Evidence for Linearity in Control of Nictitating Membrane Responses by Retractor Bulbi Motor Units

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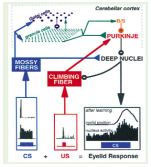
1 Introduction

How does the cerebellum produce precisely timed conditioned responses in eyeblink conditioning?



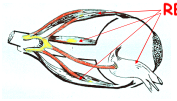
View #1

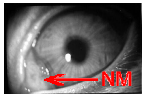
Many models assume that the position of the external eyelid or nictitating membrane is a simple linear reflection of activity in the deep cerebellar nuclei (e.g. Medina and Mauk [1]).

View #2

"it is somewhat unlikely that the actual discharge rate of interpositus neurons could be correlated with the profiles of CRs determined from the nictitating membrane displacement, as this is a passive, highly damped movement" Delgado-García and Gruart [2], p.375

2 The Nictitating Membrane Response

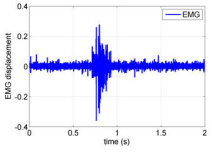




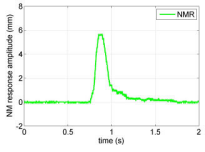
The four slips of the retractor bulbi (RB) muscle contract to pull the globe back into the orbit.

The retracting globe pushes against Harder's gland, which slides to move the nictitating membrane (NM) across the globe.

A typical EMG recording of muscle activity from an inserted electrode is:



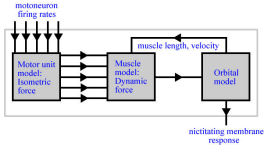
A typical NM response is:

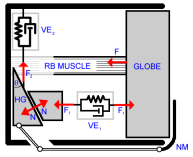


3 A Detailed Biophysical Model

Bartha and Thompson [3] have constructed a detailed model of the NM response to a motoneuron spike train.

Their model calculates the RB muscle force from the motoneuron signal. This force is used as input to a model of orbital mechanics.





As the RB muscle contracts it pulls the globe back in the orbit.

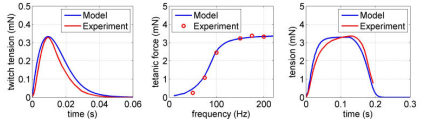
The retracting globe compresses Harder's gland via visco-elastic tissue (VE_1).

This gland then slides laterally against the resistance of visco-elastic tissue (VE_2).

As it slides it pushes the NM in front of the globe.

4 Model Details

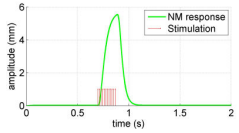
(1) The model reproduces Lennerstrand's measurements [4] of the isometric twitch and tetanic force for a retractor bulbi motor unit.



Note: It is clear that there is a significant non-linearity in the simulated tetanic-force response to motoneuron frequency. This non-linearity arises from the activation equations for muscle function.

(2) The model also gives a plausible profile for the nictitating membrane response to a realistic motoneuron stimulus.

(The figure shows the response to a 200 ms burst at 75 Hz.)

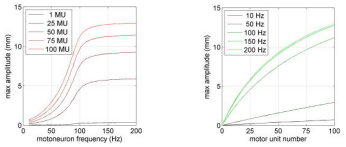


5 Response to Basic Control Strategies

An important feature of Bartha and Thompson's model is that individual motor units are explicitly represented. Hence recruitment strategies can be investigated as well as frequency modulation . The two basic control strategies are:

1) Frequency modulation: all motor units (MUs) fire together, frequency of firing is varied.

2) Recruitment: frequency is kept constant, the number of MUs varies.



For both basic control strategies, maximum NMR amplitude varies non-linearly with input signal

Note: The non-linear response to frequency results from the dynamics of muscle function (Panel 4). The non-linear response to recruitment arises from the variation in muscle tension with muscle length.

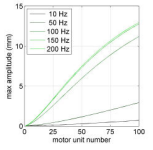
6 Strategies for a Linear Response

The above model can behave more linearly if suitably constrained. Two linearising control strategies are:

1) Varying the motor unit strength so stronger units are recruited later.

The figure shows the maximum NMR amplitude when the n^{th} motor unit strength is proportional to $\sqrt{n}$.

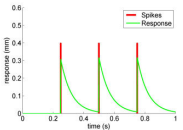
2) Appropriately modulating the motoneuron frequency as new motor units are recruited. (Figure not shown but similar to one on right.)



A linear model is characterised by its (impulse) response to a single spike input because any output is a linear sum of such responses.

