J. Indian Inst. Sci.
A Multidisciplinary Reviews Journal
ISSN: 0970-4140 Coden-JIISAD

REVIEW ARTICLE

Reflex Circuits and Their Modulation in Motor Control: A Historical Perspective and Current View

*Pratik K. Mutha**

Abstract | Sensorimotor reflexes have long been, and continue to be, an area of tremendous research in movement neuroscience. Here I aim to provide an account of some studies that have been crucial in advancing our understanding of the organization of reflex circuits, their function and their modulation during motor control. I review research ranging from early experiments in reduced animal preparations that investigated the basic building blocks of reflex circuits to more recent studies in humans that demonstrate remarkable tunability of reflexes in response to variety of contingencies related to the task, the body and the environment. By providing such an integrated account of the historical aspects and current view on reflex function, I attempt to bring out the stunning complexity of reflex machinery, as well as the incredible adaptability of this machinery despite its underlying complexity.

Keywords: *Reflexes, Modulation, Motor control*

Robert Whytt[1] was probably the first to demonstrate that a response to a stimulus could be evoked without the "will" being involved.[2] Although Whytt called this the process of "sympathy", it was close to the notion of a reflex as it came to be understood later on. The word "reflex" was probably first used by Georg Prochaska in 1784,[3] who described the "…reflexion of sensorial into motor impressions…" which could occur "….either with consciousness or without….". Hall[4] later discovered that spinal reflexes could be influenced by higher centers and was the first to use the word "arc" to describe reflex pathways. Characteristics of reflex circuits such as the wide convergence of sensory input onto multiple muscles ("irradiation"[5]), and the summation of sub-threshold stimuli to produce a reflex response ("bahnung"[6]) were then identified.[7] However, it was not until the pioneering work of Sir Charles Sherrington that the nature of the neural circuitry underlying reflex responses was investigated in significant detail.

1 Sherrington's Contributions

Sherrington's primary interest was in studying "integration" within the central nervous system. Perhaps the most influential of Sherrington's work was the "*The Integrative Action of the Nervous System*",[8] in which he proposed that "the unit reaction in nervous integration is the reflex" and that coordination involved the simultaneous and orderly coadjustment of simple reflexes. Crucial to the development of this view were his early experiments performed on spinalized and decerebrate animals; such a reduced preparation led to substantial rigidity in extensor muscles of most joints of the body, particularly the elbow, knee and neck. Among many seminal observations, Sherrington noted that when the forefoot of a spinalized cat was excited, rigidity in the hindlimb that was on the side of stimulation increased, but rigidity in the forelimb decreased. However, the opposite response was seen on the side contralateral to the stimulation. Sherrington labeled these limb motor patterns as "crossed-extension" reflexes, and then demonstrated that

Department of Biological Engineering and Center for Cognitive Science, Indian Institute of Technology Gandhinagar, Block 5, 316A, Palaj, Gandhinagar 382355, Gujarat, India
** pm@iitgn.ac.in*

Springer IISc Press

muscle activity that led these patterns bore a striking resemblance to that observed during reflexly elicited stepping behavior in spinalized animals.[9] Sherrington suggested that these stepping patterns combined with the erect standing reflex[9] were amplified into the performance of actual walking "…..to a certain measure of effective locomotion". Thus, Sherrington believed that activities such as walking or running were of reflex origin, a view that did not hold up completely to further experimentation. In particular, the demonstration of central pattern generator networks (see Ijspeert[10] for a review), which could produce rhythmic patterns of locomotor activity even in completely deafferented and spinalized animals, served to undermine Sherrington's proposal that locomotion was an activity determined by reflex action.

