

# MOTOR OUTPUT VARIABILITY IN A JOINT CONTROL SYSTEM – A SIMULATION STUDY

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## KEYWORDS

Physiological simulations, permutation, posture control.

## ABSTRACT

The plasticity of the nervous system during the processing of sensory information is of major interest to interdisciplinary neurobiology research. Here, we used an insect model system with stereotyped behavioral patterns for the investigation of how the nervous system can switch between two different motor outputs, walking and standing, despite having the same sensory input, in a computer simulation based on the known network structure. The strengths of 16 specific information pathways which integrate sensory information were permuted and the resulting database of more than 43 million network outputs was analyzed. Two independent analysis show that the same neural network can produce two different behaviors by specifically altering the weighting of several information pathways. We obtained specific combinations of pathway transmission levels that produced these behaviors. This means, that solely changing the strength with which a pathway transmits sensory information is sufficient to switch between different behaviors, like from standing to walking. The predictions that derive from our results can now be used in physiological experiments.

## INTRODUCTION

All animal behavior is characterized by its response to sensory stimuli and the movement of the body. The investigation of the processing of sensory information and the control of movements by the nervous system are thus of major interest to neurobiologists, physicists, computer and robotics scientists. Interdisciplinary efforts try to combine the physical structure of the nervous system with the activity of nerve cells and the required computation within the nervous system. Biological systems, especially the vertebrate brain, are very complex and usually possess a large number of nerve cells to produce very flexible behaviors. Therefore, model systems with a lower number of nerve cells and more stereotyped behavioral patterns are used for the investigation of nervous system functions. For walking, the knee of stick insects is used rather than the human knee. While the mechanisms of walking are the same in both species, the number of contributing nerve cells is reduced from several millions in humans to some dozen in insects. In such a small system, it might be possible to

answer a fundamental question in neurobiology, namely how a defined set of neurons can produce several different tasks and how to switch between these tasks. Here, the nervous system has to switch from a static joint control during standing to movement control of the limb when the animal starts to walk.

In biological experiments, the process of switching between those two states can often only be investigated by recording the responses of single neurons or a small set of involved neurons at a time. In combination with several degrees of freedom, a meaningful interpretation of experimental data can only be achieved by computational simulations. Here, we investigated the capability of the nervous system of the stick insect to switch between standing and walking with a simulation based on the known network structure. The strength of specific information pathways was permuted and the resulting database of more than 43 million network outputs was analyzed.

## BIOLOGICAL BACKGROUND

The neuronal control system of the knee joint (Femur-Tibia joint) of stick insects processes information in three main levels: (1) The sensory information about joint angle (position) and passive or active leg movements (velocity) is measured by the femoral chordotonal organ (Hofmann et al., 1985) and encoded in electrical discharges (spikes). Both sensory parameters are separately transmitted either directly or indirectly via spiking interneurons to (2) a layer of parallel pathways (identified nonspiking interneurons; Büschges 1990, Sauer et al, 1995, Stein & Sauer, 1998), in which the parameter channels are integrated. These nonspiking information pathways finally converge with a context-specific transmission strength onto (3) a single spiking extensor motoneuron (MN), which reflects the previous weighting of position and velocity parameters so that it either contributes to a stiffening of the joint during standing or to active leg movements during walking.

Physiological experiments indicate that for both situations the same underlying set of neurons is computing the sensory information, but leads to opposite motor outputs: a **resistance reflex** that stabilizes the leg during standing or a reflex reversal, the **active reaction** (as defined by Bässler 1976) during walking. Both behaviors can readily be monitored in the spike activity of the motoneuron when a single ramp-and-hold stimulus (i.e. flexion and extension) is applied to the leg. Due to experimental restrictions, it is still unclear whether the known network is sufficient to

produce both motor commands and to switch between them or if additional neurons (of several thousands available in the central nervous system) are needed. We addressed this question in a simulation, which included the structure of the Femur-Tibia network in as much detail as is known from physiological experiments (Fig. 1, an extended version of Sauer et al., 1996). Neurons were modeled with the simulation environment *madSim* (Mader et al., 2003) as a soma with three additional unbranched dendritic compartments with active and passive properties according to Hodgkin-Huxley equations (Hodgkin & Huxley, 1952). The sensory information was separately simulated with current injections to provide position and velocity input to

