INFERENCE ABOUT MULTIPLE PATHWAYS IN MOTOR CONTROL LIMB IN LOCUST

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Abstract: In locust local circuits that control limb movements, the neural signals are processed by both spiking and nonspiking interneurons that operate in parallel to process sensory information. These interneurons receive sensory inputs from leg mechanoreceptors and together project to leg motor neuron pools. The main feature of the nonspiking interneurons is their ability to communicate with other neurons without the intervention of nerve impulses, or spikes, so that they exert graded control over their postsynaptic motor neurons, while spiking local interneurons communicate by means of action potentials and are involved in the integration of sensory signals. Our work presents an investigation from different classes of neurons driven by random Gaussian excitatory movements to a proprioceptor at the knee joint. The underlying aim of this work was to use information theory in understanding connectivity in the neural network.

1 INTRODUCTION

To improve the performance of robots many studies have focused on understanding how animals such as insects (Fourtner, 1976) perform complex movements using relatively simple neuromuscular reflex control systems (Delcomyn, 2004). To produce a reflex movement of a limb, the neuromuscular control system must transform an external stimulus into a limb movement and in doing so must generate a movement driven by appropriate neuronal patterns (Burrows, 1996).

In many arthropods, and locusts in particular, it is possible to perform measurements of the underlying control signals (patterns of a neural activity) at the level of the relatively few neurons responsible for controlling movements of the legs. Locusts have a distributed nervous system with a brain and a series of segmental ganglion. Those in the thorax are responsible for generating the local movements of the three pairs of legs (Burrows, 1996). The movements of the tibia relative to the femur of a hing leg are monitored and encoded by a sensory structure containing approximately 90 sensory cells, the femoral chordotonal organ (FeCO) that converts a mechanical stimulus into electrical neuronal signals (Kondoh et al., 1995). These sensory signals are processed in neuronal networks containing different types of interneurons that use both digital and analogue signalling to control the activation of eleven excitatory motor neurons (9 causing flexion and 2 causing extension) that activate the tibial limb muscles to generate movement of the tibia (Newland and Kondoh, 1997).

In a number of studies (Schreiber and Schmitz, 2000; Bialek et al., 2001; Ebeling, 2002) the idea that a natural approach to analyse non-linear and stochastic signals should be based on *information theory* has been suggested. Information theory (Shannon, 1948; Cover and Thomas, 2006) quantifies statistical uncertainty in random processes and statistical dependencies between multiple random processes (Cover and Thomas, 2006). *Entropy* is a measure of uncertainty of a random vector with a probability distribution function (pdf) $p_X(x)$ (Cover and Thomas, 2006; Shannon, 1948). In addition, *divergence* is a generalization of variance to processes with non-Gaussian distributions (Cover and Thomas, 2006) while *mutual information* is a measure of statistical dependency and may be interpreted as a generalization of correlation to arbitrary non-linear relationships between multiple processes with arbitrary probability distributions (Erdogmus and Principe, 2006; Li, 1990).

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The main limitation to mutual information is due to its inability to differentiate the direction of association between two signals (Schreiber, 2000). To overcome this limitation (Schreiber, 2000) introduced a quantity called *information transfer* that shares some of the desired properties of mutual information but takes into account the dynamics of information transport. These quantities quickly spread to different areas; from econometrics (Marschinski and Kantz, 2002) to biomedical engineering (Ward and Mazaheri, 2008).

In general information theory approaches makes few assumptions about the relationship among the system variables, but does require strict stationarity (Nichols, 2006). Time-delayed mutual information quantifies co-dependence between variables by looking at shared previous information content as a function of time lag (information flow) (Paluš et al., 2001; Vastano and Harry, 1988).

Our study addresses the question of delayed mutual information estimated from a large multivariate biological data set based on data used in (Kondoh et al., 1995) and (Newland and Kondoh, 1997). Knowing the time-delay and information flow strength between two signals will inform understanding of the neural network function underlying limb motor control in locusts. These insights and methodological developments are part of our wider interest in neuromuscular (dys)function and bioinspired sensing and control. The key challenge is how to combine the recordings made in different animals into one map of neuronal interconnections. In this experimental setting (as is also often the case in related work), it is not possible to record simultaneously from more than perhaps two neurones, due to the physical size of the preparation.