Nevertheless, after the first publication of *The Integrative Action of the Nervous System*, Sherrington continued his work on reflexes for about three decades. One highlight of this period was the discovery of the "stretch reflex".[11] These experiments grew out of Sherrington's prior work on rigidity in decerebrate animals in whom he had shown a development of resistance to passive extension of a limb. Liddell and Sherrington[11] attached a fully freed tendon of the quadriceps to an optical myograph, while the femur, which carried the proximal end of the muscle, was rigidly attached to a tabletop. Lowering the tabletop resulted in a sustained stretch of the muscle and tension was rapidly developed in it, similar to the resistance observed when attempting to passively extend the knee joint in the decerebrate animal. The increase in muscle tension could be observed by stretching the muscle by only 0.8% of its length and occurred at very short latency, within 20 ms of the stretch onset. Tension continued to increase with stretch, while cessation of the stretch caused a reduction in the tension. Development of this tension was greatly reduced upon severing the nerve supply to the muscle, suggesting that its origin was central in nature. Crucially, further experimentation showed that the source of the reflex causing the contraction was confined to the muscle being stretched and was particularly dependent on an intact afferent nerve coming from the muscle. The authors concluded that "…..the contraction evoked in the quadriceps by the pull is……from receptors thus mechanically stimulated from in the muscle itself, in short, that it is a proprioceptive reflex excited by the stretch of the muscle".

2 Introduction of Electrophysiology for Studying Reflex Circuitry

The development of techniques to record intracellularly from individual neurons opened up possibilities to understand the spatiotemporal characteristics of the responses described by Sherrington. Specifically, using the "monosynaptic test reflex" developed by Renshaw[12] as a tool, Lloyd[13] showed that the "phasic" component of the stretch reflex, or in other words, the excitation of muscle fibers from the fastest muscle afferents, was monosynaptic in nature. A short latency inhibition of the antagonist muscles was also shown. Eccles and colleagues[14] expanded these findings by demonstrating that excitatory potentials from the fastest Ia afferents converged onto multiple muscles that acted as synergists for a particular action. Moreover, Eccles and colleagues also showed that the inhibition of the antagonist muscles observed when afferents of a certain muscle were stimulated was *disynaptic*[15,16] and mediated through an inhibitory interneuron, called the "Ia inhibitory interneuron".[17,18] These inhibitory components of the Ia response were also shown to be extensively spread out.[19] These diverse excitatory and inhibitory patterns of Ia action were speculated to play a significant role in locomotor activity. Another landmark finding that emerged from the use of electrophysiology was the demonstration of inhibition from Ib afferents onto the homonymous muscle. Bradley and Eccles[20] had shown that group I afferents could be divided into two groups depending on their threshold of stimulation and conduction velocity, the Ia and Ib. Stimulation of the Ib afferents, which originated from the Golgi tendon organ and were sensitive to the force in the muscle, resulted in inhibition of the homonymous muscle[19] and this inhibition appeared to be quite widespread. The inhibitory effect was then shown to be mediated through the action of the "Ib inhibitory interneuron", which received inputs from a wide variety of sources including the Ia afferents and several descending tracts.[21,22] The convergence of these inputs onto the interneuron was believed to be useful in modulating the inhibition in a task-dependent manner. Moreover, the Ia excitatory reflex combined with the Ib inhibitory reflex was later suggested to play a large role in regulating the overall stiffness of the muscle.[23]

While detailing the organization of these reflex circuits, Eccles and colleagues also demonstrated that incoming afferents, as well as interneurons mediating these reflexes received

a great deal of input from descending tracts. It was proposed that these converging inputs could be used to modulate the final response of the motor neuron to the incoming afferent information. Eccles and colleagues built upon the early work of Frank and Fuortes[24] and demonstrated that one mechanism by which modulation of the Ia and Ib reflexes could occur was through presynaptic inhibition of the incoming afferent information by descending signals from the reticulospinal, vestibulospinal, rubrospinal as well as corticospinal tracts.[25–30] The existence of such presynaptic inhibitory effects in humans has also been demonstrated.[31,32] Besides presynaptic inhibition, modulation of the stretch response could also be achieved through changes in its threshold such that excitatory input lowered the threshold, whereas inhibitory input increased it to longer lengths,[33] a result confirmed by Feldman and Orlovsky[34] who showed threshold modulation with tonic stimulation of various descending pathways. Further, inhibition of a muscle through the Ia inhibitory interneuronal pathway, which otherwise could not be achieved by the action of an inhibitory post-synaptic potential, was readily evoked following the facilitation of pathways from sensorimotor cortex.[35,36] Similar facilitatory action from descending centers was found on other afferents as well as on spinal interneurons mediating stretch responses.[36–39]

