THE COMPLEXITY OF THE ORDINARY: THE NEUROBIOLOGY OF LOCOMOTION[1]

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The aim of *Neurobiology* is to understand the functioning of the nervous system, including aspects such as perception, learning, cognition and movement. All these functions of the central nervous system enable an animal to behave independently in its environment. In addition to basic research that provides an understanding of the mechanisms and function of the nervous system, neuroscientists also often aim to address questions with a direct bearing on the human condition, a goal that is usually not possible to address directly. Today's talk will deal with an aspect of the nervous system that on first glance appears rather simple: the neurobiology of locomotion. This is true because locomotor movements appear ordinary and automatic to us. This accounts for our own movements, such as walking, as well as for our observation of moving animals around us. In ethological terms, locomotion represents a "Mehrzweckverhalten" (multi-purpose behavior). This means that locomotion is a behavioral component in a multitude of other more complex behavioral programs, such as searching for food, searching for a partner, avoidance of a predator and flight in response to a threat. Today's talk will introduce the current state of knowledge about the neural mechanisms underlying the generation of locomotor movements. It will highlight the in-depth knowledge on this topic that has been gathered from specific animal model systems.

When we think about locomotion, locomotor programs like flying, walking and swimming immediately come to mind. Although these three modes of locomotion take place in completely different environments, they share striking similarities: all three movement patterns are characterized by a two-phase structure, consisting of a power stroke and a return stroke of the locomotor organ. During flight, the wing generates lift mainly during its downstroke, while the function of the upstroke is primarily the return of the wing back

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to its initial position to start the next power stroke. The same is true for walking. During the ground phase of the leg, the so-called stance phase, the body of the organism is moved relative to the substrate, representing the power stroke, while during the swing phase, i.e., the return stroke, the leg is moved back through the air to its starting position for the next power stroke. In an insect leg, more than a dozen muscles serve to control the movement of the four main leg segments. In vertebrates, the number can be even higher, with over 30 employed during movement of the cat hindlimb. In swimming vertebrates, the musculature of both sides of the body contracts in alternation and thereby establishes a pattern of return and power strokes in order to generate undulatory propulsive contraction sequences. These patterns travel along the body of water-dwelling organisms such as fish, but also in fish-like organisms such as lampreys, leeches and tadpoles. In summary, it is clear that these three motor patterns are generated in the basis of a two-phased template that consists of power stroke and return stroke.

In the analysis of the mechanisms underlying the generation of locomotion, one has to consider six different levels (Fig. 1): the *behavioral level*, the level of *biomechanics and kinematics*, the underlying *neural networks*, the individual *neurons* involved, the *ion channels* in the neuronal membranes and finally the *subcellular machinery*. Those levels will be introduced in the following, some of them in detail, others rather general, as we focus in on terrestrial locomotion, i.e., walking. As indicated before, on the behavioral level, walking represents one behavioral component in a variety of behavioral programs. The locomotor movements of the organism are generated by the locomotor organs, the limbs. The kinematic analysis describes the movements of limbs and their individual segments. This enables a reconstruction of the locomotor movements. Biomechanical studies analyze the properties of the skeleton-muscle-system and try to determine how these biomechanical properties of the walking system contribute to its performance. Specifically, recent investigations have highlighted the significance of muscle properties on the basis of their complex length-force and velocity-force relationships, most prominently reflected by work in the labs of Ian Brown, Geral Loeb, Felix Zajac, and Robert Full. The skeleton-muscular system is controlled by the action of neural networks in the spinal cord of vertebrates and the thoracic nerve cord of invertebrates that drive the motor neurons innervating muscle fibers of the locomotor organs. These neural networks are ensembles of neurons connected to each other by synaptic (cell-to-cell) contacts. Based on their specific connectivity, such networks can generate the basic rhythmic activity of the motor neurons. At all times, the activity of the neurons is tuned by their specific properties, e.g. the ability of many neurons

to generate long-lasting activity in response to a brief activation or the ability to escape from inactivation by themselves without input from other neurons. This so-called network level leads to the level of the underlying membrane structures of the neurons that control nerve cell activity. Nerve cells function on the basis of their electrochemical properties, i.e., current flow across their membranes. Ions traveling through specific ion channels are the source of their activation or inactivation. The opening and closing of these ion channels can be mediated either by voltage changes across the membrane or by ligands, or neurotransmitters, that open them by binding after being secreted into the extracellular space at the synapse. The actual excitability of a neuron is determined on the subcellular level, i.e., its intracellular machinery. This biochemical machinery affects intracellular ion presence and ion channel availability, in part by modifying protein synthesis.