the subsequent information pathways (Büschges, 1994). 16 separate pathways (representing excitatory (E-types) and inhibitory (I-types) nonspiking interneurons) then read out this sensory information so that they comprised different weightings of position and velocity parameters. The differentially computed information conveyed by these pathways was integrated by the extensor motoneuron, which subsequently produced the motor command as a sequence of spikes. We tested whether changes in the transmission strength of these separate pathways can produce both motor outputs and switch between resistance reflex and active reaction.

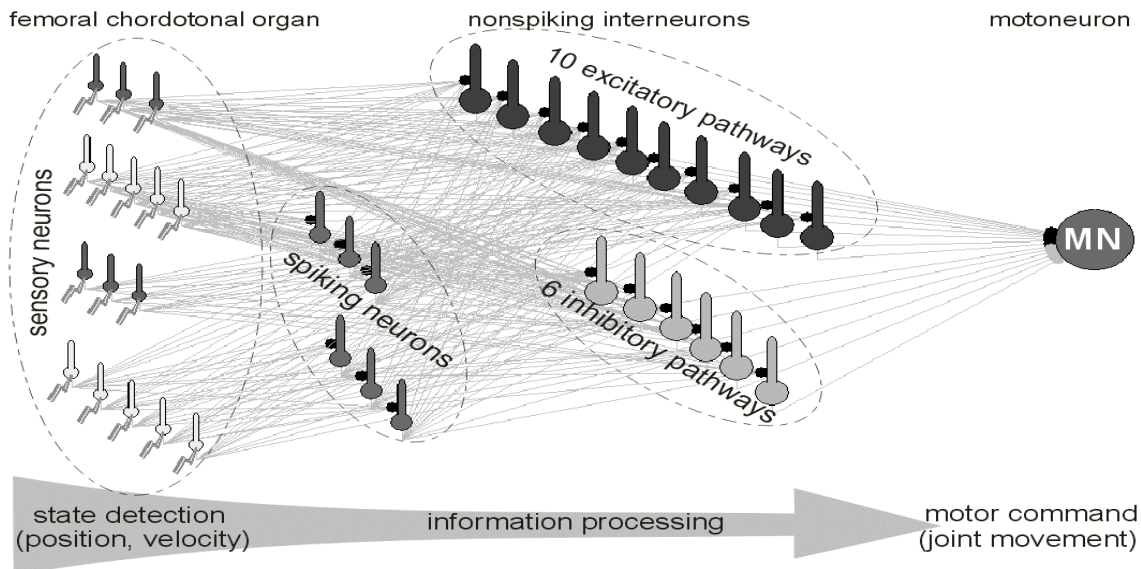


Figure 1: Structure of the Femur-Tibia Control Network and Direction of Information Flow. Small Arrows: Current Injections.

## PERMUTATION

Complex biological systems like the nervous system are nonlinear in several levels, like transmitter release, firing frequencies or membrane potential. Therefore, we selected a permutation to test whether the network was capable of generating both, resistance reflex and active reaction. We created a database of motor commands by independently altering the transmission strengths between nonspiking interneuron pathways and the motoneuron. 16 different pathways with three levels of synaptic transmission (low=5 nS, medium=50 nS, high=400 nS) resulted in a database of 43,046,721 motor outputs. To speed up the calculation of the permutations all feedforward parts of the network were calculated only once and the results of this calculation were stored and subsequently used in all following permutations. This reduced calculation time from 175 days to 6 days. Motor outputs tend to stay stable over a broad parameter range, but can also suddenly change with a small alteration of parameters. Methods that reduce the resulting database by driving the system in a certain direction once a sensible motor output is generated, like error back propagation or simulated annealing, would thus increase the probability of losing network results. Additionally, we wanted to study the capability of our network to produce motor outputs without giving it a bias or expectation of what motor output would be meaningful. Instead, we used two tests for scanning the complete database in order to classify motor

outputs according to their spike sequence and subsequently look for meaningful results.