This investigation uses mechanical excitation by random Gaussian displacements of a joint movement sensor (the FeCO) to analysis of *possible* pathways leading to electrical signal collected at different points within the neural network, Fig. 1(C). In addition, a surrogate test procedure (Schreiber and Schmitz, 1996; Schreiber and Schmitz, 2000) was used to infer if any relationships were significantly above the noise level. The final result represents a functional connectivity map displayed using a graph tools to show the time differences in neurophysiological measurements along the processing chain, combining measurements from many different recordings.

2 THEORY

Consider $X = \{x_i\}$ a discrete random signal. The entropy H_X is defined by (Cover and Thomas, 2006) as $H_X = -\sum_{x \in \chi} p_X(x) \log_2 p_X(x)$ where χ represents the set of symbols used in this codification, $p_X(x)$ the probability density function (*pdf*) of event x, and H_X quantifies the mean number of bits (when using base two in log) that can optimally code random variables. Entropy is a measure of disorder or more precisely unpredictability. For example, systems with equiprobable states have maximum entropy, since there is no way to predict what will come next. A system that could have many states but is held in just one particular state has zero entropy. Most data collections in the real world lie somewhere between such extremes.

If $p_Y(.)$ is the *pdf* of variable Y, then $D_{\mathrm{KL}}[p_Y \| p_X] = \sum_i p_Y(i) \log_2 p_Y(i)/p_X(i)$ is the Kullback-Leibler divergence (Cover and Thomas, 2006) quantifying the difference between p_Y and p_X. It can be observed from the previous equations that if $p_Y = p_X$ then the $D_{\mathrm{KL}} = 0$. It should point out that $D_{\mathrm{KL}}[p_Y \| p_X] \neq D_{\mathrm{KL}}[p_X \| p_Y]$ and thus it is not symmetric.

The mutual information from two random variables X and Y, $I(X;Y)$, quantifies the average shared information or how the knowledge from one time series informs about another (Cover and Thomas, 2006). This equation has been derived in many references (Cover and Thomas, 2006; Shannon, 1948; Paluš and Vejmelka, 2007) $I(X;Y) = H(Y) - H(Y|X) = H(X) + H(Y) - H(X,Y)$ and expressed from probabilities is:

$$I(X;Y) = \sum_{x \in \chi} \sum_{y \in \phi} p_{XY}(x,y) \log_2 \frac{p_{XY}(x,y)}{p_X(x) p_Y(y)} \qquad (1)$$

where $p_{XY}(x,y)$ is the joint probabilities distribution regarding X and Y, $H(Y|X)$ is the conditional entropy of Y given X. Since $H(Y) \geq H(Y|X)$ then $0 \leq I(X,Y) < \infty$ (Dionisio et al., 2004), the equality is archived only when X and Y are independent. From Eq. 1 it can easily be seen that $I(X;Y) = D_{\mathrm{KL}}[p(x,y) \| p(x)p(y)]$ is the "distance" from $p_{XY}(x,y)$ to $p_X(x)p_Y(y)$, i.e. the assumption that X and Y are independent.

The conditional entropy (Paluš and Vejmelka, 2007), $H(Y|X)$, quantifies the remaining uncertainty (entropy) of a random variable Y given another random variable, X, and it is evaluated as:

$$H(Y|X) = \sum_{x \in \chi} \sum_{y \in \phi} p_{XY}(x,y) \log_2 p_{Y|X}(y|x). \qquad (2)$$

The conditional mutual information $I(Y;X|Z)$ characterizes the dependence between X and Y without the possible influence of another variable Z (Cover and Thomas, 2006; Paluš and Vejmelka, 2007). This measure assesses the interaction $X \rightarrow Y$