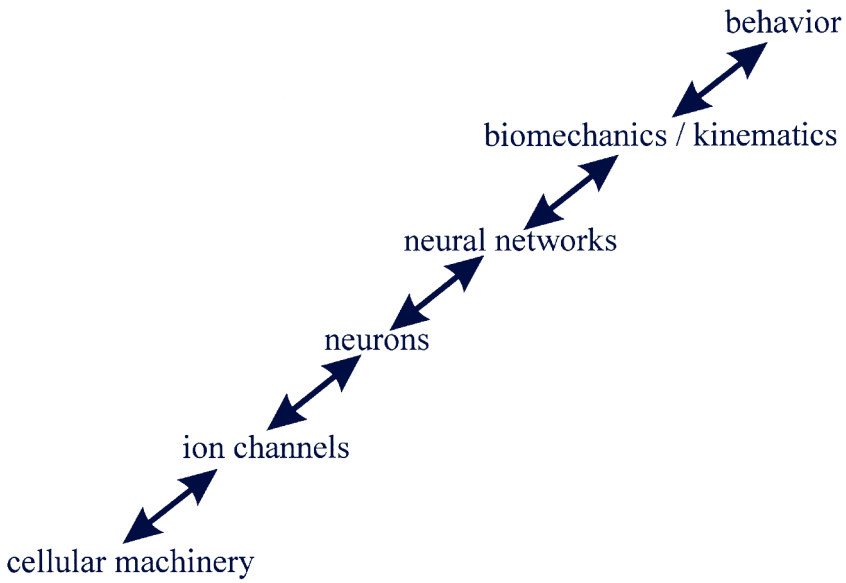


Fig. 1: Levels of analysis for understanding the neural control of locomotion. For details, see text.

The challenge and fascination of studying the neural control of locomotion derives from the fact that there are excellent animal model systems available that permit investigations on several levels, in some cases down to the subcellular machinery. In such systems, specific questions can be asked like: What function does one specific ion channel play in the generation of a specific neural activity during locomotion? What role does one neuron play in the generation of a specific behavior or muscle activation?

Before we can address more specific issues, we have to clarify the different functions that the nervous system serves in order to generate and control locomotion (Fig. 2). Higher order centers in the brain of a vertebrate and the cerebral ganglion of an invertebrate provide the command for initiation of locomotion. Descending pathways transmit this signal down to the segmental structures of the central nervous system on the level of the locomotor organs. These commands have to be continuous in order to maintain locomotion, but are not themselves patterned. The steering and postural control during the execution of the locomotor program is also guided by descending pathways from higher brain areas. In addition, the goal direction is controlled by descending commands within the nervous system, i.e., the spinal cord in vertebrates and the thoracic nerve cord in invertebrates. On the intersegmental level, the actions of the individual appendages are coordinated by neural mechanisms that establish sets of rules for coordination. On the segmental or local level, each leg has to generate successful stance-swing and swing-stance transitions in each locomotor cycle. In doing so, each leg joint has to be appropriately controlled, and finally muscle activity always has to be controlled "online" in the locomotor cycle, regardless of how the animal is walking. A detailed account of all the information currently available will not be possible within the framework of this presentation, but a simple introduction highlighting important issues and findings will be given.

Let us now first consider the generation of stepping movements for an individual appendage. Alternating activation of antagonistic motor neurons and muscles is a key feature in the generation of walking. Flexors and extensors in the vertebrate limb alternate, with the extensors generating the stance phase of the leg on the ground and the flexors generating the swing phase, i.e., the return stroke of the leg. In invertebrate limbs, similar alternation in motor neuron and muscle activation occurs, e.g. with retractor activation during leg stance in forward walking and protractor activation during leg swing. It was about 100 years ago, in 1906, that G. Brown presented the first evidence that the isolated central nervous system was capable of generating alternating activity in antagonistic leg motor neurons and muscles, without input from the sense organs in the periphery. Today it is

