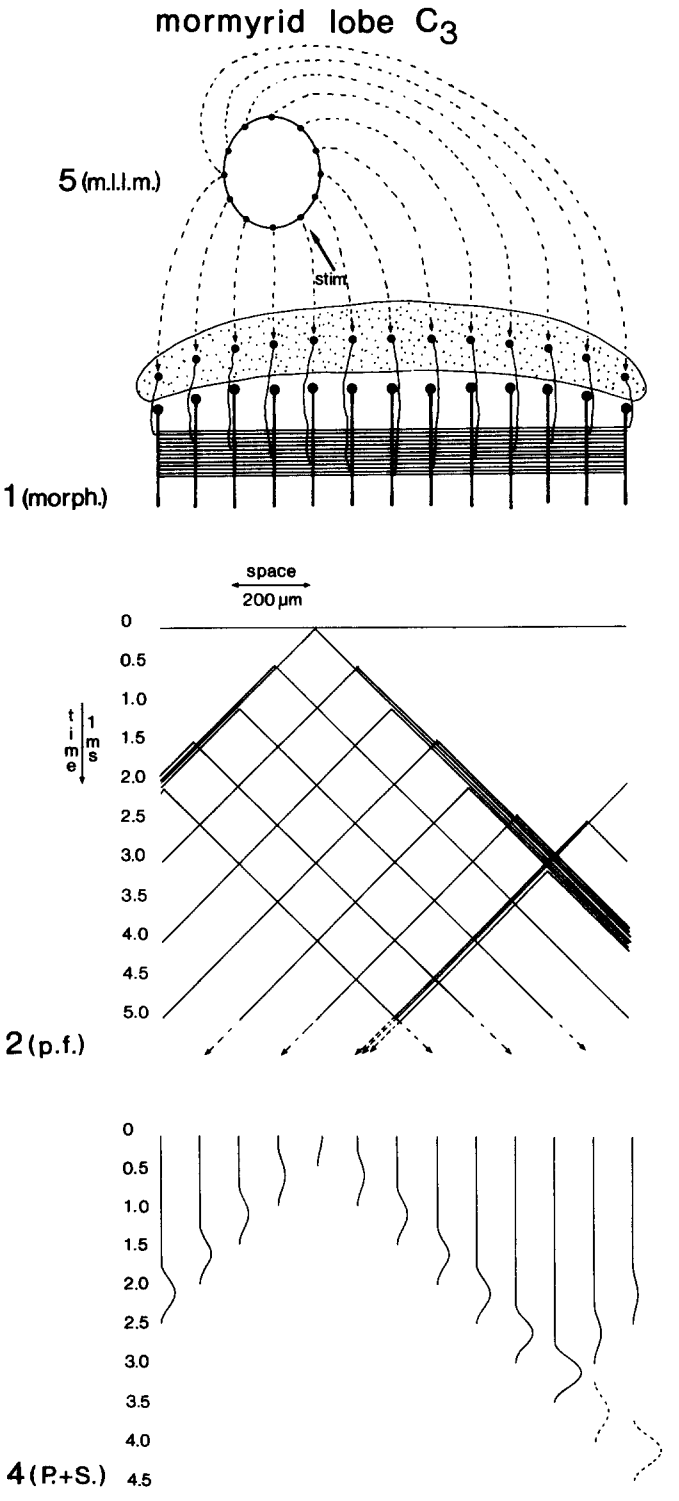

Fig. 13. Visualization of some aspects of the intracerebellar mechanisms presumed to be involved in coincidence detection in the mormyrid cerebellar lobe C_3 and the corpus cerebelli of other teleosts. For details see legend of Fig. 7 and Section 3.4.2.

poral input patterns when a considerable amount of overlap in mossy fiber input would appear to be present. It is clear that a further evaluation of the significance of coincidence-detecting mechanisms in cerebellar subdivisions with basally located granule cells requires more detailed knowledge of the structural and functional organization of the granule cell layer.

Although coincidence detection is optimally achieved by means of very thin, slow-conducting

parallel fibers, the present example, lobe C_1, also contains thick parallel fibers.[65] It is presently uncertain how these interact with the thin parallel fibers. One possibility is that it occurs in a unidirectional manner as outlined in Example 2, on the basis of conduction velocity differences. However, this is very unlikely because of the large difference in conduction velocity involved and the small width of lobe C_1, which would not allow for any significant temporal discrimination. More likely, thick fibers may activate all Purkinje cells in a certain transverse plane simultaneously, thus providing a kind of gating mechanism for the detection of coincidence peaks between the slowly conducting parallel fibers. In this respect, they resemble climbing fibers, to which similar functions are ascribed.[38] Climbing fibers are also present in lobe C_1, although they do not climb into the molecular layer.[65] Consequently, lobe C_1 is not only involved in the detection of coincidence peaks between slowly conducted parallel fiber activity, but these are also probably matched in some way with thick parallel fiber activity as well as with climbing fiber activity to yield optimal responses in Purkinje cells (see also section 3.5.3.).

Configurations similar to those of lobe C_1, i.e. a molecular layer of restricted width and laterally as well as basally located granule cells, occur in the transition zone between valvula and corpus cerebelli of several teleosts (Fig. 2). In the valvula itself all kinds of variations lying between Examples 1 and 3 may be encountered in different teleosts (for e.g. see Fig. 2). Only when additional data about the physiological properties of these cerebellar subdivisions become available will the significance of the present hypothesis on coincidence detection for such cerebellar configurations be more fully evaluated. Further research is also required for a greater insight into the possible functional significance and involvement of these cerebellar specializations.

3.4. *Example 4: mormyrid lobe C_3*

3.4.1. *Conceptual framework* 4. The last example in the present analysis is lobe C_3 of the mormyrid cerebellum, which is an example of the general organization of the corpus cerebelli of teleosts (see above). In our present analysis we consider lobe C_3 as a rostrocaudally folded or foliated sheet of cerebellar cortex, with a width twice as large as lobe C_1, with exclusively basally located granule cells, and thus being, in several aspects, comparable with one parasagittal zone of the mammalian cerebellar cortex. Consequently, the present example is especially useful in evaluating the possible implementation of our hypothesis on coincidence detection in mammalian cerebellar circuitry.

