

Computational Mechanisms of Sensorimotor Control

David W. Franklin^{1,*} and Daniel M. Wolpert¹

¹Computational and Biological Learning Laboratory, Department of Engineering, University of Cambridge, Cambridge CB2 1PZ, UK

*Correspondence: dwf25@cam.ac.uk

DOI 10.1016/j.neuron.2011.10.006

In order to generate skilled and efficient actions, the motor system must find solutions to several problems inherent in sensorimotor control, including nonlinearity, nonstationarity, delays, redundancy, uncertainty, and noise. We review these problems and five computational mechanisms that the brain may use to limit their deleterious effects: optimal feedback control, impedance control, predictive control, Bayesian decision theory, and sensorimotor learning. Together, these computational mechanisms allow skilled and fluent sensorimotor behavior.

Introduction

The sensorimotor control system has exceptional abilities to perform skillful action. For example as an opposing ice hockey player skates in on the net and shoots, within a split second the goalie reaches out, catches the puck, and prevents the goal. However, there are several issues that make this a difficult computational problem for the brain to solve. The first is uncertainty: although the goalie sees the puck coming toward the goal, he cannot be certain when and where the player will aim or where the puck will actually go. Second, once the goalie estimates the puck's likely trajectory, he must determine which of the over 200 joints and 600 muscles he will use in order to move his body or stick to block the puck—this is the problem of redundancy. Third, both his sensory feedback, such as the puck's visual location, and his motor outputs are corrupted by noise. This noise in combination with the variable environment, such as the unevenness of the ice surface, leads to variability in both perception and action. Fourth, both the sensory feedback processing and motor outputs are subject to delays, with visual perception of the puck location, for example, already around 100 ms out of date. The fifth issue is nonstationarity—the system's physical properties do not remain constant. Throughout a game the goalie must correct for weaker muscles as he fatigues, and changes in the ice surface. Finally, the entire neuromuscular system is nonlinear: for example the output of the muscle (force) is dependent on the descending activation command in a complexly nonlinear manner based on the muscle state. We will discuss each of these issues and then describe five computational mechanisms that the sensorimotor control system uses to solve the complex problem of motor control, which it does with so much skill. Our primary focus will be at the computational and behavioral level because, at present, rather little is known about how these computations are implemented. Our hope is that the neurophysiological community will see ways in which different neural areas and circuits might be mapped onto these computations.

Redundancy

The human motor system has a very large number of degrees of freedom with around 600 muscles controlling over 200 joints. These physical properties make the motor system redundant because there are multiple, often an infinite number of, ways that the same task could be achieved leading to an abundance

of possible solutions. For example when reaching from one point in space to another, there are an infinite number of paths that can reach the target and a variety of hand speeds along each possible path. Moreover, there are an infinite number of joint angle trajectories that can generate the specified hand path and speed. Because most joints are controlled by multiple muscles, the same joint motion can be achieved both by different combinations of muscles and with different levels of cocontraction or stiffness. Despite the apparent abundance of solutions, humans and other animals are highly stereotyped in the type of movements they choose to make. A major focus in sensorimotor control has been to understand why and how one particular solution is selected from the infinite possibilities and how movement is coordinated to achieve task goals.

Noise

Our nervous system is contaminated with noise, limiting both our ability to perceive accurately and act precisely (Faisal et al., 2008). Noise is present at all stages of sensorimotor control, from sensory processing, through planning, to the outputs of the motor system. Sensory noise contributes to variability in estimating both internal states of the body (e.g., position of our hand in space) and external states of the world (the location of a cup on a table). Noise also contaminates the planning process leading to variability in movement endpoints (Gordon et al., 1994; Vindras and Viviani, 1998) and is reflected in neuronal variability of cortical neurons that can predict future kinematic variability in reaching (Churchland et al., 2006). In addition, variability in action can arise through noise in motor commands (van Beers et al., 2004). Importantly, the noise in motor commands tends to increase with the level of the motor command (Jones et al., 2002; Slifkin and Newell, 1999), termed signal-dependent noise. There is evidence that the major reason for the signal-dependent nature of this variability may come from the size principle of motor unit requirement (Jones et al., 2002).

Delays

Delays are present in all stages of sensorimotor system, from the delay in receiving afferent sensory information, to the delay in our muscles responding to efferent motor commands. Feedback of sensory information (that we take to include information about the state of the world and consequences of our own actions) is subject to delays arising from receptor dynamics as well as conduction delays along nerve fibers and synaptic relays. These

delays are on the order of 100 ms but depend on the particular sensory modality (e.g., longer for vision than proprioception) and complexity of processing (e.g., longer for face recognition than motion perception). Therefore, we effectively live in the past, with the control systems only having access to out-of-date information about the world and our own bodies, and with the delays varying across different sources of information. In addition there are delays on the efferent control signals, both in terms of neural conduction delays and the low-pass properties of muscle. Although the fastest conduction delays, such as the monosynaptic stretch reflex pathway, are on the order of 10–40 ms, depending on the length and type of nerve fiber, this delay increases by 20–30 ms for the cortical component of the long-latency stretch reflex response (Matthews, 1991). Moreover, the rise in the force generation within a muscle (termed the electromechanical delay) can take another 25 ms (Ito et al., 2004). This means that a descending command from the motor cortex takes around 40 ms to produce force in the muscle because the conduction delay from the motor cortex to the arm muscles is around 16 ms (Merton and Morton, 1980). Other modalities can take even longer, with the delay in involuntary motor responses due to visual stimuli of around 110–150 ms (Day and Lyon, 2000; Franklin and Wolpert, 2008; Saijo et al., 2005). Even the vestibulo-ocular reflex, one of the fastest involuntary responses due to the short connections, takes 10 ms from stimulus onset (Aw et al., 2006). At one extreme, such as a saccadic eye movement, the movement duration is shorter than the sensory delay, meaning that feedback cannot be used to guide the movement because the sensory information regarding the movement itself arrives after the completion of the movement. For slower movements, delays make control difficult because information can be out of date, and it is possible for the system to correct for errors that no longer exist, leading to potential instability.

Uncertainty

Uncertainty reflects incomplete knowledge either with regard to the state of the world or of the task or rewards we might receive. Although uncertainty about the present state can arise from both noise and delays, there are many other sources of uncertainty; for example, it can arise from the limitations in receptor density and the representation of an analog world with the digital neural code. Uncertainty can also arise from the inherent ambiguity in sensory processing, such as ambiguity that arises when the three-dimensional world is projected onto the two-dimensional retina (Yuille and Kersten, 2006). Other components of uncertainty arise from the inherent ambiguity of the world. When we first see or even handle a new object, we may be unsure of its properties such as its dynamics. Similarly, when we first experience a novel environment, such as forces applied to the arm during a reaching movement (Shadmehr and Mussa-Ivaldi, 1994), we only receive partial information about the environmental properties even if we had perfect sensory information. Other situations, such as those that are unstable (Burdet et al., 2001) or unpredictable (Scheidt et al., 2001; Takahashi et al., 2001), add to uncertainty about the environment. Moreover, in the real world outside the laboratory, we can be uncertain what our tasks are and which actions or tasks might lead to reward rather than punishment. Such uncertainty makes the control problem more difficult.

Nonstationarity

The motor system is also nonstationary, in that its properties can change on multiple timescales. Throughout growth and development, the properties of our motor system change dramatically as our limbs lengthen and change in weight. Similarly, our muscles become stronger, so that similar activation patterns give rise to larger forces. Nerve conduction delays initially decrease in the first 2 years after birth but then increase in proportion to the lengthening of the limbs (Eyre et al., 1991). As we age, other changes occur with delays becoming larger (Dorfman and Bosley, 1979) and muscle strength decreasing (Lindle et al., 1997) due to the decrease in cross-sectional area (Jubrias et al., 1997) and changes in muscle fiber properties (Brooks and Faulkner, 1994). Moreover, sensory acuity also decreases with age, for example, visual acuity is reduced as we become older (Owsley et al., 1983), adding uncertainty to the visual feedback. On a shorter timescale the way our motor system responds to our motor commands can change as we interact with objects or as our muscles become fatigued. The ever-changing nature of the motor system places a premium on our ability to adapt control appropriately.

Nonlinearity

Control is further complicated by the highly nonlinear nature of our motor system. In linear systems, once the response to two different time series of motor command is known, it is straightforward to predict the response to both applied together as simply the sum of the responses. This makes control of linear systems relatively simple, because by knowing the response of the system to a simple input such as a pulse, one knows the response to any arbitrary input. For nonlinear systems this is no longer the case.

The descending motor command undergoes a highly nonlinear transformation as it is converted into endpoint force or movement. Although the output from the nervous system sets the activation level of the motor neuron pool, the number, strength, and temporal properties of the motor units that are activated exhibit nonlinearity. Although the measured activation level of muscle fibers exhibits a roughly linear relation with muscle force in an isometric situation, this simple relation disappears once the muscles and limbs move. The force of a muscle depends on activation level in a very nonlinear manner with respect to both the muscle velocity and muscle length and is further affected by tendon properties (for a review see Zajac, 1989). In addition, the moment arms of muscles can vary by a factor of three as the joint angles change during limb movements (Murray et al., 1995, 2000). Finally, the multijointed, multi-link structure of the skeleton, independent of the muscle, has nonlinear dynamics. Even the simplified two-link structure of the limbs during constrained reaching exhibits complex nonlinear dynamics (Hollerbach and Flash, 1982).

These nonlinearities within the motor system provide a major challenge for the sensorimotor control system, even if none of the other problems existed; however, the inclusion of these other problems makes the task even more challenging. Progress has been made into the computations that the sensorimotor system can perform to alleviate these problems. The remainder of the review will examine these computations and how they relate to the five problems of sensorimotor control we have highlighted.

Bayesian Decision Theory

Bayesian decision theory is a framework for understanding how the nervous system performs optimal estimation and control in an uncertain world. It is composed of two components, Bayesian statistics and decision theory. Bayesian statistics involves the use of probabilistic reasoning to make inferences based on uncertain data, both combining uncertain sensory estimates with prior beliefs and combining information from multiple sensory modalities together, in order to produce optimal estimates. We use the term Bayesian inference in this review to refer to probabilistic reasoning and not simply to the application of Bayes' rule (see below). Based on these inferences, decision theory is used to determine the optimal actions to take given task objectives.

Multisensory Integration

Different sensory modalities can often sample the same information about the state of our body (e.g., proprioceptive and visual location of the hand) or the state of the external world (e.g., auditory and visual location of a bird). When these different modalities are experimentally put in conflict, for example by mismatching the vision and sound of a person speaking, the percept corresponds to something intermediate between the percept of each modality alone (McGurk and MacDonald, 1976). Recent work has developed and tested the computational framework that underlies such multisensory integration. Even for normal sensory inputs, our sensory apparatus is variable and can have biases. Therefore, the estimates from different modalities are unlikely to be the same. Within the Bayesian framework, we can ask what is the most probable state of the world that gave rise to the multiple sensory inputs. Such a Bayesian model predicts that a scalar estimate from two different modalities, such as the visual and haptic width of a held object, should be weighted and averaged to produce an optimal estimate. Critically, the weighting of each modality should depend on its reliability (or the inverse of its variability due to noise), with the more reliable modality contributing more to the final estimate. Such a model of multisensory integration is supported by experimental studies of size estimation from visual and haptic cues (Ernst and Banks, 2002), location from visual and auditory cues (Körding et al., 2007b), and has been suggested to explain ventriloquism (Alais and Burr, 2004). Similar computations are used to estimate the state of our body; for example, when combining visual and proprioceptive information to estimate hand and joint location (Sober and Sabes, 2005; van Beers et al., 1996). In addition to integrating multiple modalities, a single modality can receive multiple cues about the same stimulus. Again, these different cues are combined optimally when estimating object size from visual texture and motion cues (Jacobs, 1999) and depth from texture and stereo cues (Knill and Saunders, 2003).

Bayesian Integration

Although multisensory integration combines information from two cues or modalities, there is another source of information available to refine estimates—the prior over possible states of the world. The prior reflects that not all states are a priori equally likely. For example, it may be that some configurations of the body are more common than others (Howard et al., 2009), and this prior distribution over configurations provides valuable information that could be used in conjunction with proprioceptive

input to determine the current configuration. Indeed, mathematically, the prior can be considered analogous to another sensory modality in that it provides information that is weighted with sensory inputs depending on how reliable the prior is relative to the sensory evidence. In general, Bayes' rule states that the probability of different states being correct (termed the posterior) is produced by combining the probability of receiving the sensory information if that state were true (termed the likelihood) with the prior probability of that state (for a review see Körding and Wolpert, 2006). The optimal estimate (or posterior), obtained by the combination of the sensory information and prior belief, always has lower uncertainty than the estimate based on the sensory information alone. This means that Bayesian estimation acts to reduce the uncertainty by combining sensory information with prior information.

Whether the sensorimotor system uses Bayesian learning, that is, whether it learns to represent the prior and likelihood and combine them in a Bayesian way, has been examined in a simple task (Körding and Wolpert, 2004). During reaching movements, a positional discrepancy was introduced between the subject's actual and visually displayed hand position. The size of the discrepancy was drawn on each trial from a Gaussian distribution, thereby experimentally imposing a prior distribution on the task. In addition, by varying the degree of visual blur, the reliability of the visual feedback was manipulated from trial to trial, thereby varying the likelihood. The subjects' task was to estimate on each trial the location of the cursor relative to their hand. The results showed that subjects did this in a Bayesian way, suggesting that they learned the prior distribution of the discrepancy, had an estimate of how reliable visual information was so as to estimate the likelihood, and combined these two sources of information in a Bayesian manner. Further evidence of Bayesian processing comes from work on force estimation (Körding et al., 2004) and interval timing (Jazayeri and Shadlen, 2010; Miyazaki et al., 2005). In fact Bayesian integration can also be used to understand previous studies; for example the finding that subjects tended to mistime the interception of a falling ball under altered gravity conditions was interpreted as evidence that the brain models Newton's laws (McIntyre et al., 2001). However, these results could arise from subjects optimally combining sensory information about the speed of the falling ball with prior information that gravity is constant on Earth. This would cause the subjects to continually miss the ball until they revised their prior estimate of the gravitational constant. Bayesian integration can also explain many visual illusions by making assumptions about the priors over visual objects (Kersten and Yuille, 2003) or direction of illumination (Adams et al., 2004). Similarly, biases in the perception of brightness (Adelson, 1993) can arise from priors over possible states of the world. Together, these studies show that Bayesian integration is used by the nervous system to resolve uncertainty in sensory information.