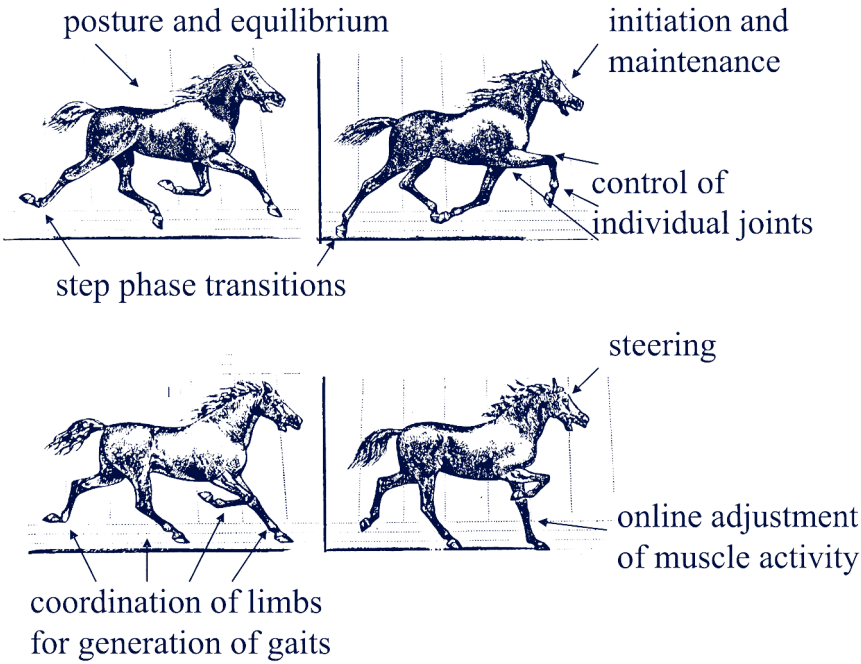


Fig. 2: Schematics exemplifying the various functions the nervous system has to serve in the generation and control of locomotor programs (for details, see text). Modified set of a series of photos taken by Muybridge in 1872.

clear that, in vertebrates, the lumbar and cervical regions of the spinal cord contain neural networks sufficient to generate alternating activity of leg motor neurons in front and hind limbs, respectively. Such neural networks in the central nervous system are called central pattern generators (CPGs), and their presence and action has been shown in a multitude of well-investigated walking systems, from insects to mammals. However, such central (and thus automatic) control of the generation of the walking motor program is not sufficient. This becomes most obvious when observing the flexibility and plasticity of the walking systems with respect to environmental factors, like the cat hind limb while walking upstairs or downstairs. Stance and swing phase of the stepping cycle are organized completely differently with respect to joint kinematics and muscle activation in each situation.

This flexibility results from the continuous influence of sensory feedback on the generation of the locomotor program. Sensory signals from length and force sensors associated with the muscles influence the generation of locomotor activity in two respects, i.e., in their magnitude and timing. A very detailed account of the current knowledge about this is presented in the excellent book by Orlovsky, Deliagina and Grillner (1999), titled *Neural Control of Locomotion*. For example, in the cat hind limb, sensory signals about hip position are able to entrain, i.e., drive and control, the activity cycle of the locomotor program for the whole limb. Depending on the actual change in hip position, alternating stance and swing phase activity of leg muscles can be generated. Our current knowledge of the role of sensory inputs has expanded dramatically within the past 10 years, prominently driven by work by Keir Pearson and his lab. The control of the magnitude of muscle activity in the locomotor cycle, as well as the transitions in activity between stance phase and swing phase, can be explained by the interplay between the CPGs and sensory feedback from the limbs (Fig. 3).

In light of the complex sensory influences on locomotor pattern generation, the question arises about the structure of the central neural pattern generating networks that are generating the basic alternating activity in leg motor neurons and muscles. Studies on the cat already conducted 20 years ago, based on work by Sten Grillner, Grisha Orlovsky, M. L. Shik and collaborators, suggested that there is not a single CPG in the central nervous system for generating the activity of the whole limb with all its joints, but that there are several CPGs present for each set of antagonistic joint muscles or even for each individual muscle. This gave rise to a hypothesis, the so-called "unit-burst-generator concept", that the neural networks for walking are composed of multiple central pattern generators. Verification of this hypothesis had to wait until the end of the last century, when confirming evidence was presented for walking systems, first in an insect, the stick insect, and later in a vertebrate, the mudpuppy. In the stick insect, it was shown that in the isolated nervous system, alternating activity in the leg motor neuron pools can be generated independently for each leg joint with very little coupling between the rhythms, indicating the presence of individual CPGs for each leg joint (Fig. 4). Today, in mammalian systems like the neonatal rat preparation, evidence has been gathered that has substantial similarities to these earlier findings. Coordination of the activity of individual CPGs in order to generate a unified locomotor program in multi-jointed limbs has been recently shown to be under the influence of the sensory feedback from the limb that contributes to intra- and interjoint coordination of motor activity. The current picture on this interaction for the generation of the stepping

