Abstract

In this chapter we report about a neural network model for early sensori-motor development and about the possible implications of this research for our understanding and, eventually, treatment of motor disorders like cerebral palsy. We recapitulate the results we published in detail in chapters two, three and four.

1 The neural circuits in the model self-organize on the basis of rhythmic activity spontaneously generated in the model. This indicates the importance of endogenously generated activity in the developing brain.

2 We also show that afferent feed-back from the mechanical part of the model is easily incorporated in the neural part of the model. In this way the model acquires reflex-related properties which have long been demonstrated in man.

In the discussion we relate these experimental findings to the variability concept from developmental neurology and show how variable motor performance is important for motor learning. We also discuss possible implications of our modelling effort for movement disorders, specifically spastic cerebral palsy.
5.1 Introduction

In this chapter we will formulate a possible mechanism for synaptic rearrangement on the basis of experiments with a computer model of the developing nervous system. We constructed a neural network model of interconnected neurons which demonstrates the capability to self-organize its neural circuits through modifications of the synaptic connections, and thus also to organize its neural activity. This self-organizing process is enabled by the spontaneous activity in the network. We postulate that our model illustrates a mechanism through which spinal cord circuits might develop in human ontogeny.

Research into early neural development is hampered by experimental restrictions. Since long animal experiments have offered an opportunity when experiments on humans are not feasible, for either technical, ethical or other reasons. Recently, with the advent of computers and increased theoretical insight into the functioning of the central nervous system, the use of computer models has become a viable experimental paradigm. We will present a model of the effects on spinal neural circuits caused by neural activity in the spinal cord at very early stages. The latter is present, and causing embryonic motility, from approximately 7 weeks postmenstrual age onwards. The research presented here aims at two aspects: (1) to increase the understanding of neural development and (2) to be a first step in providing the clinical community with an experimental model that might be part of an investigation into treatment techniques for developmental neural disorders like cerebral palsy.

Neuronal activity is a basic aspect of the central nervous system from the earliest stages of development. From in-vitro studies it is known that neurons start to generate and propagate action potentials as soon as they are interconnected (Stafström et al., 1980), while interconnected neurons will generate patterned activity because of endogenous properties of the neurons (Streit, 1993). The nervous system rapidly develops into a highly complex system, which is both spontaneously active and interacting with its environment. Part of the development is genetically determined, but neural activity itself is an important factor in the organization of the CNS. What are the mechanisms involved in this organizing process and to what extent are synaptic rearrangements critical to the formation of functional neural circuits?

From animal models it is known that primitive muscle fibers (myotubes) are able to contract as soon as they are innervated by motorneurons (Landmesser and Morris, 1975). In human embryos patterned motility can be detected, using ultrasound methods, at about 7 weeks postmenstrual age (de Vries et al., 1982; de Vries et al., 1985; Prechtl, 1989). Shortly before the stage where motility starts, connections between spinal neurons have formed (Okado and Kojima, 1984). It is concluded that the neural
activity leading to motility is endogenously generated in the spinal cord (Provine and Rogers, 1977; Prechtl, 1984). In general it seems that patterned activity is an emergent property in networks of interacting neurons, caused by the interaction of intrinsic membrane properties and synaptic interactions, see review in Marder and Calabrese, (1996). Shortly after its onset, embryonic motility develops into recognizable motor patterns (Birnholz et al., 1978; de Vries et al., 1982). This patterning implies that the neural circuits responsible for embryonic motility become organized rapidly after the onset of motility. Indeed, animal experiments indicate that the neural output of embryonic, precursory locomotor circuits is highly organized. This has been shown for chick embryos (Bekoff et al., 1975; Landmesser and O'Donovan, 1984a; O'Donovan, 1989), mouse fetuses (Kodama and Sekiguchi, 1984) and rat fetuses (Bekoff and Lau, 1980; Greer et al., 1992).

At about the same time that spontaneous motor activity can be observed, reflexes can be elicited in exteriorized fetuses (Hooker, 1952; Humphrey, 1964). However, in the exteriorized fetuses spontaneous motor activity was not present. This can be attributed to the terminal state the fetuses were in. The observed reflexes corroborate neuroanatomical studies in which it was demonstrated that afferent connections are formed between the peripheral sensory neurons and dorsal horn neurons at about 8 weeks postmenstrual age (Okado et al., 1979).