Because of the large dimensions of lobe C_3 compared with lobe C_1 we assumed, staying within the same space–time framework previously considered, an ordered (indirect) connectivity pattern between the complete circumference of the animal's body and the granular cerebellar layer. For lateral line input, this would mean connections with free neuromasts (Fig. 13.1), but somatosensory connections might equally well be considered. The remaining aspects of the conceptual framework used in the analysis of intracerebellar mechanisms are similar to those presented previously (see Examples 1, 2 and 3).

3.4.2. *Coincidence detection* 4. Figure 13 shows that similar rules hold for the present example as for Example 3. Thus, maximal coincidence of parallel fiber activity, yielding simultaneous stimulation of all parallel fiber contacts of a certain Purkinje cell, is only achieved when mossy fiber activity waves converge from both the left and right sides towards the location of that Purkinje cell, with a velocity equal to parallel fiber conduction velocity. The greater width of lobe C_3 as compared with lobe C_1 (see Example 3) allows for the detection of a larger range of time differences (6 instead of 3 ms in our framework). Under the conditions assumed in Fig. 13, this yields an optimal design to detect the direction of a stimulus on the basis of specific spatio-temporal (lateral line) wave patterns on the surface of the animal. However, other physically determined wave patterns in or around the body or muscles can also be detected, depending on the real cerebellar input. Stellate cells have an equal function in this model as described for Example 3, i.e. they serve as a d.c. filter for noisy, insignificant parallel fiber input and enhance spatial intracerebellar resolution of coincidence detection (Fig. 13.4).

3.4.3. *Possible functional significance* 4. The functional significance of lobe C_3 and the corpus cerebelli of other teleosts is equally as uncertain as that of the teleostean cerebellar structures previously used as an example in this paper. A major source of mossy fiber input is again nucleus lateralis valvulae.[68] Remarkably, the subpopulation of neurons in this nucleus that project to lobe C_3[68] receives a major input from the telencephalon.[107] The same holds for the part of nucleus lateralis valvulae that projects to the corpus cerebelli of Xenomystis (Nieuwenhuys and Meek, unpublished observation), which is in line with powerful cerebellar responses after telencephalic stimulation in the catfish.[48,49] Thus, the corpus cerebelli of several teleosts seems partly involved in the analysis (and correction?) of spatio-temporal properties and left–right differences in activity patterns generated in the telencephalon—a function resembling that of the mammalian cerebellum, which receives massive telencephalic input by way of the pontine nuclei.

Additional input to lobe C_3 originates from pretectal nuclei (one of which receives electrosensory input), and an isthmic nucleus with unknown function.[68] Electrophysiological studies on the corpus cerebelli of Gnathonemus are absent. Apart from telencephalic responses,[48,49] somatosensory and visual responses have also been recorded in catfish.[47] Consequently, the teleostean corpus is not only involved in the analysis of telencephalic input, but also in a