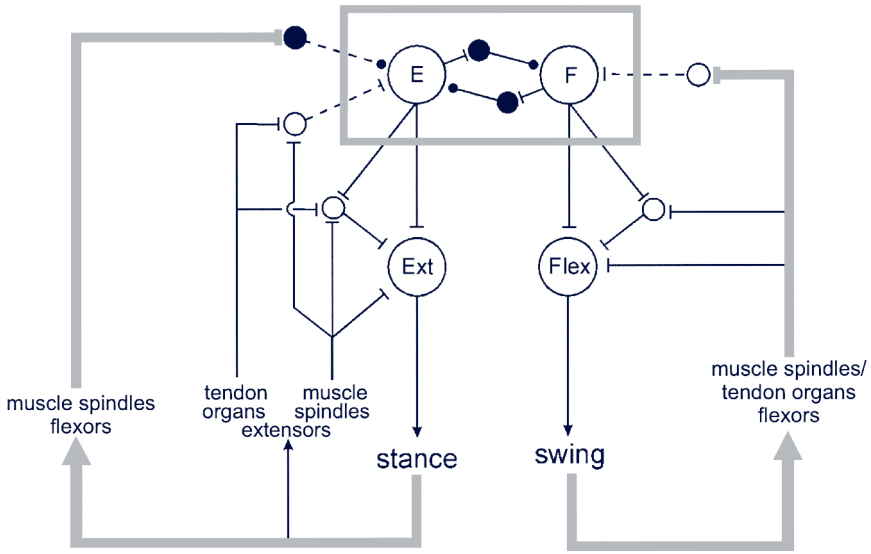


Fig. 3: Schematic presentation of the sensory control of the cat hind limb walking pattern generation based mostly on work by Keir Pearson and coworkers. The box represents the spinal central pattern generator (CPG) network with a simplified network of interneurons (E and F) that inhibit each other. The CPG is located in the lumbar spinal cord and generates the basic alternating locomotor activity in extensor (Ext.) and Flexor (Flex.) motor neurons. The circles denote neurons or groups of neurons. The lines denote the axons by which neurons transmit information to their output regions with which they make contact with other neurons, the synapses. Two kinds of synaptic connections are present: bars indicate excitatory connections, filled circles indicate inhibitory connections. Arrows denote causal influences. Please note that there are two different kinds of input from sense organs measuring either movement or force generated: the first kind of influence affects and determines the phase of the activity of the CPG (thick line); the second kind modulates the actual strength of the activity (thin lines). Figure modified from Keir Pearson (Pearson and Gordon 2000).

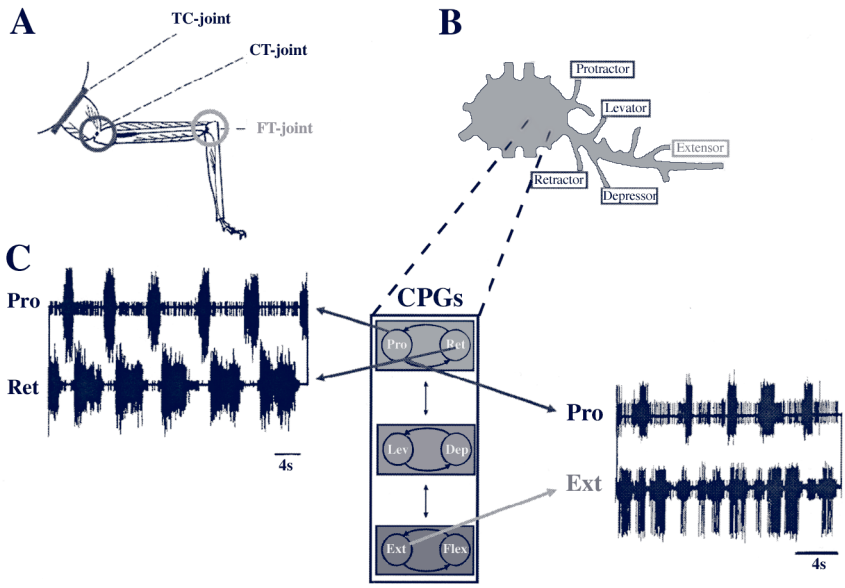


Fig. 4: Modular structure of central pattern generators of the stick insect leg muscle control system. **A** Anatomical structure of the stick insect leg showing the three main leg joints: the thoraco-coxal (TC) joint, the coxa-trochanteral (CT) joint and the femur-tibia (FT) joint. **B** Anatomy of the mesothoracic ganglion including the nerves innervating the main leg muscles serving the TC-, CT- and FT-joint. **C** The box in the middle represents the three independent CPGs of the main leg joints, the TC-joint, the CT-joint and the FT-joint. To the left and the right, experimental evidence is presented from the rhythmically active deafferented locomotor system. Motor neuron activity was recorded by extracellular electrodes from the leg motor nerves indicated: left – antagonistic motor neuron pools of each joint can generate alternating activity, exemplified for the activity of the coxal motor neuron pools; right – rhythmicity in the motor neuron pools of the different leg joints is not coordinated, i.e. different inherent frequencies are generated and no cycle-to-cycle coupling is present, exemplified for the activity of a coxal (Pro) and a tibial (Ext) motoneuron pool. The underlying data derive from work by the groups of Ulrich Bässler and Ansgar Büschges.

cycle in the stick insect middle leg is shown in Fig. 5. Note that the sensory information comes from local sources, i.e., sense organs in the limb that measure either movements, load or force. In summary, both in the stick insect and the cat walking system, current knowledge of the neural control of the generation of the leg stepping pattern has reached a level of substantial detail.

