

# Spinal oscillators in man under normal and pathologic conditions

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## Abstract

1. *Single-fibre action potentials (APs) were recorded from lower sacral nerve roots of brain-dead humans (HTs) and two paraplegics with thoracical spinal cord lesions. Impulse patterns of single oscillatory firing  $\alpha_2$  and  $\alpha_3$ -motoneurons were identified and analysed. An  $\alpha_2$ -motoneuron fired typically with 3 AP impulse trains every 160 msec.*
2. *In stable spinal oscillators of HTs the oscillation period was 70 msec plus 30 msec times the number of APs per impulse train; the respective values in paraplegics were 35 msec plus 40 msec times the number of APs per impulse train. These linear relationships indicate that spinal oscillators consist of at least 2 kinds of nerve cells.*
3. *Successive interspike intervals (IIs) of the impulse trains increased from about 3.5 msec to over 10 msec in paraplegics similarly as was the case in HTs.*
4. *The distributions of the first IIs (of impulse trains) and of the oscillation period of unstable continuously oscillatory firing  $\alpha_2$ -motoneuron showed similar peaks. By relating the peak values of the first II and the oscillation period, a shortest II of 3.5 msec was obtained in a HT and a paraplegic, and a shortest oscillation period of 70 msec was measured in a HT and 40 msec in a paraplegic. The derivation of the shortest II of 3.5 msec from the oscillation itself is taken as an indication for  $\alpha_2$ -motoneurons being included in the spinal oscillator function, since the shortest soma-dendritic spike intervals of motoneurons is expected to be 3.5 msec.*
5. *The spinal oscillator of a paraplegic showed more and higher activity changes than that in a HT as if spinal oscillators in paraplegics were insufficiently damped.*
6. *By interpreting the peaks in oscillation period distributions of unstable oscillators as being different oscillation loop pathways, it is speculated that the oscillators consist of the motoneuron, to which different interneuron pathways are connected. A contrasting of pathways with increasing excitation of the oscillator was observed.*
7. *The comparison of possible loop pathways of oscillation between paraplegics and HTs (closer to normal) indicates that the loss of descending tracts in paraplegics and the adaptation to it result in an increase of the oscillation pathways for  $\alpha_2$ -oscillators from 1 to 3 in HTs to up to 6 in paraplegics.*
8. *Different measured and theoretically predictable spinal  $\alpha_2$ -oscillators can cover altogether a frequency range between 5 and 10 Hz. A single unbalanced spinal  $\alpha_2$ -oscillator of a paraplegic can already cover a frequency range between 4 and 13.5 Hz, which is the full frequency range of the ankle clonus, postural and physiological tremor.*

*Key-words: Humans — Spinal oscillators — Frequencies — Impulse trains — Interspike intervals — Loop pathways — Paraplegics.*

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## Introduction

In previous publications (11, 12) the recruitment of motoneurons was analysed in the low activity mode of occasionally firing. It was further shown previously that when higher activity levels were needed for the continence of the urinary bladder, a sphincteric  $\alpha_2$ -motoneuron switched from the occasional firing mode via the transient oscillatory firing mode into the continuous oscillatory firing mode (13). Including measurements in paraplegics, the functions of spinal oscillators will further be analysed and differences will be shown in their functions between the lesion being sited at the brain stem (HTs) and at the lower thoracic level (paraplegics).

The existence of oscillations or rhythmic activity in the human nervous system is a long known phenomenon. Rhythmic oscillations were observed in respiration, locomotion and mastication (9, 13, 16). Physiological tremor, postural tremor and ankle clonus cover a frequency range between 5 and 12 Hz (1, 5, 7, 16). The discovery of spinal oscillators for the continence in urination and defecation (13) offers the opportunity to study probably comparable simple structured oscillators in humans. In locomotion the functions of the central rhythm generators are subserved by the pattern generator (2) and are not easily measurable.

It was shown that sphincteric  $\alpha_2$ -motoneurons fire repeatedly with impulse trains consisting of 1 to 4 action potentials (APs) at periods between 110 and 160 msec (6-9 Hz). An  $\alpha_3$ -motoneuron was identified in a dorsal S3 root, which fired with impulse trains of about 40 APs every 1.4 sec. Interspike intervals (IIs) of the impulse trains of  $\alpha_2$  and  $\alpha_3$ -motoneurons varied between 3.5 and more than 10 msec (13). In this paper a decisive step forward will be done in the understanding of the function of the spinal oscillators in humans, including the calculation of constants of oscillation itself. The results suggest that the somehow self-organizing oscillators spread with a higher activation into the interneuronal network with simultaneous contrasting of its different oscillation pathways. The oscillatory firing  $\alpha_2$ -motoneurons, acti-

vated for the continence of the urinary bladder and the rectum, fire at frequencies within the range of those of tremor and clonus. It is therefore likely that these oscillations are basic mechanisms of the human central nervous system (CNS).

## Materials and methods

Single-fibre action potentials (APs) were recorded as described previously (11, 12, 13), with two pairs of wire electrodes. With the electrode polarities employed, the efferent APs point downwards and the afferent APs upwards. The basic data recorded from brain-dead humans (HTs) and paraplegics (Para), used for recruitment analysis in the occasional firing mode, and are stored on video tapes, were used now to analyse impulse patterns and activity levels of oscillatory firing motoneurons. The previously constructed conduction velocity frequency distribution histograms with their velocity ranges for the different motoneuron groups and the conduction velocities of single APs, were used to identify the APs and the groups they belong to. By recognizing certain additional AP wave forms and impulse patterns, APs of single motoneurons in the oscillatory firing mode could be identified and their time course followed up. Some oscillatory firing motoneurons were mainly identified by the firing patterns and could therefore be picked up from the summed impulse traffic of the nerve root fibres, only when active in the transient or continuous oscillatory firing mode.

## Results

### *Spinal oscillators*

Figure 1 shows recordings of impulse trains of oscillatory firing  $\alpha_2$  and  $\alpha_3$ -motoneurons from two humans with spinal cord lesions. Recordings from HTs have been presented in previous works and can be seen in the papers to follow. In figure 1A an impulse train (3 of 4 APs are shown) of continuous oscillatory

## Oscillatory firing of $\alpha_2$ and $\alpha_3$ -motoneurons

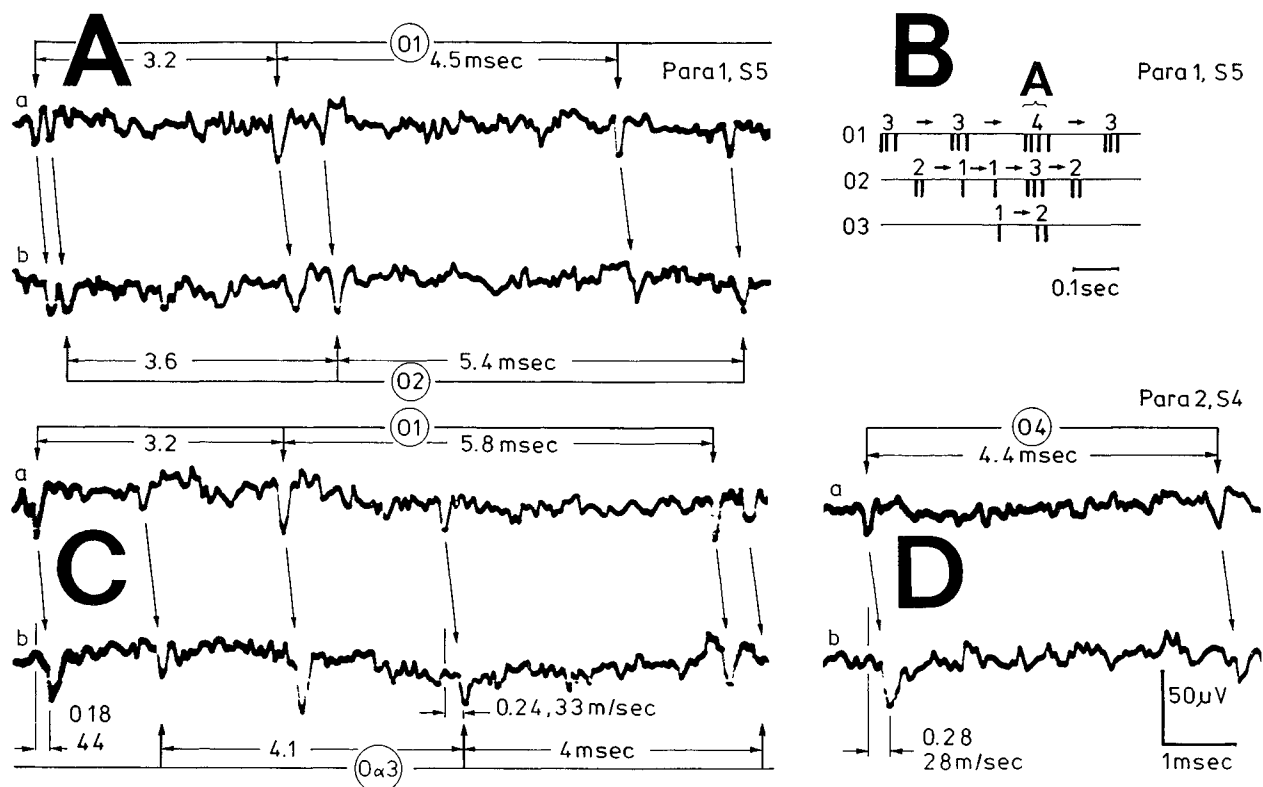


Fig. 1. — Recordings of impulse trains of oscillatory firing motoneurons in paraplegic 1 and 2.