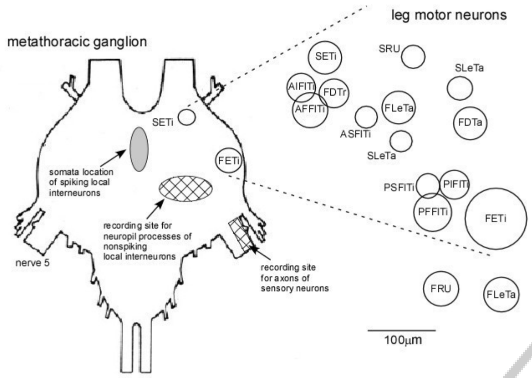


Figure 1: Diagram of the recording locations in the metathoracic ganglion of the locust. The spiking local interneurons were recorded from their somata on the ventral midline of the metathoracic ganglion, whereas nonspiking local interneurones were recorded in their neuropil processes withing the area indicated by cross-hatching. Sensory neurones were recorded in their axons in the anterior half of nerve 5, while identified motor neurons were recorded from their somata, the locations of which are shown.

Table 1: Description of main neurones described in Fig. 1, and used in signal acquisition.

Movement about knee:	
ASFlTi	*Anterior Slow Flexor tibia motor neurone*
AFFlTi	*Anterior Fast Flexor tibia motor neurone*
AIFlTi	*Anterior Intermediate Flexor tibia motor neurone*
PSFlTi	*Posterior Slow Flexor tibia motor neurone*
PFFlTi	*Posterior Fast Flexor tibia motor neurone*
PIFlTi	*Posterior Intermediate Flexor tibia motor neurone*
SETi	*Slow Extensor Tibia motor neurone*
FETi	*Fast Extensor Tibia motor neurone*
Movement about ankle:	
SleTa	*Slow Levator Tarsus*
FleTa	*Fast Levator Tarsus*
SDTa	*Slow Depressor Tarsus*
FDTa	*Fast Depressor Tarsus*
Movement of claw:	
SRU	*Slow Retractor unguis motor neurone*
FRU	*Fast Retractor unguis motor neurone*
Movement about shoulder:	
FLeTr	*Fast Levator Trochanter motor neurone*
FDTr	*Fast Depressor Trochanter motor neurone*

that is not only due to the parent random variable Z, i.e. $Z \to X$ and $Z \to Y$ (Pearl, 2009).

Like mutual information, conditional mutual information can be expressed as a Kullback-Leibler divergence $I(X;Y|Z) = D_{\mathrm{KL}}[p(x,y,z)\|p(x|z)p(y|z)p(z)]$ or as an expected value of simpler Kullback-Leibler divergences: $I(X;Y|Z) = \sum_{z\in Z} p(Z = z)D_{\mathrm{KL}}[p(x,y|z)\|p(x|z)p(y|z)]$.

(Nichols, 2006; Alonso et al., 2007) and others have examined the structural dynamics of different systems (the first study was on interactions from muscle activity in pathological patient conditions and the second used simulated mechanical system) based on *mutual information* and *conditional mutual information*.

Time delayed mutual information quantifies the dependencies between dynamical variables by looking at shared information content as a function of time lags τ between X and Y. The delayed mutual information that is (Nichols, 2006)

$$I(X,Y_\tau) = \sum_{x\in\chi}\sum_{y\in\phi} p_{XY}(x_i,y_{i+\tau})\log_2 \frac{p_{XY}(x_i,y_{i+\tau})}{p_X(x_i)p_Y(y_{i+\tau})}. \quad (3)$$

If the information present in signal X at a discrete time i is also present in signal Y at discrete time $i+\tau_0$ there will be a peak in the curve $I(X,Y(\tau))$ at $\tau_0 > 0$ as the joint probability density increases. If the peak occurs at $\tau_0 < 0$, that implies that the information is being transported from Y to X (reverse order). At this point it is assumed that X and Y are stationary and the joint probabilities will depend only on the time lag τ (Nichols, 2006).

The evaluation of interaction between random variables X and Y has been presented in many articles (e.g. (Schreiber, 2000; Paluš et al., 2001; Paluš and Vejmelka, 2007; Paluš and Stefanovska, 2003)) and is expressed using conditional entropies $I(Y;X_\tau|X)$ (Nichols, 2006). Due to peculiarities of system topology, Fig 1 (B,C) the approach adopted to analyse this system is $I(Y;X_\tau|Z)$ where Z is the recorded mechanical driver signal and τ varies from $-T \to T$ to include analysis in both directions.

