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## Feedback Modulation: A Window into Cortical Function

A recent study demonstrates involvement of primary motor cortex in task-dependent modulation of rapid feedback responses; cortical neurons resolve locally ambiguous sensory information, producing sophisticated responses to disturbances.

David W. Franklin  
and Daniel M. Wolpert

An emerging theory in sensorimotor neuroscience, termed optimal feedback control, postulates that complex actions result from the intelligent modulation of sensory feedback gains [1–3]. That is, skilful movements are formulated by the sensorimotor control system by specifying time-varying feedback gains on states of the body (for example, the limb position and velocity). The ensuing movement arises from the interaction of these feedback gains with the mechanics of the musculoskeletal system, neural noise and disturbances from the environment.

Optimal feedback control has been supported by several studies showing that feedback responses are clearly modulated throughout movement [4] and depend on the task being performed [5–7]. In addition, perturbations invoke involuntary feedback responses — the long latency stretch reflex — that approximate, in direction and magnitude, the later

task-dependent voluntary responses [8]. This provides further support for optimal feedback control and suggests that the control system sets a unified set of gains that act both on the involuntary and voluntary systems, suggesting the same neural circuitry may underlie both forms of control and blurring the distinction between them [3].

The long-latency feedback response is known to involve cortical pathways [9,10]. Moreover, recent transcranial magnetic stimulation (TMS) studies have shown that stimulation of primary motor cortex can change the task-dependent modulation of the long-latency feedback response [11,12]. As primary motor cortex is also implicated in voluntary control [13,14], this is a prime candidate for the integrated control of both voluntary and feedback control.

A recent paper [15] reports evidence that primary motor cortex neurons actively function in the task-dependent modulation of feedback pathways. Specifically, this new work shows that primary motor cortex neurons resolve ambiguous local motion at the joints in

order to produce intelligent and sophisticated compensation to disturbances. The study uses a combination of neural recordings from primates and TMS studies in man to support this finding.

Pruszynski *et al.* [15] used a robotic interface to apply perturbations to the arm consisting of different combinations of elbow and shoulder joint torques. This requires each joint to compensate for the torque it experiences. The design of the study exploited a fundamental biomechanical property of a multi-joint limb: that is, many different combinations of externally applied joint torques can give rise to identical local motion at a single joint. Therefore, it is not possible to disambiguate the appropriate response at the shoulder joint based only on shoulder motion information (or only on elbow motion information). In other words, shoulder motion alone provides highly ambiguous information as to applied shoulder torques, which can only be disambiguated by also considering elbow motion. Therefore, to compensate for the perturbation, feedback responses need to take into account information about motion at both the shoulder and elbow joints [16]. The research specifically investigated neurons that demonstrate primarily shoulder tuning in feedforward (voluntary) control tasks, in other words have neural tuning indistinguishable from single joint shoulder muscles.

These neurons, therefore, have to resolve locally ambiguous sensory information [17].

Pruszynski *et al.* [15] noted that applying a flexion torque at only the elbow joint creates an extension motion of the shoulder (Figure 1A) even though no torque is applied at the shoulder. Therefore, they examined two different sets of joint torques, one with a flexion torque at both the shoulder and elbow joints (Figure 1B) and one with extension torques at both joints (Figure 1C). Critically the shoulder torque size was chosen so that the interaction effects of the elbow torque on the shoulder cancelled out the shoulder motion in both situations. Nevertheless, to compensate for these different perturbations requires the participants to generate torques at the shoulder in different directions (extension in Figure 1B and flexion in Figure 1C) despite the fact that the shoulder joint does not move.

Importantly, the neurons exhibited a tuned response — starting 50 ms after perturbation onset — that responded to the underlying torque perturbations rather than the local joint motion (Figure 1D). This demonstrates that the primary motor cortex neurons receive information from various sensory inputs, allowing it to resolve the locally ambiguous information and produce the optimal response to the imposed disturbances. Interestingly, the initial responses of the neurons to the perturbations (20 ms following perturbation onset) did not reflect local information about either the joint motion or torque, but instead a general non-specific excitatory reaction to the disturbance. This general increase in descending drive may act to reinforce any spinal response or increase co-contraction maintaining stability [18].