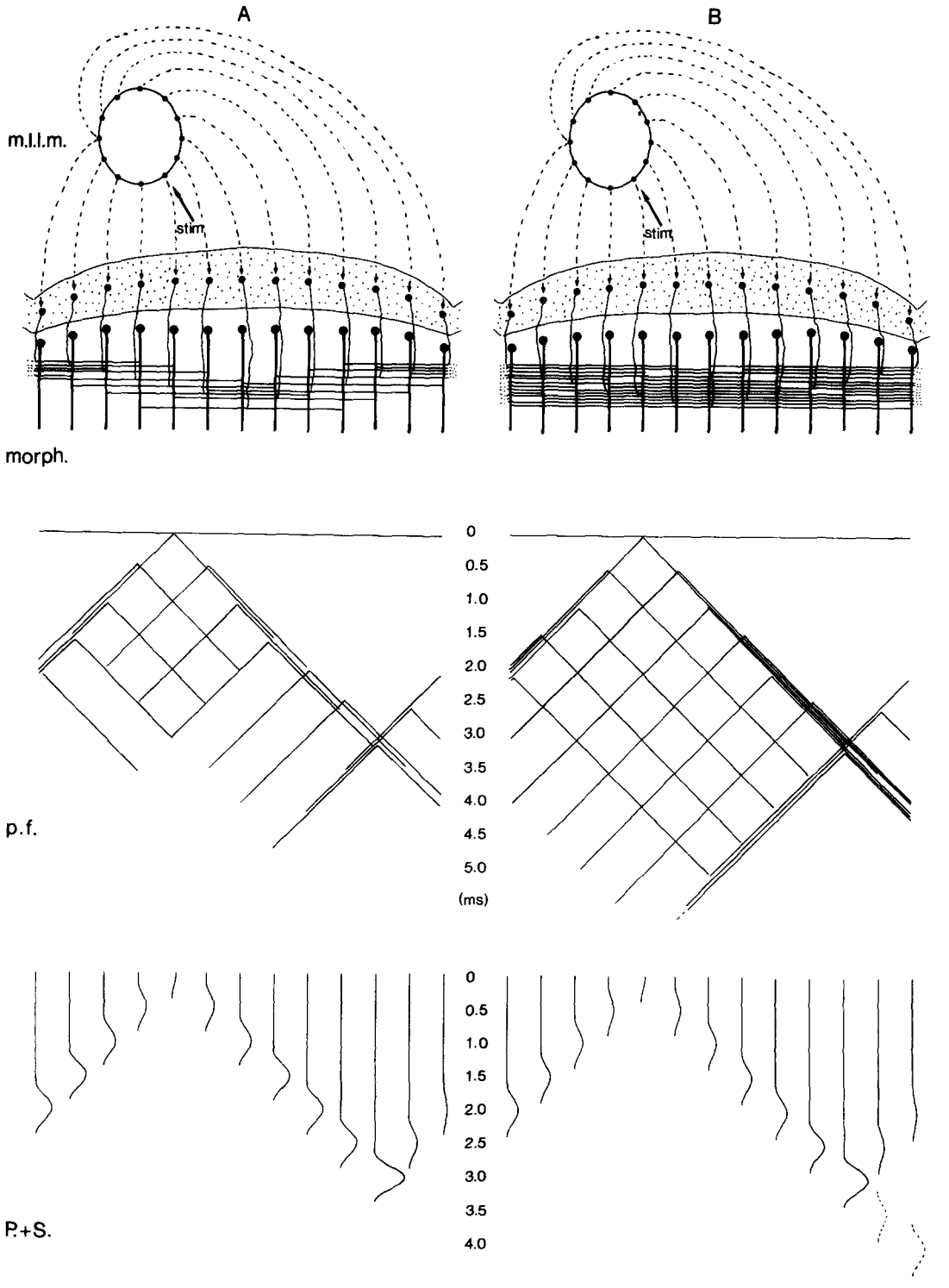

Fig. 14. Visualization of the effect of different lengths and extensions of parallel fibers, as compared with Fig. 13, for intracerebellar mechanisms presumed to be involved in intracerebellar coincidence detection. Compared with the previous figures, the parallel fibers are now not co-extensive in the transverse plane, but all symmetrical with respect to the T-bifurcation. At the left side, their length is equal to that of lobe C_1 (Example 3), and at the right side equal to that of lobe C_3 (Example 4). For further details, see legend of Fig. 7 and Section 3.4.4.

variety of other functions. To evaluate the possible functional significance of coincidence detection for these functions, more physiological experiments are necessary.

3.4.4. *Discussion* 4. The present example, illustrated in Fig 13, starts from co-extensive, symmetrical as well as asymmetrical parallel fibers of equal length, since this is probably the case in lobe C_3 and other

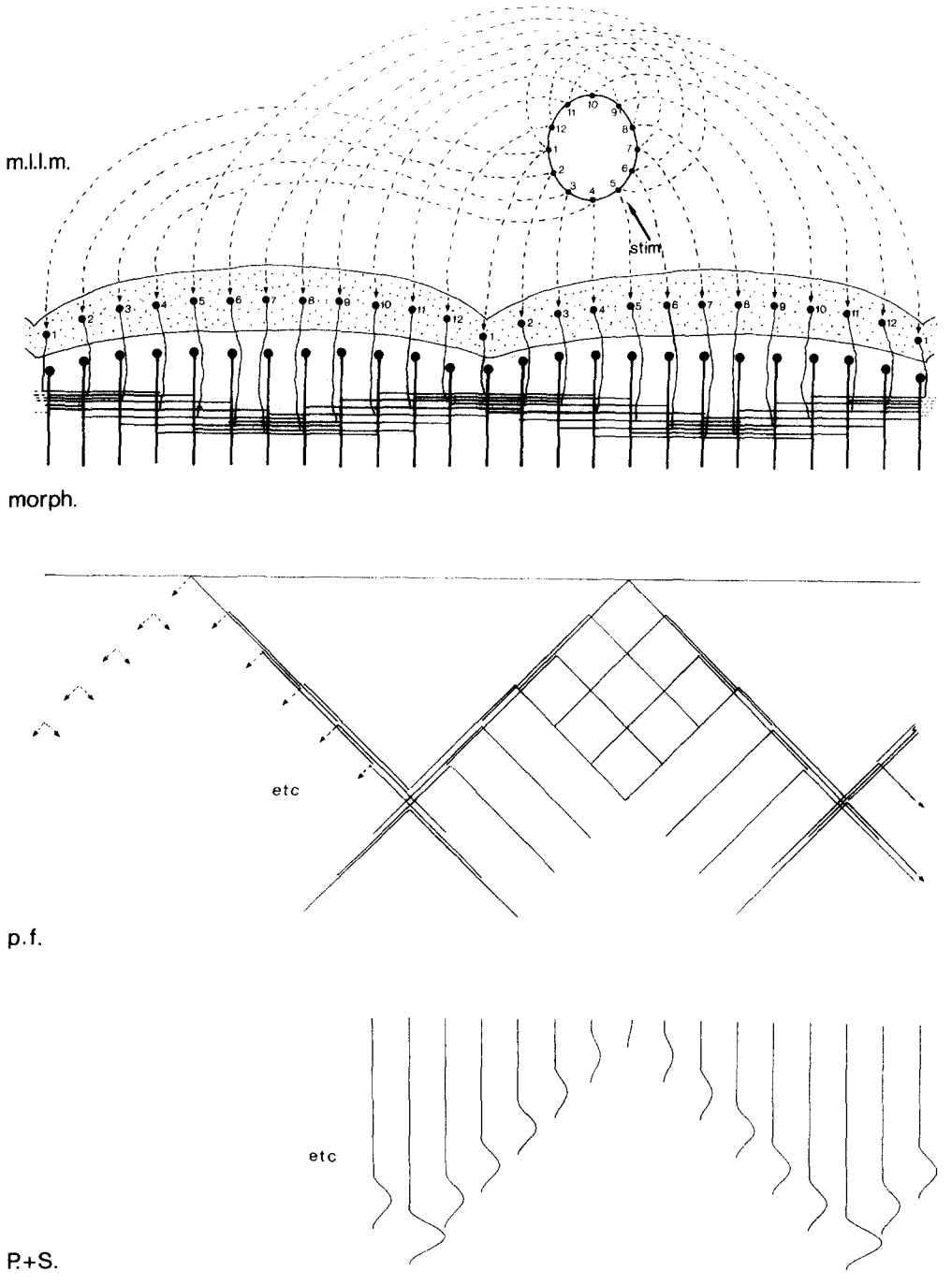

Fig. 15. Visualization of the possible effect of lateral repetition of input in two neighbouring sagittal cerebellar zones for intracerebellar coincidence detection. For further details, see legend of Fig. 7 and Section 3.4.4.