3 Physiological Characteristics of the Muscle Spindle and Their Influence on Reflex Responses

It is obvious from the previous paragraphs that during the 1950s and 1960s there was great interest in understanding the interplay between peripheral stimuli and descending commands on motor neuron output. At about the same time, there was also a large effort dedicated towards understanding the physiology and properties of the peripheral afferent sources that gave rise to these effects in the spinal cord. Sherrington[40] had previously demonstrated that afferents from the muscle originated in the muscle spindle, establishing the spindle as a sensory organ. Two types of afferents innervating the fibers inside the spindle were identified, the primary and secondary (Ia and II, respectively). This was done by demonstrating a higher threshold of activation for the secondary endings and a difference in the response rate when the muscle was stretched.[41] Later histological work showed that the spindle comprised of two types of fibers, the nuclear bag and the nuclear chain.[42,43] It was also shown that the primary afferent fibers innervate both these "intrafusal" fibers[42] and that these intrafusal fibers were innervated by efferent neurons, called the gamma motor neurons.[42,44,45]

The two types of sensory fibers were suggested to provide distinct functional advantages. While recording from dorsal root filaments from intact cats, Cooper[46] showed that stretches applied at similar rates produced very distinct responses in the primary versus secondary endings of the afferent fibers from the spindle. While there was no marked change in the response in the secondary fibers, there was a large variation in the responses of the primary fibers during the dynamic phase of the stretch. It was suggested that these two channels send distinct but linked information to the spinal cord, which increased the versatility of the spindle. It was then established that the secondary ending sent information about changes in length, while the primary ending provided information on changes in lengths and its derivatives.[47] The greater responsiveness of the primary ending to the velocity of the stretch indicated that the central nervous system received information about even the smallest stretches. This mechanism thus ensured that the firing rate of the spindle afferents did not drop significantly under cases of very small stretch which could occur say during maintenance of posture, versus large stretches occurring during movement.

Anatomical data, as well as experimental results showed that motor innervation of the spindle fibers could also be divided into two functional groups, the static and the dynamic gamma motor neurons. Similar to the two types of afferent fibers, differences between the two types of gamma motor fibers were also evident when the muscle was stretched rather than when it was maintained at a constant length. Matthews[48] showed that while stimulation of all gamma motor neurons increased the overall discharge in a primary afferent, the stimulation of only some gamma motor neurons (gamma dynamics) increased the discharge of the afferent axon during the dynamic phase of a ramp stretch. Stimulation of the other group of gamma motor neurons (gamma statics) in fact resulted in a decrease in the afferent neuron response during the dynamic phases of stretch. It must be emphasized that these findings were of great importance. Not only did they confirm anatomical data, but they also attached functional relevance to the two types of gamma motor neurons. The fact that stimulation of these two different gamma motor neurons resulted in distinct responses in the *same* afferent neuron implied that the gamma system regulates

the *sensitivity* of the spindle to stretch.[47] In other words, the amount of afferent discharge could be modulated by tuning the level of gamma activation, ultimately altering the gain of the stretch response.[49]