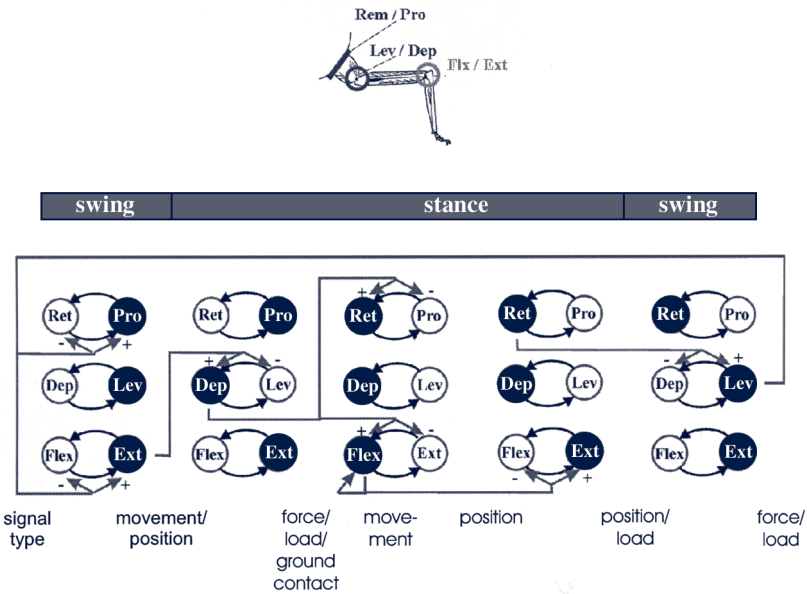


Fig. 5: Sensory influences on the timing of joint oscillators that contribute to pattern generation in the stick insect middle leg presented in a simplified state-based diagram for the action of the individual joint oscillators. Please note that specific sensory signals guide the generation of the functional stepping pattern, i.e., the generation of swing and stance phase by intra- and interjoint influences. The kind of sensory information is indicated in the bottom line. The underlying data derive from work by the groups of Ansgar Büschges and Holk Cruse.

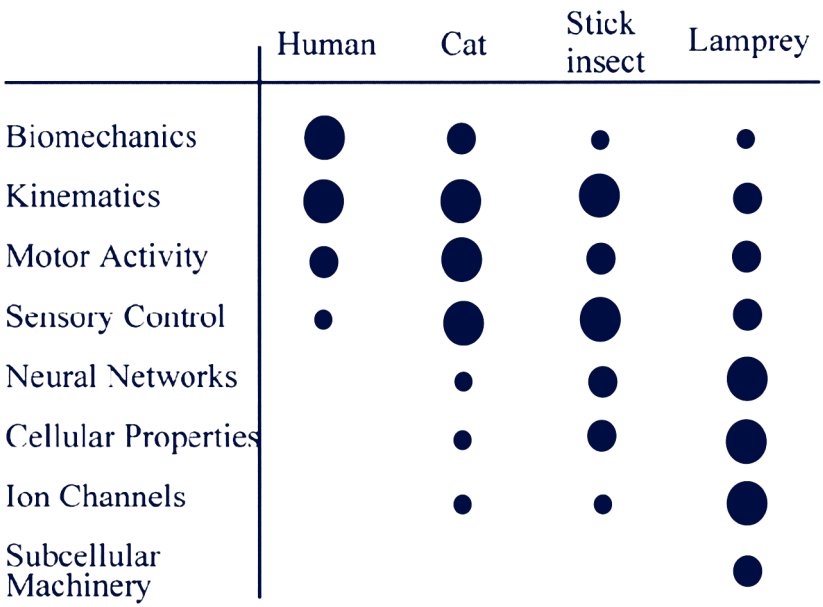


Fig. 6: Comparison of current knowledge about the levels underlying locomotor pattern generation in human, cat, stick insect and lamprey. The size of the filled circles is chosen relative to the actual state and detail of knowledge (see text for further details).

How are the underlying neural networks constructed, how do their neurons operate and how are their cellular properties controlled? In both the stick insect and cat walking systems, these investigations are a main focus of current research, but no global picture is available yet and common principles on this level are only just beginning to emerge. The situation is even more obvious for the other walking systems that have been studied in some detail, like humans, other higher mammals including the rat and the mouse, other invertebrates, like the cockroach, crayfish or locust. Fig. 6 gives a schematic comparison of the current state of knowledge for human, cat and stick insect locomotion. For introducing these levels of analysis, i.e., the neural networks, the cellular properties and the subcellular

aspects, I will present to you the spinal locomotor network for swimming in the lamprey, a lower vertebrate. Concerning these aspects, this system can be considered the most thoroughly investigated locomotor system. The reason for this is at least threefold: (i) the locomotor program for swimming is simple compared with terrestrial locomotion; (ii) the lamprey as a lower vertebrate has a rather simple nervous system, with a relatively smaller number of neurons compared with higher mammals; the lamprey central nervous system is relatively easily accessible due to the fact that they do not have bones and (iii) a motor pattern very similar to the *in vivo* pattern can be generated in the presence of neurotransmitter-agonists *in vitro* in the isolated spinal cord. For these reasons, the lamprey has given neurobiologists a very successful glimpse into the action of their neural networks and the neurons involved, with many of the important breakthroughs coming from the lab of Sten Grillner.