System identification methods showed that the impulse response under both linearising strategies is well approximated by an instantaneous NM displacement that decays exponentially.

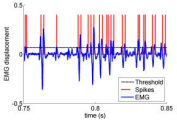
(first order filter with one pole and no zeros.)



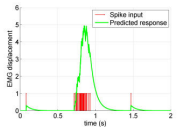
7 Testing Linearity of EMG-NMR Data

EMGs were recorded from 5 subjects with multi-unit electrodes inserted in the retractor bulbi muscle during classical conditioning of the NMR to a tone CS using methods described previously [5].

'Spikes', corresponding to action potentials, were extracted from EMG records by locating above-threshold local maxima.



The best-fit first-order filter (panel 6) for predicting NMR responses from EMG records was found by conventional system identification methods.



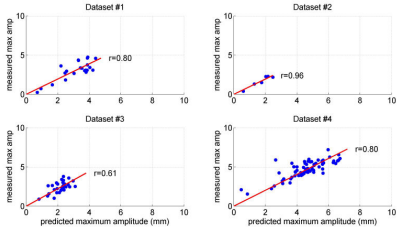
The predicted and measured NMRs could then be compared to test for linearity.

8 Result: EMG-NMR Data is Linear

Multi-unit data were provided by 4/5 animals.

One measure of similarity between predicted and measured NMRs is the maximum response amplitudes. In the figure below, the predicted amplitudes are plotted against the measured amplitudes (best fit lines in red).

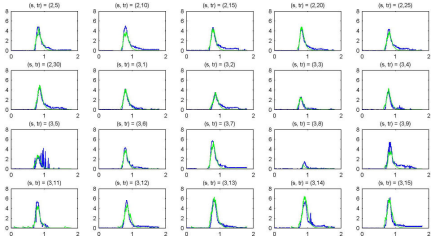
The good agreement between prediction and measurement suggests that over the range studied motoneuron input is linearly related to NMR output.



9 Individual Trials are Well-Fitted

The accuracy of the above linear model can also be seen in the predictions over individual trials.

In the figure below the NMR data is shown in blue and the predicted response in green. Trials are from data set #4.

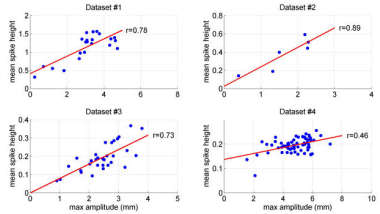


10 Between-Trial Recruitment

Both linearising strategies described in slide 6 require recruitment of motor units.

In three of the four data sets the mean height of the tallest (top 10%) spikes increases with NMR amplitude.

This is consistent with recruitment of new motor units, some of which are closer to the electrode, giving larger spike heights.

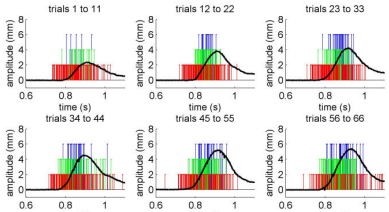


In dataset #4 which does not show this effect it appeared that only a small number of units were being recorded.

11 Within-Trial Recruitment

Cluster analysis of spikes from data set #4 allowed identification of three distinct spike shapes, possibly corresponding to distinct motor units.

Occurrences of the three spike types (red, green, blue) are marked on the figure. The red motor unit consistently fires first, then the green unit, and finally the blue unit as the amplitude rises to its maximum.



12 Conclusions and References

- **A detailed biophysical model of the NMR gives nonlinear responses to simulated motoneuron input for either frequency modulation or simple recruitment, consistent with view #2 (panel 1).**
- **However, the model responses can be linearised by appropriate recruitment strategies.**
- **Data from EMG recordings during classical conditioning of the NMR indicates both that the system is approximately linear, and that motor units in the retractor bulbi muscle are recruited.**
- **These data are consistent with view #1, provided the relation between the firing of deep cerebellar nucleus neurons and motoneurons is linear.**
- **How linearising recruitment strategies are implemented is unknown.**

References

1 Medina, J.F. and Mauk, M.D. (2000) Nature Neuroscience, 3, 1205-1211

2 Delgado-García J.M. and Gruart, A. (2005) Brain Research Reviews, 49, 367-376.

3 Bartha, G. and Thompson, R. (1992) Biological Cybernetics, 68, 135-143, 145-154.

4 Lennerstrand, G. (1974) Journal of Physiology, 236, 43-55.

5 Attwell, P.J.E., Rahman, S. and Yeo, C.H. (2001) Journal of Neuroscience, 21, 5715-5722.