## Stimulus Dependent Data Analysis

We classified the output of the network by creating a rating system for how close the output resembled (a) resistance reflex or (b) active reaction. (a) Results from physiological experiments were used to determine the optimal spike distribution of a resistance reflex. The simulation time was divided into several sections of different durations according to the ramp-and-hold stimulus. The optimum result was defined with a spontaneous firing activity of 7 Hz, a firing frequency of 90 Hz during the flexion phase, 12 Hz during the holding phase and 0 Hz during the relaxation stimulus. The spike activity of all permutations was compared to the optimum by a rating factor, which was calculated by the sum of the square difference between the current and optimum firing frequency of all time sections. Similarly, an optimal template was created for the active reaction. A spontaneous firing frequency of 40 Hz was assumed, which was followed by a complete lack of activity beginning 40ms after the onset of the flexion stimulus. When the flexion stimulus reached a certain position, strong firing activity resumed with 90 Hz. All events after the end of the flexion stimulus were not rated.

## Stimulus Independent Data Analysis

Our second analysis of the database was stimulus independent: In general, biological neural networks can either produce no, tonic, burst-like (salvo of spikes) or irregular activity. By definition, no, tonic or irregular activity do not represent one of the desired motor patterns. Both, active reaction and resistance reflex are best described by a burst-like activity: In the latter, a single burst is generated with a maximum activity during the flexion part of the stimulus. During an active reaction, two bursts of activity are separated by a lack of spike activity during the flexion part of the stimulus. We searched the database according to the flowchart (Fig. 2) in which the spike activities of the motoneurons were classified in the categories mentioned above.

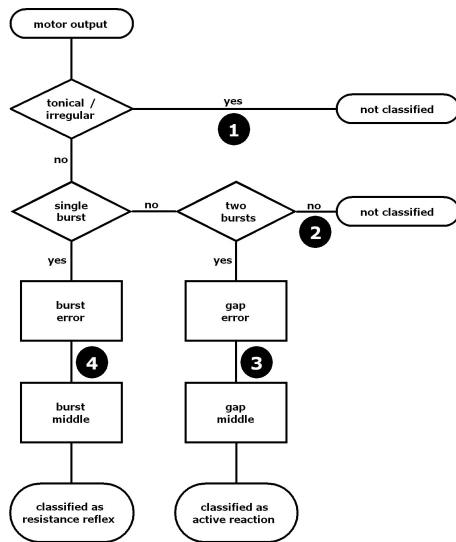


Figure 2: Flowchart for Classification of Motor Outputs

As a result, all database entries without activity or with tonic or irregular firing patterns were eliminated (1). The remaining bursters were then separated into single bursters or multiple bursters. Multiple bursters were then split into bursters with two bursts or bursters with more bursts, which subsequently were eliminated from our analysis (2). The remaining single bursters were assigned a variable that held the "burst error", which represents the deviation from an optimum burst duration of 200ms. After that, the center and the duration of the burst were determined and allocated to additional variables (3).

Simulations with two bursts were assigned the variable "gap error" which held the deviation from a) the optimum duration (100ms) of the lack of activity (which represents the active reaction) and b) from the expected firing frequencies. Subsequently, the center and the duration of the gap were determined (4).

## PERMUTATION RESULTS

### Stimulus Dependent Analysis (Resistance Reflex)

All simulation results were rated according to the expected motor output. Fig. 3 shows a comparison of the activity of the best resistance reflex (rating factor 101.80), which fits physiological data very well, and the simulation with the

worst rating (rating factor 83,115.00). Bars indicate the synaptic transmission levels of the 16 nonspiking pathways. A plot of the rating factor against the number of simulations sorted by the rating factor revealed that the best 150 simulations showed a steady, but slow rise in rating factor. From simulation 150 on, the rating factor deteriorated more quickly. The regression coefficients of the first 150 and the following 150 simulations were significantly different ( $P < 0.05$ ,  $N = 150$ , t-test). We thus grouped the best 150 simulations and classified them as the best possible result. From these simulations, the synaptic transmission strengths of all 16 pathways that relay velocity and position information from the leg onto the motoneuron were used to determine which pathways need to be strong to achieve the desired motor output and which pathways must be weak.