Summarizing these neurodevelopmental data, it appears that in the period from 6 to 8 weeks postmenstrual age a rapid cascade of events takes place: neuno-neuronal connections are formed, muscle fibers are formed by fusion of myoblasts, efferent and afferent neuromuscular connections develop, and spontaneous neural activity causing motility starts. Endogenous activity, spontaneously originating in the spinal cord, is present most eminently, but re-active activity, which could also be termed reflexive activity, is certainly also a property of the brain and spinal cord from a very early developmental stage onwards.

Which further course does the development of fetal motility take after its onset? Within the first half of gestation the fetus develops an extensive motor repertoire and at the end of this period this comprises generalized movements in which the whole body partakes, isolated movements of arms, legs, head and even lips, tongue, eyelids, eyes, hands and feet (de Vries et al., 1982; de Vries et al., 1985). All these fetal movement patterns can also be recognized in the newborn infant (Prechtl, 1984). Apparently, no new motor patterns arise during the second half of gestation. Rather it seems that during this period motor patterns are refined and calibrated so as to be well adapted to the sensorial changes after delivery (Prechtl, 1984).

Normal motility is characterized by variability, which is the ability to vary motor performance (Touwen, 1976; 1978; 1993; 1998). Variability manifests itself in two different ways: a temporal one, which may be inter- as well as intra-individual and
inter- as well as intra-functional, and a performal one. The latter shows two phases:

1. variations in the execution of movement patterns; this is termed ‘primary variability’.
2. the ability to choose from the available options so as to perform a specific motor task adaptively; this is the so-called ‘secondary variability’.

During gestation the (primary) variability in the performance of fetal motor patterns steadily increases (de Vries et al., 1985; Touwen, 1993). Concomitantly, a decrease of variability is a reliable indication of fetal stress (Bekedam et al., 1985; Visser et al., 1985; Prechtl, 1990; Sival et al., 1992).

In general, brain function can be described in terms of a ratio between activity and reactivity. Limiting ourselves to the fetal period, we hypothesize that the development of variability may be initially due mainly to spontaneous endogenous activity, but later also to the emergence of re-activity to external stimuli and the interplay between these two forms of activity. Neural activity, initially endogenous but later also re-active, directs an explorative phase, during which the nervous system makes an inventory of its actions and the consequences of these actions. This explorative phase forms the primary variability: unspecified modes of execution of motor patterns. In a later phase of development the child – then toddler – learns to select the most appropriate and feasible option given the circumstances from this large repertoire of motor options (Touwen, 1993). This latter process is secondary or adaptive variability. Since the spinal cord is the first operational part of the CNS, it follows that variability is also a property of the spinal cord on its own. The concept of variability should therefore also be valid in our research, which in the present form is limited to the first appearance of spinal cord functions. In this chapter we want to discuss two things.

1. What can, on the basis of computer simulations of processes taking place during early ontogeny of the central nervous system, be said about the neural mechanisms responsible for the first motility and their impact on the development of primary spinal cord circuits? For this purpose we studied the developmental changes in simulated primary spinal neural circuits induced by the first motility, stylized into a flexion/extension movement pattern of the upper extremity.
2. Do we find indications for variability of motor performance in our computer simulations of spinal activity and what does this tell us about the early development of motor function?

We will conclude the chapter with some remarks on the possible consequences of computer models in general, and of our model more specifically, for further research and for possible clinical implications.
5.2 Model

In our model we have stylized embryonic motility into a flexion and extension movement of a single joint. The neural model to drive and control this system consists of motorneurons, sensory neurons and interneurons. In the chapters two, three and four we have described our model in detail. In the present section we will introduce the concepts of the model.

5.2.1 Basic model elements: neurons

Single neurons are complex entities. However, a neuron can functionally be seen as a signal relay and processing unit. Our study is concerned with the behaviour of collections of cells, or cell assemblies, allowing us to choose a relatively simple single neuron model: a frequency coding neuron model (Segev, 1992). In this model the activity of a neuron is expressed as a number between 0 and 1, 0 meaning no activity, 1 meaning maximally active.