State Estimation

In the sections on multisensory integration and Bayesian integration, we have focused on the static situation of receiving two sources of information to inform us of the state (e.g., the width of an object). However, sensorimotor control acts in a dynamic and evolving environment. For example we need to maintain an estimate of the configuration of our body as we move so as

to generate appropriate motor commands. Errors in such an estimate can give rise to large movement errors (Vindras et al., 1998). Making estimates of time-varying states requires some extension to the computations described above as well as the need to consider the delays in sensory inputs.

Optimal state estimation in a time-varying system can be considered within the Bayesian framework. As before, the likelihood assesses the probability of receiving the particular sensory feedback given different states of the body. The prior now reflects the distribution over states. However, this prior is not simply the distribution over all states but is the distribution over states given our best estimate of the current distribution. This can be calculated by considering our previous state estimate (in essence the distribution over previous states) together with the motor command we have generated to update the states. The physics of our body and the world mean that the next state depends on the current state and the command. In order for the CNS to estimate the next state from the current state and the command, a model of the body is needed to simulate the dynamics. Such a predictive model is termed a forward model, which acts as a neural simulator of the way our body responds to motor commands. If the forward model is not perfect, however, the estimate of the future state will drift away from the actual state. Therefore, this estimate is combined with the sensory inputs in a Bayesian way—with the prediction of the state acting as the prior that is combined with the sensory evidence.

For linear systems with noise on the sensory input and motor output, the system that implements recursive Bayesian estimation is termed the Kalman filter (Kalman, 1960). The estimate from the Kalman filter is more accurate than the estimate that could be obtained by any single measurement alone. The Kalman filter uses a model of the expected change in the state based on the previous state plus an update based on the commands and the laws of physics. For example it has been shown that the brain combines sensory information with the expected physics of the world in motor prediction (McIntyre et al., 2001).

State estimation has been suggested to occur within the cerebellum (Paulin, 1993). To test this, TMS was applied over the cerebellum just before subjects were asked to interrupt a slow movement to intercept a visual target (Miall et al., 2007). The results suggested that when the cerebellum was interrupted by TMS, the intercept movement was disturbed, causing errors in the final movement. Analysis of these results suggested that during these TMS trials, the reaching movements were planned using hand position that was 140 ms out of date. This supports the idea that the cerebellum is used to predict the current and future state, without which the brain must rely on delayed feedback, resulting in incorrect movements. Consistent with such findings, the analysis of Purkinje cell firing in the cerebellum during arm movements found that cell firing best predicted movement kinematics, but not muscle activity 100–200 ms in the future (Ebner and Pasalar, 2008). Although motor-related activity in the brain must precede motor-related activity in the periphery, this paper demonstrated that the firing pattern was more consistent with a forward model (or state estimator) than an internal model that would correlate with muscle activity. Other

lines of research have suggested that the posterior parietal cortex is involved in state estimation (Desmurget et al., 2001; Wolpert et al., 1998a) through receiving predicted information (see the section “Forward Models and Predictive Control”) via the cerebellum (Shadmehr and Krakauer, 2008).

Bayesian decision theory is made up of both Bayesian statistics and decision theory. The three topics we have covered so far relate to Bayesian statistics in which inferences are made based on uncertain or noisy information. Once Bayesian inference provides an accurate state estimate, decision theory can be used to determine the optimal actions given the task objectives. In decision theory the objectives are formulated as a loss function that describes the desirability (or lack of desirability) of possible outcomes. The optimal action is, in general, the one for which the expected loss is minimized, and the selection of such an optimal action leads to the frameworks of optimal feedback control (OFC) and optimal impedance.

Optimal Feedback Control

Extensive research has been performed over the years to investigate why humans choose one particular manner of performing a task out of the infinite number possible. Initially, this has focused on reaching trajectories that tend to exhibit roughly straight-line paths with bell-shaped speed profiles, although certain movements have some path curvature depending on gravitational constraints (Atkeson and Hollerbach, 1985) or visual feedback (Wolpert et al., 1994). The majority of planning models have been placed within the framework of optimizing a cost. The idea is that a scalar value, termed cost, is associated with each way of achieving a task, allowing all possible solutions to be ranked and the one with the lowest cost selected. Different costs then make different predictions about the movement trajectory. For example, models that have been able to account for behavioral data include minimizing the rate of change of acceleration of the hand—the so-called minimum jerk model (Flash and Hogan, 1985)—or minimizing the rates of change of torques at the joints—the minimum torque change model (Uno et al., 1989). In these models, the end result is a desired movement. Although noise and environmental disturbances can act to disturb this process, the role of feedback is simply to return the movement back to this desired trajectory. Although able to account for many features of the empirical trajectories, these models have several features that make them somewhat unattractive in terms of explanatory power. First, it is not clear why the sensorimotor systems should care about costs such as the jerkiness of the hand. Second, even if it did, to optimize this would require measurement of third derivatives of positional information, and for this to be summed over the movement is not a trivial computation. Third, these models often do not provide information as to what should happen in a redundant system because they only specify endpoint trajectories. Finally, it is hard to generalize these models to arbitrary tasks such as a tennis serve.

In an effort to reexamine trajectory control and counter these four problems, a model was developed based on the assumption that there was one key element limiting motor performance, i.e., noise. In particular, motor noise over a reasonable range of motor activity is signal dependent, with the standard deviation

of the noise scaling with the mean level of the signal—a constant coefficient of variation. Therefore, for faster, more forceful movements, the noise is greater than for slow movements, naturally leading to the speed-accuracy trade-off. However, the idea that this type of noise may be responsible for many of the characteristics of human movement was formalized by the connection between motor planning and signal-dependent noise (Harris and Wolpert, 1998). Within this framework, the goal of the motor system is to optimize some statistic of the movement such as minimizing the endpoint variance. An optimal movement is one that minimizes the deleterious effects of noise while subject to boundary constraints such as reaching a target (on average) in a specified time. This optimization was able to predict movement trajectories for both the eye and arm (Harris and Wolpert, 1998; Haruno and Wolpert, 2005). The benefit of this model is that the cost, i.e., accuracy, is a natural variable the sensorimotor system should care about. The cost is easy to measure because it is just how far away the hand or eye ends up from a target. The model can deal with redundancy because the noise is at the muscular level, so effects on task performance take into account the kinematics of the body (Haruno and Wolpert, 2005). Finally, any task can be placed within the framework of optimizing the statistics of movement. For example the optimal tennis serve can be specified as the movement that has the highest probability of winning the point or has the highest speed at a particular average location with a variance that means it has a 90% chance of being within the service area. However, the solutions obtained for this model were feedforward, and the incorporation of feedback required a major extension to the model.

OFC was developed as a model that combined ideas on optimization with feedback control tuned to task demands (Todorov and Jordan, 2002). OFC finds the best possible feedback control law for a given task that minimizes a mixed cost function with components that specify both accuracy and energetic costs. Subject to the dynamics of the task and the noise in the sensory and motor system, OFC finds a particular feedback control law, in other words, how particular feedback gains change throughout the movement, such that the minimal expected cost is achieved. In contrast to inverse models that map desired state and current state into a motor command, OFC does not need to specify a desired state at each point in time. Instead, given a cost function that specifies a penalty on, for example, the state at some fixed time and the integrated effort, it uses the current state as an input to generate the motor command. Therefore, an important feature of these feedback control laws is that they will only correct for deviations that are task relevant and will allow variation in task-irrelevant deviations—the so-called minimum intervention principles. This matches studies that show that feedback does not always act to return the system back to the unperturbed trajectory but often acts in a manner to reduce the effect of the disturbance on the achievement of the task goal (Kurtzer et al., 2009).

OFC is important as a framework because it combines trajectory generation, noise, and motor cost within a single framework and provides a clear comparison for the results of experimental work. The control law and, hence, predicted trajectory depend on the relative weighting of each of the costs (e.g., energy costs, error costs). We have yet to understand how a task determines

the relative weighting, and therefore, this is a free parameter often fit to the data. The evidence that the sensorimotor system uses OFC can be broken down into two main categories. The first is the feedforward changes in trajectories and coordination patterns predicted by OFC, whereas the second is changing parameters in feedback control. We review each of these in turn.

Coordination and Redundancy

The theory of task optimization in the presence of signal-dependent noise (Harris and Wolpert, 1998) suggests that one movement is chosen from the redundant set of possible movements so as to minimize the variance in the endpoint location, thereby maximizing accuracy. This theory suggests that smoothness and roughly straight-line movements are simply by-products of the desire for accuracy in the presence of signal-dependent noise. As such it provides a principled way in which many of the redundancies—particularly the trajectory and joint angles—could be solved. This was further expanded by the optimal control framework (Todorov, 2004; Todorov and Jordan, 2002). Optimal control has so far been very successful in predicting the trajectories that subjects use in a number of tasks, including eye movements (Chen-Harris et al., 2008; Harris and Wolpert, 2006), arm movements (Braun et al., 2009), adaptation to novel dynamics (Izawa et al., 2008; Nagengast et al., 2009), and posture (Kuo, 2005).

The framework can also be applied to solve the problem of redundancy within the muscle system (Haruno and Wolpert, 2005). In particular, when multiple muscles are able to perform similar actions, the sensorimotor control system can choose how to partition the motor commands across the muscle space. A second aspect in which OFC has been successfully applied to solve the issue of redundancy is within multiple degrees of freedom (Guigon et al., 2007; Todorov and Jordan, 2002). As outlined previously, the motor system has over 200 degrees of freedom from which it chooses several to perform actions. Within optimal control, one can have cost functions, which are minimized, and constraint functions, which need to be achieved. By including the start and end locations as fixed constraints, OFC can be used to determine how to use multiple degrees of freedom to perform actions similar to those in a variety of experimental studies without parameter tuning (Guigon et al., 2007).

Task-Dependent Modulation of Feedback

The aim of OFC is not to eliminate all variability, but to allow it to accumulate in dimensions that do not interfere with the task (Todorov and Jordan, 2002) while minimizing it in the dimensions relevant for the task completion (minimum intervention principle). This means that OFC predicts that the feedback gains will both depend on the task and vary throughout the movement. In particular the theory predicts that perturbations that do not interfere with the task completion will be ignored, whereas perturbations that interfere with the task will be appropriately counteracted (Scott, 2004; Todorov, 2004). There are several results that support this finding. When subjects make reaching movements with their two arms and have the endpoint of one arm perturbed to either side of the movement, the reflex response in the perturbed arm only will act to return the hand back to the trajectory. However, when the two arms are acting together in a reaching movement, controlling a single cursor that is displayed at the spatial average of the two hands,

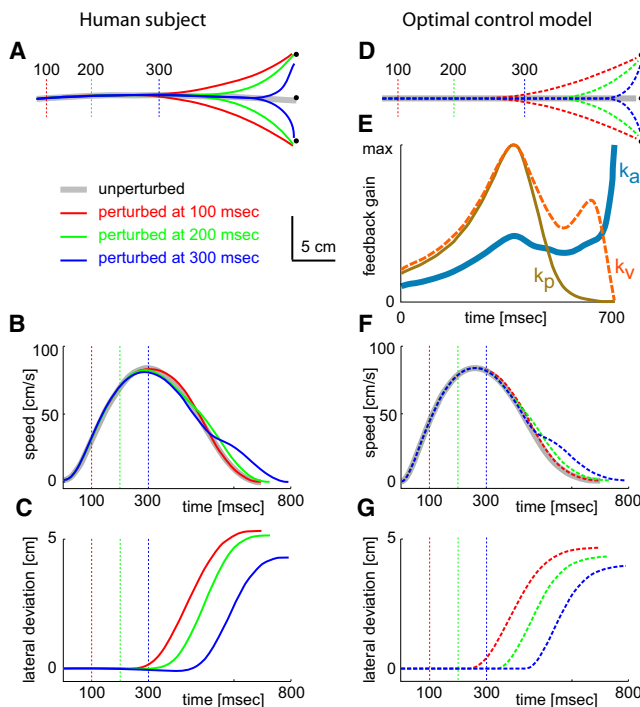


Figure 1. OFC Predicts Adaptive Feedback Responses

(A) Paths of reaching movement in the horizontal plane viewed from above. Although moving toward a target (central black circle), the target location could jump laterally (top or bottom targets) at three different times after movement start. These produce different feedback responses depending on the timing of the target shift.

(B) Speed profiles for the movements shown in (A).

(C) Lateral deviation (toward the displaced target and perpendicular to main movement direction). Subjects make different corrective movements depending on the time of the target shift.

(D) An OFC model predicts similar trajectories to human subjects.