4 Hypotheses About Reflex Function

The growing knowledge about spindle structure, afferent and efferent projections within the spinal cord and the effects of descending signals on spinal circuits led to the emergence of a number of hypotheses about reflex function. The first and perhaps the most prominent among the hypotheses of reflex function was the "servo-hypothesis" proposed by Merton.[50] He postulated that reflex pathways function as a mechanism for regulating muscle length, or in other words, as a length-servo. Merton proposed that the gamma motor neuron activation established a reference length that the muscle was supposed to be at. Spindle discharge due to gamma activity served as a "misalignment signal" and subsequent alpha motor neuron activation ensured that this reference muscle length was achieved/maintained relatively independent of external disturbances, which could arise, say, from changes in external loads. Merton suggested that this action was mediated by a high gain in the length sensitive pathways arising from the muscle spindle and that the threshold of activation of the inhibitory pathway from the Golgi tendon organs was too high to interfere with the length-regulating property of the spindle pathway.

This hypothesis seemed very attractive and remained the most dominant hypotheses about stretch reflex function for several years. Unfortunately, it did not hold up to further experimentation. Recordings from alpha and gamma motor neurons demonstrated the near simultaneous activation of these neurons,[51] arguing against Merton's proposal that gamma motor neurons were activated prior to alpha motor neurons for establishing a reference length. In addition, the high gain for the length sensitive pathway combined with the loop delay inherent to the stretch reflex arc could not produce the desired result of length regulation without causing instability.[52] Other experiments in *intact* animals[53–56] showed that gamma motor neuron activity might not be the primary driver for the modulation of spindle afferent discharge. These studies demonstrated that the highest frequency of Ia discharge occurred when a muscle was passively stretched by voluntary activation of the antagonist muscle rather than in response to gamma motor neuron activation. These observations challenged several aspects of the servo hypothesis, ultimately leading to its retreat as the description of stretch reflex function.

The question then became that if the stretch reflex is not a length servo, what else might it be useful for? Some insight into this issue was provided by the seminal work of Houk and colleagues.[57,58] They developed a conceptual model of the proprioceptive reflex pathways, including the length sensitive Ia excitatory pathway from the spindle as well as the force sensitive Ib inhibitory pathway from the Golgi tendon organ, and called it the "motor servo". Through careful experimentation, these authors suggested that not length or force, but a relationship between the two, or in other words, *stiffness* might be the regulated property of the motor servo reflexes. The argument that they made was that because the length feedback pathway resulted in larger force in the muscle through increased motor neuron activation while the force feedback pathway from Golgi tendon organs led to a decrease in motor neuron output thereby decreasing muscle force, it was clear that length and force could not be regulated at the same time. Through a simple mathematical derivation, Nichols and Houk[57] suggested that these reflex pathways might regulate the ratio between changes in force and changes in length, i.e., stiffness. It is obvious that the length dependent pathway acts to increase stiffness, whereas the force feedback pathway acts to decrease it. This reflex stiffness, in combination with the intrinsic stiffness of the muscle determines the total mechanical stiffness, which appeared to be the regulated variable. For example, greater reflex action was shown at low levels of initial force in the muscle to compensate for the low intrinsic stiffness of the muscle at these low force levels. It must be pointed out that the notion of stiffness being the regulated property of reflex action does not imply that stiffness is *controlled*. It simply means that the pattern of reflex action is such that it tends to reduce variations in total stiffness. In other words, reflex action compensates for the force and length dependent variations in the intrinsic stiffness of the muscle. These actions of the reflex pathways aid in maintaining the total stiffness of the muscle constant.[57,58]

How much each reflex pathway contributes to the regulation of total mechanical stiffness depends upon the "gain" of these pathways. While early reports suggested that the gain of the reflex circuits could not be altered,[23,33,59] later experimentation showed that reflex gain could be under descending control.[49] This gain

for the reflex pathways could be set by a variety of mechanisms including selective activation of gamma motor neurons, presynaptic modulation of afferent information and/or gating of inputs to interneurons.