The total input to a neuron is the summation of the contributions from all other neurons projecting to it. These contributions are weighted using connection weights, as a model for the strengths of the synaptic transfers. The weighted input to a neuron determines its membrane potential. The output of the neuron is a non-linear function of the membrane potential.

An important assumption in the model is that the type of a neuron is not determined by activity-dependent processes, but by its position in the developing structure (cf. motorneurons in the ventral horn and sensory (inter)neurons in the dorsal horn). We further presume, consistent with experimental evidence, that the initial synaptic connections in the spinal cord are highly specific: a neuron makes only connections with neurons it is determined to connect to (Mendelson and Frank, 1991; Snider et al., 1992; Silos-Santiago et al., 1995). Indeed, there is experimental evidence that target recognition relies on activity-independent mechanisms (Goodman and Shatz, 1993; Tanabe and Jessell, 1996). These two assumptions imply that the type of a neuron is determined through its connections with other neurons. For example, a neuron which innervates a muscle is a motorneuron, precisely because it innervates a muscle, while a neuron that is innervated by sensory neurons and inhibits the motorneurons of the antagonistic muscle is an inhibitory interneuron, again because of its connectivity. A group of neurons with the same connectivity is called a ‘cluster’.

As said in Sect. 5.1, the earliest activity in the spinal cord of various animal models, causing embryonic motility, is generated endogenously. In our model spontaneous neural activity is modelled by specialized neuron clusters called ‘Spontaneous Activity Clusters’, or S.A.C.s. The neurons in such a cluster are spon-
taneously active, i.e. without any neural input. There are two S.A.C.s, one for each muscle. During training the neurons in the S.A.C.s are rhythmically active.

### 5.2.2 Training the model: a Hebbian learning rule

The initial connection weights between neurons have a random value, which is small initially. During training the values of the connection weights are changed according to Hebbian learning. Hebbian learning is based on the work by the psychologist Hebb, who wrote: “When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes part in one or both cells such that A’s efficiency, as one of the cells firing B, is increased.” (Hebb, 1949, p. 62). There is evidence for Hebbian learning schemes in neuronal plasticity, see review in Fregnac (1995). The Hebbian learning scheme is an unsupervised, local learning scheme: the weights are modified on the basis of the activities of only the pre- and postsynaptic neurons. In contrast to Hebbian learning stand supervised, non-local learning schemes, in which a measure of the performance of the whole network is needed to update every weight.

### 5.2.3 Lay-out of the model

The full model consists of two parts, a neural part representing the CNS and a mechanical part representing the muscles and joint. The combined neural and mechanical parts are depicted in Fig. 5.1. The neural part contains two motorneuron clusters which innervate the two muscles. It also contains two clusters of sensory neurons connected with velocity sensitive receptors in the muscles, representing the neurons in the dorsal root ganglia. Finally, there are two clusters of inhibitory interneurons, interposed between the clusters of motorneuron and sensory neurons, which mediate Ia-afference. Each cluster contains 10 neurons, because this appeared to be the smallest number of neurons that could reflect the essentially continuous nature of a population of neurons adequately without imposing an inordinate computational burden.

The two clusters of interneurons inhibit the opposite cluster of motorneurons and reciprocally inhibit each other. A sensory cluster excites its homonymous motorneuron cluster and its homonymous interneuron cluster. As a model for the spontaneous neural activity two S.A.C.s are included. Both S.A.C.s excite both motorneuron clusters and both interneuron clusters. The neurons in the two S.A.C.s produce sinusoidal signals, with the neurons in one S.A.C. being in opposite phase to the neurons in the other S.A.C. As indicated by the box around the two S.A.C.s, they are best viewed as two elements of one neural generator of patterned activity, the arrow between the two S.A.C.s signifying that the activities of the two S.A.C.s
are coupled. One S.A.C. would have sufficed, but for reasons which will become clear in Sect. 5.3.2 it appeared to be advantageous to have two S.A.C.s.