- A. Impulse train of the continuously oscillatory firing  $\alpha_2$ -motoneuron O1 (3 of the 4 APs are shown) together with the impulse train of the transiently oscillatory firing  $\alpha_2$ -motoneuron O2. Interspike intervals are indicated.
- B. Impulse patterns of the 3 oscillatory firing  $\alpha_2$ -motoneurons O1, O2 and O3: O1 continuously oscillatory firing, O2 and O3 transiently oscillatory firing. "A" marks the sweep piece shown in A. Paraplegic 1.
- C. Impulse train of the  $\alpha_2$ -motoneuron O1 together with a part of the impulse train of the oscillatory firing  $\alpha_3$ -motoneuron O $\alpha$ 3. Interspike intervals, conduction times and conduction velocities are indicated. Paraplegic 1, S5 root.
- D. Impulse train (consisting of 2 APs) with the corresponding interspike interval, conduction time and conduction velocity of the continuously oscillatory firing  $\alpha_2$ -motoneuron O4. Paraplegic 2, S4 root.

firing  $\alpha_2$ -motoneuron O1 of paraplegic 1 (Para 1) is shown. The first two interspike intervals (IIs) are marked with 3.2 and 4.5 msec. Figure 1A shows further the impulse train of a second, but transient oscillatory firing,  $\alpha_2$ -motoneuron O2. The durations of the IIs are marked with 3.6 and 5.4 msec. There is no third transient oscillatory firing  $\alpha_2$ -motoneuron appearing in that sweep piece. In figure 1B the simultaneously measured impulse patterns of the 3 oscillatory firing  $\alpha_2$ -motoneurons (O1, O2 and O3) are represented by a schematic

latory firing, and O2 and O3 are transiently oscillatory firing. "A" shows approx. the same time period shown in figure 1A. The oscillation periods in B (approx. 160 msec for O1) of the oscillatory firing are drawn to scale, the IIs of the impulse trains are not. Figure 1C shows the recording of a part of the impulse train of the oscillatory firing  $\alpha_3$ -motoneuron O $\alpha$ 3 from Para 1 in comparison with the impulse train of motoneuron O1. Again IIs are indicated. Conduction times (0.18 msec, 0.24 msec) and conduction velocities (44 m/sec, 33 m/sec) of  $\alpha_2$  and  $\alpha_3$ -motoneurons are indicated. By comparing

| Case<br>Root<br>Sex<br>Age   | No                   | Kind<br>of<br>oscill.                  | $\bar{T}_{osc}$<br>[msec] | $\bar{f}_{osc}$<br>[Hz]     | Length of<br>impulse<br>train | II <sub>1</sub><br>[msec]   | II <sub>2</sub><br>[msec] | II <sub>3</sub><br>[msec] | $T_{osc}$<br>[msec] | $f_{osc}$<br>[Hz]  | Activity<br>[sec <sup>-1</sup> ] |
|--|----------------------|--|---------------------------|-----------------------------|-------------------------------|-----------------------------|---------------------------|---------------------------|---------------------|--------------------|----------------------------------|
| Para 1<br>S5 root<br>female<br>37 years<br>leason:<br>13 years ago<br>leason level:<br>T8 incomplete<br>T12 complete<br>centr. Temp.<br>35°C<br>root Temp.<br>25°C?<br>bladder<br>dyssynergia<br>from<br>200 ml on | 01<br>cont.<br>osc.  | $\alpha_2$                             | 161                       | 6.2                         |                               | 3.26±.2<br>n=119<br>3.2 n=1 | 5.5±.9<br>n=118<br>4.4    | 6.6                       | 161<br>166          | 6.2<br>6.0         | 18.6<br>21                       |
|  | 02<br>trans.<br>osc. | $\alpha_2$                             |                           |                             |                               | n=1                         |                           |                           | 68                  | 14.7               | 14.7                             |
|  |                      |  |                           |                             |                               | 5.7 n=3                     |                           |                           | 100                 | 10                 | 15                               |
|  |                      |  |                           |                             |                               | 5.8 n=2                     |                           |                           | 118                 | 8.5                | 17                               |
|  |                      |  |                           |                             |                               | 4.6 n=2<br>3.5              | 5.8                       |                           | 135                 | 7.4                | 18.5                             |
| 03<br>trans.<br>osc.   | $\alpha_2$           |  |                           |                             | 5.7 n=7                       |                             |                           | 68/82/<br>112             | 14.7/12.1/<br>8.9   | 14.7/12.1/<br>8.9  |                                  |
|  |                      |  |                           |                             | 6.5 n=5                       |                             |                           | 82/112/<br>142            | 12.1/8.9/<br>7.0    | 18.1/13.4/<br>10.5 |                                  |
|  |                      |  |                           |                             | 4.5 n=2                       | 7.5 n=2                     |                           | 112/127/<br>142           | 8.9/7.9/<br>7.0     | 17.8/15.7/<br>14   |                                  |
|  |                      |  |                           |                             | 6.2<br>5.2                    | 11.2                        |                           | 127/142                   | 7.9/7.0             | 15.7/14            |                                  |
| 0α3<br>cont.<br>osc.   | $\alpha_3$           | 285±<br>18.5<br>n=7<br>(256 to<br>302) | 3.5<br>(3.9 to<br>3.3)    | <br>6 to 15 APs<br>mean=8.4 | see Fig.3B                    |                             |                           |                           |                     | 29.4               |                                  |

|   |    |            |  |       |     |                                 |                                   |               |                 |                |                  |
|---|----|------------|--|-------|-----|---------------------------------|-----------------------------------|---------------|-----------------|----------------|------------------|
| Para 2<br>S4 root<br>male<br>23 years<br>leason:<br>2 years ago<br>level: T8<br>centr. Temp. 36°C<br>root Temp. ?<br>bl.dyssynergia:<br>> 200ml | 04 | $\alpha_2$ |  |       |     | 5.3±.9<br>n=71<br>(4.2/4.6/5.6) |                                   |               | 85/100/<br>110  | 11.8/10<br>9.1 | 23.6/20/<br>18.2 |
|   |    |            |  |       |     | 5.3±1<br>n=58<br>(4.2/5.6)      | 8.7±2.3<br>n=59<br>(4.4/8.8/12.8) |               | 100/110/<br>150 | 10/9.1/<br>6.7 | 25/22.8/<br>16.7 |
|   |    |            |  |       |     | 5.7±2<br>n=8                    | 7.2±3<br>n=8                      | 10.2±3<br>n=8 | 120/150         | 8.3/6.7        | 25/20            |
|   |    |            |  |       |     |                                 |                                   |               | 160/200         | 6.25/5         | 22/17.5          |
| HT5<br>dS3root<br>female<br>58 years<br>centr. Temp.<br>38°C  | 04 | $\alpha_2$ |  |       |     | 4.4                             |                                   |               | 168             | 6.0            | 12               |
|   |    |            |  |       |     |                                 |                                   |               | 184             | 5.4            | 10.9             |
|   |    |            |  |       |     | 3.8(6.8)                        | 7.0                               |               | 168/184         | 6.0/5.4        | 18/16.2          |
|   |    |            |  |       |     | 3.8/4.3                         | 4.5/6.8                           | 7/8/9/<br>10  | 172?/184        | 5.4            | 18.9             |
|   |    |            |  |       |     |                                 |                                   |               | 184             | 5.4            | 21.6             |
| HT6<br>dS4 root<br>female<br>37 years<br>c.Temp. 35.5°C   | 02 | $\alpha_2$ |  |       |     | 7.4±.5<br>n=6                   |                                   |               | 125/160         | 8/6.25         | 16/12.5          |
|   |    |            |  |       |     | 4.5/7.45                        |                                   |               |                 |                | 19               |
|   | 01 | $\alpha_2$ |  | 110.5 | 9.0 |                                 | 6.0                               |               |                 |                | 18.1             |