teleostean cerebella[65] (see Introduction). In such a situation, an increase in the range of time detection can be correlated with a decrease in intracerebellar spatial resolution of time difference detection (c.f. Examples 3 and 4; Figs 12.4B and 13.4B). Consequently, the importance of stellate cells in maintaining significant signal–noise ratios becomes even more important than as already discussed for Example 3. Only in the presence of a well-balanced stellate and/or basket cell inhibition system will insignificant coincidences, visible as stippled peaks in Fig. 13.4, be significantly reduced. Another problem of the configuration of lobe C_3 is the occurrence of undesired boundary effects (see Conceptual framework 3) at the side contralateral to that where significant coincidence peaks occur. Comparison of the structure of the teleostean corpus with that of a parasagittal mammalian cerebellar zone shows that the latter seems to have reduced these problems substantially.

The first difference between the teleostean corpus cerebelli and a parasagittal rat cerebellar zone, which have a notably similar width of 1–2 mm,[66] is that mammalian cerebellar parallel fibers are presumably not asymmetrical and not co-extensive in the transverse plane, but are, on average, symmetrical and thus discongruent in their extension. Figure 14 shows the significance of such an organization with respect to the problems outlined above for two presumed lengths of parallel fibers (one equal to Example 3 and one equal to Example 4). Comparison with Fig. 13 shows that this yields a similar or even enhanced spatial intracerebellar differentiation of coincidence detection, with a similar or larger difference in neighbouring peaks and with fewer stippled peaks.

A second difference between the teleostean corpus cerebelli and a parasagittal mammalian cerebellar zone concerns the relationship of the latter with neighbouring zones. When a similar mossy fiber connectivity pattern is presumed for neighbouring zones, this would eliminate the undesired boundary effect for the zone under consideration, since there is no boundary remaining (Fig. 15). Such a configuration would, in addition, have the general advances of repetition of signal processing, i.e. a better signal–noise ratio. When the output of both zones is integrated, the general performance of the system is better than that of one zone alone. Figure 15 shows that this requires multiple projection of each source of mossy fiber input over different cerebellar zones, which is indeed a common observation in mammalian cerebella. Many investigations have shown multiple, patchy mossy fiber projections to the cerebellum[106] and the present suggestion of repetition in coincidence detection in order to decrease undesired boundary effect and to increase signal–noise ratios might be one aspect of the functional significance of these projections.

As discussed in section 3.3.4., cerebellar configurations with basally located granule cells require a certain topographic organization of the granule cell layer for useful coincidence detection, and the scale of the resulting (continuous or patchy) maps determines the range of time differences that can be analysed. The multiple mossy fiber projections observed in mammals might, apart from eliminating boundary effects, also have a function in adapting mossy fiber projection scales to specific and different temporal activity patterns which can be analysed. For our lateral line model (see Figs 13–15) this would imply that cerebellar coincidence detecting mechanisms could not only discriminate between different stimulus directions, but also between stimuli of different velocities, each of which would require a mossy fiber projection map with a different scale which would be inversely proportional to the stimulus conduction velocity. Although this is merely hypothetical for the teleostean cerebellum, it might well be important for the mammalian cerebellum, which has to analyse a multitude of exteroceptive and proprioceptive wave patterns with multiple spatiotemporal relations in order to regulate the fine balance and interactions between a variety of muscles.

3.5. *General Discussion*

The present paper presents evidence for the hypothesis that the parallel organization of parallel fibers generates coincidence peaks of parallel fiber activity at specific locations that depend on small time differences in mossy fiber input. The location of these peaks is detected by Purkinje cells, which thus subserve spatial encoding of temporal differences. This means that the mossy fiber–parallel fiber–Purkinje cell system can be regarded as a timing device, as suggested previously by several authors.[12,13,33,34] This paper presents a straightforward mechanism on which this function might be based, and analyses the implications of this mechanism for a number of cerebellar configurations encountered in teleosts. The four examples analysed show that the intracerebellar mechanism proposed would lead to straightforward detection of small temporal differences in the input of cerebellar configurations with a bilateral or a unilateral location of granule cells (Examples 1 and 2), while the same mechanism might allow for the analysis of specific spatio-temporal input patterns in mammalian-like configurations with basally located granule cells, i.e. underneath the layer of Purkinje cells (Examples 3 and 4).

The attraction of our hypothesis is that it is simple and can easily be tested by physiological experiments designed to record Purkinje cell activity after stimulation of granule cells at two locations with varying time intervals. In addition, the present hypothesis accounts for the significance of most, if not all, characteristics of the molecular layers considered in Examples 1–4, including: the parallel course of parallel fibers; their thin caliber—and thus the lowest conduction velocity possible in the central nervous system; their large number (Discussion 1) and the existence of two parallel fiber conduction velocities in unidirectional molecular layers (Discussion 2); the many spines of Purkinje cells and the sagittal orientation of their dendritic tree in bidirectional molecular layers (Discussion 1), but their non-sagittal, more random orientation in unidirectional molecular layers (Discussion 2); the absence of spines on stellate cells (Discussion 1) and the function of these inhibitory interneurons as well as basket cells in enhancing spatial differentiation of coincidence detection (Discussion 2) and reducing Purkinje cell responses to insignificant, noisy parallel fiber activation (Discussion 3), as well as the specific significance of the bilateral (Discussion 1), unilateral (Discussion 2) and basal location of granule cells (Discussion 3) encountered in teleostean cerebella. Finally, the hypothesis proposed seems to fit well in the organizational characteristics of the mammalian cerebellar cortex (Discussion 4).

In addition to the many aspects already discussed in the more specific Discussions 1–4 summarized above, the general discussion will concentrate mainly on two items: the critical evaluation of the present conceptual framework and the possible functional significance of the mormyrid palisade pattern. It concludes with a few comments on parallel fiber–climbing fiber interactions.