The reason to include a mechanical model is that we need sensory feedback. Therefore we connect the neural part with a simple mechanical part, consisting of a one degree of freedom joint actuated by two identical muscles. The forearm (i.e. the moving part) has an inertia which is comparable to that in human extremities. The forearm is actuated by two antagonistic muscles, for which a muscle model including excitation-contraction dynamics, force-length characteristics and force-velocity characteristics has been implemented.

5.3

Training and testing the model

The model is tested in two distinct manners. First, its motor behaviour is trained until a motor pattern has developed which resembles the in-vivo situation. Second, after training, the acquired motor performance inventory, introduced in Sect. 5.1, can be investigated: is the network able to control a movement and is it able to
counteract a mechanical perturbation? In other words, has the network been able to derive general motor control principles from the training phase?

5.3.1 Training the model

Based on the conception that actual early motor development is initially spontaneous and feedback develops later, training also takes place in two stages: the first training stage proceeds without sensory feedback, the second stage with sensory feedback. The earliest activity in the network, again in concordance with animal experiments, is periodic during both training phases (O'Donovan, 1989; O'Donovan and Chub, 1997). The neurons in the two S.A.C.s produce sinusoidal signals with a period of 1 s. As said, the neurons in one S.A.C. are in phase with each other, but in opposite phase to the neurons in the other S.A.C.

At the start of the first training phase the output of the neural part of the model, i.e. the output of the two motorneuron clusters, is approximately zero. This measure of the model output can be compared to a recording from the peripheral motor nerve, so as to get the average activity of the motorneuron pool. However, during training the two motorneuron clusters appear to become alternatingly active, causing a continual flexion and extension movement of the forearm, i.e. causing the two muscles to become each other’s antagonist. In the neural part of the model, two opposite channels emerge: an agonist and an antagonist channel. The separation of the two channels is accomplished through the development of reciprocal inhibition between the two interneuron clusters: when one channel is active, the activity in the other channel is inhibited. The first training phase ends when the synaptic strengths do not change any more, which indicates that the system has become stable: the network is able to coordinate its activity.

At the start of the second training phase sensory feedback is added. Now the network also receives signals from the velocity-sensitive receptors in the muscles through the clusters of sensory neurons (Fig. 5.1). During this second phase the output of the network hardly changes: the two motorneuron clusters remain alternatingly active, and so the flexion and extension continues. Apparently, the two clusters of sensory neurons become easily integrated into the network. This endows the network with the capability to track the expected state or react to an unexpected state of the forearm. This capability is investigated in the next section, Sect. 5.3.2.

5.3.2 Motor control properties

Afference-related spinal cord properties develop very early in ontogeny as they are important prerequisites for the consecutive development of motor patterns. This
allows us to test our (developmental) network for properties which have so far only been tested on the adult spinal cord.

In the following experiments there are three inputs to the network, see Fig. 5.2. Two of these inputs, A₁ and A₂, enter the two opposite channels and signal the desired state of the two muscles. The combination (A₁, A₂) thus specifies the desired joint angle. The third input, P, is common to both channels and signals the desired amount of co-contraction, or joint stiffness. There is evidence that there are separate systems specifying joint angle and joint stiffness (Humphrey and Reed, 1983). To relay these three signals to the network, the function of the previously rhythmically active neurons in the S.A.C.s is modified. During testing, these neurons relay these three constant signals.

Now the introduction of two S.A.C.s becomes clear. During training the neurons in a S.A.C. provide the network with periodic signals, during testing they generate constant signals. This change in S.A.C. function has not been caused by any developmental process. The only function of a S.A.C. is to relay signals; initially the signal is periodic, later it becomes a constant signal. The neurons in one S.A.C. generate A₁ + P, the neurons in the other S.A.C. generate A₂ + P. This state of affairs can be compared to the biological situation in which the commands from the brain are given to spinal circuits. In the training phase the S.A.C.s model the spontaneous rhythmic activity in the network. During testing they model the neurons through which the putative signals for joint angle and joint stiffness are relayed.
The first property we have tested is the capability of the network to move the forearm to a specified joint angle at varying levels of co-contraction (i.e. joint stiffness). In comparison: the brain commands the spinal cord to implement motor activity in order to reach an object at different positions, with varying speeds and intensity. This means that joint angle can be specified separately from joint stiffness. Because of the non-linear properties of neurons this independence depends critically upon interaction between the two opponent channels through inhibitory interneurons (Bullock and Contreras-Vidal, 1993).