(E) The complex time varying feedback gains of the optimal feedback controller that give rise to the predicted movements. k_p , accuracy of final position; k_v , limiting movement velocity; k_a , limiting activation; max, maximum. (F and G) Speed and lateral deviation predicted by the optimal control model. Similar to human subjects, the model predicts that when time allows, minimal corrective movements are made to reach the shifted target (low gains in E). On the other hand, when the target jump occurs late in the movement, both the speed and lateral movement are changed, and some undershoot of the movement trajectory is produced (adapted with permission from Liu and Todorov [2007]).

a physical perturbation of a single limb elicits feedback responses in both limbs to adjust the cursor's position (Diedrichsen, 2007). This demonstrates the flexibility of OFC. Because noise is signal dependent, the optimal response is to divide the required change in the control signal between the actuators. Another example involved manipulating the visual environment in which subjects reached. During reaching movements a sensory discrepancy produced by a difference between the visual location and the proprioceptive location of the hand could be either task relevant or irrelevant. By probing the visuomotor reflex gain using perturbations, it was shown that the reflex gain was increased in task-relevant but not for task-irrelevant environments (Franklin and Wolpert, 2008). Similarly it has been shown that target shape modulates the size of the visuomotor reflex response (Knill et al., 2011).

Liu and Todorov (2007) investigated another predicted feature of optimal control. The theory itself predicts that feedback should be modulated differently during a movement depending on the distance to the target. At the beginning of the movement, the feedback is less important because there is sufficient time to correct for errors that might arise in the movement. However, near the end of the movement, errors are likely to cause the target to be missed. This was investigated by having subjects make reaching movements to a target, and jumping the target lateral to the direction of movement at different times (Figure 1A). As predicted, the subjects responded more strongly when the target jump occurred close to the end of the movement (e.g., blue paths), producing both a change in the movement speed and lateral movement to the target (Figures 1B and 1C). Interestingly, in this case, subjects also failed to completely compensate for the target displacement. For target jumps occurring near the start of movement, no change occurred in the movement speed, and the movement trajectories slowly converged to the shifted target location over the rest of the movement. These results were explained by an OFC model of the task that was able to reproduce the characteristics of the human movements (Figures 1D–1G). The optimal control model has three time-varying feedback gains that act throughout the movement (Figure 1E). In order to have the movements stop near the target, the feedback gain acting to minimize movement velocity (k_v) is much larger than the one acting to enforce target accuracy (k_p), similar to over-damping the system at the end of the movement. This explains the failure of the subjects to completely compensate for the target shift when it occurred late in the movement because the velocity feedback gain prevented complete adaptation of the endpoint position.

Finally, if the brain utilizes some kind of OFC, then the reflex responses should exhibit the same kind of responses as seen in voluntary control because the same neural structures must be responsible for both (Scott, 2004). This means that not only will the responses vary according to the physical demands of the task being performed but that these responses approximate the later “voluntary” responses (Pruszynski et al., 2009). Although the short-latency (monosynaptic) stretch reflex responds only to muscle stretch, the long-latency response has long been known to respond to other factors (e.g., Lacquaniti and Soechting, 1986). However, more recently, it has been shown that the long-latency stretch reflex responses actually reflect the internal model of the limb, corresponding to the required joint torques to offset the overall disturbance of the limb (Kurtzer et al., 2009; Kurtzer et al., 2008).

Forward Models and Predictive Control

Both time delays and noise in the sensorimotor system impede our ability to make accurate estimates of relevant features of movement, such as the state of our limbs. Motor prediction, as instantiated by a forward model, is a key computational component that can alleviate this problem (Desmurget and Grafton, 2000; Miall et al., 1993; Wolpert and Kawato, 1998). We have touched upon this issue previously in our description of the Kalman filter, in which a combination of motor output and sensory input is used to estimate the current state. A forward model is a putative computational element within the nervous

system that predicts the causal relation between actions and their consequences (Wolpert and Kawato, 1998). The forward model instantiates a model of the neuromuscular system and external world, thereby acting as a neural simulator that makes predictions of the effect of motor commands. A necessary input to the forward model is a copy of the motor output (termed efference copy) that will act on the neuromuscular system. The output of the model can then be used for state estimation, prediction of sensory feedback, or for predictive control.

Forward models are not only useful to counteract the effects of delays and noise but also can help in situations where identical stimuli can give rise to different afferent signals depending on the state of the system. For example by modulating the γ static and γ dynamic drive to the muscle spindles, the sensorimotor system will receive different sensory responses for the identical physical input (Matthews, 1972). To infer state in such situations, the sensorimotor system needs to take into account the motor output to interpret the sensory input. Therefore, only by combining multiple signals (e.g., γ dynamic drive, γ static drive, α motor neuron drive) within a forward model of the system can inferences be made to interpret the state of the system from ambiguous afferent signals.

Evidence for Forward Models and Predictive Control

There have been many studies that have investigated whether forward models can be found within the sensorimotor system. However, conclusive evidence for a forward model in the sensorimotor system has been very difficult to produce. This is because the output of the forward model, a prediction of a future event, is not a measurable output but, instead, used to guide the control of the motor system (Mehta and Schaal, 2002). Several studies supporting the use of forward models in the sensorimotor system have used different techniques, for example sinusoidal tracking with induced delays (Miall et al., 1993) or virtual pole balancing with feedback blanking (Mehta and Schaal, 2002). In one study the existence of a forward model was probed by asking subjects to report the final hand position at the end of reaching movements that had been physically perturbed without visual feedback (Wolpert et al., 1995). The systematic errors and the variability in the errors in the estimated positions were indicative of a forward model similar to the Kalman filter. Using saccades during reaching movements to probe the underlying predicted hand position, several studies have provided evidence that estimates of body state use both sensory feedback and a model of the world (Ariff et al., 2002; Nanayakkara and Shadmehr, 2003). They asked subjects to visually track the position of their hand during full-limb reaching movements. They found that saccades tended to move to a position 196 ms in advance of the position of the hand (Ariff et al., 2002). By disturbing the arm position with unexpected perturbations, they demonstrated that saccades were initially suppressed (100 ms following the disturbance), then following a recalculation of predicted position, the eyes moved to a predicted position (150 ms in advance, suggesting access to efferent copy information). In contrast when the perturbation also changed the external dynamics (i.e., adding a resistive or assistive field), this recalculation was incorrect, and subjects were unable to accurately predict future hand position. This work suggests that the prediction of future hand position was updated using both the sensory feedback of the

perturbation and a model of the environment. When the model of the environment was incorrect, the system was unable to accurately predict hand position. On the other hand, when the altered environment could be learned, the saccade accurately shifted to the actual hand position, demonstrating that the model of the environment could be adaptively reconfigured (Nanayakkara and Shadmehr, 2003).

Prediction for Perception

Prediction can also be used for perception. In particular, sensory prediction could be performed by predicting the state of the body and using this sensory prediction to cancel out the sensory consequences of moving (reafference) (von Holst and Mittelstaedt, 1950). This cancellation of self-generated sensory feedback would be used to increase the detection of any environmentally generated sensory information (Wolpert and Flanagan, 2001). One of the ways that this theory was tested was by using the observation that self-generated tickle was much less ticklish than externally generated tickle. By using robotic manipulation to separate the self-generated motion to perform the tickle and the tactile input on the skin (giving rise to the tickle sensation), it was demonstrated that as the sensation was changed from the self-generated motion by adding small delays or changes in movement direction, the tactile input became more ticklish (Blakemore et al., 1999). This demonstrates that the prediction mechanism used in sensory perception was precise, both spatially and temporally. A similar effect was found in force generation, where self-generated forces are felt less intensively. This was used to explain the finding of force escalation (Shergill et al., 2003). Support for this idea that the efference copy is used to predict the sensory consequences of movement and remove this for sensory perception has also been found in self-generated head movements where the predicted cancellation signal is subtracted in the vestibular nuclei (Roy and Cullen, 2001, 2004).

Research on eye movements has also provided strong evidence for the use of efference copy in a manner that illustrates many of the properties of the forward model, in particular for this transformation from motor to sensory representation (Roy and Cullen, 2001, 2004; Sommer and Wurtz, 2002, 2006). In the visual system, the change in afferent feedback produced by the movement of the eye needs to be determined in order to discount accurately the self-generated movement (reafference) from the externally generated movement in the world (exafference). This could be done using the motor signals sent to the muscle of the eye. Saccades are generated from the frontal eye field (FEF) via descending drive through the superior colliculus (SC) (for a review see Andersen and Buneo, 2002); therefore, it was hypothesized that signals from the SC could act as efference copy back to the FEF (Sommer and Wurtz, 2002). One candidate pathway, therefore, was via the medial dorsal nucleus (MD) of the thalamus, which increases activity just prior to the saccade and signals the direction of the saccade (Sommer and Wurtz, 2004a) (Figure 2A). In the double-step saccade task (Figure 2B), two targets are flashed sequentially during fixation, to which the eye is then required to make a saccade in sequence. The location of the second target is only available as a vector from the initial fixation position. This means that once the first movement is made, information about the first movement must be

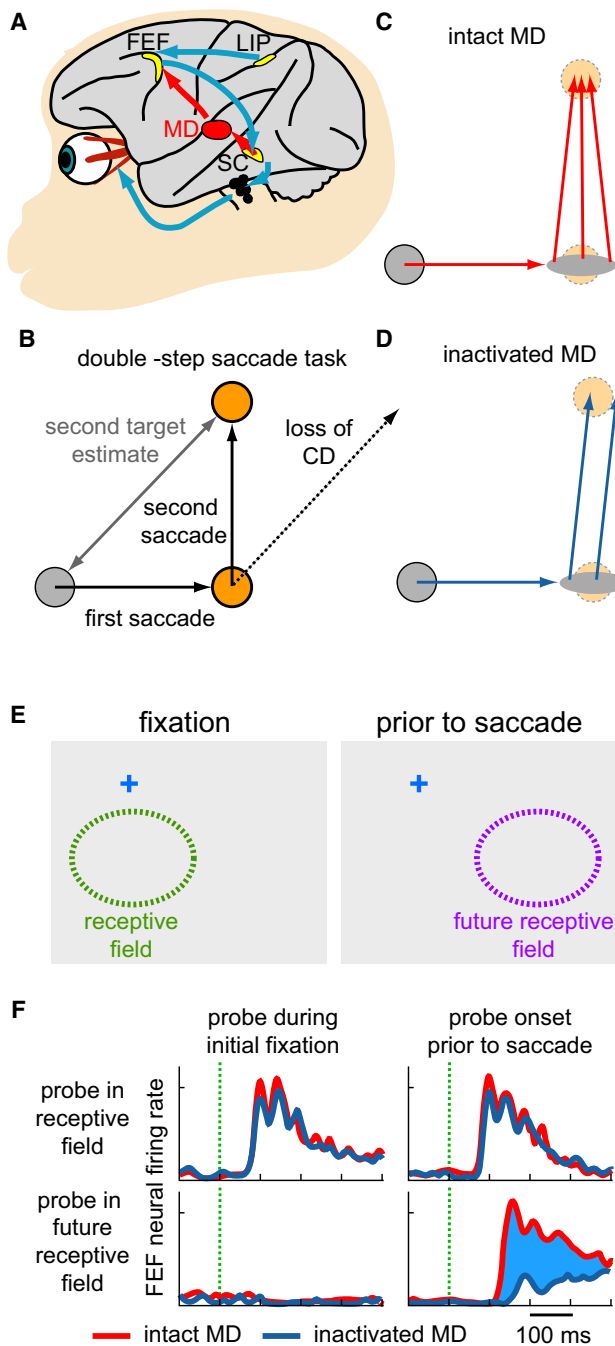


Figure 2. Forward Models in the Sensorimotor System: Evidence from the Saccadic System

(A) The neural pathway investigated between the visual brain areas and the motor system responsible for saccades. A major visual to motor pathway (blue arrows) takes information from the ventral and dorsal streams, via lateral intraparietal area (LIP) to the FEF. The FEF conveys information to the SC, which triggers saccades via nuclei within the brain stem. The saccadic system also has a motor to visual pathway (red arrows), which was proposed to carry corollary discharge (CD) of the motor actions from the SC to the FEF via the MD of the thalamus. In a series of experiments, Sommer and Wurtz (2002, 2004b, 2006) inactivated the MD relay neurons by injecting muscimol to test if this pathway provided motor information about impending eye saccades to higher visual areas (FEF) similar to forward models.

combined with the second target location to provide an updated target estimate relative to the current eye fixation position. Normally, the first saccade will produce a range of endpoints due to noise. However, the second saccade was found to change angle to compensate for the distance of the first saccade, suggesting that information about the actual distance moved in the first saccade was combined with the second target estimate (Figure 2C). The MD relay neurons were then inactivated by injecting the GABA agonist muscimol. When this region was inactivated, the second saccade exhibited significant directional errors corresponding to the direction that the eye would move in, as if it did not take into account the state change produced by the first saccade (Figure 2D) (Sommer and Wurtz, 2002). However, by examining the trial-by-trial variability, Sommer and Wurtz (2004b) also demonstrated that the second saccade no longer corrected for the trial-by-trial variability of the first saccade. Therefore, this work shows that the MD was transmitting motor signals from the first saccade to update the sensory representation to guide the second saccades. Second, Sommer and Wurtz (2006) looked at neurons in the FEF that shift their receptive field prior to the saccade (indicative of efference copy) (Duhamel et al., 1992) (Figure 2E). Normally, when the eye is fixated, these neurons respond only to light shone within their receptive field (Figure 2F, left column). However, just prior to a saccade to a new location, these neurons will respond both to a light in the current receptive field and in the future receptive field (Figure 2F, right column). However, after inactivation of the MD, whereas the receptive field sensitivity is unaffected (Figure 2F, top), significant deficits were found to probes in the future receptive field (Figure 2F, blue region). Thus, these FEF neurons do not shift their receptive fields when the MD is inactivated (Sommer and Wurtz, 2006). This demonstrates that

(B) The double-step saccade task. Although the eye is fixating the starting location (gray circle), two targets (orange circles) are flashed briefly that need to be fixated in turn. No visual feedback is present during either of the two saccades. The location of the second target is only available as a vector from the original staring location. Once the eye has made a saccade to the first target, information from the motor system about the movement that occurred is used to update the location of the second target relative to current eye fixation position. If this corollary discharge information is lost, then the position of the second saccade would not be updated, and the second saccade would miss the target (dotted arrow).