The alternating activity pattern of the myotomal muscles along the body of a lamprey is generated by segmental networks of neurons in the spinal cord. The crucial network component underlying the alternating activity is the reciprocal inhibition between neurons of both sides of the spinal cord (Fig. 7), which interact like neuron 1 and neuron 2 in the scheme in Fig. 7A. When neuron 1 is active, neuron 2 is switched off via synaptic inhibition from neuron 1 and vice versa. In the lamprey spinal cord, these neurons are the commissural crossed inhibitory interneurons (CC). Their interaction with their contralateral counterparts, as well as with other spinal neurons on their ipsilateral side, establishes the alternating activity pattern of myotomal motor neurons on both sides of each spinal segment, called "fictive swimming" (Fig. 7B). However, network topology is only the first aspect controlling the generation of rhythmic locomotor activity. The intrinsic properties of the neurons are the second one. A simplified presentation of the intrinsic properties of neurons during the generation of rhythmic activity is schematically presented in Fig. 8. The intrinsic properties tune the activity of a neuron, i.e., increase or decrease neural activity in the locomotor cycle, by acting on top of the modulations in membrane potential resulting from synaptic inputs from other neurons. For example, bistable characteristics, so-called plateau potentials, prolong the activity of a neuron in response to synaptic excitation, without continuous excitatory synaptic inputs. A decline in neural activity is not only produced by inhibitory network interactions, but each neuron may also possess intrinsic mechanisms that eventually result in its inactivation. Thus, a complex interplay between the neural network topology and specific intrinsic properties of the neurons underlie the generation of the basic

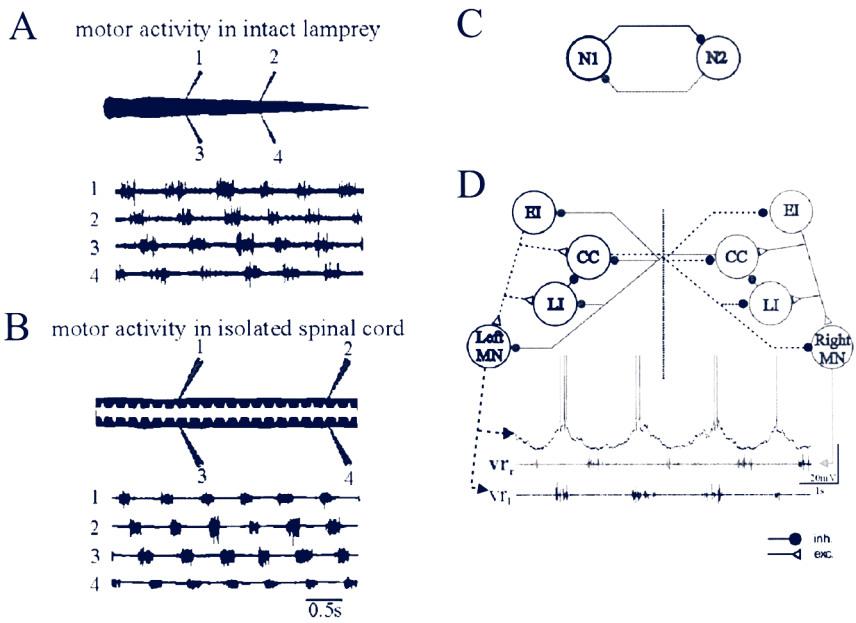
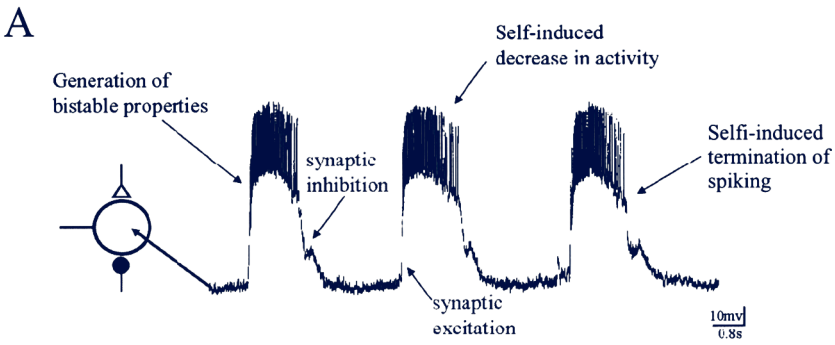