It was investigated whether for various levels of co-contraction $P$, up to approximately 30% of the maximum force of the muscles, a combination $(A_1, A_2)$ would always lead to the same joint angle. The results are shown in Fig. 5.3.

The plot shows that a control signal (the command), consisting of a combination $(A_1, A_2)$, always leads to practically the same joint angle, independent of the amount of co-contraction $P$. In chapters three and four we explicitly showed that here reciprocal inhibition between the clusters of inhibitory neurons is crucial.

Secondly we tested the neural and mechanical reactions to an externally applied mechanical perturbation of the model forearm. Put differently: we tested whether training has endowed the network with appropriate reflexes. We tested this in two ways. The first subtest was to measure the neural response, i.e. the change in the output of the motorneuron clusters, to a mechanical disturbance of constant angular velocity. The manner in which we measure the neural response has been explained in detail in chapter four. The second subtest was to determine the mechanical response, in terms of joint stiffness, for varying amounts of background activity in the muscles.

In Fig. 5.4 the size of the neural response to a mechanical perturbation is shown. At four different levels of background activity in each of the muscles (as a fraction of the maximal activity) we applied perturbations of a moment $M = 10.0 \text{ Nm}$ during $t = 0.03 \text{ s}$. We calculated the average of the angular velocity during the interval from 0.02 s to 0.05 s after the start of the perturbation as well as the neural response as a function of the angular velocity. Our findings were that, firstly, the size of the neural reaction turned out to be linearly dependent on the size of the perturbation, indicated by the almost straight lines in the plot. This is in agreement with Gottlieb and Agarwal (1979). Secondly, the size of the neural reaction turned out to be almost independent of the background activity in the muscles, indicated by the almost coincident lines. To test the influence of the second training phase (the phase in which afference is present and in which we presume that afference becomes incorporated into the neural part), we also measured the size of the neural response in a network before the second training phase. These results are also shown in the figure. In this experiment the background activity in the muscles was 0.16. It is clear that the size of the neural response is much smaller, indicating
that reflex activity is almost absent. This confirms our hypothesis that during the second training phase the effect of afference is incorporated in the network.

We also determined the mechanical response to a perturbation, i.e. joint stiffness, by applying a constant perturbing moment \( M = 10.0 \text{ Nm} \) for 0.1 s and measuring

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**Figure 5.3**

Shown are five curves of the attained joint angle as a function of the difference S.A.C.1 - S.A.C.2 of the average activities in the S.A.C.s for varying amounts of a common activity, or co-contraction, \( P \). The almost overlapping curves indicate that the joint angle can be established independently of the amount of co-contraction, which is a measure for the joint stiffness.

**Figure 5.4**

For various amounts of background activity the size of the neural reaction, in arbitrary units, to a mechanical perturbation was determined as a function of the size of the perturbation. The size of the perturbation is the angular velocity of the joint shortly after the onset of the perturbing input. The size of the neural reaction appears to be (almost) linearly related to the angular velocity of the joint caused by the perturbation. Also shown is the neural response of a network before the second training phase at a background activity of 0.16. It appears that afference has not yet been incorporated in the model at that stage.
the resulting change in joint angle. From the size of the applied moment and the change in joint angle the joint stiffness can be calculated. The experiment was performed at various levels of background activity and also both in the presence and the absence of afference. The results are displayed in Fig. 5.5. The lower line which is almost straight is the intrinsic joint stiffness. This is the stiffness caused by intrinsic muscle properties, like passive elasticity of the muscles. The upper, more curved line is the total joint stiffness, which is the sum of the intrinsic joint stiffness and the reflex joint stiffness, caused by the stretch reflex. The figure shows that the intrinsic joint stiffness is almost linearly dependent on background activity in the muscle, in agreement with other investigations (Hoffer and Andreassen, 1981; Sinkjaer et al., 1988; Kearney et al., 1997). The shape of the reflexive component, namely the difference between total joint stiffness and the intrinsic component, is slightly curvilinear. This is very similar to neurophysiological experiments in cats (Hoffer and Andreassen, 1981) and in humans (Sinkjaer et al., 1988). It has a maximum at intermediate levels of background activity and is relatively smaller at lower and at higher levels, indicated by the gap between the two lines. The larger stiffness in the presence of feedback can be attributed to the stretch reflex. The shape of the interval representing the reflexive component illustrates that the size of the reflexive activity is a function of the background activity of the muscles.