5 Stretch Responses in Intact Humans

The unraveling of reflex circuitry and understanding their potential role in motor control was possible primarily because of the use of reduced animal preparations in which muscles were typically functionally isolated. Such techniques clearly could not be used in humans and so the nature of reflex circuitry in humans was investigated through indirect techniques. Moreover, most studies in humans focused on the idea that if length and force sensitive reflexes act to regulate stiffness as suggested by Houk and colleagues,[23,57,58,60] this stiffness must be modulated to alter the effective impedance presented to mechanical loads under varying dynamical conditions.[52] Before getting into the details of these studies, it is important to describe the typical response observed in a muscle when it is rapidly stretched in healthy humans and the circuitry that mediates the generation of these responses.

The force in a muscle is a function of its length and the external load acting on it. Equilibrium is defined when the force in the muscle counterbalances the external load force. Deviations from equilibrium can be imposed by positional perturbations or by changing the load. The application of such perturbations stretches the muscles and activates the Ia, Ib and II afferents to elicit stretch reflexes. The corresponding patterns of muscle activity following a stretch have been typically recorded using electromyographic (EMG) techniques. While animal studies in reduced preparations show a clear burst of muscle activity that can be attributed to regional segments located exclusively within the spinal cord, responses in intact humans have been consistently shown to consist of more than one burst. For example, Lee and Tatton[61] described the response to a rapid stretch of wrist extensors to consist of a number of distinct peaks of activity occurring at distinct latencies. These bursts have been attributed to specific neural pathways primarily based on their latency following the stretch stimulus. While the 20 ms delay between the application of stretch and emergence of the earliest (M1) response appears to be too short to be a result of anything but spinal circuitry,[62] the later (M2 and M3) responses occurring at about 50–80 ms have been attributed to long-loop pathways between the spinal cord and supraspinal structures, particularly primary motor cortex or M1.[62–67] However, studies in decerebrate and spinalized cats deprived of any cutaneous input have shown the existence of a strong medium latency response suggesting that part of this response may be spinal.[52,68] In addition, polysynaptic pathways from the Ia sensory neurons as well as slower neurons from the group II sensory fibers have been demonstrated to contribute to the medium latency M2 and M3.

6 Modulation of Reflex Responses

How is this complex reflex architecture exploited to regulate limb stiffness, as proposed by Houk and colleagues? Detailing the experiments that uncovered the specific mechanisms underlying reflex modulation, is beyond the scope of this review. We focus here instead on the factors that lead to the modulation of reflex responses. With regard to the mechanisms, it may suffice to say that modulation of reflex responses could be achieved by varying either the threshold of activation (through changes in sub-threshold depolarization of motor neurons) or the gain (through pre-synaptic inhibition or gamma stimulation) of the reflex circuits. Changes in either of these parameters could lead to changes in limb stiffness, ultimately changing the impedance that a limb offers to a load.

A vast body of research has attempted to understand the factors that cause reflex-mediated changes in impedance, both for the lower and the upper limbs. For brevity, we limit our discussion to just the upper extremity (see Zehr and Stein[3] for a review on modulation of lower limb reflexes). Hammond[69–71] was the first to demonstrate that the medium and long-latency components of the stretch reflex could be modulated based on subject intent. He applied a constant velocity perturbation to the forearm when the arm was initially held abducted by about 80°. 18 ms after the perturbation, a reflex response was observed in the biceps muscle. This short latency burst was followed by a longer latency response when the subject was instructed to resist the perturbation prior to task onset. When the instruction was to let go, the long latency response was inhibited. Other studies corroborated these findings using "resist/let go",[72,73] "flex/extend"[74] or "compensate/do not intervene"[67,75,76] instructions, and psychophysical analogues of these instruction-based paradigms were developed more recently.[77,78] In these psychophysical studies, the arm was perturbed such that it was

either pushed into a target (similar to a "do not intervene" instruction), or had to be brought into a target by countering the applied perturbation ("react" instruction). Larger reflex responses were observed when subjects had to react to the perturbation compared to when the arm was pushed into the target. While these results were similar to those obtained using verbal instructions, the authors were able to considerably expand on previous studies by demonstrating modulation of the long latency response with the amplitude and the direction of the visual target. Crucially, while recording from M1, Pruszynski et al.[78] showed that neuronal activity was also tuned to the response required, at a latency that could account for the responses in the arm musculature.