Fig. 7: Introduction to the swimming network of the lamprey. **A** Presentation of the swimming motor pattern by EMG recordings from the segmental myotomal muscles along the lamprey. **B** Activity of the ventral roots innervating the myotomal muscles in the isolated spinal cord preparation. Note the similarity in intra- and intersegmental coordination of the activity pattern in **A** and **B**. **C** Schematic presentation of the network topology of the spinal swimming network of the lamprey. Top: Kernel of the locomotor network consisting of two neurons that inhibit each other mutually. Bottom: Detailed presentation of the segemental network topology: EI – excitatory interneuron; CC – contralateral commissural interneuron; LI – lateral interneuron; MN – motor neuron. For clarity, the lower three traces give simultaneous recordings from an experiment in which the two contralateral ventral roots of one segment were recorded extracellularly together with one motoneuron that was recorded intracellularly. A, B are modified from Pearson and Gordon (2000).

locomotor pattern in the lamprey spinal cord. Synaptic inputs and intrinsic properties exert their influence via the action of ion channels in the neuronal membrane. The ion channels that are contributing to the mediation of synaptic inputs are controlled by neurotransmitters. Fig. 8B gives lists of neurotransmitters and neuromodulators currently known to be present in the neurons of the lamprey spinal cord, as well as a list of the known ion channels. The significance of ion channels for the generation of rhythmic locomotor activity can be investigated by the use of specific antagonists. For example, blocking one specific "high-voltage-activated (HVA)" calcium channel subtype that is involved in the mediation of synaptic transmission results in a decrease in synaptic efficacy and consequently induces a loss of function of the spinal locomotor network. Rhythmic activity ceases in the presence of the antagonist in the spinal cord.

In the light of such detailed knowledge, two questions arose some years ago: Are the insights into the spinal locomotor network of the lamprey sufficient to explain the generation of swimming movements, or are there specific areas that need further attention? To answer this question, a simulation of the lamprey swimming network was developed by Anders Lansner, Örjan Ekeberg and coworkers that combined a neural network simulation with a biomechanical model of the lamprey. The lamprey locomotor system was therefore the first system for which a computer simulation has been developed that bridges the gap between the level of the cellular machinery and the behavior. The goal of such endeavors is different from building biologically inspired robots, a field that has been growing substantially in past years. In robotics, the emphasis is to combine engineering solutions with biological insights in order to improve the performance of animats, while the generation of simulations adds a new approach to biological motivated basic research. Since its start, this approach has been very successful for the research conducted on the spinal mechanisms in the lamprey, specifically to test (i) the current state of knowledge, (ii) to test hypotheses drawn from the data, as well as (iii) to highlight topics that need further research.

Similar programs are urgently required to understand complex movement sequences, such as walking. Successful execution of such programs has immediate application. Recent advances in our knowledge of the neurophysiological mechanics controlling walking in tetrapods and insects as outlined above encouraged us to develop a research program aimed at creating computer simulations for testing hypotheses emerging from the neurophysiological findings. Thus a special research group on "Neural Control of Locomotion" was formed for the academic year 2001/02 at the Wissenschaftskolleg zu Berlin that brought



B

transmitters & modulators	ion channels
glutamate	Na^+
glycine	K^+
GABA	K^+_{Ca}
5-HT	Ca^{++}_{HVA}
dopamine	Ca^{++}_{LVA}
tachykinins	NMDA
NPY	AMPA

Fig. 8: **A** Schematic presentation of the main mechanisms determining neural activity. Excitation of the neuron is initiated by synaptic inputs. Bistable properties can keep the neuron active, outlasting the excitatory influence of synaptic inputs on it. Activity of the neuron can be attenuated by mechanisms of self-induced decrease in activity and finally terminated either by inhibitory synaptic inputs or by self-induced termination of activity. **B** Listing of the most thoroughly investigated transmitters and neuromodulators acting in the lamprey spinal locomotor network as well as a list of the ion channels underlying membrane potential alteration and, through that activity, control (for details see Grillner et al. 2000).