3.5.1. *Critical evaluation.* The present paper has explored possible intracerebellar functional mechanisms by defining those conditions that would lead to simultaneous stimulation of all parallel fiber contacts of a certain Purkinje cell. It has been outlined in the Introduction that we started from the assumption that optimal stimulation of Purkinje cells by parallel fiber activity is reached when all contacts with parallel fibers are activated in such a way that the resulting EPSP's reach the axon hillock simultaneously. Because of the effects of different distances between proximal and distal contacts with the axon hillock, the ultimate stimulus conditions fulfilling the criteria necessary to reach our true starting point differ slightly from the first approximation obtained by conditions leading to simultaneous stimulation of parallel fiber contacts. However, for any given Purkinje cell configuration, the relation between both conditions is fixed and predetermined, and thus the results under both conditions lead to similar conclusions. The refined differences in stimulus conditions necessary to meet our real or simplified starting point will be discussed below under the heading 'palisade pattern'. With respect to the starting point the following further comments can be made.

The temporal aspect of our starting point (i.e. simultaneous stimulation, or simultaneous effects on the axon hillock) is essential for the present analysis, and represents the only way of ascribing functional specificity to teleostean Purkinje cells. In teleostean cerebella parallel fibers are co-extensive in the transverse plane, and thus there is no spatial differentiation in the parallel fiber input of more medially or more laterally located Purkinje cells (Fig. 3). Consequently, only temporal differentiation can lead to functional specificity. The fact that not all parallel fibers that traverse a dendritic tree of a Purkinje cell make synaptic contact with that Purkinje cell (only about 20%)[38,65] does not necessarily interfere with this conclusion. Presumably, the ultimate pattern of parallel fiber–Purkinje cell synaptic contacts (i.e. which of the parallel fibers that traverses a Purkinje cell dendritic tree makes a synaptic contact with that tree), is determined by stochastic rules, and does not reflect any further specific organization.

The quantitative aspect of our starting point (stimulation of all parallel fiber contacts being necessary) is not an absolute prerequisite for the present hypothesis and analysis. When there is an intra- or post-cerebellar mechanism comparing relative differences in Purkinje cell activity independent of their absolute intensity level, the cerebellar configurations analysed in Examples 1–4 would also be well equipped to detect coincidences in the activity of only subpopulations of parallel fibers. However, to maintain the capacity of coincidence detection throughout the whole intensity range of parallel fiber activity possible, it is still necessary to presume that maximal Purkinje cell activity is exclusively related to maximal parallel fiber stimulation. Otherwise, when submaximal parallel fiber activity would already yield maximal Purkinje cell stimulation, coincidence detection would not be possible at levels higher than such a submaximal parallel fiber activity.

For convenience, the present paper starts from a linear relationship between parallel fiber input and Purkinje cell output, but non-linear relationships would also be compatible with the present coincidence detections hypothesis as long as parallel activity is not inversely related to (thereby inhibiting) Purkinje cell activity. A linear relationship compared with, for example, an exponential one, would reduce coincidence detection sensitivity at low levels of parallel fiber activities but enhance coincidence detection at higher levels. A saturating exponential relationship would do the reverse. The dendritic spines of Purkinje cells probably play a crucial role in the determination of the balance and relationships between parallel fiber input and Purkinje cell output[65] (see Discussion 1). It should be noticed than non-linear aspects of the input–output relationships of Purkinje cells,[38,53] and inhomogenities in their receptive surfaces,[100] are related to their climbing fiber input. Consequently, it seems most realistic to start from a basically linear relationship between parallel fiber input and Purkinje cell output, the level of which is set (and thus may also continuously be changed and adapted) by means of spine properties[92] as well as climbing fiber input (see section 3.5.3. for a further discussion of the latter).

We have argued that coincidence detection of time differences is a very probable function of the cerebellar cortex, and that most, if not all, aspects of the design of the molecular layers evaluated in Examples 1–4, including the organizational features of parallel fibers, the orientation of Purkinje dendrites and the presence of stellate cells, seem to be optimally adapted to such a function. However, the actual performance of such a system greatly depends on the spatio-temporal aspects of the input provided to it. The resolution of coincidence detection will be much better for sharply tuned mossy fiber activity peaks than for prolonged, blurred waves. In this respect we noted that precerebellar nuclei are always of the closed type,[57] which means that they have a restricted volume without overlap with other regions, and that the neurons thus have a dendritic tree restricted to the nucleus which does not protrude into neighbouring regions. The best known example is the inferior olive, which gives rise to climbing fibers, but the same holds for precerebellar nuclei giving rise to mossy fiber

projections. In teleosts, the nucleus lateralis valvulae is the clearest example, and in mammals the best examples are the pontine and dorsal funicular nuclei. Possibly, the 'closed' organization of these nuclei optimizes temporal tuning of precerebellar signals and reduces temporal spread or blurring of signals. It would be interesting to know whether nucleus lateralis valvulae and other precerebellar nuclei have a similar function in synchronizing cerebellar input as has been shown for the inferior olive.[51,52] Such a mechanism would greatly enhance the cerebellar capacity for coincidence detection.

The actual functional performances of a possible intracerebellar coincidence detecting mechanism do not only depend on the temporal organization of cerebellar input, but also on the spatial distribution of cerebellar mossy fiber input in the mediolateral direction, in particular when basally located granule cells are involved (Examples 3 and 4). In teleosts, nothing is known about cerebellar precision and organization in this respect, but in mammals a substantial overlap exists between the projections of individual mossy fibers because of the convergent–divergent organization of the granule cell layer.[31] Consequently, intracerebellar signal processing is faced with an overlap that does not seem optimal for coincidence detection from the theoretical point of view. On the one hand, the lack of precision in intracerebellar mossy fiber organization may be determined by the general constraints of the organizational capacity of the central nervous system. On the other hand, it might well represent a compromise between spatial order, intensity maintenance and/or temporal tuning mechanisms. It should be mentioned, however, that in spite of these and other 'blurred' aspects of cerebellar input organization, the intracerebellar parallel fiber–Purkinje cell organization still seems the best one to achieve maximal degrees of coincidence detection (see Discussion 1), and that feedback loops, as established by Golgi cells and Purkinje axon collaterals, might also help to optimize coincidence detection conditions.