(C) When the SC-MD-FEF pathway is intact, saccades to the first target exhibit a spread of endpoints (gray ellipse) due to noise; however, the second saccades are angled appropriately to compensate for the variation in starting postures.

(D) When the MD relay neurons have been inactivated, the second saccade is not directed at the appropriate angle to the second target. Moreover, the trial-by-trial variations in the endpoint of the first saccade were not compensated for accurately in the second saccade (Sommer and Wurtz, 2002, 2004b).

(E) Shifts of the FEF receptive field occur prior to saccade. When fixating (blue cross), an FEF neuron has a receptive field within a particular location (green circle); however, just before a saccade, the receptive field of the neuron shifts to its future location (purple circle). After the saccade, this new location is the receptive field.

(F) With an intact SC-MD-FEF pathway (red), probes in the receptive field location elicit neural firing prior to the saccade to the new location (upper plots). Moreover, probes in the future receptive field also elicit neural firing directly prior to the saccade (lower plots), indicating that the receptive field shifts prior to the saccade. When the MD is inactivated (blue), the neural firing in the receptive field is unaffected, but significant deficits (light-blue region) were found to probes in the future receptive field (F adapted by permission from Macmillan Publishers Ltd: Nature, Sommer and Wurtz [2006]).

this pathway is used to convey predictive eye position to the FEF to allow shifts in the receptive fields in advance of saccade onset. Therefore, in the visual system, efference copy (corollary discharge) is used to change the sensory feedback and thereby the perception. In this case the signals are likely used to maintain the perceptual stability of the visual image. Similar results have been found in other perceptual systems such as the vestibulo-ocular system in primates, which takes into account self-generated movements (Roy and Cullen, 2001, 2004).

Forward Models in the Nervous System

Given the evidence that the motor system uses prediction for control, and the support for forward modeling in state estimation, the question is where such modeling is actually performed for effectors other than the eye. Forward modeling has been proposed to occur within the cerebellum (Bastian, 2006; Miall et al., 1993; Paulin, 1993; Wolpert et al., 1998b) and has been supported by several lines of evidence. The first is indirect evidence in brain imaging (Blakemore et al., 2001; Boecker et al., 2005; Desmurget et al., 2001; Kawato et al., 2003); however, this is supported by more direct evidence related to deficits associated with cerebellar damage (Müller and Dichgans, 1994; Nowak et al., 2004, 2007; Serrien and Wiesendanger, 1999). For example when we drop a weight from one of our hands onto an object held by the other hand, our grip force on the object increases predictively just before impact of the object (Johansson and Westling, 1988). If on the other hand, someone else dropped the weight, then, without visual feedback, we would have no predictive control, and the increase in grip force would occur reflexively at delays of around 100 ms. In patients with cerebellar degeneration, all of the responses to a dropped object, whether made by the experimenter or by the patient themselves, exhibited this delayed increase in grip force suggesting that the patients with cerebellar damage were unable to make a predictive coupling of grip force (Nowak et al., 2004). Another predictive mechanism in sensorimotor control is the reduction in force when we lift a heavy object off of one hand by using the other. If we lift off the object ourselves, then we reduce the required force in a predictive manner such that our hand does not move. However, if someone else performs this action, then we are unable to predict the reduction in force accurately enough, causing an elevation of our hands upward as the load is reduced faster than our prediction. When this mechanism was examined in patients with cerebellar damage, it was found that whereas the patients maintained some ability to predict the unloading, deficits were still found in the timing and scaling as well as the inability to remap this predictive control to new stimuli such as unloading via a button press (Diedrichsen et al., 2005). In addition to cerebellar evidence for forward models (Ebner and Pasalar, 2008; Miall et al., 2007; Tseng et al., 2007), there appears to be evidence that prediction can be seen at many levels, from posterior parietal cortex (Desmurget et al., 2001; Shadmehr and Krakauer, 2008; Wolpert et al., 1998a) to the muscle spindles, where the afferents contain information related to movements 150 ms in the future (Dimitriou and Edin, 2010). It has been suggested that the type of predictive information transmitted as efferent copy may vary depending on the level within the stream of processing (Sommer and Wurtz, 2008). For example at lower levels within the motor system, efference

copy may signal muscle activity commands, whereas at higher levels, such signals may signal spatial planning. This may explain why evidence of such forward model signals can be found at various levels in both the central and peripheral nervous system.

Impedance Control

The computational mechanisms we have so far described, such as forward models and OFC, are primarily applicable to situations that are predictable; however, many motor tasks have unpredictable components that arise through two possible mechanisms. First, unpredictability can arise from an inability to model fully the system, such as when holding the lead of a dog that can pull on the lead in random directions. Second, it can arise in a system that may be easy to model but that is unstable, such as when using a handheld knife to cut an apple, but in which noise can lead to an unpredictable outcome, such as a rightward or leftward slip off the apex (Rancourt and Hogan, 2001). In such unpredictable tasks the sensorimotor system relies on responses at a variety of delays to minimize any errors that arise. At one extreme are the instantaneous responses to any physical disturbance produced by the mechanical properties of the body and muscles—in particular the inertia of the body segments, and the intrinsic properties of the muscles (stiffness and damping). Later responses (at various delays) to the perturbations can be produced by reflex responses. As the delay increases, these responses can be tuned according to the task (Pruszynski et al., 2008). However, such adaptive responses, delayed by 70 ms, may be too late to prevent a task failure, especially in an unstable environment (Burdet et al., 2001). In such cases the neural feedback pathways may be insufficient to maintain stability (Mehta and Schaal, 2002). Therefore, in these situations the CNS controls the mechanical properties of the muscles, regulating the impedance of the system to ensure stable smooth control.

Control of Impedance

Mechanical impedance is defined as the resistance to a displacement. In a standard lumped model of impedance, three main components are present: stiffness, the resistance to a change in position; damping, the resistance to a change in velocity; and inertia, the resistance to a change in acceleration. Although the inertia can be controlled only by changing posture (Hogan, 1985), the viscoelastic properties (stiffness and damping) can be controlled by changing muscle activation or endpoint force (Franklin and Milner, 2003; Gomi and Osu, 1998; Weiss et al., 1988), coactivating muscles (Carter et al., 1993; Gomi and Osu, 1998), changing limb posture (Mussa-Ivaldi et al., 1985), and modulating reflex gains (Nichols and Houk, 1976). It has been suggested that the sensorimotor system could control the impedance of the neuromuscular system to simplify control (Hogan, 1984, 1985). Such a strategy has been observed, in which subjects increase their limb stiffness when making reaching movements in unpredictable (Takahashi et al., 2001) or unstable environments (Burdet et al., 2001). In sensorimotor control, increases in stiffness are not the only manner in which impedance control is used. For example when trying to avoid obstacles, subjects will choose a low-impedance (admittance) strategy so that interactions will lead to the hand deviating so as to move around the obstacle (Chib et al., 2006).

To examine adaptation to instability, subjects reached in a force environment in which instability was only present orthogonal to the direction of movement (Burdet et al., 2001). They found that stiffness increased only in the direction of the instability, but not in the direction of movement. This suggests that the sensorimotor control system can coordinate the coactivation of muscles to tune the orientation of the stiffness of the limb to match task demands (Burdet et al., 2001), thereby reducing the energetic cost relative to scaling up the entire stiffness of the limb (Franklin et al., 2004). Indeed, this was shown to be the case. When subjects adapted to a series of unstable environments, each with different directions of instability, subjects adapted the endpoint stiffness so that it was roughly aligned to each direction of instability (Franklin et al., 2007b). Moreover, an examination of the muscle activity associated with each unstable environment showed that this tuning of the endpoint stiffness was achieved partially through selective coactivation of different muscles, each contributing to increased stiffness in different directions.

Feedback Control of Impedance

Although muscular coactivation increases impedance thereby producing an instantaneous response to any disturbance, it also requires higher energy to maintain. Thus, there is a trade-off between the stability and metabolic cost. However, feedback components that do not induce such a metabolic cost can also increase the stiffness of the muscle to perturbations, albeit with a small delay (Nichols and Houk, 1976). The reflex gain also changes when the stability of the task changes (Akazawa et al., 1983; Perreault et al., 2008). This reflex contribution to stability has strong support from studies examining unstable tasks such as posture control when standing (Loram and Lakie, 2002; Morasso and Sanguineti, 2002) or while catching a ball (Lacquaniti and Maioli, 1987). However, the relevant timescale for corrections is markedly longer for such posture control compared to control of object interaction (Morasso, 2011). As this time decreases, feedback mechanisms for controlling impedance become less useful and direct coactivation control more necessary. However, even for control of object interaction, reflex contributions still matter. Several studies have provided evidence that the sensorimotor control system can and does regulate feedback gains for impedance control (Franklin et al., 2007b; Krutky et al., 2010).

Interactions between Impedance and Noise

Impedance control is another method in which the brain can counteract the effects of noise. Although the increase in muscle activation responsible for increased muscle stiffness causes an increase in signal-dependent motor noise, the stiffness increases faster than the noise so that overall a reduction in the disturbance is produced (Selen et al., 2005). This means that noise at the level of the joint or endpoint of a limb does not necessarily increase linearly with the size of the control signals. As multiple muscles are recruited across a joint, the stiffness adds because the muscles are in series with one another. However, the noise produced by each muscle will average out as long as the noise is not correlated across the muscles. Therefore, the noise will increase at a smaller rate than the stiffness as long as the descending drive to all of the active muscles is not giving rise to highly correlated changes in muscle force. Indeed,

recent studies have found very low correlations between forces in individual muscles (Kutch et al., 2010).

Because increased impedance reduces the effect of noise, and decreased noise decreases the endpoint errors (van Beers et al., 2004), this provides an excellent strategy for increasing the accuracy of movements. A series of experiments have investigated this possible relationship between impedance and accuracy (Gribble et al., 2003; Lametti et al., 2007; Osu et al., 2004). These studies have shown that the variability in movements, especially in movement endpoints, occurs primarily when the stiffness or cocontraction levels are low (Lametti et al., 2007). Moreover, when accuracy needs to be increased, subjects increased the cocontraction of muscles (Gribble et al., 2003; Osu et al., 2004) and the joint stiffness to adapt to the accuracy demands at the end of the movement.

Within the geometry of a multiple link, multiple muscle limb, there is a further complication added to this interplay between noise and stiffness. Due to the geometry of the limb, each muscle will contribute differently to the limb stiffness, endpoint force, and endpoint noise. Specifically, each muscle contributes to these properties in a particular direction at the endpoint of the limb, which varies depending on the posture of the limb. Therefore, these complex interactions can be exploited by the sensorimotor control system in order to optimize the trade-offs between noise, metabolic cost, stability, and task success. The inclusion of geometry allows the system to manipulate the control strategy such that any motor noise at the endpoint could be orientated in a task-irrelevant direction. Indeed, an object manipulation study demonstrated that the nervous system modulates the limb stiffness in an optimal manner so that the stiffness may not be increased purely in the direction of the instability but increases in the direction that balances the increase in stiffness in the appropriate direction with the increase in motor noise (Selen et al., 2009).

Optimal Control of Impedance

Although there are mathematical difficulties with incorporating nonlinear muscular properties within the stochastic OFC framework, some work has already been produced that attempts to bridge this gap (Mitrovic et al., 2010). In this study, impedance control is presented as the technique for dealing with uncertainties in the internal model; for example, when novel dynamics are experienced, before the learning is completed, there is a large uncertainty about what the dynamics are and how to compensate for them. Within this framework, the coactivation of muscles to increase the stiffness or impedance of the system results as an emergent property acting to reduce the uncertainty of the internal model. This fits within the experimental work because coactivation is seen as one of the first responses to changing dynamics whether or not such coactivation is required for the final adaptation to the dynamics (Franklin et al., 2003; Osu et al., 2002; Thoroughman and Shadmehr, 1999).

Impedance Control in the Nervous System

Only a limited amount of work has been done so far to investigate the neural underpinnings of impedance control. It has been suggested that the cerebellum is the brain area most likely involved in impedance control (Smith, 1981). This has been supported by changes in cerebellar firing during coactivation (Frysinger et al., 1984) and several fMRI studies investigating the coactivation

involved in stabilizing an unstable object compared to a matched stable object (Milner et al., 2006, 2007). However, in these two fMRI studies, it is not clear that a forward model could be separated from an impedance controller (because both could have been used for the unstable task, but not for the stable task). Earlier work also proposed that there are separate cortical areas for the control of movement/force and joint stiffness (Humphrey and Reed, 1983), a finding supported by psychophysical studies (Feldman, 1980; Osu et al., 2003), but not conclusively. In terms of the adaptive control of feedback gains that change with the environmental compliance, the results are much clearer. Recent studies using single-cell recordings in monkeys and TMS in humans have shown that these task-dependent feedback gains are dependent on primary motor cortex (Kimura et al., 2006; Pruszynski et al., 2011; Shemmell et al., 2009).

Learning

Finally, we examine the issue of learning. As already discussed, one of the features that makes control difficult is nonstationarity. Both over the long timescale of development and aging as well as on the short timescales of fatigue and interactions with objects, the properties of the neuromuscular system change. Such changes require us to adapt our control strategies—in other words, learn. In sensorimotor control, two main classes of learning have been proposed: supervised learning, in which the (possible vector) error between some target of the action and the action itself drives learning (Jordan and Rumelhart, 1992; Kawato et al., 1987); and reinforcement learning, in which a scalar reward signal drives learning (Dayan and Balleine, 2002; Schultz and Dickinson, 2000). The third main type of learning, unsupervised learning, has been a focus primarily in the modeling of sensory processing (Lewicki, 2002; Olshausen and Field, 1996).

