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# CLIMBING FIBER PURKINJE CELL TWINS ARE FOUND

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## ABSTRACT

*At the IJCNN'93 in Nagoya we have pronounced a challenging goal: to get activity patterns of pairs of Purkinje cells (PC), controlled with the same climbing fiber (CF), - a CF PC Twins problem [2]. Here, for the first time in cerebellar studies, CF PC twins have been identified and studied. Several important features of the CF PC twins activity are demonstrated: (1) High constancy of conduction time of impulses of cells of inferior olives to the targeted PCs, (2) A relatively high failure rate (0.05 - 0.18) of impulse propagation into terminal branches of CF, (3) A salient difference in complex spikes (CS) - simple spikes (SS) interaction between the PC twins, (4) SS cross-correlation between twin cells is zero, thus contradicting a naïve prediction of several cerebellar learning theories.*

## 1. Introduction

The PC of the cerebellum gets synapses from numerous Granule Cells (GrCs): from 4000 (frog), up to 500000 (human), and multiple synapses of a single CF. In higher vertebrates each CF controls about 10 different PCs, while only one climbing fiber contacts an individual PC. Since 1969, an unconfirmed hypothesis asserted that a climbing fiber plays the role of a teacher in supervised learning in the cerebellar cortex [11]. That means that those PCs, which are controlled with one climbing fiber, are being taught to the same training signal. This consideration has been put into basis of problem formulation for a search of pairs of PCs, controlled with the same CF, - CF PC twins problem [2]. The problem seems to be *a priori* hopelessly hard: there are 100000 - 1000000 PCs in cerebella of mammals, while ten of them are controlled with the same CF. The experiment success probability is thus about  $10^{-4}$  -  $10^{-5}$ . This is almost zero, as any animal experiment has lot of other unpredictable obstacles. Nevertheless, we began systematic work in this direction, understanding that the experiments are similar to rare events search in High-Energy Physics [3]. The search problem is formulated as follows. A criterion of dealing with Purkinje cells with a common CF should be based on the fact, that PC's complex spikes (CS) are invoked by unitary impulses in the CF. In CF PC twins, these impulses should be practically synchronous. The goal of experiments is to find pairs of PCs with virtually synchronous CSs. An evaluation of the twin PCs

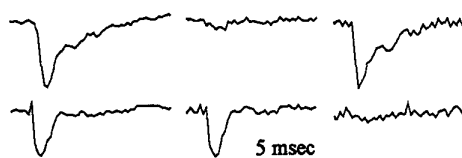
connections with GrCs could be obtained by comparison of their simple spike (SS) activity, which is known to be elicited by incoming excitation of GrCs.

## 2. Methods

Blocks of 2-6 tungsten electrodes were used for recording focal potentials and spontaneous extra-cellular neuron activities in a cortex (*vermis*) of a guinea pig cerebellum (experimental details in [4, 5]). Records of potentials, picked up by pairs of electrodes were thoroughly analyzed for a presence of synchronous CSs. We expected revealing of complex spikes, which always appear in two recording channels with the same time shift between them with a precision in a range of few hundreds of microseconds. The distance between electrodes (more than 200  $\mu\text{m}$ ) excluded recording of activity of the same PC [4] by two electrodes. 255 tracks of paired potential records in 6 animals have been analyzed.

## 3. Results

Two instances of synchronous CSs with parameters in the expected range have been revealed. They are described below separately.



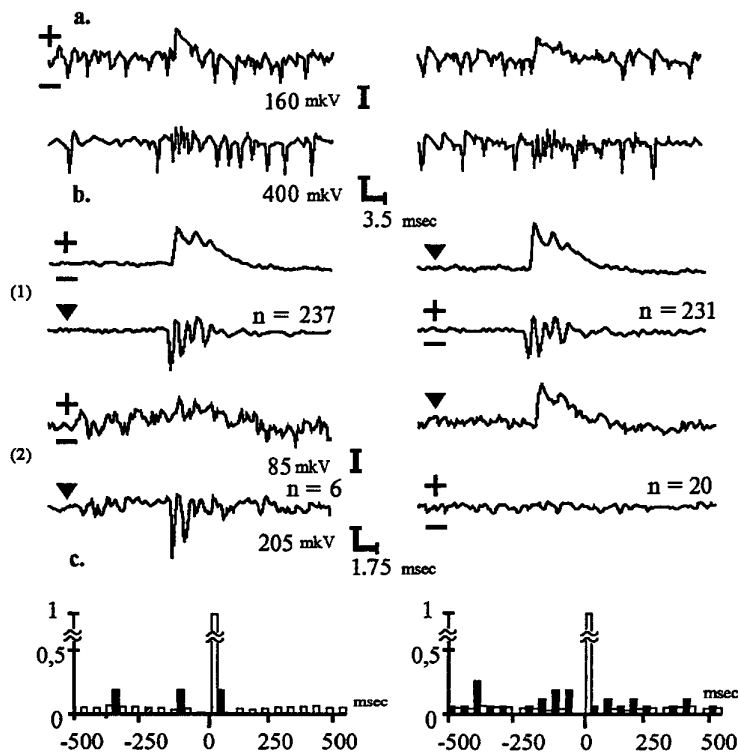
**Fig. 1. Twin complex spikes, case 1**

Upper and lower traces are obtained at the distance of 800  $\mu\text{m}$ . Averaged data: left: 164 CSs in channel I; center: 25 CSs in channel II only; right: 35 CSs in channel I only.