In addition to the regular organization of the cerebellum, a number of 'repetitive' aspects of cerebellar organization might allow for the increase of signal–noise ratios for coincidence detection. The most important one is the large number of similar parallel fibers which has already been dealt with in Discussion 1. In addition, repetitive projection of input in space, either in the rostrocaudal or mediolateral direction (see Discussion 4), might also substantially increase signal–noise ratios. Moreover, repetitive stimulation, in time, could equally enhance the coincidence detecting capacity of the intrinsic cerebellar organization, when an intra- or postcerebellar averaging mechanism exists for coincidence peaks within a certain time window. In fact, many sensory, motor and other neural signals are not single but repetitive, and thus could lead to enhanced intracerebellar coincidence detection, provided their frequency is low enough to survive stellate cell inhibition (Examples 3 and 4).

Coincidence detection has also been put forward as the neural mechanism involved in the detection of time discrepancies in the acoustic system of mammals and birds[16,18,40,71] and in the electrosensory lateral line system of gymnotid teleosts,[16,17,20] where it is used to detect the location of a sound on the basis of phase differences between the left and right ear or for jamming avoidance responses, respectively.[16] Several interesting comparisons can be made between the cerebellar coincidence detecting mechanism proposed, and similar acoustic and lateral line coincidence detecting mechanisms present in nucleus laminaris of the barn owl and the torus semicircularis of gymnotids. All are similar in their dependence on the presence of neurons that require simultaneous activation of their input, which is achieved by delay lines that are matched with temporal differences in the input.[16] The nucleus laminaris of the barn owl[18] is particularly similar in this respect to the organization of the lobus transitorius (Example 1), since in both systems coincidence detection is based on inputs entering from two opposite sides. However, several differences may also be noticed.

The acoustic and lateral line input pathways involved in coincidence detection consist of relatively few, large neurons with axosomatic club endings and/or gap junctions[23,72] and several other properties that maintain or even enhance the phase locking of the input. This is provided by sensors that produce one spike per cycle.[16] In contrast, cerebellar molecular layer input is provided by numerous small neurons, located in the granule layer as well as in precerebellar nuclei such as the nucleus lateralis valvulae. Although several features of these neurons and their proximal synaptic connections resemble those of the acoustic and lateral line input pathways that maintain or enhance temporal orders of input, the organization of cerebellar input seems less precise and is certainly not as fast. In general, cerebellar coincidence detection seems to have a more stochastic character than the fast and precise acoustic and lateral line systems, which may detect temporal disparities of only 0.5–1.0 μs.[16] Comparison of both systems suggests that acoustic and lateral line coincidence detection allows for rapid analysis of phase differences in relative simple, repetitive input of relatively high frequency (an acoustic or electric tone), whereas cerebellar coincidence detection might be involved in slower analysis of temporal differences of single or low-frequency repetitive inputs with a more complex and noisy shape or pattern.

The functional involvement of a cerebellar coincidence detecting mechanism as proposed in the present paper may be manifold. As a conceptual framework, several implications of a possible involvement in mechanosensory lateral line input processing have been considered and discussed in Examples 1–4, but other possibilities are equally as compatible with the

present hypothesis as long as the external or internal physical parameters involved in the spatio-temporal aspects of cerebellar input match with parallel fiber conduction velocity and intracerebellar dimensions. Possible functional significances of cerebellar coincidence detection include: (i) the detection of time disparities between sensory inputs of the same modality at different locations; (ii) comparison of temporal aspects of sensory input of different modalities (e.g. mechanosensory lateral line and somatosensory input); (iii) analysis of the spatio-temporal pattern of muscle contractions as registered by proprioceptive input; (iv) analysis of the degree of synchrony of the neural activity of different brain nuclei or regions, e.g. between the left and right component of paired nuclei; (v) comparison of temporal aspects of exafferent or reafferent input with corollary (or expected) signals; and (vi) all kinds of combinations of the five previous possibilities. All are in line with previously suggested cerebellar functions,[1,9,24,38] and the present hypothesis on coincidence detection of parallel fiber activity offers a mechanism which may allow for all these functions, since they all depend on the analysis (and subsequent corrections, when necessary) of spatio-temporal aspects of cerebellar input.

3.5.2. *The palisade pattern.* The Purkinje cells in the mormyrid cerebellar subdivisions used as examples in the present paper have a very regular dendritic organization. The distal, spiny dendrites are oriented parallel to each other, and run, mostly unbranched, from deep to superficial in the molecular layer, perpendicular to the surface, which is known as the dendritic palisade pattern of mormyrid Purkinje cells.[65,77-80] The degree of regularity is different in different cerebellar parts being, for example, larger in lobe C_1 than in lobe C_3[65] (see Fig. 16). Since the functional significance of this pattern is still unknown,[65] the question may be raised whether the present hypothesis might help to explain its functional significance.

The palisade pattern of mormyrid Purkinje cells points out that not only the cerebellar organization in the mediolateral or left–right direction should be considered, as has been done in the present paper until now, but also the organization in the two other orthogonal dimensions, i.e. the apical-basal and rostrocaudal. To evaluate the possible significance of a regular organization in these directions, it is necessary to return to our starting point, which assumes that Purkinje cells are optimally stimulated by parallel fibers when all contacts with parallel fibers are activated in such a way that the resulting postsynaptic potentials reach the axon hillock simultaneously. The palisade might well represent a specialization that increases the refinement or tuning of Purkinje cells for coincidence detection of specific patterns of parallel fiber activity on the basis of this starting point.