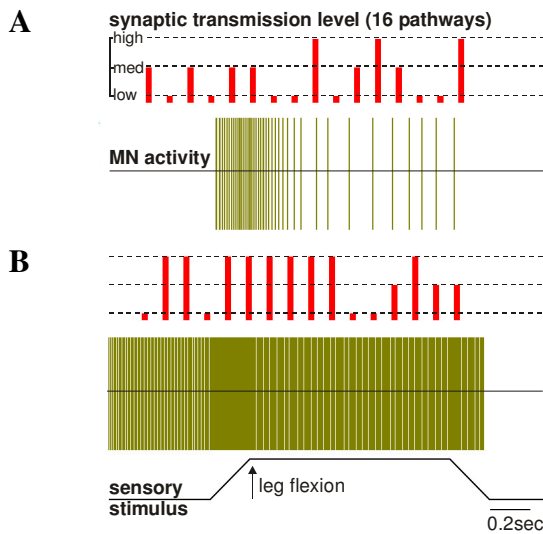


Figure 3: Best (A) and Worst (B) Resistance Reflex

In the best-rated simulations, specific synapses showed a clear preference for a certain synaptic transmission level (Table 1, resistance reflex). If this level was completely unimportant for determining the motor output, one would expect an equal distribution in all pathways, i.e. 33% occurrence for each level (50 in 150 simulations).

Table 1: Occurrence of Synaptic Strengths for different Pathways during Resistance Reflex and Active Reaction

pathway (name)	resistance reflex			active reaction		
	low	med	high	low	med	high
1 (I4)	55	61	34	2	3	84
2 (E10)	97	53	0	3	3	83
3 (I2)	62	50	38	20	18	51
4 (IE1)	79	31	40	18	23	48
5 (I3)	79	52	19	29	26	34
6 (E6)	61	87	2	32	37	20
7 (E3)	83	65	2	30	51	8
8 (E4)	56	79	15	53	36	0
9 (E5)	69	78	3	54	35	0
10 (E2)	102	48	0	53	36	0
11 (E7)	122	28	0	51	38	0
12 (E8)	131	19	0	41	48	0
13 (E1)	44	58	48	48	41	0
14 (E9)	3	6	141	45	44	0
15 (I8)	2	3	145	48	33	8
16 (I1)	0	0	150	57	32	0

The preference of certain pathways for specific synaptic transmission levels shows the importance of these synapses for the resistance reflex. Two examples, one for a pathway with strong preference (16, nonspiking interneuron I1) and one with a weak preference (13, nonspiking interneuron E1) are shaded.

The difference between the importance of the 16 pathways is most obvious when normalized for each synaptic transmission level (Fig. 4, left). The expected occurrence is 0.33, or, in other words, if all 43 Mio simulation results were plotted, one would obtain an equal distribution of 0.33 for all synaptic transmission levels. As is obvious from our results, the weighting of the different nonspiking pathways is critical for the expression of the resistance reflex.

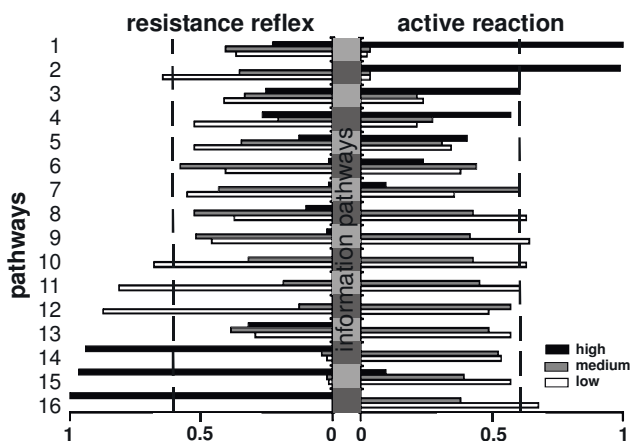


Figure 4: Normalized Occurrence of Synaptic Strengths for all Pathways during Resistance Reflex and Active Reaction

Physiological experiments suggest that the spontaneous activity of the motoneuron may not originate from within the network itself (Bässler, 1983). Our results support this hypothesis, because none of the high rated motor outputs showed spontaneous activity.