The data were also analysed to determine whether they expressed any significant underlying dynamics (Kugiumtzis, 2002). The validation procedure was based on null hypotheses statistical tests for the observed data (Urbach, 2000). To this end surrogate data analysis was used (Schreiber and Schmitz, 1996; Schreiber and Schmitz, 2000; Kugiumtzis, 2002). The basic idea from the surrogate data analysis was to compute the statistics of interest for the original data set and for each of the ensemble of surrogate data sets with equivalent amplitude distribution and power spectra but forming independent from X, Y and Z. If the computed statistics for the original data set are significantly different from the values obtained for the surrogate sets it is possible to infer that the output data are related by the input signal.

For univariate time series the most common method is the use of Fourier Transformation of the data, randomising the phase and inverting the transform. This removes any correlation between signals. The surrogate data will have the same power spectrum of the original and considering the *Wiener-Khintchin* *theorem* the same autocorrelation function. The literature presents many improvements on this algorithm (Venema et al., 2006) in particular with reference to amplitude distribution.

3 MATERIALS & METHODS

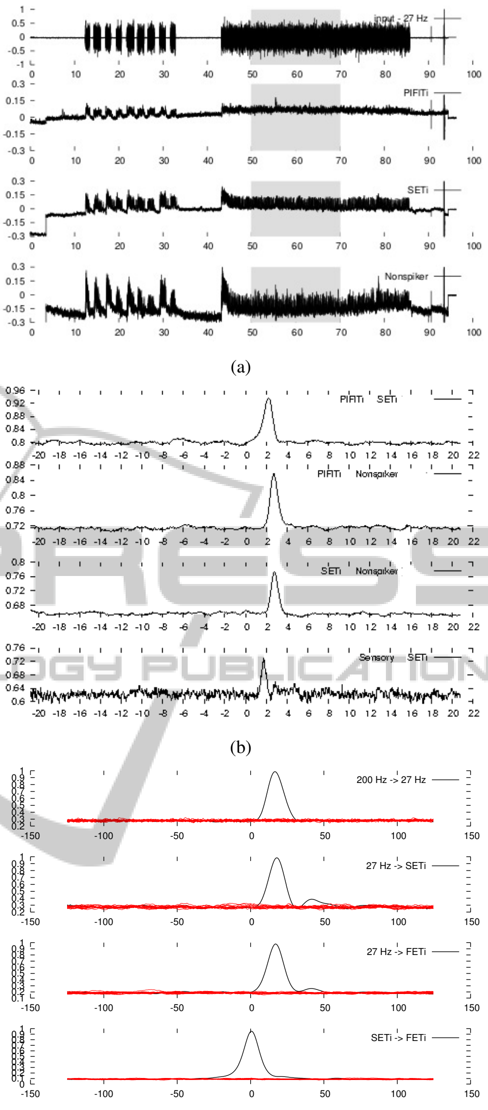
Adult male and female desert locusts, *Schistocerca gregaria* (Forskål) were used for all experiments. Locusts were mounted ventral-side-uppermost in modelling clay and the apodeme of the FeCO exposed by opening a small window of cuticle in the distal anterior femur (Kondoh et al., 1995), grasped between the tips of fine forceps attached to a vibrator and cut distal to the forceps. The metathoracic ganglion was exposed by making a small window in the ventral thorax and removing air sacs and connective tissue. Microelectrodes with DC resistances of 50 – 80 MΩ were driven through the sheath and into the neuropilar proceses of the spiking and nonspiking interneurons, Fig. 1.

The forceps holding the FeCO were moved with a Gaussian white noise (GWN) signal produced by filtering a pseudorandom binary sequence band-limited to 27 Hz with a fourth order Chebyshev low-pass filter. Stimulus and evoked responses of the interneurons were stored on magnetic tape using a PCM-DAT data recorder. Subsequently, all signals were sampled at a rate of 10 kHz offline to a PC for later analysis.

3.1 The Algorithms

The algorithms were developed in plain Python 2.67 running on a Linux (Ubuntu 10.10) i7 computer with 12 GB of RAM. During the execution process 2 computers were used with the same specification and communications base on SSH. The code used mainly the resources of parallel programming from the iphython (Pérez and Granger, 2007) environment. The main libraries used in this work were: numpy, scipy and matplotlib.