While the primate experiments demonstrated that the cortical neurons resolve the ambiguous sensory information and produce a response — mirrored in the muscles — one cannot from this data imply causality. To address this issue, TMS was applied over the primary motor cortex in human subjects to excite the local cortical circuitry and examine whether primary motor cortex directly influences this integrated response to locally ambiguous sensory information. Single-pulse TMS excites cortical circuitry, causing a supralinear response when

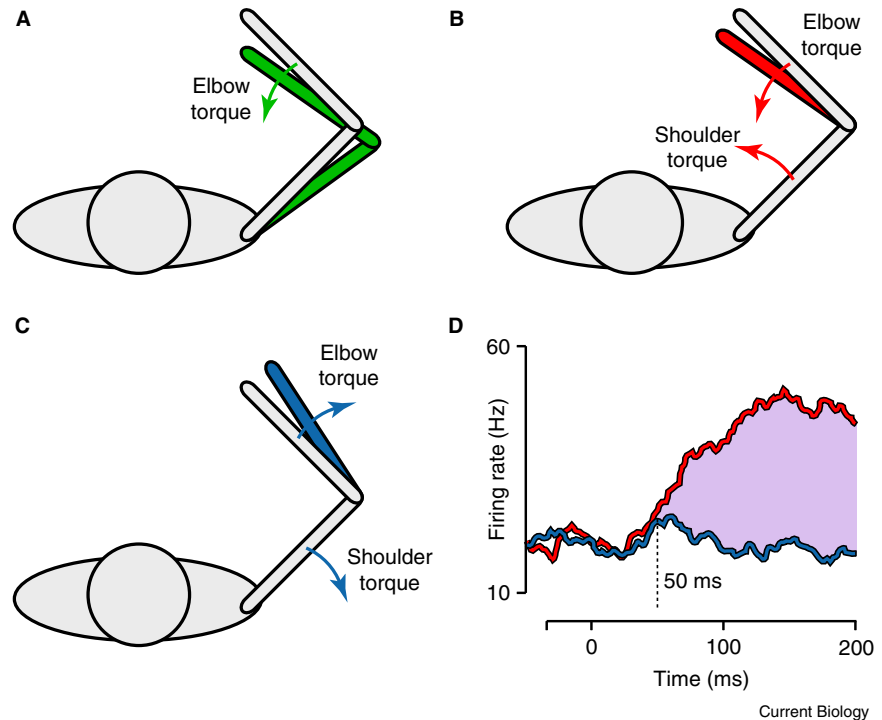


Figure 1. Biomechanical properties of the multi-joint limb are exploited to demonstrate the involvement of primary motor cortex in task-dependent modulation of rapid feedback responses.

(A) A flexor torque (green arrow) applied only at the elbow produces movement at both the elbow (flexion) and the shoulder (extension) due to the reaction forces. Arrows represent joint torques applied by the robotic interface. (B) By also applying a flexor torque at the shoulder to counteract the shoulder motion (red arrow), the shoulder joint is stationary and motion is only produced at the elbow (flexion). However, counteracting this disturbance requires both elbow and shoulder joint torques. If subjects only generated an elbow extension torque, then motion of the shoulder would be produced due to the underlying shoulder torque. (C) Extension torques applied at the elbow and shoulder joint (blue arrows) can result in pure elbow extension. (D) The population responses in shoulder-tuned primary motor cortex neurons to the disturbances in (B) (red trace) and (C) (blue trace). At a delay of only 50 ms from the perturbation onset, the shoulder neurons exhibit tuned responses to the underlying joint torques (purple region) despite no motion of the shoulder. (Adapted from [15]).

synchronized with the long latency stretch response, but only a linear response when synchronized with the short latency reflex that involves spinal circuitry [19]. Pruszynski *et al.* [15] combined this technique with the locally ambiguous perturbations. They found supralinear responses in the shoulder muscle activity only when the TMS was applied so as to interact with the long latency feedback responses. This demonstrates that the cortical circuitry not only disambiguates the local sensory information, but is causally involved in producing this sophisticated feedback response to the perturbations.