←  
 Table 1. — *Oscillatory firing modes of  $\alpha_2$  and  $\alpha_3$ -motoneurons from 2 paraplegics (Para 1, 2) and 2 HTs (brain-dead humans). Centr. Temp. = central temperature; cont. osc. = continuously oscillating; trans. osc. = transiently oscillating.  $\bar{T}_{osc}$  = mean oscillation period;  $\bar{f}_{osc}$  = mean oscillation frequency;  $II_1, II_2, II_3$  = first, second and third interspike interval of the impulse train; activity measured in action potentials (APs) per second. Downward bars in the schematically drawn activity modes indicate APs of the repetitive activity.  $\pm$  = error (standard deviation);  $n$  = number of observations. O1, O2, O3, O4, O $\alpha_3$  = designations of oscillatory firing motoneurons, which will be referred to in all figures. For other details of the oscillatory firing  $\alpha_2$ -motoneurons of the HT5 and HT6 and of the oscillatory firing  $\alpha_3$ -motoneuron of the HT5 see Ref. 13. Further details of the oscillatory firing  $\alpha_2$ -motoneurons O4 (para 2) and O4 (HT5) in the form of probability distributions are given in the figures 4, 5, 6, 11. The central temperature of 38°C in HT5 was due to an infection.*

the conduction velocities of the two motoneurons with distribution histograms of the conduction velocity frequencies (Fig. 2B of the previous paper (12)) it can be seen that the value of 44 m/sec falls within the  $\alpha_2$ -range and the value of 33 m/sec in that of  $\alpha_3$ -motoneurons. The motoneuron type could have also been identified by the number of APs per impulse train and the oscillation period, since  $\alpha_2$ -motoneurons fire at about 2 to 4 APs per impulse train and an oscillation period of between 100 and 190 msec, whereas  $\alpha_3$ -motoneurons fire at more APs per impulse train and longer oscillation periods. Figure 1D shows a recording from  $\alpha_2$ -motoneuron O4 of Para 2. The conduction velocity of 28 m/sec shows that this continuous oscillatory firing  $\alpha_2$ -motoneuron is of  $\alpha_2$ -type (cf. this value with the velocity ranges of  $\alpha_2$  and  $\alpha_3$ -motoneurons of the Para 2; Fig. 2E of the previous paper (12)).

The firing pattern of the continuously oscillatory firing  $\alpha_2$ -motoneuron O1 was rather constant as for the length of the impulse train (and the number of APs per train) as well as for the oscillation period; the firing pattern of the continuously oscillatory firing  $\alpha_2$ -motoneuron O4 of Para 2 varied in the number of APs per impulse train and the length of the oscillation period. Including the stable and unstable continuously oscillatory firing  $\alpha_2$ -motoneurons of the brain-dead human cadavers HT6 and HT5 (13) a pool of oscillatory firing motoneurons is available for an analysis from impulse patterns of human spinal oscillators. As already illustrated in figure 1, the oscillators driving sphincteric motoneurons are situated in the lower spinal cord, since their functions could be measured in the two paraplegics. The number of APs per impulse train and the oscillation

periods of oscillators measured in the paraplegics and in some of the HTs are summarized in table 1.

#### *Relation between oscillation period and number of APs per impulse train*

Since more often in HTs than in paraplegics the motoneurons fired in the high activity mode with a certain number of APs per impulse train and a more fixed oscillation period, stability seems to be closer to physiologic conditions. The most stable oscillators were taken to plot the relation between the number of APs and the oscillation period  $T$  (Fig. 2A). As can be seen, the relationship is a straight line not crossing the origin. The approximate equation derived for this linear relation is: Oscillation period = 70 msec + 30 msec  $\times$  (number of APs per impulse train). For rather normally firing  $\alpha_2$  and  $\alpha_3$ -motoneurons, this means that the oscillation period increases by 30 msec if the number of APs increases by one AP per impulse train. Since in addition always another interval of 70 msec is needed for a complete oscillation period, the linear relationship is interpreted by the oscillator consisting of at least 2 kinds of elements: one element always present and contributing 70 msec to the oscillation period, and a set of other elements which contribute according to their numbers, a multiple of 30 msec to the oscillation period.

Assuming that the oscillator consists of the motoneuron itself and of time determining interneurons, each one responsible for a time consumption of 30 msec, the motoneuron oscillating with one interneuron, would yield an oscillation period of 70 msec + 30 msec

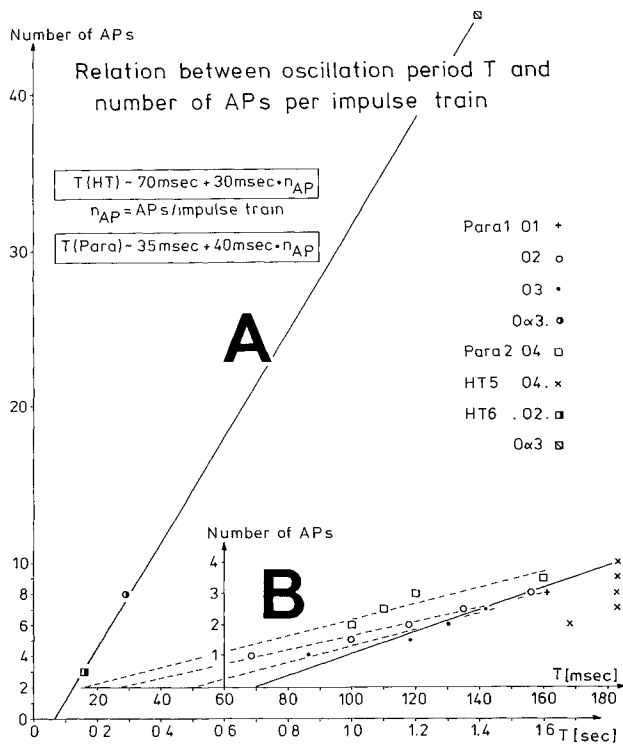


Fig. 2.

- A. Relation between the oscillation period (T) and the number of action potentials (APs) per impulse train of stable continuously oscillatory firing  $\alpha_2$  and  $\alpha_3$ -motoneurons. The straight line can be described by the relation  $T(\text{HT}) = 70 \text{ msec} + 30 \text{ msec} \times n_{\text{AP}}$ .
- B. Expanded scales. The solid line is the straight line from A. The dashed lines characterise the relationship between the numbers of APs and the oscillation period for the oscillatory firing systems of the paraplegics where the motoneurons fired with different impulse train lengths. T(Para) describes the different linear relations. Note that the unstable oscillatory firing  $\alpha_2$ -motoneuron in HT5 behaves differently.

(10 Hz). If the motoneuron oscillates with 2, 3 or 4 time consuming interneurons, the oscillation periods will be 130 (7.7 Hz), 160 (6.25 Hz) or 190 msec (5.3 Hz).

*Relation between oscillation period and number of APs per impulse train in more extensive pathology*

Since there was a tendency for stable  $\alpha_2$ -oscillator to oscillate with a certain number of APs per impulse train (e.g. 3) and a rather fixed

oscillation period (e.g. 160 msec), it might be interesting to plot the oscillation period against the number of APs per impulse train for the situation where the oscillator changes the oscillation period and the number of APs per impulse train for different stimulations. Variation of first IIs of the impulse trains and of the oscillation period (frequency) occurred on average more often in paraplegics than in HTs. It is followed that changing first IIs (for a fixed number of APs per impulse train) and frequencies is an indication for more extensive pathologic oscillatory firing.

Figure 2B (insert) shows (the dashed lines) the relationship between the oscillation period and the number of APs per impulse trains for the unstable, more pathologic, oscillators. Averaging the 3 dashed lines gives, for these more pathologic cases, an oscillation period of approximately 35 msec plus 40 msec times the number of APs per impulse train. On the background of the previously drawn oscillation picture this would mean that the contribution to the oscillation period of the motoneuron and the time consuming interneurons have changed. As can be seen from figure 2B, the most unstable oscillator measured in HTs (crosses) showed a variability different from those of unstable oscillators in the paraplegics. This phenomenon will be analysed in more detail below.