The data set consist of signals from 20 different nonspiking local interneurons, 35 spiking local interneurons, 20 sensory neurons and 34 identified motor neurons. All neuron pathways were stimulated for at least 40s. We chose to analyse approximately 25 percent of each dataset where signals were approximately stationary (grey area in Fig. 2(a). The main consequence of this long acquisition period is that each analysed signal (discounting the transients and zero input) has from 200.000 - 400.000 samples. For regular signal analysis it took over 20 min to analyses each file. Moreover, 35 repetitions of surrogate data were also performed. The full analysis of this data took approximately 35 days in a continuous parallel environment and at least one extra month was required to analyse these initial results.



(a)

(b)

(c)

Figure 2: (A) Simultaneous intracellular recordings from two motor neurons PIFlTi, SETI, and a nonspiker during stimulation applied to the FeCO. The grey areas represents the signal selection used in this analysis and the horizontal axis is time in seconds. (B) Delayed Conditional Mutual Information from combinations of signals shown in (A) and the horizontal axis is delay between signals in milliseconds. (C) This plot shows the delayed conditional mutual information (line associate with the peak) between signal indicated at the legend and delayed conditional mutual information using surrogate date with 35 repetitions (baseline). The vertical axis, left, has a normalized values and each mark correspond to a step of 0.1.

The estimation of probability density used a histogram approach, while for joint probability distributions bidimensional histograms were used. In both cases the number of bins was fixed at 128. The delayed mutual information and conditional mutual information were implemented as a function of a *lag*. Each lag was executed in a different core of the computers.

4 RESULTS

For evaluation of the algorithms we used simulated signals (with a linear and non-linear system with Gaussian random input signals) and real experimental signals. In many signal records there were both 200 Hz and 27 Hz data. The time delays from 200 Hz → 27 Hz, Fig.2(c) first plot, agreed with time-delay specifications of the low-pass filter used and when reversing input and output, 27 Hz → 200 Hz, the correct negative lag were obtained.

Simultaneous recordings from interneurons and motor neurons showed that they received either excitatory or inhibitory inputs during stimulation applied to the FeCO, Fig.2(a). This conclusion is based on extensive previous work (Kondoh et al., 1995; Newland and Kondoh, 1997; Vidal-Gadea et al., 2010) and parallel work not further reported here.

We evaluated the time delay from recording sites, 1, considering the peaks of delayed mutual information and delayed conditional mutual information. Different combinations of these sites were evaluated and distinct peaks with relatively short delays were clearly apparent (all graphics in Fig.2(b)). In Fig.2(b) (top to down, three first graphics) the analyses was performed with delayed mutual information and last plot from delayed conditional mutual information where the conditional was 27 Hz signal. Using this approach we analysed the delayed (conditional) mutual information from responses of sensory neurons, spiking and nonspiking local interneurons and motor neurons resulting from stimulation of the FeCO.

The results of our analysis are summarised in Fig.3 in which the presumed interconnections based on delayed (conditional) mutual information are shown. The numbers on the arrows give the mean time-delay (ms).

Some of recorded signal were collected at the same place in neuronal ganglia from different animals. In this case, data were average and in few cases outliers were removed from mean evaluation. In one case (Nonspiker1 and Nonspiker2 in Fig.3) there were enough data to cluster into two different sets, with different mean delay value and the graph was rerouted to accommodate this split state. Also, in part of the data there were signals with two peaks with similar amplitude time delay mutual information that were statistically significant. In these cases the peaks were considered as representing different pathways.

The results reveal a number of important points. First, that neurons sharing similar functions and that are closely located in the network give similar time-delays. For example, all identified flexor motor neurons recorded from anterior and posterior groups, that generate flexion movements of the tibia, have only short delays of only a few milliseconds relative to each other. Similarly, the two extensor motor neurons (the slow, SETi, and fast, FETi) that produce extension movements of the tibia share information with similar short delays.