With respect to the apical-basal organization of the cerebellar molecular layer, it is clear that basally located parallel fiber contacts are, on average, closer to the axon hillock than those distally (or apically) located. Thus, postsynaptic potentials generated at these sites will reach the axon hillock earlier than simultaneously generated potentials at distal locations, and coincidence at the axon hillock will only be reached when a specific apical-basal wave of parallel fiber activity is present that matches the conduction velocity of the dendritic potentials of Purkinje cells. Obviously, the palisade dendrites allow for sharper tuning of specific apical-basal gradients in parallel fiber activity than, for example, the mammalian Purkinje cell dendritic organization (Fig. 16). Starting from a similar apical-basal gradient in parallel fiber activity, the latter would introduce considerably more noise and spread in the temporal properties of membrane potentials arriving at the axon hillock than the mormyrid palisade pattern. Consequently, palisade dendrites add at least one dimension to our previous conclusion based on the coincidence detection hypothesis, namely that Purkinje cells are optimally tuned for cerebellar neural activity waves directed towards the Purkinje cell under consideration. This does not only seem to hold for mossy fiber activity waves in the mediolateral or latero-medial direction, as explained for Example 3, but also for parallel fiber activity waves in the apico-basal direction. Unfortunately, nothing is known about the parallel fiber organization in the apico-basal direction, i.e. about differences in the location or other properties of parent granule cells of apically or basally located parallel fibers. For a further evaluation of the functional significance of possible apico-basal gradients in parallel fiber activity, more insight into the functional organization of the granule cell layer is necessary.

The palisade pattern of lobe C_1 Purkinje cells adds a third dimension of regularity to the mormyrid molecular layer organization, namely the rostrocaudal direction. Whereas the regularity of Purkinje cells in lobe C_3 is restricted to two directions (the sagittal orientation of the dendritic tree and the apico-basal regularity of the palisade dendrites), the dendritic tree of Purkinje cells in lobe C_1 also has a rostrocaudal regularity or hierarchy[65] (Fig. 16). Consequently, these cells do not only seem to be tuned to specific mediolateral and apico-basal input gradients, but also to specific rostrocaudal spatio-temporal patterns. For lobe C_1 Purkinje cells, maximal coincidence of parallel fiber input at the level of the axon hillock is reached by input waves directed towards the cell under consideration from all directions—mediolaterally, apico-basally and rostrocaudally. In other words, concentric centripetal mossy fiber/parallel fiber activity gradients, matched with the conduction velocity of parallel fibers in the mediolateral direction, and with the dendritic signal conduction velocity in the rostrocaudal and apico-basal directions. The same probably holds for other Purkinje cells, including mammalian ones, but the sharpest tuning

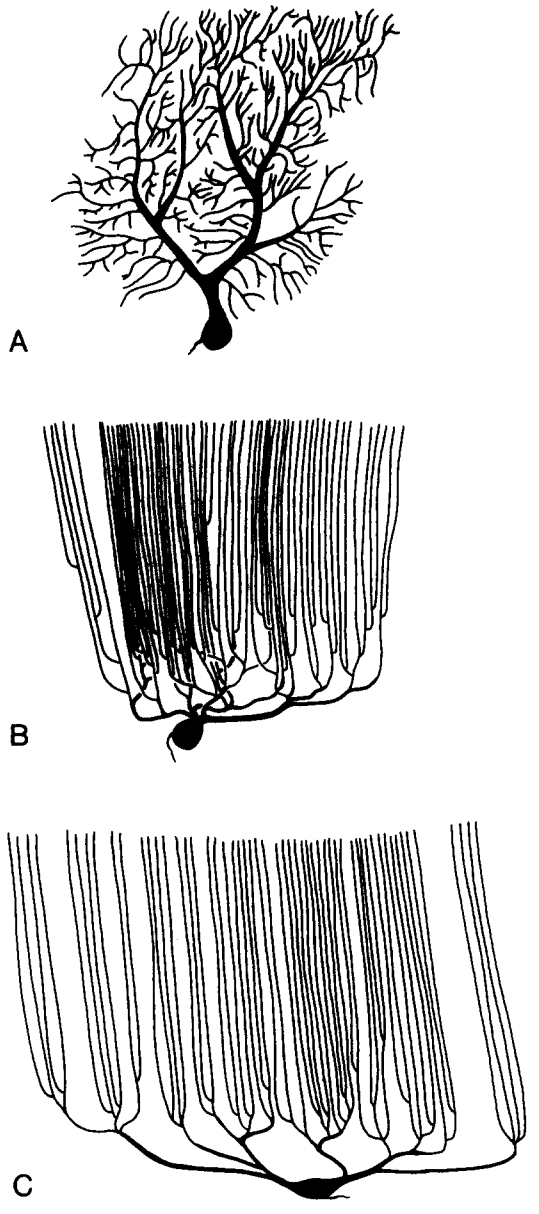

Fig. 16. The dendritic organization of Purkinje cells in the mammalian cerebellum (A), mormyrid lobe C_3 (B) and mormyrid lobe C_1 (C), according to the description of Meek and Nieuwenhuys.[65] The spiny dendritic tufts that make spiny contacts with parallel fibers have been drawn thinly, with omission of the numerous spines. For further details, see Section 3.5.2.

for such specific spatio-temporal gradients may be expected for Purkinje cells organized as in lobe C_1.

With respect to the functional significance of a rostrocaudal dendritic regularity as observed in lobe C_1 the following may be noticed. In general, the rostrocaudal cerebellar organization seems to be spatiotopic, as demonstrated, for example, in the mormyrid and other teleostean cerebella by the ordered projection of several inputs in this direction.[31,67,68] Within our conceptual framework of an ordered connection between the lateral line canal organs and the mormyrid lobus transitorius and lobe C_1, it is clear that such a rostrocaudally ordered projection indeed would not only lead to the coincidence detection in the left–right direction, as explained in Examples 1 and 3, but also to rostrocaudal or caudorostral gradients of input activity towards any level under consideration. Determination of the stimulus position in the transverse plane would then primarily depend on temporal aspects of the input. In the rostrocaudal direction, it would primarily depend on spatial aspects of the input, with similar center–surround interactions as in the spatio-topically organized visual and somatosensory systems, but restricted to the rostrocaudal direction. The specific rostrocaudal distribution of axon-terminals in lobe C_1 is in line with this suggestion.[65] However, other aspects of input organization, such as repetition of input to increase signal–noise ratios, might also be present in the rostrocaudal direction, although it is at present not clear what the functional significance of a palisade pattern as observed in lobe C_1 would be for such an input organization.