There has been extensive work in sensorimotor control suggesting that an internal model of the external environment is learned (for a review see Kawato, 1999; Wolpert and Kawato, 1998). This has focused on the adaptation of limb movements to novel dynamics. When subjects are presented with a change in the external dynamics during movement, causing a disturbance to the trajectory, subjects gradually adapt, producing straight movements (Lackner and Dizio, 1994; Shadmehr and Mussa-Ivaldi, 1994). This learned adaptation is not simply a rote learning of the compensations required for a particular trajectory but generalizes across the work space for a variety of movements (Conditt et al., 1997; Goodbody and Wolpert, 1998; Shadmehr and Mussa-Ivaldi, 1994), suggesting that the sensorimotor control system develops an internal representation of the external world that it can use to generalize for novel movements. Although the introduction of novel dynamics induces large errors and, hence, large feedback responses, these are gradually reduced as the feedforward control is learned (Franklin et al., 2003; Thoroughman and Shadmehr, 1999). There is evidence that such fast trial-by-trial learning relies on the cerebellum because patients with cerebellar damage are impaired in such adaptation across many task domains (Diedrichsen et al., 2005; Smith and Shadmehr, 2005; Tseng et al., 2007).

The way learning evolves both spatially and temporally has been studied extensively using state space models. For example

during learning the errors experienced for a movement in one direction show spatial generalization to movements in other directions with a pattern determined by a decaying generalization. This has been suggested to occur through the adaptation of neural basis functions that are broadly tuned across neighboring movement directions and velocities (Thoroughman and Shadmehr, 2000; Thoroughman and Taylor, 2005). Specifically, what this means is that the learning of the dynamics is not local but is used for control at nearby regions in state space. Therefore, the learning generated in any one movement is used to update a neural basis function that is used for control in a variety of similar movements. This allows the learning function to generalize control across the reachable state space so that movements that have never been performed can be appropriately predicted and performed. In the temporal domain, recent experiments have shown that there are two learning processes that contribute to the adaptation process: a fast process that learns quickly and forgets quickly, and a slow process that learns but also forgets more slowly (Smith et al., 2006). Extensions of this basic two-rate model suggest that there is a single-fast process used for all environments but a multitude of slow processes, each gated by contextual information (Lee and Schweighofer, 2009). This may explain the conflicting results that have been found when investigating the consolidation of motor memories (Brashers-Krug et al., 1996; Caithness et al., 2004). Recent experiments have only been able to demonstrate the consolidation of opposing force fields for fairly dramatic contextual information (Howard et al., 2008; Nozaki et al., 2006).

Learning Signals for Adaptation

Signals that drive motor learning can arise in different modalities, such as through vision or proprioception, and have differential importance in driving learning. For example visual feedback of hand trajectories is not required for adaptation to novel stable (DiZio and Lackner, 2000; Scheidt et al., 2005; Tong et al., 2002) or unstable dynamics (Franklin et al., 2007a). This result may not be unexpected because congenitally blind individuals are able to walk and use tools (two examples of adaptation to unstable dynamics), and can adapt to the perturbing effects of a Coriolis force field (DiZio and Lackner, 2000). This demonstrates that visual feedback is not critical for adaptation to dynamics. Interestingly, when subjects were presented with no visual information regarding the errors perpendicular to the movement direction, they could straighten their movements (adapting to the dynamics) but were unable to modify their movement direction and, therefore, unable to reach the original targets (Scheidt et al., 2005). This suggests that visual information appears to be responsible for learning the direction of the movement and path planning. Indeed, subjects without proprioception are able to adapt to visuomotor rotations (Bernier et al., 2006), suggesting that the visual signal is enough for the remapping of movement direction planning. However, subjects without proprioception are unable to learn the correct muscle activation patterns to adapt to their self-produced joint-interaction torques during reaching (Ghez et al., 1995; Gordon et al., 1995). Visual feedback does provide useful information for dynamical control, in particular to select different internal models of objects (Gordon et al., 1993). However, whereas visual feedback may predominantly affect the learning and remapping of path planning, it

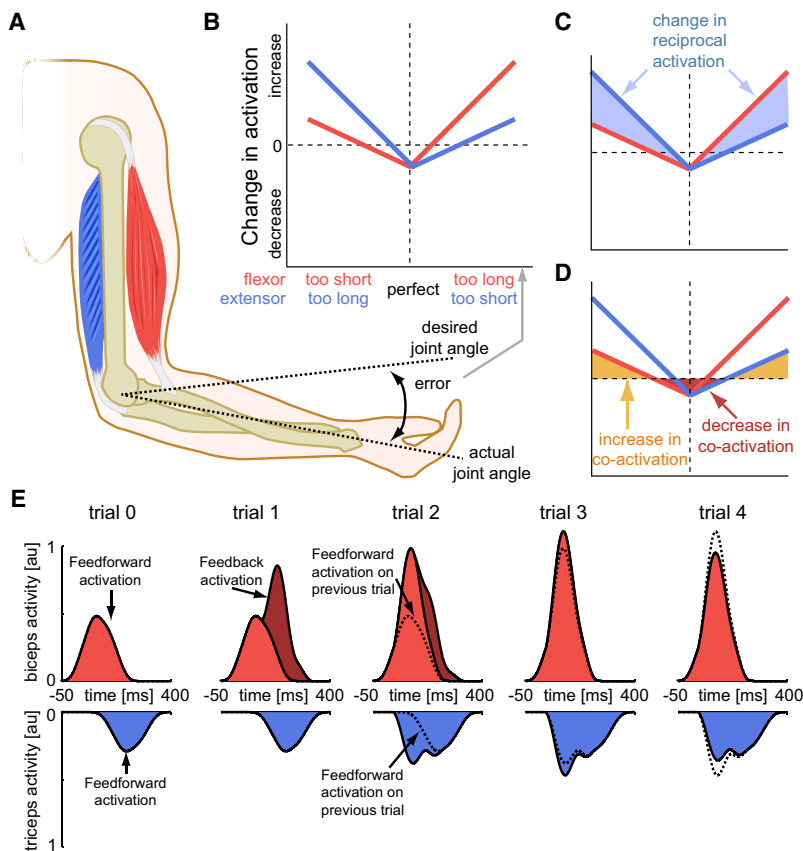


Figure 3. Error-Based Learning Algorithm Predicts Changes in Muscle Activation and Coactivation

(A) We consider a single-joint motion for simplicity. In this example, the elbow joint is controlled by two antagonist muscles, the biceps (red) and triceps (blue). During a movement the current joint angle is compared to the desired joint angle to give rise to a sequence of errors.

(B) Each error measure is used by the V-shaped update rule to determine the change in muscle activation for the next repetition of the movement. This change in muscle activation is shifted forward in time on the subsequent trial to compensate for the delays. The V-shaped learning rule for each muscle (biceps, red; triceps, blue) has a different slope depending on whether the error indicates that the muscle is too long or too short at each point in time.

(C) The different slopes for stretch or shortening of each muscle lead to an appropriate change in the reciprocal muscle activation that drives compensatory changes in the joint torques and endpoint forces.

(D) Large errors lead to an increase in coactivation, whereas little or no error leads to a reduction in the coactivation.

(E) Changes in muscle activation patterns during repeated trials. In the steady-state condition a movement may be produced by coordinated feedforward activation of an agonist-antagonist pair (trial 0). The introduction of a disturbance that extends the elbow joint (trial 1) produces a large feedback response in the biceps muscle (dark red). On the subsequent trial (trial 2), the learning algorithm changes both the biceps and triceps activation pattern (shifted forward in time from the feedback response). Due to this action, a smaller feedback response is produced on this trial. In the next trial (trial 3), the feedforward activation is again increased based on the error on the previous trial such that the disturbance is compensated for perfectly. This leads to a reduction in the coactivation on the next trial (trial 4).

(B)–(D) were redrawn with permission from Franklin et al. (2008).

appears that proprioceptive feedback predominately drives the learning and generalization of dynamics.

Optimality and Learning

Models of trial-by-trial adaptation have been developed to relate errors experienced on one trial to the update of internal representation of the forces or joint torques that will be produced on the subsequent trial (Kawato et al., 1987; Scheidt et al., 2001; Thoroughman and Shadmehr, 2000). However, this approach is limited in several respects. First, it has been shown not to function in unstable environments, where the control of the limb impedance is required (Burdet et al., 2006; Osu et al., 2003). Second, within the optimal control framework, motor learning should not be viewed as a process that only acts to reduce error. Indeed, other factors such as energy consumption (Emken et al., 2007), risk (Nagengast et al., 2010), and reward play a role in the determination of the manner in which adaptation occurs and may explain why subjects change to curved movements under certain circumstances (Chib et al., 2006; Uno et al., 1989). Optimal control can predict the trajectories learned after force field adaptation (Izawa et al., 2008). Similarly, optimal control can model the trajectories seen after adaptation to complex objects (Nagengast et al., 2009). However, these frameworks for adaptation still do not explain the learning of impedance for adaptation to unpredictable or unstable dynamics. By considering a simple optimization process (Figure 3) that trades off energy consumption and error for every muscle, adaptation to

unstable environments and the resulting selective control of impedance can be explained (Franklin et al., 2008). Unlike most other algorithms, this one (Franklin et al., 2008) can predict the time varying changes in muscle activation and learning patterns seen during human adaptation to similar environments (Franklin et al., 2003; Milner and Franklin, 2005; Osu et al., 2003). The learning algorithm posits that the update of muscle activation during learning occurs as a function of the time-varying error sequence from the previous movement similar to feedback error learning (Kawato et al., 1987). During a movement, the current joint angle is compared to the desired joint angle to give rise to a sequence of errors. Each error measure is used by a V-shaped update rule to determine the change in muscle activation for the next repetition of the movement (Figure 3B). This change in muscle activation is shifted forward in time on the subsequent trial to compensate for the delays. Such a phase advance may occur through spike timing-dependent plasticity (Chen and Thompson, 1995). The V-shaped learning rule for each muscle has a different slope depending on whether the error indicates that the muscle is too long or too short at each point in time. Unlike many learning algorithms, a large error produces increases in both the agonist and antagonist muscles. On the other hand, a small error induces a small decrease in the muscle activation on the next trial. The different slopes for stretch or shortening of each muscle lead to an appropriate change in the reciprocal muscle activation that drives compensatory

changes in the joint torques and endpoint forces (Figure 3C). However, large errors lead to an increase in coactivation that directly increases the stiffness of the joint, decreasing the effects of noise and unpredictability, whereas small errors lead to a reduction in the coactivation, allowing the learning algorithm to find minimal muscle activation patterns that can perform the task (Figure 3D). Therefore, this algorithm trades off stability, metabolic cost, and accuracy while ensuring task completion.

The learning algorithm works to reshape the feedforward muscle activation in a trial-by-trial basis during repeated movements. When a movement is disturbed, for example, extending the elbow and causing a large feedback response in the biceps (Figure 3E, trial 1), the learning algorithm specifies how this is incorporated in the subsequent trial. On the subsequent trial (Figure 3E, trial 2), the learning algorithm changes both the biceps and triceps activation pattern (shifted forward in time from the feedback response), producing both a change in joint torque to oppose the disturbance and an increase in joint stiffness to reduce the effects of the disturbance. Due to this action, a smaller feedback response is produced on this trial. In the next trial (Figure 3E, trial 3), the feedforward activation is again increased based on the error on the previous trial such that the disturbance is compensated for perfectly. This leads to a reduction in the coactivation on the next trial (Figure 3E, trial 4). Through the incorporation of the error-based changes in muscle activation, the learning algorithm tunes the time varying feedforward activation to the nonlinear nonstationary changes in the environment (Franklin et al., 2008). This algorithm can adapt the muscle activation and limb impedance to optimally counteract changes in noise in the interaction between the human and the environment. Although the current algorithm still requires the inclusion of a desired trajectory for the error estimate, the integration of the model within an optimal control framework (e.g., Mitrovic et al., 2010) may provide an understanding of the process by which adaptation occurs. Specifically, this algorithm may explain the mechanism behind the fast adaptation process of the multirate model (Smith et al., 2006).

Many models have suggested that the sensorimotor system changes the motor command in proportion to the size of the error experienced (e.g., feedback error learning) (Franklin et al., 2008; Kawato et al., 1987). However, experimental studies have shown conflicting results, with the change in command corresponding only to the direction of the error with no effect of error size (Fine and Thoroughman, 2006, 2007). There are several explanations for these results. The first is simply that the adaptation was a result of the primitives that make up the adaptation process, which exhibit a combination of position and velocity tuning (Sing et al., 2009). Therefore, any adaptation after an error will be a linear scaling of the primitives, resulting in what appears to be an invariant adaptation to the error. The second explanation is that one must consider sensorimotor adaptation within the framework of Bayesian decision theory. The ideal strategy for adaptation was actually found to be nonlinear (Wei and Körding, 2009), where small errors would be compensated for in a linear fashion, but large errors would be discounted. This arises because the sensorimotor control system must weight the information provided by the uncertainty it has in such a signal. A single large error is much more unlikely than small errors and

should, therefore, not be compensated for equally. In fact any sensory feedback experienced during a movement must be considered within the overall uncertainty of the current model of the environment, and the uncertainty of the sensory feedback itself (Wei and Körding, 2010). This will lead to fairly linear responses to error that fall within the expected variance for the environmental conditions (e.g., Franklin et al., 2008) and nonlinear and nonspecific adaptation to single trials that exceed expectation (e.g., Fine and Thoroughman, 2007; Wei et al., 2010).

