

Dr. Wolfgang Stein
Institute of Neurobiology
Ulm University
D-89069 Ulm, Germany

Phone: +49 (0)731 50 22636
Fax: +49 (0)731 50 22629
Email: wstein@neurobiologie.de
www: www.neurobiologie.de

Statement of research interests.

Plasticity and behavior.

The plasticity of the nervous system plays a key role in everyday life, because it continuously adapts behavior to the changing requirements of the body and the environment. The perception of environmental cues and proprioceptive signals from inside the body thus represents a pivotal requirement without which complex organisms would not be able to survive. Consequently, the processing of sensory signals is a vitally important task of the nervous system and at the same time one of the most intriguing research fields in systems and computational neuroscience.

The goal of my research is to obtain a general understanding of how the nervous system generates behaviorally relevant activity. I am focusing on the influence of sensory signals on the functional flexibility of behavior. Since rhythmic activity governs most parts of our behavior (such as breathing, walking or chewing) I have selected two well-characterized arthropod systems which generate rhythmic motor activity (see below). I aim at combining cellular, pharmacological and anatomical approaches to elucidate general principles about motor pattern selection from multifunctional networks.

Since many of the same organizing principles pertain to network activity in all animals, including humans, my work aims to better elucidate how the nervous system generates a functionally correct behavior. This will also facilitate the understanding of dysfunctional sensorimotor circuits, and what to target in them for functional recovery, such as occurs after spinal cord injury or stroke. My research includes work on the modulation of network function, and will also contribute insight into health related issues, like aberrant circuit function occurring as a consequence of drug addiction. My research will thus also guide comparable studies in the numerically larger and experimentally less accessible mammalian nervous system.

1) Selection of motor programs by sensory pathways and descending pathways from the brain. At the cellular level, we aim at determining how distinct motor patterns are elicited by different sensory and descending inputs to multifunctional neural networks that underlie behavior. Previous work in many model systems showed that one common principle underlying behavioral plasticity in the nervous system is that single neural networks produce many different neural activity patterns. The multifunctional character of such networks arises from the actions of modulatory neurotransmitters which alter the cellular and synaptic properties of the network neurons. We are addressing these issues by using the quite unique accessibility of identified sensory, projection and circuit neurons in the stomatogastric nervous system of the crab *Cancer pagurus*. This system contains the well-defined gastric mill (chewing) and pyloric (filtering of chewed food) central pattern generators, located within the stomatogastric ganglion, plus several descending projection neurons from higher centers of the nervous system (such as the brain) that modulate these circuits. Several peripheral systems which modulate gastric mill and pyloric activity, largely via activation of specific projection neurons, are also identified. Functionally, this system is comparable to mammalian motor circuits in the spinal cord, and their descending innervation from the brain. We are using multiple simultaneous intracellular and extracellular recordings from identified projection and circuit neurons with standard and dynamic clamp-mediated electrical perturbation of neuronal activity to investigate the principles of functional plasticity in pattern generation and the consequences of realistic sensory feedback.

2) Sensory regulation of locomotion. The principles of motor network operation and the generation of locomotion have been studied in great detail in arthropods such as stick insect and locust. This research has led to the development of cybernetic appliances, e. g. autonomously walking robots and motor driven artificial limbs. Sensory feedback to locomotor networks significantly shapes the motor patterns in all animals, and is a prerequisite for the correct functioning of these networks. Loss of sensory feedback causes numerous diseases. We are studying sensory feedback to motor networks in the stick insect walking system and the locust flight system as a model for sensorimotor circuit function in vertebrates. Both networks have extensively been studied and they share the same principle structures. Central pattern generators produce the underlying rhythmic motor pattern, which is then modified by external and internal sensory feedback to better suit the current environmental needs. In both systems, network structures as well as single network neurons are identified. Since one of the major problems in systems theory and its application to robotics is the processing of simultaneously occurring sensory input, we are characterizing the interaction of different sensory inputs to these motor systems

and, thereby, elucidating the question of how such an interaction determines the motor pattern. Our experiments are supported by the use of computer-based network simulations, in which experiment-derived hypotheses can be tested and new ideas about network functioning are revealed.

Future directions.

It is commonly recognized that the fundamental roles of the central nervous system and sensory feedback are separate. The sensory system continuously re-adjusts the activity produced by the central nervous system such that the resulted behavior fits changing circumstances. Pattern-generating networks are thus generally studied assuming feed-forward architecture with sensory feedback that modifies the network output. This approach has provided considerable insight. However, sensory organs often show complex dynamics and take part in the processing of the information, and in rhythmically active networks, sensory feedback is often active in coordination with the motor pattern.

Any functional analysis of a network presumes the identification and characterization of all components (neurons) contributing to the generation of the motor output. So, even complete knowledge of all network connections can only be a starting point for the investigation of the network dynamics, because the output of the network will, as a general rule, depend on modulatory processes such as synaptic dynamics and intrinsic cell properties. As a consequence, it is an obsolete approach to infer the function of a network or of a sensory input to that network from the investigation of individual network components. Due to the interaction between different network components and between motor networks and sensory feedback, emergent properties will determine system output. In this regard, a more comprehensive analysis of the holistic network behavior is required.

We will thus employ the methods of functional network analysis to study the integration and processing of rhythmic sensory input with a combination of electrophysiological experiments and computational modeling during locust flight and in the crab stomatogastric nervous system. Both systems belong to the most thoroughly characterized systems in neurobiology, now enabling us to apply complex methods of network analysis which require detailed knowledge of the structure and function of the underlying networks. The prominent structural differences between both systems will allow a general interpretation and thus a more conceptual understanding of how sensory feedback influences pattern generating networks. Beginning with a model-based analysis of coupled oscillators we will test the functional impact of sensory feedback loops on motor output. It is our goal to characterize emergent network properties and functional flexibility of pattern generating networks and, thereby, to show the general principles of how behaviorally relevant motor activity is generated. This will also help to improve currently available biomechanical prostheses used to replace or control body parts after traumatic injury.

We will then employ realistic sensory feedback to the isolated nervous system by a unique experimental approach. By means of the dynamic clamp method, computer-generated sensory feedback loops can be connected to the biological nervous system in real-time. In this manner, the model-derived hypotheses on the interaction between central and sensory oscillator can be tested with the biological preparation and thus serve the iterative improvement of these hypotheses.

Methods used.

Extra- and intracellular recordings of central and sensory neurons; pharmacological treatment; immunohistochemical staining; computer-based modeling; real-time computer feedback.