In concluding our discussion on the mormyrid palisade pattern, we might also reverse our reasoning, and state that the presence of a palisade pattern in mormyrids is a strong argument in favor of the importance of coincidence detection mechanisms in cerebellar input processing. The only functional significance that can be attributed to such an organization is a sharper tuning for coincidence detection of specific spatio-temporal patterns of input. Other functions suggested for cerebellar Purkinje cells, not implying coincidence detecting processes, could equally or better make use of less regularly organized dendritic trees. Since it seems unlikely that the mormyrid palisade pattern has no functional significance at all, the presence of this parallel fiber specialization of Purkinje cell organization[65] indeed suggests the presence of coincidence detecting mechanisms in cerebellar circuitry.

3.5.3. *Climbing fiber–parallel fiber interactions.* Having argued that the mormyrid palisade pattern optimizes tuning for coincidence detection, one might ask why, for example, mammals do not have palisade-like Purkinje dendrites. The most important factor involved seems to be the cerebellar climbing fiber input.

Although the present paper concentrates on the cerebellar mossy fiber–parallel fiber input, it should be stressed that the cerebellum also receives climbing fiber input, and that both parallel and climbing fiber input converge on the receptive surface of Purkinje cells. As already shown,[65] mormyrid climbing fibers have rather primitive properties, including a restricted proximal location and an absence of a 1:1 relationship with Purkinje cells. This leaves all degrees of freedom involved in dendritic tree organization available for specialization of parallel fiber–Purkinje cell interactions. In contrast, mammals have highly specialized climbing fibers, related 1:1

with Purkinje cells and penetrating the molecular layer, thus reducing their distance to parallel fiber input on the receptive surface of Purkinje cells allowing for subtle and refined mutual interactions.[65] Apparently, the establishment of climbing fiber–Purkinje cell synaptic contacts within the molecular layer reduces the degrees of freedom available for parallel fiber-Purkinje cell interactions and is incompatible with the presence of long, homogeneous (palisade) dendrites exclusively involved in parallel fiber input processing.

Phylogenetic comparison suggests that the difference in climbing fiber organization between teleosts and mammals might be related to the restricted movement repertoire of the former compared with the latter. Climbing fibers may enhance as well as inhibit the effect of parallel fiber input on Purkinje cells[10,11,27–29] and subserve a kind of instruction[2,58,92] or gain control function[10,11] on parallel fiber–Purkinje cell interactions. In view of the present hypothesis, an important function of climbing fibers thus might be to enhance or attenuate coincidence detection at certain cerebellar sites or zones, depending on the position or phase of movement of the animal at a given time. Conceivably, this is less crucial and refined in fish, with their aquatic environment and restricted movement repertoire, than in mammals, with their specialized, complex extremities and high demands for refined sensorimotor co-ordination due to their mobile terrestrial lifestyles.

Unfortunately, details about the interactions between climbing fibers and parallel fibers in teleosts are lacking, while a further discussion of these interactions in mammals, including their involvement in 'learning processes', is obviously out of the scope of the present paper. However, the present hypothesis on coincidence detection of parallel fiber activity might not only present some clues for increased insight in the functional organization of the cerebellar mossy fiber–parallel fiber input but also for a better understanding of climbing fiber–parallel fiber interactions.

4. CONCLUSION

We have seen that the orthogonal organization and specific granule cell locations of teleostean cerebellar configurations represent an optimal arrangement for the detection of small time differences, either between two sets of mossy fiber input or between specific spatiotemporal mossy fiber input waves, and that similar functions might take place in the mammalian cerebellum. Parallel fibers are considered as tapped delay lines,[12,13] and Purkinje cells as coincidence detectors of parallel fiber activity, tuned for parallel fiber activity waves that simultaneously reach their receptive surface (or more precisely, whose excitatory postsynaptic potentials simultaneously activate their axon hillock). Purkinje cell spines are considered as attenuators, and inhibitory stellate as well as basket cells as noise filters and coincidence peak enhancers. Climbing fibers are supposed to inhibit or enhance coincidence detection at specific cerebellar sites or zones, depending on the position or movement phase of the animal. The specialized palisade pattern of Purkinje cells present in some teleosts, probably represents the ultimate optimization for cerebellar coincidence detection.

Our hypothesis on cerebellar coincidence detection can be tested in a variety of cerebellar subdivisions by physiological experiments designed to activate two sets of mossy fibers and/or granule cells instead of one. This is in order to investigate the response of postsynaptic Purkinje cells in relation to small temporal differences in the activation of these sets. Since the present hypothesis assumes a certain synchrony in the activation of sets of granule cells, and a certain degree of topographic organization of mossy fiber–granule cell projections—either single or multiple, continuous or patchy—it can be substantiated further by studies on the precise functional anatomy of the cerebellar granule cell population. It is hoped that this paper will stimulate further research on both these temporal and spatial organizational aspects of the cerebellar mossy fiber–granule cell–parallel fiber–Purkinje cell system, in teleosts as well as mammals.

Acknowledgements—I wish to thank Dr R. Nieuwenhuys for his continuous interest and stimulating remarks during preparation of the manuscript and Dr Ch. Nicholson for critical reading of the manuscript. I am grateful to Dr A. B. A. Kroese for his information about the mechanosensory lateral line system and to Mrs M. v.d. Coevering for secretarial assistance and typing the manuscript.

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(*Accepted* 2 *December* 1991)