### Stimulus Dependent Analysis (Active Reaction)

The structure of the simulated network was derived from experimental data in standing animals, and thus during the generation of resistance reflexes. To test, whether the same network is capable of producing the opposite motor output, the active reaction, despite having the same sensory input, we searched the database for active reactions. 89 motor patterns that resembled an active reaction were found. The best result according to the rating factor is shown in Fig. 5.

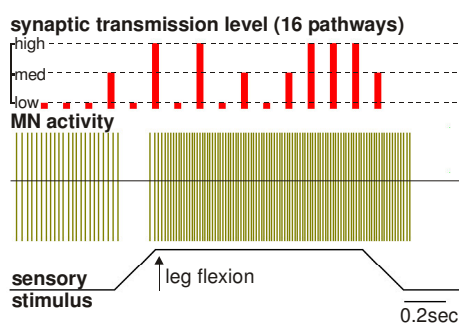


Figure 5: Best Active Reaction with corresponding Synaptic Strengths

Like the experimental original, the simulation showed a high spontaneous activity before the beginning of the stimulus, which was turned off during the flexion phase of the stimulus. Before the end of this stimulus, strong motoneuronal activity resumed.

As with the resistance reflex, the strengths of the 16 pathways differed in their occurrence for this motor pattern (Table 1). Here, a different set of nonspiking pathways became important. Two examples, one for a pathway with strong preference (14) and one with a weak preference (13) are shaded (Table 1). Fig. 4 (right) shows which pathways showed preferences for a certain strength and the obvious difference in the occurrences of transmission levels for specific pathways between resistance reflex and active reaction (compare left and right). For example, the highest occurrence of the synaptic transmission level of pathway 2 (nonspiking interneuron E10) changed from low during the resistance reflex to high during the active reaction. This means that this pathway is important for both motor outputs, but needs to be weighted differently. To change the motor output from a resistance reflex to an active reaction, the synaptic transmission level needs to be adapted from the level with the largest bar on the left side to the largest bar on the right side. Going from an active reaction to a resistance reflex requires the reverse procedure.

To test whether the obtained distribution of synaptic transmission levels truthfully drive the network into generating either resistance reflex or active reaction, we calculated 4 permutations with partly fixed synaptic transmission levels. In the first permutation, the synaptic transmission levels of those pathways that had a higher normalized occurrence than 0.6 (dashed line, Fig. 4) during a resistance reflex were fixed to that value, while the transmission levels of all other pathways were permuted (high, medium and low settings). The rating factor for the resistance reflex was used to assess the results. For comparison, a second permutation was calculated in which the synaptic transmission levels of the same pathways were fixed to the value with the lowest probability of occurrence. When we compared the ratings of these two permutations (Fig. 7), the first permutation showed a highly significant ( $P < 0.0001$ ,  $N = 19683$ , Mann-Whitney test) better rating than the second permutation, which further supports our hypothesis, that the differential weighting of the pathways is important for the generation of a specific motor command. Keeping synaptic transmission levels of those pathways with high occurrence at the correct value was sufficient and necessary to generate resistance reflexes.

Similarly, we calculated two permutations for the active reaction. The permutation with fixed parameter settings for those pathways with high occurrence produced highly significantly better results ( $P < 0.0001$ ,  $N = 2187$ , Mann-Whitney Test) than the second permutation. This shows that also for the active reaction the weighting of the nonspiking pathways is of great importance and that a specific weighting is sufficient and necessary to produce an appropriate motor output.