Secondly, nonspiking interneurons can be partitioned into two distinct groups (marked as nonspiker 1 and 2) with short and long time delays with respect to the stimulus input, reflecting their potential roles in the neural pathways controlling limb movements. Third, while the dataset on which this analysis was based was very large, it should be considered as a small sample probing network characteristics. It is impossible to record from all combinations of neurons and so many potential interconnections are missing or have few repetitions. Additional recordings are clearly needed for a more complete analysis of the network.

Clearly it would be desirable to confirm the analysis with detailed anatomical studies of the neuronal connections of the actual cells from which the data was collected. However, this would be challenging and was not carried out in this data set. In addition, the connections with longer time-lags are unlikely to be mono-synaptic, and such connectivities would be difficult to disentangle from anatomical studies. Thus while agreement between anatomy and the current study would provide supportive evidence for the approach taken, disagreement would not necessarily imply that the proposed signal processing method failed. It is a strength of the current method that connections are identified based on information transmission, rather than direct neuronal connections.

It should also be pointed out that the current method based on the simultaneous recordings from only one or two neurons cannot clearly indicate if connections are direct or indirect.

5 CONCLUSIONS

Previous work (Kondoh et al., 1995; Newland and Kondoh, 1997) has analysed the anatomical connections between neurones, but such methods are not able

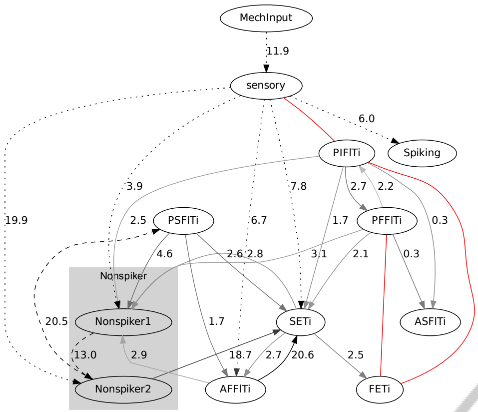


Figure 3: Graph showing the presumed interconnections based on delayed conditional mutual information analyses with edge labels showing the mean time delays through nodes in ms. The red edge labels indicate presumed connections with incomplete data. Solid lines represent pathways that were evaluated directly from each dataset. Dotted lines were inferred under the conditions that FeCO movement activates sensory neurons whose time delays were not included in the analyses. Dashed lines represent the partitioning of nonspiking interneurons into two nodes.

to identify the activation of these connections during the GWN stimulation used in the current study and related work. The functional connections identified in the current study broadly match those known from the anatomical studies.

In previous work on this data we have used linear and non-linear system identification approaches to study connectivity. However, this form of analysis is limited by the class of models chosen (Volterra-Wiener using polynomial non-linearities) whereas the current information theoretic approach does not impose such a constraints. Mutual information is thus a better suited tool for mapping the connectivity in the network. However, mutual information only shows strength of connections (this will be considered in further studies) and delays (considered here), but not detailed input-output relationships.

The analysis of this data was realized using a computer with multiple cores and with no downsampling of the data. The approach was computationally intensive and without a multiple core computer and a high performance computational environment could not be complete within a reasonable time. A key feature of our analysis is that it can be used to understand the interconnections between neurons in neural networks composed of both spiking (digital action potentials) and nonspiking (analogue synaptic) signals.

We found that neurons that share similar functions, for example flexor or extensor motor neurons that drive muscle activity (Newland and Kondoh, 1997) share similar time delays with respect each group indicating their combined activity in controlling movements. Knowledge such as this can help further understand the structure of neural pathways within local circuits and can help inform further neurophysiological analysis

(Burrows, 1996) suggested that the interactions between nonspiking interneurons could lead to them acting in many different ways to process the signals from the FeCO. We found that a subset (4 and 6 measurements of 14) of a population of nonspiking local interneurons showed two distinct delayed mutual information time delays. Also, the last 4 measures from nonspinking had 2 peaks with similar delays from 2 sets described before. This revealed itself in distinct peaks in their responses indicating the presence of two main pathways to the same neurone and points to differences in the function of the two types of interneuron in local networks, a feature not documented from previous neurophysiological analyses.

The next steps in our study will be to include more experimental samples in data analysis. The data analysis will also include an analysis of transfer entropy and a Bayesian model to group partial graph information.

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