Learning and Credit Assignment

The sensorimotor system is able to learn multiple internal models of external objects (Ahmed et al., 2008; Krakauer et al., 1999; Wolpert and Kawato, 1998), physical parameters of the world (McIntyre et al., 2001), and internal parameters of the neuromuscular system (Takahashi et al., 2006). These models need to be appropriately adapted when faced with errors. This means that our motor control system needs to determine how to assign the sensory feedback used to drive learning to the correct model. Several studies have investigated how adaptation can be assigned to the internal model of the arm rather than an internal model of a tool (in this case a robot) (Cothros et al., 2006; Kluzik et al., 2008). The results suggested that the more gradual the change in dynamics, the stronger was the association with the subject's internal model of the arm rather than of the robot (Kluzik et al., 2008). Similarly, if errors arise during reaching, we need to determine whether to assign the error to our limb dynamics or external world and thereby update the appropriate model. The problem of credit assignment can be solved within a Bayesian framework (Berniker and Körding, 2008). In this probabilistic framework, the sensorimotor system estimates which internal model is most likely responsible for the errors and adapts that particular model. A recent study has shown that motor learning is optimally tuned to motor noise by considering how corrections are made with respect to both planning and execution noise (van Beers, 2009). Rather than examining adaptations to perturbations, this study investigated how the sensorimotor control system adapts on a trial-by-trial manner to endpoint errors. The system still needs to assign the errors as either due to errors produced by execution noise that cannot be adapted to, or to central planning errors, which can be corrected for. The results suggest that the adaptation process adapts a fraction of the error onto the command of the previous trial so that the adaptation process is robust to the execution noise. Together, these recent studies highlight the issue that sensory feedback cannot simply be integrated into the feedforward control, but needs to be accurately assigned to the respective models while taking into account the manner in which different noise sources will play into both the planning and execution processes. This demonstrates that learning, which is used to solve many of the problems faced by the sensorimotor control system—nonlinearity, nonstationarity, and delays,—is optimally performed to take into account the other difficulties, namely noise and uncertainty.

Conclusions

We have presented five computational mechanisms that the sensorimotor control system uses to solve the difficult problems involved in motor control. Returning to our original example of

the hockey goalie, we can see that Bayesian decision theory will help to deal with the noise in the sensory system, the uncertainty of the location of the puck, and combining the sensory feedback with prior information to reduce uncertainty in the system. OFC can be used to solve the redundancy of the motor system while minimizing the effects of noise in the motor system—find the optimal set of muscles to activate to position the glove as accurately as possible to catch the puck. Predictive control or forward models are able to deal with the delays throughout the sensory, processing, and motor systems, and deal with the issue that sensory feedback is always out of date. Impedance control can be used to deal with feedback delays (ensure that the impact of the puck does not move the arm into the net), uncertainty in the ice surface (controlled stiffness of the interaction between the skates and the ice), and further limiting the effects of motor noise in reaching the correct hand location. Finally, learning allows the sensorimotor control system to correctly tune the neuromuscular system to the nonstationarity of the physical properties, the nonlinearity of the muscles, and the delays in the system.

Many of the concepts we have reviewed are currently being unified with a normative framework (e.g., [Berniker and Kording, 2008](#); [Kording et al., 2007a](#); [Mitrovic et al., 2010](#); [Todorov, 2004](#)). Normative models posit that the nervous system is (close to) optimal when solving for a sensorimotor control problem. To determine such an optimal solution, the normative model specifies two key features of the world. First, how different factors, such as tools or levels of fatigue, influence the motor system: the so-called generative model. Second, how these factors are likely to vary both over space and time—that is the prior distribution. The structure of the generative model and the prior distribution together determine how the motor system should optimally respond to sensory inputs and how it should adapt to errors. Although we presented each computational mechanism separately, they interact both in their use and possibly within their neural implementation. For example both Bayesian decision theory and forward modeling will be used to make the best estimate of the state of the body that is necessary for OFC.

Although evidence for these five computational mechanisms being used by the sensorimotor control system comes from extensive modeling work and behavioral experiments, the neurophysiological implementation of these mechanisms is less well understood. Throughout this review we have linked some of the neurophysiological studies to the computational mechanisms, and some recent reviews have discussed the possible neural implementations of some of these computational mechanisms, e.g., [Bastian \(2006\)](#), [Shadmehr and Krakauer \(2008\)](#), and [Sommer and Wurtz \(2008\)](#). However, the neural system evolved along with the complex mechanical structures of the body; therefore, some of these computational mechanisms may even be encoded at lower levels such as in spinal circuitry ([Bizzi et al., 2008](#)). Although this review focuses primarily on the algorithmic part of sensorimotor control, we believe that the important open questions are where and how these computational algorithms are implemented in the neural structures.

ACKNOWLEDGMENTS

This work was supported by the Wellcome Trust.

REFERENCES

- Adams, W.J., Graf, E.W., and Ernst, M.O. (2004). Experience can change the 'light-from-above' prior. *Nat. Neurosci.* 7, 1057–1058.
- Adelson, E.H. (1993). Perceptual organization and the judgment of brightness. *Science* 262, 2042–2044.
- Ahmed, A.A., Wolpert, D.M., and Flanagan, J.R. (2008). Flexible representations of dynamics are used in object manipulation. *Curr. Biol.* 18, 763–768.
- Akazawa, K., Milner, T.E., and Stein, R.B. (1983). Modulation of reflex EMG and stiffness in response to stretch of human finger muscle. *J. Neurophysiol.* 49, 16–27.
- Alais, D., and Burr, D. (2004). The ventriloquist effect results from near-optimal bimodal integration. *Curr. Biol.* 14, 257–262.
- Andersen, R.A., and Buneo, C.A. (2002). Intentional maps in posterior parietal cortex. *Annu. Rev. Neurosci.* 25, 189–220.
- Ariff, G., Donchin, O., Nanayakkara, T., and Shadmehr, R. (2002). A real-time state predictor in motor control: study of saccadic eye movements during unseen reaching movements. *J. Neurosci.* 22, 7721–7729.
- Atkeson, C.G., and Hollerbach, J.M. (1985). Kinematic features of unrestrained vertical arm movements. *J. Neurosci.* 5, 2318–2330.
- Aw, S.T., Todd, M.J., and Halmagyi, G.M. (2006). Latency and initiation of the human vestibuloocular reflex to pulsed galvanic stimulation. *J. Neurophysiol.* 96, 925–930.
- Bastian, A.J. (2006). Learning to predict the future: the cerebellum adapts feedforward movement control. *Curr. Opin. Neurobiol.* 16, 645–649.
- Bernier, P.M., Chua, R., Bard, C., and Franks, I.M. (2006). Updating of an internal model without proprioception: a deafferentation study. *Neuroreport* 17, 1421–1425.
- Berniker, M., and Kording, K. (2008). Estimating the sources of motor errors for adaptation and generalization. *Nat. Neurosci.* 11, 1454–1461.
- Bizzi, E., Cheung, V.C., d'Avella, A., Saltiel, P., and Tresch, M. (2008). Combining modules for movement. *Brain Res. Brain Res. Rev.* 57, 125–133.
- Blakemore, S.J., Frith, C.D., and Wolpert, D.M. (1999). Spatio-temporal prediction modulates the perception of self-produced stimuli. *J. Cogn. Neurosci.* 11, 551–559.
- Blakemore, S.J., Frith, C.D., and Wolpert, D.M. (2001). The cerebellum is involved in predicting the sensory consequences of action. *Neuroreport* 12, 1879–1884.
- Boecker, H., Lee, A., Mühlau, M., Ceballos-Baumann, A., Ritzl, A., Spilker, M.E., Marquart, C., and Hermsdörfer, J. (2005). Force level independent representations of predictive grip force-load force coupling: a PET activation study. *Neuroimage* 25, 243–252.
- Brashers-Krug, T., Shadmehr, R., and Bizzi, E. (1996). Consolidation in human motor memory. *Nature* 382, 252–255.
- Braun, D.A., Aertsen, A., Wolpert, D.M., and Mehring, C. (2009). Learning optimal adaptation strategies in unpredictable motor tasks. *J. Neurosci.* 29, 6472–6478.
- Brooks, S.V., and Faulkner, J.A. (1994). Skeletal muscle weakness in old age: underlying mechanisms. *Med. Sci. Sports Exerc.* 26, 432–439.
- Burdet, E., Osu, R., Franklin, D.W., Milner, T.E., and Kawato, M. (2001). The central nervous system stabilizes unstable dynamics by learning optimal impedance. *Nature* 414, 446–449.
- Burdet, E., Tee, K.P., Mareels, I., Milner, T.E., Chew, C.M., Franklin, D.W., Osu, R., and Kawato, M. (2006). Stability and motor adaptation in human arm movements. *Biol. Cybern.* 94, 20–32.
- Caitness, G., Osu, R., Bays, P., Chase, H., Klassen, J., Kawato, M., Wolpert, D.M., and Flanagan, J.R. (2004). Failure to consolidate the consolidation theory of learning for sensorimotor adaptation tasks. *J. Neurosci.* 24, 8662–8671.

- Carter, R.R., Crago, P.E., and Gorman, P.H. (1993). Nonlinear stretch reflex interaction during cocontraction. *J. Neurophysiol.* 69, 943–952.
- Chen, C., and Thompson, R.F. (1995). Temporal specificity of long-term depression in parallel fiber–Purkinje synapses in rat cerebellar slice. *Learn. Mem.* 2, 185–198.
- Chen-Harris, H., Joiner, W.M., Ethier, V., Zee, D.S., and Shadmehr, R. (2008). Adaptive control of saccades via internal feedback. *J. Neurosci.* 28, 2804–2813.
- Chib, V.S., Patton, J.L., Lynch, K.M., and Mussa-Ivaldi, F.A. (2006). Haptic identification of surfaces as fields of force. *J. Neurophysiol.* 95, 1068–1077.
- Churchland, M.M., Afshar, A., and Shenoy, K.V. (2006). A central source of movement variability. *Neuron* 52, 1085–1096.
- Conditt, M.A., Gandolfo, F., and Mussa-Ivaldi, F.A. (1997). The motor system does not learn the dynamics of the arm by rote memorization of past experience. *J. Neurophysiol.* 78, 554–560.
- Cothros, N., Wong, J.D., and Gribble, P.L. (2006). Are there distinct neural representations of object and limb dynamics? *Exp. Brain Res.* 173, 689–697.
- Day, B.L., and Lyon, I.N. (2000). Voluntary modification of automatic arm movements evoked by motion of a visual target. *Exp. Brain Res.* 130, 159–168.
- Dayan, P., and Balleine, B.W. (2002). Reward, motivation, and reinforcement learning. *Neuron* 36, 285–298.
- Desmurget, M., and Grafton, S. (2000). Forward modeling allows feedback control for fast reaching movements. *Trends Cogn. Sci. (Regul. Ed.)* 4, 423–431.
- Desmurget, M., Gréa, H., Grethe, J.S., Prablanc, C., Alexander, G.E., and Grafton, S.T. (2001). Functional anatomy of nonvisual feedback loops during reaching: a positron emission tomography study. *J. Neurosci.* 21, 2919–2928.
- Diedrichsen, J. (2007). Optimal task-dependent changes of bimanual feedback control and adaptation. *Curr. Biol.* 17, 1675–1679.
- Diedrichsen, J., Verstynen, T., Lehman, S.L., and Ivry, R.B. (2005). Cerebellar involvement in anticipating the consequences of self-produced actions during bimanual movements. *J. Neurophysiol.* 93, 801–812.
- Dimitriou, M., and Edin, B.B. (2010). Human muscle spindles act as forward sensory models. *Curr. Biol.* 20, 1763–1767.
- DiZio, P., and Lackner, J.R. (2000). Congenitally blind individuals rapidly adapt to coriolis force perturbations of their reaching movements. *J. Neurophysiol.* 84, 2175–2180.
- Dorfman, L.J., and Bosley, T.M. (1979). Age-related changes in peripheral and central nerve conduction in man. *Neurology* 29, 38–44.
- Duhamel, J.R., Colby, C.L., and Goldberg, M.E. (1992). The updating of the representation of visual space in parietal cortex by intended eye movements. *Science* 255, 90–92.
- Ebner, T.J., and Pasalar, S. (2008). Cerebellum predicts the future motor state. *Cerebellum* 7, 583–588.
- Emken, J.L., Benitez, R., Sideris, A., Bobrow, J.E., and Reinkensmeyer, D.J. (2007). Motor adaptation as a greedy optimization of error and effort. *J. Neurophysiol.* 97, 3997–4006.
- Ernst, M.O., and Banks, M.S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. *Nature* 415, 429–433.
- Eyre, J.A., Miller, S., and Ramesh, V. (1991). Constancy of central conduction delays during development in man: investigation of motor and somatosensory pathways. *J. Physiol.* 434, 441–452.
- Faisal, A.A., Selen, L.P., and Wolpert, D.M. (2008). Noise in the nervous system. *Nat. Rev. Neurosci.* 9, 292–303.
- Feldman, A.G. (1980). Superposition of motor programs—II. Rapid forearm flexion in man. *Neuroscience* 5, 91–95.
- Fine, M.S., and Thoroughman, K.A. (2006). Motor adaptation to single force pulses: sensitive to direction but insensitive to within-movement pulse placement and magnitude. *J. Neurophysiol.* 96, 710–720.
- Fine, M.S., and Thoroughman, K.A. (2007). Trial-by-trial transformation of error into sensorimotor adaptation changes with environmental dynamics. *J. Neurophysiol.* 98, 1392–1404.
- Flash, T., and Hogan, N. (1985). The coordination of arm movements: an experimentally confirmed mathematical model. *J. Neurosci.* 5, 1688–1703.
- Franklin, D.W., and Milner, T.E. (2003). Adaptive control of stiffness to stabilize hand position with large loads. *Exp. Brain Res.* 152, 211–220.
- Franklin, D.W., and Wolpert, D.M. (2008). Specificity of reflex adaptation for task-relevant variability. *J. Neurosci.* 28, 14165–14175.
- Franklin, D.W., Osu, R., Burdet, E., Kawato, M., and Milner, T.E. (2003). Adaptation to stable and unstable dynamics achieved by combined impedance control and inverse dynamics model. *J. Neurophysiol.* 90, 3270–3282.
- Franklin, D.W., So, U., Kawato, M., and Milner, T.E. (2004). Impedance control balances stability with metabolically costly muscle activation. *J. Neurophysiol.* 92, 3097–3105.
- Franklin, D.W., So, U., Burdet, E., and Kawato, M. (2007a). Visual feedback is not necessary for the learning of novel dynamics. *PLoS One* 2, e1336.
- Franklin, D.W., Liaw, G., Milner, T.E., Osu, R., Burdet, E., and Kawato, M. (2007b). Endpoint stiffness of the arm is directionally tuned to instability in the environment. *J. Neurosci.* 27, 7705–7716.
- Franklin, D.W., Burdet, E., Tee, K.P., Osu, R., Chew, C.M., Milner, T.E., and Kawato, M. (2008). CNS learns stable, accurate, and efficient movements using a simple algorithm. *J. Neurosci.* 28, 11165–11173.
- Frysinger, R.C., Bourbonnais, D., Kalaska, J.F., and Smith, A.M. (1984). Cerebellar cortical activity during antagonist cocontraction and reciprocal inhibition of forearm muscles. *J. Neurophysiol.* 51, 32–49.
- Ghez, C., Gordon, J., and Ghilardi, M.F. (1995). Impairments of reaching movements in patients without proprioception. II. Effects of visual information on accuracy. *J. Neurophysiol.* 73, 361–372.
- Gomi, H., and Osu, R. (1998). Task-dependent viscoelasticity of human multijoint arm and its spatial characteristics for interaction with environments. *J. Neurosci.* 18, 8965–8978.
- Goodbody, S.J., and Wolpert, D.M. (1998). Temporal and amplitude generalization in motor learning. *J. Neurophysiol.* 79, 1825–1838.
- Gordon, A.M., Westling, G., Cole, K.J., and Johansson, R.S. (1993). Memory representations underlying motor commands used during manipulation of common and novel objects. *J. Neurophysiol.* 69, 1789–1796.
- Gordon, J., Ghilardi, M.F., and Ghez, C. (1994). Accuracy of planar reaching movements. I. Independence of direction and extent variability. *Exp. Brain Res.* 99, 97–111.
- Gordon, J., Ghilardi, M.F., and Ghez, C. (1995). Impairments of reaching movements in patients without proprioception. I. Spatial errors. *J. Neurophysiol.* 73, 347–360.
- Gribble, P.L., Mullin, L.I., Cothros, N., and Mattar, A. (2003). Role of cocontraction in arm movement accuracy. *J. Neurophysiol.* 89, 2396–2405.
- Guigon, E., Baraduc, P., and Desmurget, M. (2007). Computational motor control: redundancy and invariance. *J. Neurophysiol.* 97, 331–347.
- Harris, C.M., and Wolpert, D.M. (1998). Signal-dependent noise determines motor planning. *Nature* 394, 780–784.
- Harris, C.M., and Wolpert, D.M. (2006). The main sequence of saccades optimizes speed-accuracy trade-off. *Biol. Cybern.* 95, 21–29.
- Haruno, M., and Wolpert, D.M. (2005). Optimal control of redundant muscles in step-tracking wrist movements. *J. Neurophysiol.* 94, 4244–4255.
- Hogan, N. (1984). Adaptive control of mechanical impedance by coactivation of antagonist muscles. *IEEE Trans. Automat. Contr.* 29, 681–690.
- Hogan, N. (1985). The mechanics of multi-joint posture and movement control. *Biol. Cybern.* 52, 315–331.
- Hollerbach, M.J., and Flash, T. (1982). Dynamic interactions between limb segments during planar arm movement. *Biol. Cybern.* 44, 67–77.