*Case 1.* Inter-electrode distance is 800  $\mu\text{m}$ . The record includes 199 instances of CS occurring at least in one of the channels. Mean interval and standard deviation - 714  $\pm$  536 msec. In 139 cases there are CSs in both channels. In 25 cases - CS at the channel I without CS at the channel II. In 35 cases, there are CSs at the channel II without a CSs at the channel I. Fig. 1 demonstrates results of potential averaging for 164 cases, when CSs were present at the channel I. Inter-CSs delay - 0.5 msec. In

this record, CSs and SS are present only at the channel I. In the channel II we could reliably distinguish only CSs. *Case 2.* In one instance, when both electrodes - test and referent recorded the CSs and SSs of Purkinje cells, the CSs at both electrodes appeared almost always simultaneously with a time shift of  $0.54 \pm 0.05$  msec.

The CS's wave-forms of the cells were notably different (Fig. 2 a). The SSs frequencies for these PCs were 58 and 46 imp/sec. At the Fig. 2 b results of averaging of CSs of the channel I (*plato-shaped*), synchronous with CS of the channel II (*oscillatory*) and vice versa are presented. It is



**Fig. 2. CS and SS activity of climbing fiber-stimulated twin Purkinje cells.**

Inter-electrode distance - 400  $\mu$ m. **a.** Fragments of original records. In two columns, two samples. Upper beam - cell I, lower beam - cell II. **b.** Averaging, synchronous with CSs: (1) averaging of CSs, left - synchronization by unit II, right - the same for I; (2) potential averaging when CSs in I (left) or in II (right) are blocked. **c.** Filled columns: histograms of CS activity in vicinity of blocked CS, in channel I (left) and in channel II (right); unfilled columns: renewal density for the whole population of CSs.

evident, that the results in both cases are virtually the same. Potential averaging of both channels synchronous with SSs of the other channel has not revealed any meaningful signals.

Our records contain 764 CSs of the channel I and 750 CSs of the channel II. In 6 cases there are CSs in II with no CSs in I, and *vice versa* in 20 other cases (Fig. 2, b2). In Figure 2 c are presented all CSs, which are generated in vicinity of the absent CSs for the both PCs along with a bi-lateral renewal function. The data show that CSs *vanish* in one of the channels predominantly in periods of increased CS firing rate. In other words, the failure probability depends on inter-CSs interval. 33% of all

impulses do not reach the cell I, and 50% impulses do not reach the cell II at inter-impulse intervals with duration,  $T < 80$  msec. At  $T < 100$  msec these figures change to 9 % and 26%. When  $T$  is in a range 200-500 msec all the impulses attain the cell I, while still 3 % of impulses can not reach the cell II.

In Fig. 3a, the influence of CSs on SS firing probabilities is demonstrated for both PCs. This influence is stronger and more prolonged for the cell I. Auto-correlation functions of SSs activity for both channels are alike. They have initial sharp minimums (obviously due to SS refractoriness), immediately followed by maximums, which are about 20% higher than a stationary level. They attain the latter exponentially with a time constant of

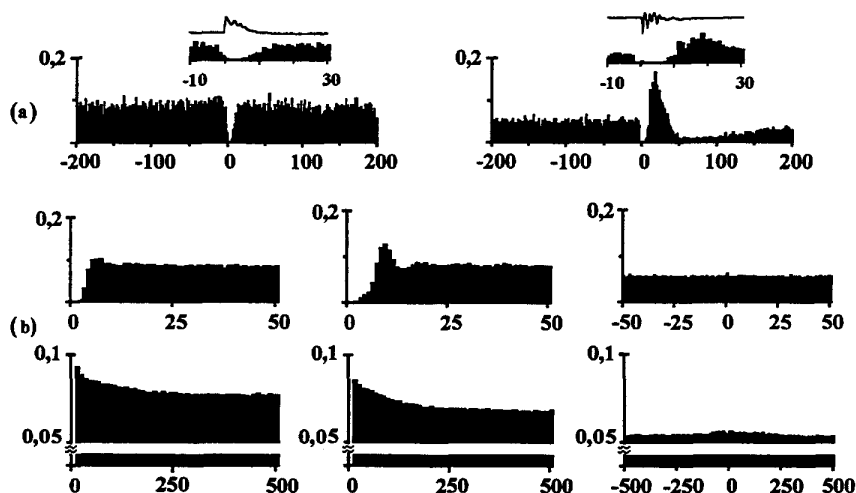
about 150 msec (Fig. 3, b: left and center). The cross-correlation function between SSs of both channels is flat at all time scales (Fig. 3 b: right).