*Successive interspike intervals of impulse trains of oscillatory firing motoneurons in pathology*

Figure 3 shows successive interspike intervals (IIs) of impulse trains of the oscillatory firing  $\alpha_2$  (Fig. 3A) and  $\alpha_3$ -motoneurons in the paraplegics (Fig. 3B). No principal differences can be seen in comparison with the IIs measured in HTs (13). Similarly as in HTs, the duration of the IIs increased from the first to the second and to the third II in  $\alpha_2$ -motoneuron impulse trains. Only the variability in the duration of the IIs was larger in the paraplegic case. Sometimes the first II was longer than the second II (not shown in Fig. 3). The successive

Successive interspike intervals from impulse trains of oscillatory firing  $\alpha_2$  and  $\alpha_3$ -motoneurons

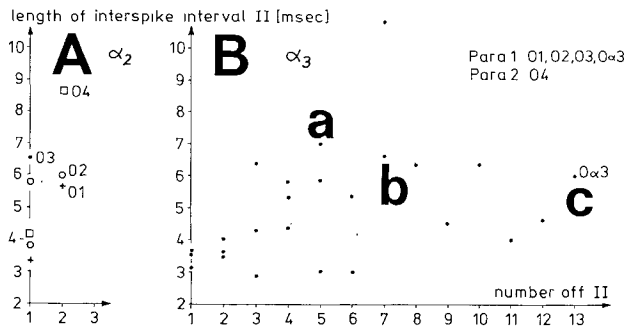


Fig. 3. — Successive interspike intervals of oscillatory firing  $\alpha_2$ (A) and  $\alpha_3$ -motoneurons (B). The designations are the same as in figures 1, 2. In B, a, b and c designate short, medium and long impulse train.

IIs of the impulse trains of the oscillatory firing  $\alpha_3$ -motoneuron O $\alpha$ 3 showed similar behaviour (increasing impulse train length) as did the IIs of the oscillatory firing  $\alpha_3$ -motoneuron impulse trains in HT5 (13): with short impulse trains the IIs increased regularly (Fig. 3Ba), and with longer impulse trains the IIs became more irregular (Fig. 3Bc).

Even though not quantified so far (and not evident from Fig. 3), it seems as if the shortest II (of about 3.5 msec) of  $\alpha_2$  and  $\alpha_3$ -motoneurons are slightly reduced in paraplegics. In rat (8) and cat (15) the shortest soma-dendritic spike interval was between 3.4 and 3.5 msec. Judged by the shortest II of the impulse trains in humans, the shortest soma-dendritic spike interval also seemed to be 3.5 msec. The on the average slightly reduced shortest soma-dendritic spike intervals could mean that the properties of the soma and the dendritic trees of the  $\alpha$ -motoneurons have slightly changed following spinal cord lesion.

#### *Similarities in the distributions of the first interspike interval and the oscillation period*

It was emphasized in a previous paper on spinal oscillators (13) that in stable oscillators the duration of the first interspike interval (II)

already provides information on how long the impulse train will be and how long the oscillation period will be. This means that complete information about the ongoing oscillation is already contained in the length of the first II. In other words, the oscillation period in stable oscillators “tells” how long the impulse train and the duration of the first II were.

In unstably continuously “swinging” oscillators this relationship between the first II and the oscillation period is not applicable. The question arises whether there are similarities in the frequency distributions of the first II and the oscillation period for unstable “swinging”  $\alpha_2$ -oscillators, suggesting an underlying more general property. As figures 4, 5 and 6 show, there are corresponding peaks in the distributions. For this analysis, the most suitable spinal  $\alpha_2$ -oscillators were chosen, oscillator O4 of Para 2 and oscillator O4 of HT5.

Figure 4 shows the II distribution for impulse trains of 2, 3 and 4 APs in paraplegic 2. Continuous integral curves were drawn over the discrete values to compensate for the author’s systematic error in the measuring procedure (e.g. preference of even to odd values). Also, the number of measurements was rather low. The number of observation for 4 AP impulse trains was too low to give real distributions. As can be seen from the distributions of the first II for 2 and 3 AP impulse trains, the mean II were nearly exactly the same (5.3 msec) whereas the distributions of the IIs are quite different. As the values 4.2 and 4.6 msec suggest, there are regularities in the distributions, which remind of coupled oscillators. Also, the distribution of the second II of the 3 AP impulse train suggest coupling of oscillators, e.g. like in two pendulums. The dashed line arrows point to the largest corresponding peaks.

Figure 5 shows the frequency distributions of the corresponding oscillation periods (A to E). Peaks can be recognized in each distribution, and the corresponding peaks of different distributions, for different impulse train length, are indicated again by dashed line arrows. With the increasing impulse train length the largest peak of the oscillation period shifts towards longer oscillation periods and, as can be calcu-

Interspike interval distributions from impulse trains of  
oscillatory firing motoneuron O4

Para 2  
vS4

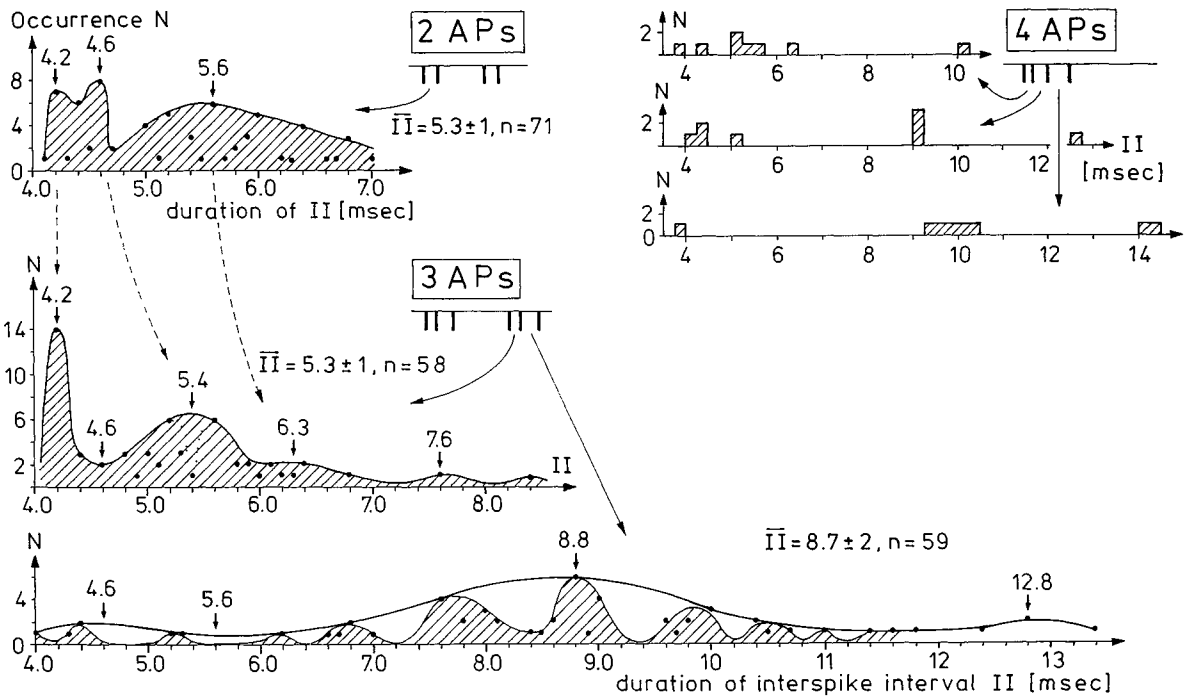


Fig. 4. — Interspike interval frequency distributions from impulse trains of the oscillatory firing  $\alpha_2$ -motoneuron O4. Owing to systematic errors, e.g. between even and odd values, enveloping curves were drawn. For impulse trains of 4 APs only histograms were plotted because of low statistic. The dotted lines mark the corresponding peaks in the occurrence patterns of the first interspike interval (II). Note that mean interspike intervals ( $\bar{II}$ ) provide only little information about the distribution of IIs. Two enveloping curves are drawn for the distribution of the second II.

lated, the activity produced by the oscillator increases (10 Hz:  $A=20$  APs/sec; 9.1 Hz:  $A=22.8$ ; 8.3 Hz:  $A=25$ ).

Considering the increased activity of the oscillator and interpreting the oscillation period as a loop spread into the space of interneurons in the spinal cord, figure 5 would suggest that with the increasing oscillator activity the oscillation loop is extended, and it probably spreads away from the motoneurons. But at the same time, the dashed lines draw near (closest in Fig. 5C). This seems to be indication of some kind of contrasting. When attributing the peaks to certain interneuron pathways, figure 5A to E show, how the interneuron pathway change with the increasing activity of the oscillator. In

A, the oscillator uses mainly 2 out of 6 pathways. In B, the oscillator still uses 6 pathways, but prefers the one with 110 msec. In C, the pathway with 120 msec is mainly used. The simplified interpretation of the oscillation loop is shown at the right side of figure 5. The double dashed line arrow (left part of Fig. 5) shows how the mean loop pathway increased. This loop pathway interpretation suggests that the oscillator can use different neural pathways and that certain pathways are preferentially used according to the activation; a kind of contrasting occurs with the increased spreading. The major contrasting in this oscillator pathways occurred for 3 APs per impulse train (Fig. 5C).