- Howard, I.S., Ingram, J.N., and Wolpert, D.M. (2008). Composition and decomposition in bimanual dynamic learning. *J. Neurosci.* 28, 10531–10540.
- Howard, I.S., Ingram, J.N., Körding, K.P., and Wolpert, D.M. (2009). Statistics of natural movements are reflected in motor errors. *J. Neurophysiol.* 102, 1902–1910.
- Humphrey, D.R., and Reed, D.J. (1983). Separate cortical systems for control of joint movement and joint stiffness: reciprocal activation and coactivation of antagonist muscles. *Adv. Neurol.* 39, 347–372.
- Ito, T., Murano, E.Z., and Gomi, H. (2004). Fast force-generation dynamics of human articular muscles. *J. Appl. Physiol.* 96, 2318–2324.
- Izawa, J., Rane, T., Donchin, O., and Shadmehr, R. (2008). Motor adaptation as a process of reoptimization. *J. Neurosci.* 28, 2883–2891.
- Jacobs, R.A. (1999). Optimal integration of texture and motion cues to depth. *Vision Res.* 39, 3621–3629.
- Jazayeri, M., and Shadlen, M.N. (2010). Temporal context calibrates interval timing. *Nat. Neurosci.* 13, 1020–1026.
- Johansson, R.S., and Westling, G. (1988). Programmed and triggered actions to rapid load changes during precision grip. *Exp. Brain Res.* 71, 72–86.
- Jones, K.E., Hamilton, A.F., and Wolpert, D.M. (2002). Sources of signal-dependent noise during isometric force production. *J. Neurophysiol.* 88, 1533–1544.
- Jordan, M.I., and Rumelhart, D.E. (1992). Forward models: supervised learning with a distal teacher. *Cogn. Sci.* 16, 307–354.
- Jubrias, S.A., Odderson, I.R., Esselman, P.C., and Conley, K.E. (1997). Decline in isokinetic force with age: muscle cross-sectional area and specific force. *Pflugers Arch.* 434, 246–253.
- Kalman, R.E. (1960). A new approach to linear filtering and prediction problems. *J. Basic Eng.* 35–45.
- Kawato, M. (1999). Internal models for motor control and trajectory planning. *Curr. Opin. Neurobiol.* 9, 718–727.
- Kawato, M., Furukawa, K., and Suzuki, R. (1987). A hierarchical neural-network model for control and learning of voluntary movement. *Biol. Cybern.* 57, 169–185.
- Kawato, M., Kuroda, T., Imamizu, H., Nakano, E., Miyauchi, S., and Yoshioka, T. (2003). Internal forward models in the cerebellum: fMRI study on grip force and load force coupling. *Prog. Brain Res.* 142, 171–188.
- Kersten, D., and Yuille, A. (2003). Bayesian models of object perception. *Curr. Opin. Neurobiol.* 13, 150–158.
- Kimura, T., Haggard, P., and Gomi, H. (2006). Transcranial magnetic stimulation over sensorimotor cortex disrupts anticipatory reflex gain modulation for skilled action. *J. Neurosci.* 26, 9272–9281.
- Kluzik, J., Diedrichsen, J., Shadmehr, R., and Bastian, A.J. (2008). Reach adaptation: what determines whether we learn an internal model of the tool or adapt the model of our arm? *J. Neurophysiol.* 100, 1455–1464.
- Knill, D.C., and Saunders, J.A. (2003). Do humans optimally integrate stereo and texture information for judgments of surface slant? *Vision Res.* 43, 2539–2558.
- Knill, D.C., Bondada, A., and Chhabra, M. (2011). Flexible, task-dependent use of sensory feedback to control hand movements. *J. Neurosci.* 31, 1219–1237.
- Körding, K.P., and Wolpert, D.M. (2004). Bayesian integration in sensorimotor learning. *Nature* 427, 244–247.
- Körding, K.P., and Wolpert, D.M. (2006). Bayesian decision theory in sensorimotor control. *Trends Cogn. Sci. (Regul. Ed.)* 10, 319–326.
- Körding, K.P., Ku, S.P., and Wolpert, D.M. (2004). Bayesian integration in force estimation. *J. Neurophysiol.* 92, 3161–3165.
- Körding, K.P., Tenenbaum, J.B., and Shadmehr, R. (2007a). The dynamics of memory as a consequence of optimal adaptation to a changing body. *Nat. Neurosci.* 10, 779–786.
- Körding, K.P., Beierholm, U., Ma, W.J., Quartz, S., Tenenbaum, J.B., and Shams, L. (2007b). Causal inference in multisensory perception. *PLoS One* 2, e943.
- Krakauer, J.W., Ghilardi, M.F., and Ghez, C. (1999). Independent learning of internal models for kinematic and dynamic control of reaching. *Nat. Neurosci.* 2, 1026–1031.
- Krutky, M.A., Ravichandran, V.J., Trumbower, R.D., and Perreault, E.J. (2010). Interactions between limb and environmental mechanics influence stretch reflex sensitivity in the human arm. *J. Neurophysiol.* 103, 429–440.
- Kuo, A.D. (2005). An optimal state estimation model of sensory integration in human postural balance. *J. Neural Eng.* 2, S235–S249.
- Kurtzer, I., Pruszynski, J.A., and Scott, S.H. (2009). Long-latency responses during reaching account for the mechanical interaction between the shoulder and elbow joints. *J. Neurophysiol.* 102, 3004–3015.
- Kurtzer, I.L., Pruszynski, J.A., and Scott, S.H. (2008). Long-latency reflexes of the human arm reflect an internal model of limb dynamics. *Curr. Biol.* 18, 449–453.
- Kutch, J.J., Kuo, A.D., and Rymer, W.Z. (2010). Extraction of individual muscle mechanical action from endpoint force. *J. Neurophysiol.* 103, 3535–3546.
- Lackner, J.R., and Dizio, P. (1994). Rapid adaptation to Coriolis force perturbations of arm trajectory. *J. Neurophysiol.* 72, 299–313.
- Lacquaniti, F., and Soechting, J.F. (1986). EMG responses to load perturbations of the upper limb: effect of dynamic coupling between shoulder and elbow motion. *Exp. Brain Res.* 61, 482–496.
- Lacquaniti, F., and Maioli, C. (1987). Anticipatory and reflex coactivation of antagonist muscles in catching. *Brain Res.* 406, 373–378.
- Lametti, D.R., Houle, G., and Ostry, D.J. (2007). Control of movement variability and the regulation of limb impedance. *J. Neurophysiol.* 98, 3516–3524.
- Lee, J.Y., and Schweighofer, N. (2009). Dual adaptation supports a parallel architecture of motor memory. *J. Neurosci.* 29, 10396–10404.
- Lewicki, M.S. (2002). Efficient coding of natural sounds. *Nat. Neurosci.* 5, 356–363.
- Lindle, R.S., Metter, E.J., Lynch, N.A., Fleg, J.L., Fozard, J.L., Tobin, J., Roy, T.A., and Hurley, B.F. (1997). Age and gender comparisons of muscle strength in 654 women and men aged 20–93 yr. *J. Appl. Physiol.* 83, 1581–1587.
- Liu, D., and Todorov, E. (2007). Evidence for the flexible sensorimotor strategies predicted by optimal feedback control. *J. Neurosci.* 27, 9354–9368.
- Loram, I.D., and Lakie, M. (2002). Direct measurement of human ankle stiffness during quiet standing: the intrinsic mechanical stiffness is insufficient for stability. *J. Physiol.* 545, 1041–1053.
- Matthews, P.B.C. (1972). *Mammalian Muscle Receptors and Their Central Actions* (London: Arnold).
- Matthews, P.B.C. (1991). The human stretch reflex and the motor cortex. *Trends Neurosci.* 14, 87–91.
- McGurk, H., and MacDonald, J. (1976). Hearing lips and seeing voices. *Nature* 264, 746–748.
- McIntyre, J., Zago, M., Berthoz, A., and Lacquaniti, F. (2001). Does the brain model Newton's laws? *Nat. Neurosci.* 4, 693–694.
- Mehta, B., and Schaal, S. (2002). Forward models in visuomotor control. *J. Neurophysiol.* 88, 942–953.
- Merton, P.A., and Morton, H.B. (1980). Stimulation of the cerebral cortex in the intact human subject. *Nature* 285, 227.
- Miall, R.C., Weir, D.J., Wolpert, D.M., and Stein, J.F. (1993). Is the cerebellum a smith predictor? *J. Mot. Behav.* 25, 203–216.
- Miall, R.C., Christensen, L.O., Cain, O., and Stanley, J. (2007). Disruption of state estimation in the human lateral cerebellum. *PLoS Biol.* 5, e316.