5.4 Discussion

In the previous sections of this chapter we have shown, using our model, how basic spinal circuits may self-organize on the basis of endogenous activity in the spinal cord and concurrently acquire adult motor control properties related to the stretch reflex. In this concluding section of the present chapter we will relate our findings to some experimentally established features in biological systems and discuss possible implications of our research.

5.4.1 Developmental neurobiology

Does our model contribute to basic knowledge and understanding in developmental neurobiology? Our research fits very well in, and corroborates, many animal experiments on spinal development. Patterned spontaneous activity in the early stages of spinal development is crucial for the formation of functional spinal circuits (Hamburger, 1963; Bekoff, 1976; Landmesser and O'Donovan, 1984a; O'Donovan, 1989; Greer et al., 1992; Kalb and Hockfield, 1992; Sillar, 1994). We have shown how spontaneous rhythmic activity in a neural network which, through its connectivity determined to control a flexion and extension movement, is indeed sufficient for the flexion and extension to develop. Moreover, spontaneous rhythmic activity in general seems an important
phenomenon during development in other parts of the central nervous system (Wong, 1993; Lippe, 1994; Katz and Shatz, 1996).

Self-organization and Hebbian learning have often been implicated as mechanisms in activity-dependent forms of plasticity (Shatz, 1990; Lo and Poo, 1991; Liu et al., 1993; Senn et al., 1996; O’Donovan and Chub, 1997). Our computer simulations add evidence and provide an extra indication that these mechanisms may play an important role and may be a general feature in the (functional) development of the central nervous system.

The networks we studied are precursors of adult locomotor circuits and there is “consensus that the basic pattern of synaptic connectivity in spinal locomotor circuits arises early in development.” (Sillar, 1994). We have shown that stretch reflex related motor control properties, essential during locomotor activity, develop in our model, although these reflexes presumably have no recognizable function yet. It was our intention to show that these basic properties are already present, either still dormant or perhaps more prominent. The properties can be integrated into more complex motor patterns at later stages of development.

Obviously, stretch reflexes still develop after the stage we modelled. For instance, in infants there is stretch-induced reflex irradiation present to homonymous and heteronymous muscles, which in healthy infants disappears during development (O’Sullivan et al., 1991; Myklebust and Gottlieb, 1993). There are many indications that a significant amount of synaptic rearrangement keeps taking place, also in reflex circuits and probably influenced by descending pathways (Leonard and Hirschfeld, 1995).
The variability concept

In the context of sensori-motor function, variability means the ability to show variation in the execution of a motor pattern, reflecting a number of different ways (neural ways) to generate the same motor pattern. Does the model exhibit variability? No, but we can draw conclusions from our model about the significance of variability during development, precisely because there is no variability in the model.

The neural origin of variability is varying neural activity, caused by endogenous neuron properties, in assemblies of interconnected neurons. The model elements which correspond best to the origin of endogenous activity are the S.A.C.s. Primary variability (secondary variability is beyond the scope of this thesis) is the property of the CNS to generate recognizably similar motor patterns executed by varying neural activity. The absence of primary variability in our model is caused by the deterministic character of the computer simulations, because the neurons in a S.A.C. do not generate varying neural activity, but only produce a sinusoidal signal with a fixed period and amplitude. This seems comparable to a very pathological condition in the case of a severely damaged brain.

One purpose of variability is that the brain, in a circular reaction, learns the transformations between the various representations of the movement. The term ‘circular reaction’ was introduced by Piaget and indicates a continuous production and perception cycle (Piaget, 1963). In neural reality, the previously mentioned spontaneously active cell assemblies act as endogenous generators of variable neural activity, leading to a stream of variable neural commands resulting in spontaneous, variable movements. The brain learns to associate the varying neural commands and their effects, at different hierarchical levels in the brain, with each other and with the resulting movement. A prerequisite to enable other parts to learn this association is that these other parts of the brain are presented with a complete spectrum of the neural commands and their effects. This can only be accomplished if the neural circuits exhibit variability. The spontaneous activity in the model, with its fixed period and amplitude, appeared to be sufficient to train our neural model to execute proper flexion and extension movements, but it is of course insufficient to present a complete representation of the potential of the underlying spinal circuitry.