Oscillation period : dependence on the number of APs per impulse train

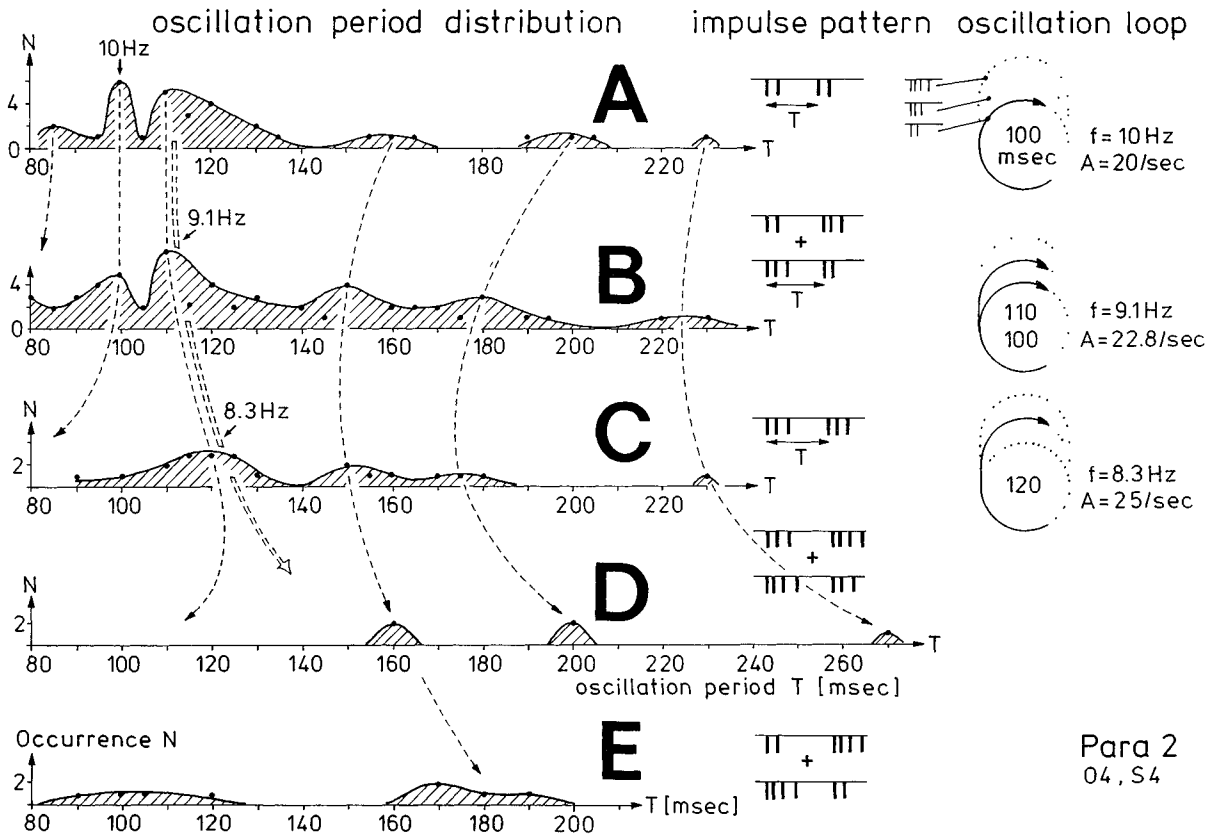


Fig. 5. — Distributions of oscillation period frequencies: impulse train lengths of 2 APs(a), 2/3 APs(B), 3 APs(C), 3/4 APs(D) and 2/4 APs(E). The corresponding distribution peaks are linked by the dashed lines. The double dashed line indicates mean shift of the distribution. A very simple loop interpretation is given for the increasing oscillation period at the right side of the figure.

Figure 6 shows the interspike interval distributions (A) and the oscillation period distributions (B) for different impulse train lengths of oscillator O4 of HT5. Again, certain peaks could be identified in each distribution of first IIs, numbered 1, 2 and 3. The dashed line arrows show correlations to those of other distributions of different impulse train lengths (a, b, d). The first II distribution peaks (1, 2 and 3) are closest for the 3 Ap impulse trains. Also, the distribution peaks (6B; 1, 2 and 3) of the oscillation period distributions for different impulse train lengths (g, h, i, j) could be correlated. The distribution peaks in figure 5B shift only little toward larger oscillation periods with the increasing impulse train length as compared to the oscillation period shift observed for Para 2 (Fig. 5).

There is no clear-cut information which can be derived from the distributions of the second and third II. Comparing the distribution of the first II (b) with those of the second (c), peaks in the first II distribution partly correspond to valleys in the second II distribution and vice versa (small arrows). A similar case is seen in figure 6e and f. If  $\alpha_2$ -motoneuron is a part of the oscillator, and this will be shown below, then this partly opposite distribution behaviour may reflect inactivation of parts of dendrites when the motoneuron oscillates in itself to produce the impulse train or when depolarization spreads further into the dendrite tree endings to produce the third and fourth somadendritic spike (see Discussion). It is not possible as yet to identify all characteristics contained in these distributions; nevertheless,

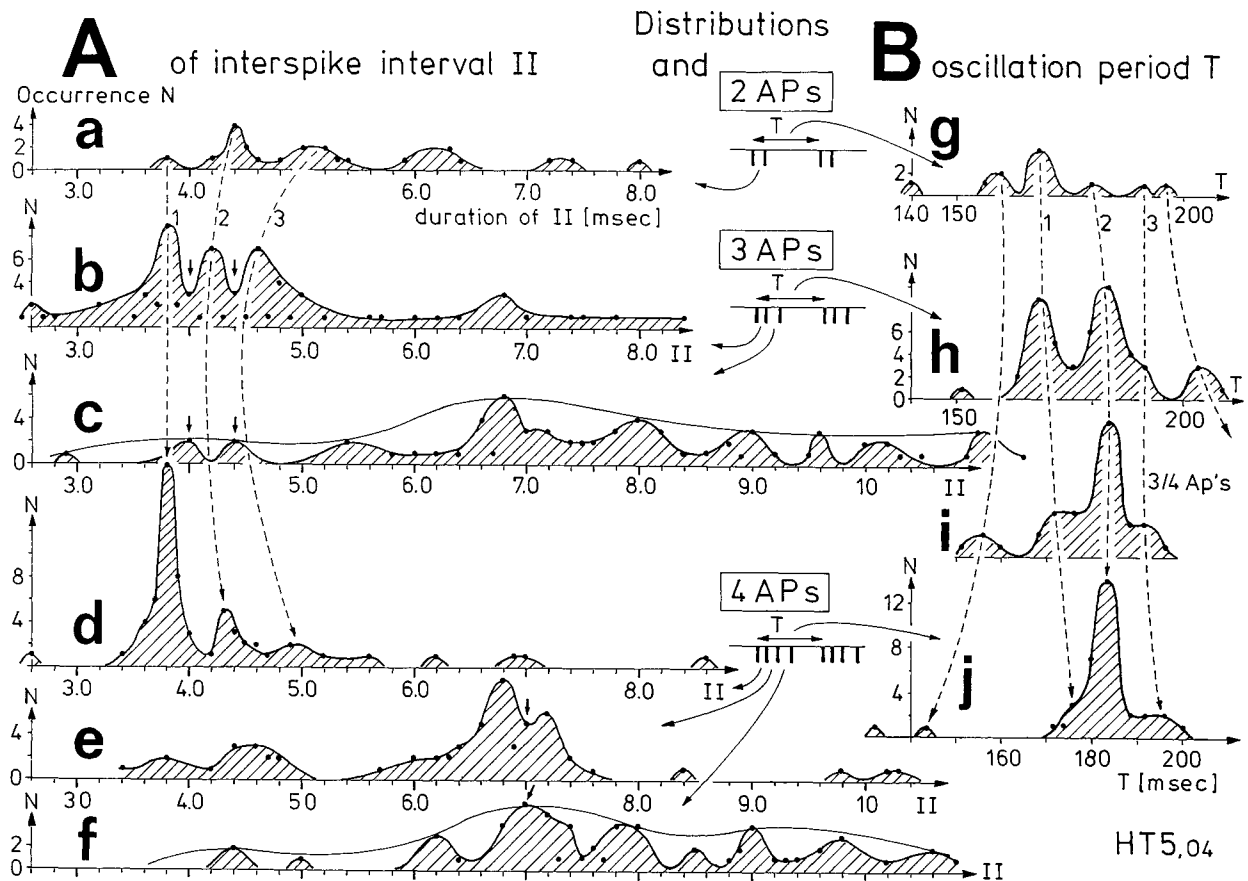


Fig. 6. — Interspike interval frequency distribution (A) and the corresponding oscillation period frequency distributions (B) for different length of the impulse trains. The corresponding distribution peaks of the first interspike intervals and the oscillation period are linked by the dashed lines. The corresponding interspike interval peaks and oscillation period peaks are labelled in the same manner (1, 2 and 3) (b and g). Distributions of the second (c, e) and third interspike intervals (f) are also shown. The small arrows indicate opposite trends of occurrence between the first (b) and the second (c), and between the second (e) and the third (f) interspike intervals.

information on some important properties of the oscillation will be extracted from the distributions in the next part of this paper.