### Stimulus Independent Analysis

The stimulus independent analysis (Fig. 2) resulted in more than 350,000 single burst (resistance reflex like) and more than 650,000 two burst (active reaction like) motor patterns.

The best rated resistance reflex and the best rated active reaction of the *stimulus dependent* analysis were present in the best 0.1% of the results.

For comparison with the stimulus dependent analysis, the 150 best rated single bursters and the 89 best rated two bursters were analyzed in detail: The single bursters had an average burst duration of  $307.67 \pm 13.73$  ms ( $n=150$ ) and burst-centers between 655 ms and 688 ms simulation time. This corresponded very well with the stimulus dependent analysis. The occurrence of synaptic transmission levels of these resistance reflex like motor pattern showed a clear preference of specific synapses for a certain strength (Fig. 6, left).

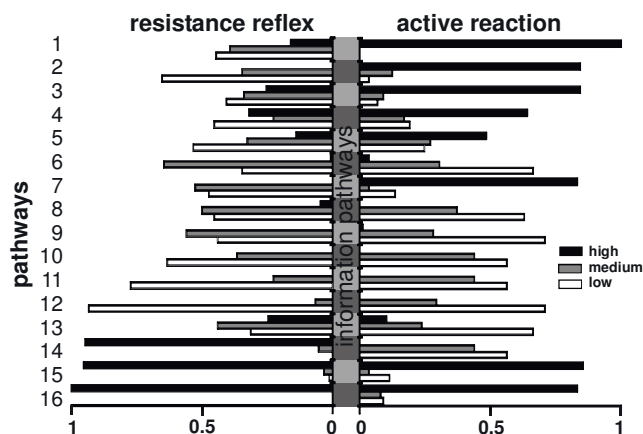


Figure 6: Normalized Occurrence of Synaptic Strengths according to the Stimulus Independent Analysis.

As is obvious, the weighting of the different nonspiking pathways was very similar to the result of the *stimulus dependent* analysis (compare to Fig. 4, left). Thus, even an analysis that did not involve the stimulus protocol detected resistance reflexes and showed that the weighting of the different pathways is critical for the expression of this motor output.

The best "two bursters" had an average burst-interval of  $72.43 \pm 9.53$  ms and the center of the interval was always between 513 ms and 643 ms. Although the interval appeared earlier than in the stimulus dependent analysis and the average interval was shorter, the motor outputs clearly resembled an active reaction. The occurrences of synaptic transmission levels (Fig. 6, right) showed great similarities with those obtained by the stimulus dependent analysis (Fig. 4, right). The most noticeable differences were pathways 15, 16 and 7, which changed from low to high synaptic strengths and from medium to high, resp. We conclude that these pathways do not strongly contribute to the reversal of the motor output, but may rather determine the timing of the active reaction and caused it to appear earlier and to be of shorter duration.

## CONCLUSIONS

Our analysis of the permutation results shows that the same neural network which stabilizes the leg during standing can also contribute to active leg movements, despite having the same sensory input. To do so, the weighting of several information pathways which integrate sensory information about joint velocity and position must be altered

specifically. We have shown which interneuronal pathways need to be changed for switching between both behaviors and that these changes are sufficient and necessary for producing these behaviors. How the change in the transmission of sensory information to the motoneuron is actually achieved was not tested, but it is conceivable that such a change would either occur directly presynaptic or directly postsynaptic (like in our simulation) to the nonspiking interneurons. Our results predict that specific interneuronal pathways need to be weakened or strengthened (Table 1) to support standing or walking. The timing of the motor output seems to depend on the weighting of the nonspiking pathways. These predictions now can be tested in physiological experiments.

In our investigation, we did not reduce the number of possible simulations by using a goal-oriented permutation. Instead, we tested whether the generation of a certain behavior is an intrinsic property of this network, which turned out to be the case. Although we did not start up with an expectation for synaptic transmission levels, we obtained specific combinations of synaptic transmission levels that produced specific behaviors. This means that solely by changing the strength with which a pathway transmits sensory information is sufficient to switch between different behaviors, like from standing to walking.

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