In order to explore the potentials of the spinal circuits it is desirable to implement a system which sends varying commands to the spinal circuits. In comparison: a wide range of volleys arrives in the spinal cord segments from various brain areas. The self-organizing process taking place because of this activity has been called motor babbling (Bullock et al., 1993) It is easy to envisage how the present model can be extended to include this next phase. A second neural part, representing higher
centres in the developing brain, may be added and the S.A.C.s will generate more variable signals. The additional neural part could then, in a self-organizing process, learn to control the spinal circuits, because it is given a full representation of the transformations taking place in the underlying circuitry.

5.4.3 Clinical considerations

The goal of our research is to better understand, diagnose and, ultimately, treat chronic developmental movement disorders which are the result of brain damage like cerebral palsy. To accomplish that goal we need basic knowledge about the motor system, more specifically about its development. Does our modelling study have clinical implications? We may illustrate possible clinical implications with the example of spastic cerebral palsy. Spastic cerebral palsy is a developmental movement disorder which seems most amenable to experiments using our model. Cerebral palsy (CP) in general is a collection of developmental non-progressive disorders; spastic CP consists of either a disturbed coordination of opposing muscle groups which originates in the spinal cord itself, or an impaired control of opposing muscle groups through disturbed (sub-)cortical control of the spinal systems. Other forms of CP, such as athetosis or ataxia, are not discussed here, because their origins are not primarily cortico-spinal, but lie in the basal ganglia or the cerebellum, leading to a more complex motor disorder.

Spasticity is caused by disturbed descending signals (corticospinal, vestibulospinal, reticulospinal), probably leading to hyperexcitability of spinal motorneuron pools (Filloux, 1996). Spasticity can also be caused by abnormal spinal development due to the absence of descending control during development (Leonard and Hirschfeld, 1995). The targets of the descending pathways are usually the spinal interneurons, on which the descending signals are resolved with segmental influences (Harrison, 1988). Consequently, interneuronal mechanisms may play an important role in spastic CP.

An important function of spinal interneurons is to coordinate the activity of one muscle with other muscles (Jankowska, 1992). The impaired coordination of opposing muscle groups in spastic CP might be attributed to spinal interneuronal malfunction and can therefore be investigated with our model. Clinical features suitable for investigation are for example:

1. characteristic co-contractions between agonist and antagonist muscles (or muscle groups), because of malfunction of reciprocal inhibition.
2. lacking disappearance of reflex radiation to heteronymous muscles.
3. disturbed velocity-dependence of stretch reflexes.
4. reciprocal excitation.
These failures seem very well suited to be studied with our model. First, one of the most prominent results from our model is the development of reciprocal inhibition, suggesting that maldevelopment of reciprocal inhibition can be studied also. Furthermore, by adding additional clusters of different interneurons to the model, like Ib-interneurons or flexor reflex afferent (FRA) interneurons, a closer look at the interaction of the different interneurons is feasible. A third option is to experiment with other descending signals. So far, there are three descending signals in the model ($A_1$, $A_2$ and $P$), which are all relayed through the S.A.C.s, but other signals could be added, e.g. signals to motorneurons or to interneurons separately.

5.4.4 Concluding remark

We have shown that computer simulations of early neural development are feasible. They can give insight in developmental processes. Furthermore, if a model of normal (healthy) development can be constructed, it might also be possible to create models of pathological development.

The presented model simulates the development of an extremely simple motor pattern, i.e. flexion and extension, and a long way has to be gone before we may properly simulate more complex motor patterns such as shown by normal and abnormal fetuses and infants. From there to a computer model based foundation of physiotherapeutic treatment is still a greater step. But we believe that the first step has been taken: it is possible to simulate the development of a recognizable sensori-motor pattern.