#### Constants of oscillation

In the first paper dealing with spinal oscillators (13) it was stated that information on the oscillation of stable oscillators is contained in the length of the first II and also in the oscillation period. In the previous paragraph it was shown that the distributions of the first II and the oscillation period are similar for unsta-

ble oscillators and that there are corresponding peaks. With the information on the oscillation in both distributions it is tried to estimate the constants of oscillation by relating the peaks of the distributions from the first IIs to those of the oscillation periods.

Figure 7 shows the correlation between peaks of the distributions of the first II and the oscillation period for the oscillator in Para 2 (Fig. 7A) and HT5 (Fig. 7B). By extrapolating the curves for different AP impulse train length to the coordinate axes one obtains the shortest II and the shortest oscillation period. Approx. 3.5 msec are obtained for the shortest II from

## Relation between peak values of interspike interval and oscillation period distributions

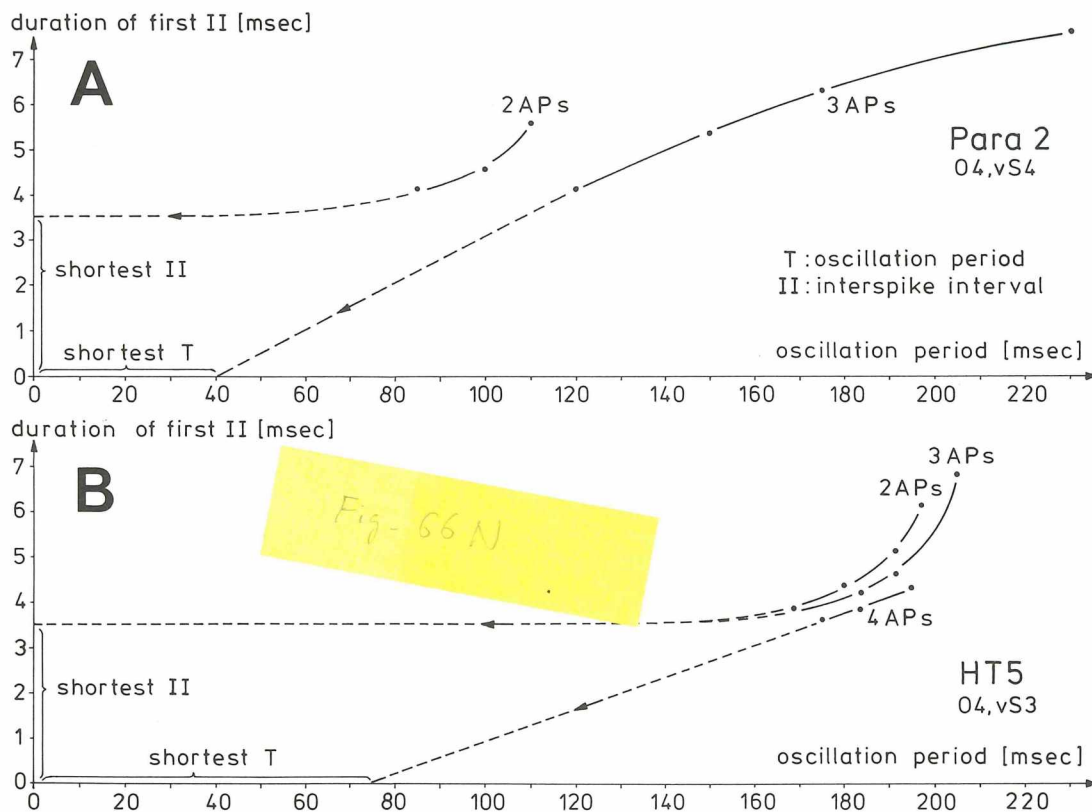


Fig. 7. — Relations between corresponding peak values of interspike interval and oscillation period frequency distributions for the  $\alpha_2$ -motoneuron O4 in paraplegic 2 (A) and O4 in HT5 (B). The relation points are obtained from figures 4, 5, 6. Lines connect the dots to show trends. The dashed lines are extrapolations into the unphysiologic range to obtain characteristic constants of the oscillation. The constants on the ordinate have the same value as the shortest soma-dendritic spike interval (Fig. 3) and those on the abscissa are values of the oscillation period for impulse trains of zero APs (Fig. 2).

the oscillation itself in Para 2 and HT5 (Fig. 7). The shortest oscillation period for Para 2 is about 40 msec, and for HT5 very approx. 70 msec. The shortest II of 3.5 msec, which is approx. the expected shortest soma-dendritic spike interval of motoneurons (no information is available about differences between different  $\alpha$ -motoneurons), is taken as an indication for the motoneuron itself being an important part of the spinal oscillator. The values of shortest oscillation period of 40 msec and 70 msec obtained from the oscillation itself for Para 2 and HT5 respectively are approx. the same as those obtained from different oscillators (Fig. 2).

### *Frequency and activity levels of spinal oscillators in Para 2 and HT5*

Figure 8 shows the frequency and activity levels of oscillator O4 in Para 2 following pin-prick (pain) (Fig. 8A) and upon no stimulation (Fig. 8B). The figures at the bottom indicate the numbers of APs per impulse train. Activity and frequency levels change in parallel. For the strong activity increase following pain 1 the frequency increased in parallel with the number of APs per impulse train. Frequency and AP number also change upon no stimulation (Fig. 8B). Figure 8C shows the frequency and the activity levels of oscillator O4 in HT5.



In comparison to HT5, the activity of oscillator in Para 2 is less stable, in particular the frequency of HT5 oscillator is more stable. Unimportant for this comparison is that the oscillator in Para 2 was excited and that in HT5 was inhibited by the pin-prick. Figure 9 shows the frequency and activity changes in Para 2 and HT5 oscillators following anal catheter pulling. Again, the changes of oscillator in Para 2 are more pronounced than those in HT5. In addition in Para 2 changes seem to occur all the time, as if the oscillator is overexcited. Some kind of a damping seemed to be missing to give the Para 2 oscillator the same stability as has the HT5 oscillator.

## Discussion

### *Structure of spinal oscillators*

It was shown in figure 2 that there is a linear relationship between the oscillation period of  $\alpha_2$  and  $\alpha_3$ -oscillators and the number of action potentials (APs) per impulse train. As the linear relation does not cross the origin, it is concluded that the oscillator consists of at least two kinds of elements. Since in addition in figure 7 it was shown that the shortest II, calculated from the oscillation itself, is about 3.5 msec and the shortest soma-dendritic spike interval of an  $\alpha$ -motoneuron is also about 3.5 msec (8, 13, 15), it may further be concluded that the  $\alpha$ -motoneuron itself is a part of the oscillator. The old working hypothesis assuming the oscillator to be a ring of interneurons or similar structures (13), is less likely. Further, if separate oscillators drive  $\alpha_2$  and  $\alpha_3$ -motoneurons, then one oscillator may drive several motoneurons. As figure 1A shows, if two  $\alpha_2$ -motoneurons fire with the same or similar impulse pattern, then they should have been detected, since such AP combinations are very easy to pick up from the summed impulse traffic. So far, identical impulse patterns have not been detected. It is therefore concluded that all motoneurons belong to their own oscillator. However  $\alpha_2$ -motoneurons can fire with rather similar impulse trains (Fig. 1A, Table 1). It was

pointed out (3) that neural networks from lower species are irrelevant in this respect. It will be tried now to schematically construct based on measurements themselves, some principles of the neural network of  $\alpha_2$ -oscillators driving anal and bladder sphincters and associated functions of the pelvic floor.