- Milner, T.E., and Franklin, D.W. (2005). Impedance control and internal model use during the initial stage of adaptation to novel dynamics in humans. *J. Physiol.* 567, 651–664.
- Milner, T.E., Franklin, D.W., Imamizu, H., and Kawato, M. (2006). Central representation of dynamics when manipulating handheld objects. *J. Neurophysiol.* 95, 893–901.
- Milner, T.E., Franklin, D.W., Imamizu, H., and Kawato, M. (2007). Central control of grasp: manipulation of objects with complex and simple dynamics. *Neuroimage* 36, 388–395.
- Mitrovic, D., Klanke, S., Osu, R., Kawato, M., and Vijayakumar, S. (2010). A computational model of limb impedance control based on principles of internal model uncertainty. *PLoS One* 5, e13601.
- Miyazaki, M., Nozaki, D., and Nakajima, Y. (2005). Testing Bayesian models of human coincidence timing. *J. Neurophysiol.* 94, 395–399.
- Morasso, P. (2011). ‘Brute force’ vs. ‘gentle taps’ in the control of unstable loads. *J. Physiol.* 589, 459–460.
- Morasso, P.G., and Sanguineti, V. (2002). Ankle muscle stiffness alone cannot stabilize balance during quiet standing. *J. Neurophysiol.* 88, 2157–2162.
- Müller, F., and Dichgans, J. (1994). Dyscoordination of pinch and lift forces during grasp in patients with cerebellar lesions. *Exp. Brain Res.* 101, 485–492.
- Murray, W.M., Delp, S.L., and Buchanan, T.S. (1995). Variation of muscle moment arms with elbow and forearm position. *J. Biomech.* 28, 513–525.
- Murray, W.M., Buchanan, T.S., and Delp, S.L. (2000). The isometric functional capacity of muscles that cross the elbow. *J. Biomech.* 33, 943–952.
- Mussa-Ivaldi, F.A., Hogan, N., and Bizzi, E. (1985). Neural, mechanical, and geometric factors subserving arm posture in humans. *J. Neurosci.* 5, 2732–2743.
- Nagengast, A.J., Braun, D.A., and Wolpert, D.M. (2009). Optimal control predicts human performance on objects with internal degrees of freedom. *PLoS Comput. Biol.* 5, e1000419.
- Nagengast, A.J., Braun, D.A., and Wolpert, D.M. (2010). Risk-sensitive optimal feedback control accounts for sensorimotor behavior under uncertainty. *PLoS Comput. Biol.* 6, e1000857.
- Nanayakkara, T., and Shadmehr, R. (2003). Saccade adaptation in response to altered arm dynamics. *J. Neurophysiol.* 90, 4016–4021.
- Nichols, T.R., and Houk, J.C. (1976). Improvement in linearity and regulation of stiffness that results from actions of stretch reflex. *J. Neurophysiol.* 39, 119–142.
- Nowak, D.A., Timmann, D., and Hermsdörfer, J. (2007). Dexterity in cerebellar agenesis. *Neuropsychologia* 45, 696–703.
- Nowak, D.A., Hermsdörfer, J., Rost, K., Timmann, D., and Topka, H. (2004). Predictive and reactive finger force control during catching in cerebellar degeneration. *Cerebellum* 3, 227–235.
- Nozaki, D., Kurtzer, I., and Scott, S.H. (2006). Limited transfer of learning between unimanual and bimanual skills within the same limb. *Nat. Neurosci.* 9, 1364–1366.
- Olshausen, B.A., and Field, D.J. (1996). Emergence of simple-cell receptive field properties by learning a sparse code for natural images. *Nature* 381, 607–609.
- Osu, R., Burdet, E., Franklin, D.W., Milner, T.E., and Kawato, M. (2003). Different mechanisms involved in adaptation to stable and unstable dynamics. *J. Neurophysiol.* 90, 3255–3269.
- Osu, R., Franklin, D.W., Kato, H., Gomi, H., Domen, K., Yoshioka, T., and Kawato, M. (2002). Short- and long-term changes in joint co-contraction associated with motor learning as revealed from surface EMG. *J. Neurophysiol.* 88, 991–1004.
- Osu, R., Kamimura, N., Iwasaki, H., Nakano, E., Harris, C.M., Wada, Y., and Kawato, M. (2004). Optimal impedance control for task achievement in the presence of signal-dependent noise. *J. Neurophysiol.* 92, 1199–1215.
- Owsley, C., Sekuler, R., and Siemsen, D. (1983). Contrast sensitivity throughout adulthood. *Vision Res.* 23, 689–699.
- Paulin, M.G. (1993). The role of the cerebellum in motor control and perception. *Brain Behav. Evol.* 41, 39–50.
- Perreault, E.J., Chen, K., Trumbower, R.D., and Lewis, G. (2008). Interactions with compliant loads alter stretch reflex gains but not intermuscular coordination. *J. Neurophysiol.* 99, 2101–2113.
- Pruszynski, J.A., Kurtzer, I., and Scott, S.H. (2008). Rapid motor responses are appropriately tuned to the metrics of a visuospatial task. *J. Neurophysiol.* 100, 224–238.
- Pruszynski, J.A., Kurtzer, I., Lillicrap, T.P., and Scott, S.H. (2009). Temporal evolution of “automatic gain-scaling”. *J. Neurophysiol.* 102, 992–1003.
- Pruszynski, J.A., Kurtzer, I.L., Nashed, J.Y., Omrani, M., Brouwer, B., and Scott, S.H. (2011). Primary motor cortex underlies multi-joint integration for fast feedback control. *Nature*. 10.1038/nature10436.
- Rancourt, D., and Hogan, N. (2001). Stability in force-production tasks. *J. Mot. Behav.* 33, 193–204.
- Roy, J.E., and Cullen, K.E. (2001). Selective processing of vestibular reafference during self-generated head motion. *J. Neurosci.* 21, 2131–2142.
- Roy, J.E., and Cullen, K.E. (2004). Dissociating self-generated from passively applied head motion: neural mechanisms in the vestibular nuclei. *J. Neurosci.* 24, 2102–2111.
- Saijo, N., Murakami, I., Nishida, S., and Gomi, H. (2005). Large-field visual motion directly induces an involuntary rapid manual following response. *J. Neurosci.* 25, 4941–4951.
- Scheidt, R.A., Dingwell, J.B., and Mussa-Ivaldi, F.A. (2001). Learning to move amid uncertainty. *J. Neurophysiol.* 86, 971–985.
- Scheidt, R.A., Conditt, M.A., Secco, E.L., and Mussa-Ivaldi, F.A. (2005). Interaction of visual and proprioceptive feedback during adaptation of human reaching movements. *J. Neurophysiol.* 93, 3200–3213.
- Schultz, W., and Dickinson, A. (2000). Neuronal coding of prediction errors. *Annu. Rev. Neurosci.* 23, 473–500.
- Scott, S.H. (2004). Optimal feedback control and the neural basis of volitional motor control. *Nat. Rev. Neurosci.* 5, 532–546.
- Selen, L.P., Beek, P.J., and van Dieën, J.H. (2005). Can co-activation reduce kinematic variability? A simulation study. *Biol. Cybern.* 93, 373–381.
- Selen, L.P., Franklin, D.W., and Wolpert, D.M. (2009). Impedance control reduces instability that arises from motor noise. *J. Neurosci.* 29, 12606–12616.
- Serrien, D.J., and Wiesendanger, M. (1999). Role of the cerebellum in tuning anticipatory and reactive grip force responses. *J. Cogn. Neurosci.* 11, 672–681.
- Shadmehr, R., and Mussa-Ivaldi, F.A. (1994). Adaptive representation of dynamics during learning of a motor task. *J. Neurosci.* 14, 3208–3224.
- Shadmehr, R., and Krakauer, J.W. (2008). A computational neuroanatomy for motor control. *Exp. Brain Res.* 185, 359–381.
- Shemmell, J., An, J.H., and Perreault, E.J. (2009). The differential role of motor cortex in stretch reflex modulation induced by changes in environmental mechanics and verbal instruction. *J. Neurosci.* 29, 13255–13263.
- Shergill, S.S., Bays, P.M., Frith, C.D., and Wolpert, D.M. (2003). Two eyes for an eye: the neuroscience of force escalation. *Science* 301, 187.
- Sing, G.C., Joiner, W.M., Nanayakkara, T., Brayanov, J.B., and Smith, M.A. (2009). Primitives for motor adaptation reflect correlated neural tuning to position and velocity. *Neuron* 64, 575–589.
- Slifkin, A.B., and Newell, K.M. (1999). Noise, information transmission, and force variability. *J. Exp. Psychol. Hum. Percept. Perform.* 25, 837–851.
- Smith, A.M. (1981). The coactivation of antagonist muscles. *Can. J. Physiol. Pharmacol.* 59, 733–747.

- Smith, M.A., and Shadmehr, R. (2005). Intact ability to learn internal models of arm dynamics in Huntington's disease but not cerebellar degeneration. *J. Neurophysiol.* 93, 2809–2821.
- Smith, M.A., Ghazizadeh, A., and Shadmehr, R. (2006). Interacting adaptive processes with different timescales underlie short-term motor learning. *PLoS Biol.* 4, e179.
- Sober, S.J., and Sabes, P.N. (2005). Flexible strategies for sensory integration during motor planning. *Nat. Neurosci.* 8, 490–497.
- Sommer, M.A., and Wurtz, R.H. (2002). A pathway in primate brain for internal monitoring of movements. *Science* 296, 1480–1482.
- Sommer, M.A., and Wurtz, R.H. (2004a). What the brain stem tells the frontal cortex. I. Oculomotor signals sent from superior colliculus to frontal eye field via mediodorsal thalamus. *J. Neurophysiol.* 91, 1381–1402.
- Sommer, M.A., and Wurtz, R.H. (2004b). What the brain stem tells the frontal cortex. II. Role of the SC-MD-FEF pathway in corollary discharge. *J. Neurophysiol.* 91, 1403–1423.
- Sommer, M.A., and Wurtz, R.H. (2006). Influence of the thalamus on spatial visual processing in frontal cortex. *Nature* 444, 374–377.
- Sommer, M.A., and Wurtz, R.H. (2008). Brain circuits for the internal monitoring of movements. *Annu. Rev. Neurosci.* 31, 317–338.
- Takahashi, C.D., Scheidt, R.A., and Reinkensmeyer, D.J. (2001). Impedance control and internal model formation when reaching in a randomly varying dynamical environment. *J. Neurophysiol.* 86, 1047–1051.
- Takahashi, C.D., Nemet, D., Rose-Gottron, C.M., Larson, J.K., Cooper, D.M., and Reinkensmeyer, D.J. (2006). Effect of muscle fatigue on internal model formation and retention during reaching with the arm. *J. Appl. Physiol.* 100, 695–706.
- Thoroughman, K.A., and Shadmehr, R. (1999). Electromyographic correlates of learning an internal model of reaching movements. *J. Neurosci.* 19, 8573–8588.
- Thoroughman, K.A., and Shadmehr, R. (2000). Learning of action through adaptive combination of motor primitives. *Nature* 407, 742–747.
- Thoroughman, K.A., and Taylor, J.A. (2005). Rapid reshaping of human motor generalization. *J. Neurosci.* 25, 8948–8953.
- Todorov, E. (2004). Optimality principles in sensorimotor control. *Nat. Neurosci.* 7, 907–915.
- Todorov, E., and Jordan, M.I. (2002). Optimal feedback control as a theory of motor coordination. *Nat. Neurosci.* 5, 1226–1235.
- Tong, C., Wolpert, D.M., and Flanagan, J.R. (2002). Kinematics and dynamics are not represented independently in motor working memory: evidence from an interference study. *J. Neurosci.* 22, 1108–1113.
- Tseng, Y.W., Diedrichsen, J., Krakauer, J.W., Shadmehr, R., and Bastian, A.J. (2007). Sensory prediction errors drive cerebellum-dependent adaptation of reaching. *J. Neurophysiol.* 98, 54–62.
- Uno, Y., Kawato, M., and Suzuki, R. (1989). Formation and control of optimal trajectory in human multi-joint arm movement. Minimum torque-change model. *Biol. Cybern.* 61, 89–101.
- van Beers, R.J. (2009). Motor learning is optimally tuned to the properties of motor noise. *Neuron* 63, 406–417.
- van Beers, R.J., Sittig, A.C., and Denier van der Gon, J.J. (1996). How humans combine simultaneous proprioceptive and visual position information. *Exp. Brain Res.* 111, 253–261.
- van Beers, R.J., Haggard, P., and Wolpert, D.M. (2004). The role of execution noise in movement variability. *J. Neurophysiol.* 91, 1050–1063.
- Vindras, P., and Viviani, P. (1998). Frames of reference and control parameters in visuomanual pointing. *J. Exp. Psychol. Hum. Percept. Perform.* 24, 569–591.
- Vindras, P., Desmurget, M., Prablanc, C., and Viviani, P. (1998). Pointing errors reflect biases in the perception of the initial hand position. *J. Neurophysiol.* 79, 3290–3294.
- von Holst, E., and Mittelstaedt, H. (1950). Das reafferenzprinzip. Wechselwirkungen zwischen zentralnervensystem und peripherie. *Naturwissenschaften* 37, 464–476.
- Wei, K., and Körding, K. (2009). Relevance of error: what drives motor adaptation? *J. Neurophysiol.* 101, 655–664.
- Wei, K., and Körding, K. (2010). Uncertainty of feedback and state estimation determines the speed of motor adaptation. *Front. Comput. Neurosci.* 4, 11.
- Wei, K., Wert, D., and Körding, K. (2010). The nervous system uses nonspecific motor learning in response to random perturbations of varying nature. *J. Neurophysiol.* 104, 3053–3063.
- Weiss, P.L., Hunter, I.W., and Kearney, R.E. (1988). Human ankle joint stiffness over the full range of muscle activation levels. *J. Biomech.* 21, 539–544.
- Wolpert, D.M., and Kawato, M. (1998). Multiple paired forward and inverse models for motor control. *Neural Netw.* 11, 1317–1329.
- Wolpert, D.M., and Flanagan, J.R. (2001). Motor prediction. *Curr. Biol.* 11, R729–R732.
- Wolpert, D.M., Ghahramani, Z., and Jordan, M.I. (1994). Perceptual distortion contributes to the curvature of human reaching movements. *Exp. Brain Res.* 98, 153–156.
- Wolpert, D.M., Ghahramani, Z., and Jordan, M.I. (1995). An internal model for sensorimotor integration. *Science* 269, 1880–1882.
- Wolpert, D.M., Goodbody, S.J., and Husain, M. (1998a). Maintaining internal representations: the role of the human superior parietal lobe. *Nat. Neurosci.* 1, 529–533.
- Wolpert, D.M., Miall, R.C., and Kawato, M. (1998b). Internal models in the cerebellum. *Trends Cogn. Sci. (Regul. Ed.)* 2, 338–347.
- Yuille, A., and Kersten, D. (2006). Vision as Bayesian inference: analysis by synthesis? *Trends Cogn. Sci. (Regul. Ed.)* 10, 301–308.
- Zajac, F.E. (1989). Muscle and tendon: properties, models, scaling, and application to biomechanics and motor control. *Crit. Rev. Biomed. Eng.* 17, 359–411.