This work supports the idea that primary motor cortex is involved in fast feedback responses as well as feedforward control. Importantly, because the neurons were selected

based on their involvement in feedforward control, and were then found to demonstrate task-dependent tuning at feedback latencies, this work provides evidence that the same neural circuitry is involved in both feedback and feedforward control. This highlights the critical importance of studying feedback modulation in sensorimotor control. Such responses can be used to elucidate the neural structures responsible for motor control without the additional complexity of conscious interaction. While this work implicates primary motor cortex in this process, it is still unknown whether this sensory information used to resolve this ambiguity is from local pathways within the motor cortex, or from other structures such as the cerebellum or somatosensory areas.

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# Plant Cytokinesis: Circles within Circles

The current model of the plant cytokinetic apparatus, describing it as being composed of treadmill microtubules, is challenged by a new study showing that these microtubules display dynamic instability.

Clive Lloyd

How does the plant cell's cytokinetic apparatus, composed of highly dynamic microtubules, maintain its bilateral symmetry as it keeps expanding outwards? Early on, just after nuclear division, the young phragmoplast — the structure that lays the new dividing wall between sister nuclei — is indistinguishable from the remnant of the mitotic spindle. Whereas the animal cell's plasma membrane constricts inwards to the spindle midzone, pinching the cell in two, the plant cell divides by directing Golgi vesicle transport along microtubules to the midline where the vesicles fuse to form a cross-wall. This membrane barrier starts a point in the centre of the separated nuclei, and grows outwards, expanding the phragmoplast until it joins the rigid mother wall. Previously, it was thought that the bilateral symmetry of the phragmoplast was maintained during its long centrifugal journey by microtubule treadmill, with two sets

of interdigitating plus-ends constantly growing towards each other (and perhaps sliding apart to prevent too much overlap) while the minus-ends of the microtubules depolymerised. Now, in this issue of *Current Biology*, Smertenko *et al.* [1] account for discrepancies that have arisen over the last twenty years by showing that the dynamicity of the phragmoplast is based instead on the dynamic instability of microtubules.

Early studies, in which addition of exogenous tubulin under non-physiological conditions formed hooks whose direction of curvature revealed the otherwise cryptic polarity of the microtubule, established that the phragmoplast is a mirror image: two opposed circular palisades of microtubules meeting at their plus-ends [2]. At that time, there was little reason to suspect that this cytokinetic apparatus is highly dynamic, for even the expansion of the double ring could be explained by its passive displacement by the wall that grows in the hollow centre.

One of the first clues of dynamicity came in 1991 when Asada *et al.* [3] extracted dividing plant cells with glycerine and added fluorescent tubulin to them. The tubulin was incorporated at the plus-ends of the two interlocking circlets of microtubules to form a single fluorescent line where the opposing plus-ends met in the midline. Unlabelled tubulin was then added to chase out the fluorescent protein, and this caused the single fluorescent line to split in two. The explanation for this result was that the unlabelled tubulin entered the microtubule lattice at the overlapping plus-ends, and treadmill of tubulin subunits displaced the fluorescent segments towards the minus-ends. However, several studies (e.g. [4]) have shown that plus-ends labelled with the fluorescent plus-end binding marker EB1 can be seen growing towards, and not just at, the midline. This observation suggests that microtubule growth is not restricted to a narrow zone at the midline and even hints at the possibility that new microtubules may arise throughout the body of the structure.

To examine this further, Smertenko *et al.* [1] took dividing tobacco BY-2 cells expressing fluorescent tubulin and then photobleached rectangle-shaped areas of the phragmoplast. If tubulin subunits