In figure 2 it was shown that the oscillation period increases by 30 msec with each AP in the impulse train. With the space interpretation of the oscillation period this means that with each AP per impulse train the oscillation spreads out by 30 msec farther into the network of interneurons. With the simplest assumption of one time consuming interneuron per 30 msec this means that if the  $\alpha_2$ -oscillator fires with 3 AP impulse trains there are at least the motoneuron and 3 time-determining interneurons included in the oscillation loop. Since in uncontrolled oscillators in paraplegics (see below) the oscillation period is not a single value but a distribution with approx. up to 6 separate peaks, there are 6 interneuron loops starting from the motoneuron. Since further there is some kind of contrasting of these different pathways (Fig. 5A to D) with the increasing activity of the oscillator (increasing number of APs per impulse train), there probably is some kind of additional lateral field inhibition by recurrent inhibiting interneurons between the 6 possible pathways. Therefore, the pathways probably consist of separate rows of interneurons. The process of contrasting of the different pathways was the strongest for 3 AP impulse trains (Fig. 5C) in the uncontrolled oscillator of Para 2. Whether this means that this uncontrolled oscillator prefers the 3 AP impulse trains is not clear. The consequences of the central control of the brain stem and higher centres is a further contrasting, fusion or reduction of the pathways, since on the average, more stable oscillators (firing always with about the same frequency) were found in HTs than in paraplegics, as can be seen from the comparison of the distributions of the oscillation periods between Para 2 (Fig. 5) and HT5 (Fig. 6B). Even though there are no measurements of oscillators of this quality from normal humans available, it seems from the comparison of the oscillators in HT5

and Para 2 that the brain stem and the higher centres regulate in a specific way these oscillators. One way of regulation could be by synchronizing spinal oscillators with oscillators of the higher centres. The loss of the descending pathways partly uncovers the spinal neural network of the oscillators. Some basic structures of  $\alpha_2$ -oscillators are illustrated in figure 10.

Not much can be said about how the oscillator oscillates. Two possibilities can be proposed. The motoneuron is controlled by a drive potential. The depolarizing part produces impulse trains at the axon hillock. The impulse train length is determined by the strength of the depolarization rather than by its duration. The hyperpolarizing potential blocks the motoneuron to other inputs and determines mainly the oscillation period (13). With the increasing depolarization amplitude and the increasing and prolonged hyperpolarization the number of APs per impulse train and the oscillation period increase. The impulse train activity excites different interneurons which depolarize and hyperpolarize the motoneuron. The actions of the neurons must be coordinated and must have certain time courses. Depolarizing and hyperpolarizing potentials have been detected among interneurons in the sacral spinal cord (10) and in the nervus pudendus (4). For further discussion see Ref. 13. A second possibility is that it is the motoneuron itself that oscillates. This activity drives interneurons which inhibit the motoneuron for some time. When the inhibition of the motoneuron is released the motoneuron starts oscillating again. The oscillation lasts for the time of the impulse train. A stronger depolarization or a longer oscillation of the motoneurons may result in an increase of the antidromic invasion of the dendrites with each successive spike (6). Second and third IIs may show then phenomena such as opposite distribution probabilities as indicated in figures 4 and 6A by small arrows. The interneurons included in the oscillation loop have different thresholds. The thresholds are regulated by the afferent input (Fig. 10). If the afferent input is low, only the short loops are channelled. With higher afferent input also the longer loops are opened. The afferent input

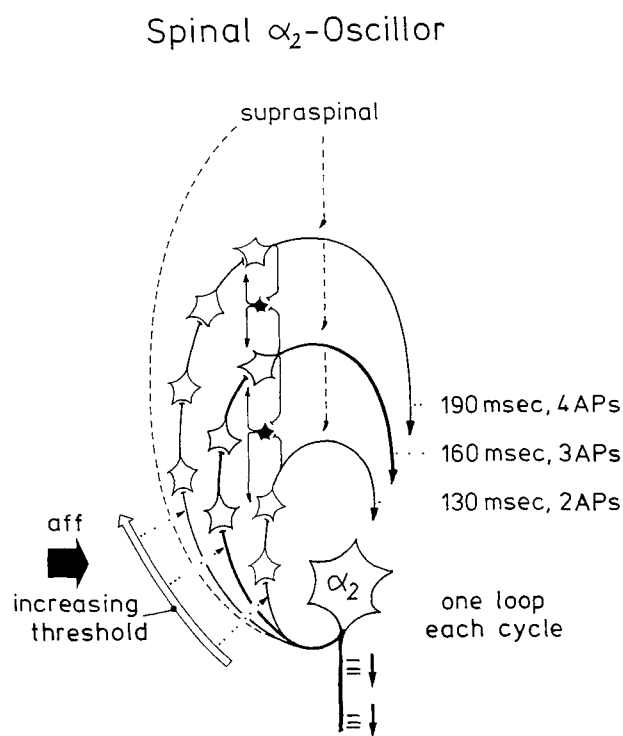


Fig. 10. — Working hypothesis of principle circuitries of the spinal  $\alpha_2$ -oscillator.  $\alpha_2$  =  $\alpha_2$ -motoneuron soma; open cell somas = interneurons; filled somas = inhibitory interneurons (2 are indicated) for lateral field inhibition (unclear whether they work pre- or post-synaptically). Three loops with sets of interneurons are indicated, up to 6 are measured. Threshold arrow indicates higher thresholds for longer loops with respect to the adequate afferent input. If all thresholds are too high, so that no loop is opened (self organized), the  $\alpha_2$ -motoneuron fires in the occasional firing mode. If working hypothesis would be right, still many more interneurons are necessary to realise the measured interspike interval and oscillation period distributions. For example the interloop interaction is not indicated, which becomes important if the afferent input changes quickly; more inhibiting interneurons are necessary; the preference for the 3 AP loop is not explained by the model; the function of the oscillator is not known: Oscillates the  $\alpha_2$ -motoneuron in itself (impulse train) and is transiently inhibited by the interneurons (time between the impulse trains) or oscillates the  $\alpha_2$ -motoneuron together with the interneurons? One loop each cycle = Probably the excitation uses in a first approximation one pathway for a certain oscillation cycle, but which pathway is taken depends on the probability distribution for a certain afferent input in similarity to figures 4, 5, 6, 11.

needs at least 3 qualifications for the regulation, namely the afferent input has to be adequate (connections), it must have a certain frequency and has to have a stable phase. These

3 conditions for the afferent input to excite the oscillator will be analysed in the publications to follow. The oscillation loops are channelled not only by the afferent input. Probably in normal humans also the descending tracts can activate and organize the oscillators to achieve continuous high activity levels in external sphincters, if required. The comparison of spinal oscillators with mechanical oscillators (16) is not justified. Apart from similar principles, mechanical oscillators are far from the human reality. Different kinds of oscillators and oscillator models in different species are discussed elsewhere (2, 3, 16).

One oscillator model is especially attractive. As figure 10 suggests, the excitatory states of the  $\alpha_2$ -motoneurons firing in the oscillatory mode could be due to "reverberatory" activity in intraspinal (segmental) interneural circuits (18). Closed intraspinal loops were already proposed in 1948 (19). The reverberatory interneuronal circuits are probably not intercalated between the secondary muscle spindle afferents and the  $\alpha_2$ -motoneuron as thought earlier (13), but closed "synfire chains" converge onto  $\alpha_2$ -motoneurons itself. The stabilisation of the reverberatory activity in positive (re-excitatory) loops could be supported by processes similar to synaptic modulation (20). Reverberatory loops, recurrent inhibition and presynaptic inhibition probably effect the synchronisation (20). The dependence of the oscillation period on the number of action potentials per impulse train (Fig. 2) and the oscillation period distribution of a very unstable oscillator (Fig. 5) suggest that the spinal oscillator could be a mixture of "dedicated-line" arrangement and "synfire chain" concept. The "synfire chain" (17) consists of a set of neurones that converge on a subsequent set, which in turn converges on another set and so forth. When the neurones in the first set fire in near-synchrony, each of the cells in the second set receives near-synchronous synaptic inputs which synchronously excite the subsequent set, and so forth. The "synfire chains" are very flexible dynamic functional entities. The chain may be turned on or off according to the spatio-temporal pattern activity in the spinal interneuronal network.

$\alpha_3$ -oscillators fire with higher activity than  $\alpha_2$ -oscillators (13) (Table 1) according to the  $\alpha_2$ -oscillator that the mean activity increases with longer impulse trains and longer oscillation periods.  $\alpha_3$ -oscillators are probably similar structured than  $\alpha_2$ -oscillators. Attributing one interneuron to one AP per impulse train, the interneuron loops can consist of up to 50 interneurons (13). Since others than the time consuming interneurons will contribute to the oscillation, several hundreds of interneurons can be involved. For longer impulse trains, strong irregularities occurred in the impulse trains (13) (Fig. 3Bc). It is possible that neighbouring  $\alpha_3$ -motoneurons may influence each other.