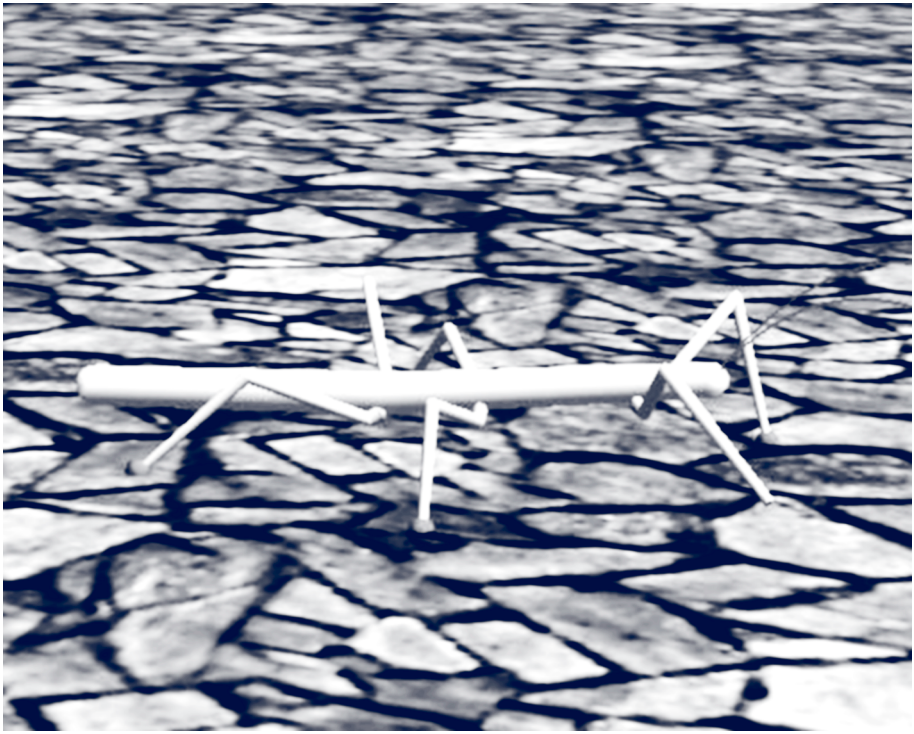


Fig. 9

together five scientists from vertebrate neurophysiology, Sten Grillner and Keir Pearson, computer modeling, Örjan Ekeberg, theoretical biology, Volker Dürr and invertebrate neurobiology, Ansgar Büschges. The goal of this group was to construct a 3-dimensional dynamic simulation of a hexapod (stick insect) and a tetrapod (cat) walking system. The present design of these simulations is shown in Fig. 9. By the end of this academic year, we want to finalize these 3-dimensional dynamic simulation platforms for hexapod and tetrapod walking systems, already including some neural control based on current knowledge. These platforms will be of great use for us and the broader field by adding an important approach to our work aiming at unraveling the neural mechanisms of one specific nervous system function that is anything but ordinary: locomotion.

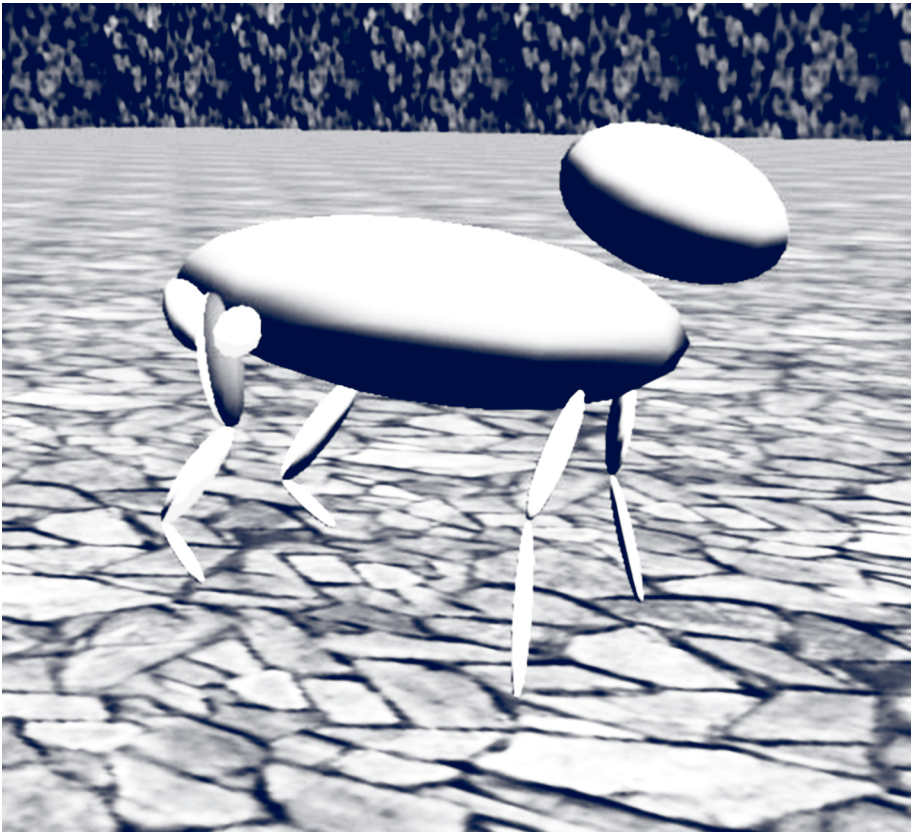


Fig. 9 and 10: Pictures of the two 3-D dynamic simulation platforms for the stick insect and the cat walking system as of April 2001 (see text for details).

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