#### 4. Discussion

We should first note that our five-year investigation has yielded first results in the targeted direction. Two pairs of CF PC twins are presented above. One of them is of less interest, as it presents only *twin CS*, i.e. complex spikes, which are generated in distant branches of the same CF. One example of *twin CS* has been published years ago [1]. Nevertheless, no data on propagation failure, comparable to our data of failure of 25 and 35 impulses for the twin case 1 and 6 and 20 failures for the case 2, have been reported beforehand. In the records, we have only results of two CF branches activation and for each of them a propagation of the initial impulse of the CF-issuing cell (CFIC) is non-reliable. We can obtain first order corrections to the number of CFIC impulses, which were probably generated by CFIC, taking into account failure frequencies and the total number of observed events. For the case 1 we get  $199 \times (25/199) \times (35/199) \sim 4$  CFIC

impulses have reached neither of the two recorded PCs. For the case 2 the correction is  $764 \times (6/764) \times (20/764)$ , which is less than 1. The empirical failure ratio is 0.14 and 0.19 in case 1, and 0.008 and 0.026 in case 2. These values, especially for case 1, are relatively large. It should be noted, however, that for the connection tuning mechanisms, which are described in an accompanying paper, even a failure probability of 0.2 would not present serious problems [6]. It is worth also to note, that for the two pairs of CS twins time lag between CS onset in neurons is practically the same: 0.5 and 0.54 milliseconds. The time shift is stable: its relative variations are less than 10%.

The most interesting case 2 presents the first discovered pair of *CF PC twins*, in which both CSs and SSs are present. This is a unique observation in the history of cerebellar research. It is important to analyze properties even of a single pair, because this is not a spontaneous random observation, but the first encountering of a long time anticipated event.



**Fig. 3. Inter-spike correlation of CF Purkinje cell twins**

**a.** Histograms of cross-correlation between CSs and SSs of the cells I (left) and II (right); In upper captures - the same at the stretched time scale. **b.** Auto-correlation (renewal functions) for SSs of the cells I (left) and II (center) and cross-correlation I → II (right) at the two time scales (upper and lower rows). Ordinate - bin filling probability, abscissa - in milliseconds.

There are several issues, which can be elucidated by the first twin pair analysis.

(1) Comparison of shapes of CS waves in the twin PCs demonstrates that periods of *fast* oscillations inside the CS are different for neurons I and II (2.2 and 1.5 msec). This fact shows mutual independence of mechanisms of

secondary CS maximums generation in these cells, which was not evident beforehand.

(2) It is well known, that PC's CSs affect an activity of their SSs. For different PCs this influence has different features [9; and others]. The SS - CS dependence, which is demonstrated at the Fig. 3 is well within the known variations [9]. Totally unexpected is the fact, that the *CF PC twins* have extremely *different* types of CS - SS

relations. It should be noted, that for the granule cells - PC connections tuning mechanisms, diversity of properties of influence of CF on different PCs, controlled with the same CF may be beneficial for elimination of excessively synchronizing feed-back [6].

(3) There are two types of PC's SS auto-correlation functions (ACF): the flat and triangle. It has been also shown, that an intensive stimulation of the CF could transform a cell with a flat ACF into a cell with a triangle one [8]. In accordance with these findings, our data show that practically the same CF input for I and II endorses them with the likely ACFs.

(4) It would be premature on a basis of data, obtained from a single pair of *CF PC twins*, to make conclusions to support or dismiss the *CF learning role*. Nevertheless, the data obtained *are contradicting* in an exact meaning pointed below to this famous hypothesis. It is indeed natural to assume that the *triangular* ACF is connected with a PC involvement into processes with a large correlation time. If the *CF PC twins* were identically trained during the whole life preceding an experiment, then time-dependent processes, in which they could be involved, should be the same [7]. That means, that the cross-correlation function of the *CF PC twins* at the time scale, matching the correlation time of the processes, in which they are involved, should be of *the same shape*, as their auto-correlation function. *This is definitely not the case* for our pair of the *CF PC twins* (Fig. 3 c). This fact means that either the learning hypothesis is totally wrong [10] or some theses in the above deduction are incorrect.

## 5. Conclusions

Purkinje cells, controlled with the same climbing fiber, have long been postulated to exist, but are difficult to find and record. This hard experimental problem, with emphasis on possible benefits of its performance, has been formulated more than two decades ago [7]. The first example of the *CF PC twins*, as described above, has been obtained after five years of goal-oriented experimental work (beginning with [2]). We suppose, that the work deserves the efforts devoted to it: an analysis of even the first two pairs of the *CF PC twins* yields substantial information on the working mechanisms of the cerebellar cortex. It seems that a comparison of this type of experiment, with the experiments in High Energy Physics could be justified [3]. In both cases, events are being searched for, which possess well described and rarely encountered features. These events analysis yields confirmation or disapproval of advanced theories on the system construction.

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