Activity properties of branches of a climbing fiber which controls different Purkinje Cells

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CLIMBING FIBER PURKINJE CELL TWINS ARE FOUND
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ABSTRACT
At the IJCN'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 4000 (frog), up to 500000 (human), and multiple synapses of a single CF. In higher vertebrates each CF controls about 4000 (frog), up to 500000 (human), and multiple synapses of a single CF. In higher vertebrates each CF controls about 30000 - 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 PCs 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 μm) 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 μm. Averaged data: left: 164 CSs in channel I; center: 25 CSs in channel II only; right: 35 CSs in channel I only.

Case I. Inter-electrode distance is 800 μm. The record includes 199 instances of CS occurring at least in one of the channels. Mean interval and standard deviation - 714 ±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 SSSs of Purkinje cells, the CSs at both electrodes appeared almost always simultaneously with a time shift of 0.54±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 (piato-shaped), synchronous with CS of the channel II (oscillatory) and vice versa are presented. It is 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

![Fig. 2. CS and SS activity of climbing fiber-stimulated twin Purkinje cells.](image-url)
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 $199 \cdot (25/199) \cdot (35/199) \approx 4$ CFIC impulses have reached neither of the two recorded PCs. For the case 2 the correction is $764 \cdot (6/764) \cdot (20/764)$, 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.

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 feedback [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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6. References