#### *Importance of spinal oscillators*

The spinal oscillators are of interest for at least 3 reasons: 1) They are important neural networks of the central nervous system, which generate the high activity mode for sphincters, and probably also for other muscles; 2) They consist, in addition to the motoneuron, of many interneurons. The spinal oscillators allow therefore the study of interneuron connectivity under physiologic and pathophysiologic conditions. With respect to the present research project (reconstruction of urinary bladder function in paraplegia (13)), it should be possible to find the reason for the dyssynergia of the urinary bladder, especially since parasympathetic activity (detrusor function) has also been identified (paper VI (14)); 3) The oscillation, namely the repeated firing with impulse trains, is easy to measure invasively from lower human sacral nerve roots, and tremor, a most likely result of the oscillation, is nearly as easily measurable noninvasively as the reflexes. The oscillators are somehow the CNS interneuron counterpart to the monosynaptic reflexes, which include only the motoneurons.

#### *Frequency ranges of spinal oscillators*

The distributions of the oscillation periods of the oscillators in Para 2 and HT5 were

transposed into frequency distributions and plotted in figure 11. The possible frequency ranges of normal humans are not known. To have an approximate comparison to the normal case, somehow normal oscillation period distributions were constructed in the following way. With the linear relation between the oscillation period and the number of APs per impulse train (Fig. 2), the frequency values of stable oscillators were plotted into figure 11. The small drift of the oscillation frequency with different stimulations has been accounted for by small cross-hatched areas. The frequency distributions of stable oscillators have also to be measured in future. The normal oscillators have to be understood in the following way. Let

a stable spinal oscillator oscillate with 6.25 Hz ( $T = 160$  msec) with 3 AP impulse trains. If a higher activity is needed, the frequency changes only little to about 6.5 Hz, but the impulse train increases by 1 AP. The cross-hatched areas represent therefore 6 oscillators each one firing with its own frequency. Only once it has been observed that a stable oscillator changed strongly its frequency for one oscillation. Such quick changes of the oscillation frequency are not possible with mechanical oscillators. Spinal oscillators have no analog of the kinetic energy of mechanical oscillators. Also, magnetic field may not occur with the loop excitation. They are run by relative timing of activity with pre- and postsynaptic potentials. In unstable oscilla-

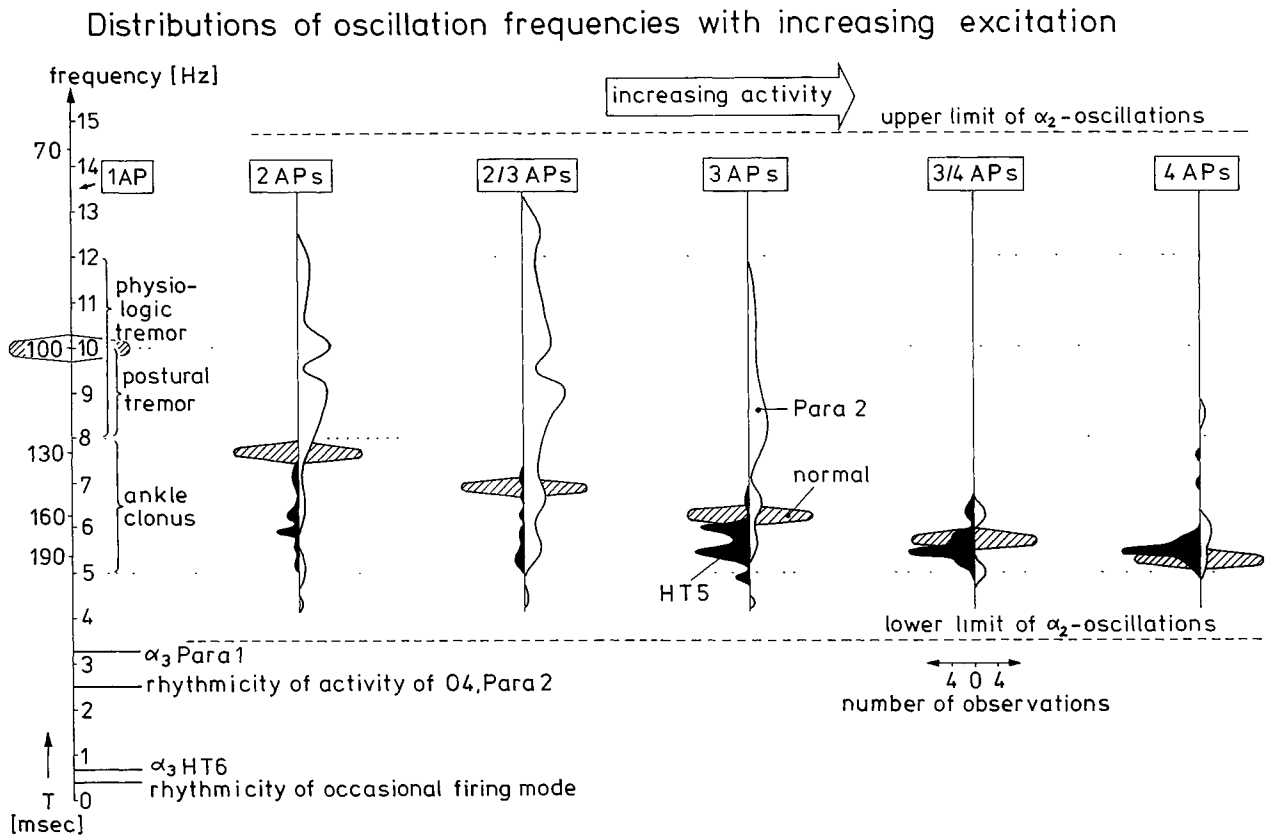


Fig. 11. — Frequency distributions of oscillation frequencies of continuously oscillatory firing  $\alpha_2$ -motoneurons with increasing number of APs per impulse train (increasing activity) in paraplegic 2 (O4, open), in HT5 (O4, filled), and probably normal human (cross-hatched, from Fig. 2). Frequencies of  $\alpha_3$ -motoneurons and rhythmic activity changes in the occasional and oscillatory firing mode are indicated. Ranges of physiologic tremor, postural tremor and ankle clonus are also drawn. Note that frequencies for the brain-dead HT5 are too low and the frequencies of the long lasting isolated spinal cord (Para 2) are too high as compared to the theoretically predicted frequency ranges (cross-hatched).



tors the frequency and the number of APs per impulse train change strongly with increasing or decreasing stimulation (afferent input). Unstable oscillators cover, for a certain AP number, a range of possible frequencies.

From figure 11 it can be seen that for low activation the oscillator in HT5 (2 APs) covers a larger frequency range than does the theoretical normal oscillator, and the frequencies are lower than normal. For high activation (4 APs) the oscillator frequency in HT5 is rather normal. That means that for low activation the oscillator in HT5 is underactivated and for high activation is rather normal. A partial spinal shock may be responsible for this underactivation for low activation. The situation is opposite for the oscillator in Para 2. For low activity demands (2 APs) the frequency distribution range is spread strongly and the oscillator is strongly overactivated. For high activation (4 APs) the frequencies are closer to normal, even though increased. Most dramatic overactivation of spinal oscillators in paraplegics are to be expected in the lower and middle activation range. As figure 11 shows, for activations with 2 to 3 APs, the oscillator in paraplegic 2 covered the whole range of frequencies for ankle clonus, postural and physiologic tremor, even though certain frequencies occurred preferentially.

Since the oscillatory firing mode represents high motoneuron activation, there was overactivation in the  $\alpha_2$ -motoneuron system in paraplegics (Fig. 11). Further, in Para 1 in a lower sacral root, 3  $\alpha_2$ -oscillators (Fig. 1B) and one  $\alpha_3$ -oscillator (Table 1) could be identified, twice the number found in measurements in HTs with no more than 2 oscillators detected in a root. This points towards a higher recruitment of the oscillatory firing mode in paraplegics than in HTs. It was reported in a previous paper that in the occasional firing mode  $\alpha_3$ -motoneurons (and maybe  $\gamma$ -motoneurons) were stronger activated (12). All these measurements point toward a situation, in which the isolated spinal cord is overactivated as compared with HTs, and maybe also in comparison to the normal case (Fig. 11). However, overactivation is not only a general increase, but acts specifi-

cally on different structures in the CNS. The summing of different effects of this kind may result in certain cases, in complete pathologic function. Since there was no opportunity to fill the urinary bladder during the surgery, which in principle should present no problem, to trigger dyssynergia, no specific information was obtained with respect to the dysfunction of the urinary bladder.

An oscillatory system only oscillates if there is energy input in phase. The system under consideration is a constant stretch reflex of the anal sphincter (and the bladder function), which is mainly activated through stretching muscle spindles. The paper to follow will therefore be concerned with the function of the stretched muscle spindles, driving the oscillators. For the sake of a later comparison to the efferent innervation of the muscle spindles (14), the impulse patterns of single encoding sites of secondary muscle spindle afferents will be analysed first before comparing muscle spindle afferent and oscillator activities.

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