Long latency responses in the upper limbs have also been shown to be strongly sensitive to task goals. In a task where subjects were required to maintain a fixed position or a fixed level of force, subjects always demonstrated a higher reflex response to a perturbation when stabilizing a position rather than force.[79–85] Hore and colleagues[83] demonstrated that the mechanism by which this modulation was achieved involved the modulation of the gain of the reflex circuits rather than co-contraction of antagonist muscles. It has been demonstrated that long latency reflexes are also tuned to the amount of sensory information accumulated during a decision process.[86,87] For example, Selen et al.[87] asked subjects to reach to targets to indicate the direction of dots moving on a screen. The number of dots moving in the same direction and the amount of time available to subjects to view the dot motion was varied. Reflex responses elicited during the decision interval (when subjects were accumulating evidence related to the motion) were tuned to the strength and the duration of motion, indicating the sensitivity of the reflex to the accumulated sensory evidence.

A number of studies have effectively employed multi-joint perturbations to uncover even greater sophistication in reflex responses. Broadly, these studies have shown that the long latency component of the stretch response are tuned not just to local stretch of the muscle, but also to the underlying torque required to compensate for the perturbation. This was first demonstrated by Lacquaniti and colleagues,[88, 89] who showed that a perturbation applied to extend the shoulder not only led to strong reflex activation of the shoulder flexors but also *elbow flexors*. They argued that the extensor perturbation at the shoulder created restoring extensor torques at the elbow and so the activation of elbow flexors was appropriate for compensating their effects. Other researchers[90–92] arrived at a similar conclusion, and this idea has recently been extended significantly by Scott and colleagues[93–96] who have consistently demonstrated that long latency reflexes elicited at a joint are sensitive to motion at that joint as well as motion at other connected joints, and compensate for the underlying multi-joint torque pattern (also see Weiler et al.[97,98]). This intricacy is again seen in the activity of M1 cells, which appear to generate motor commands that integrate information about shoulder and elbow motion to counter the underlying torque at very short latency (~ 50 ms) following the perturbation. Perreault and colleagues have suggested that the strength of the modulation may be sensitive to knowledge of not just the mechanics of the limb, but also the properties of the environment.[67,99,100] These authors showed that while the same muscles were active when subjects interacted with either a stiff or compliant environment, the magnitude of reflex activation was quite different, pointing to the incorporation of environmental conditions into the reflex response. Similar conclusions were drawn by Kimura et al.[101] who showed modulation of the long latency response based on prior knowledge about an upcoming dynamical environment that the limb would encounter during movement. The general view emerging from these studies is that reflex responses show a phenomenal degree of sophistication, identical to motor responses for voluntary control of movement.[102]

One major limitation of almost all the studies that have examined modulation of reflex responses in the upper limb is that contingencies of the task and the characteristics of the perturbation are typically known in advance. For instance, task goals remain fixed and the timing, magnitude and direction of the perturbations are fairly predictable. Under such predictable conditions, what appears as a modulated reflex may actually be an early release of a voluntary movement that is appropriately tuned to task conditions.[76,103] This suggests that reflex modulation might be confounded by the simultaneous imposition of a triggered response when task conditions are predictable. To examine reflex modulation under conditions where task goals could unexpectedly change, Mutha et al.[104] asked participants to reach to a visual target that occasionally jumped to a new location during movement initiation, thus changing the task goal during the course of motion. Unpredictable mechanical perturbations were occasionally applied, 100 ms after the target jump. Both short and long latency reflex

responses were tuned to the direction of the target jump: response amplitudes were increased or decreased depending on whether the perturbation opposed or assisted achievement of the new task goal, respectively. It was also shown that this reflex modulation resulted in a change in the mechanical impedance to the perturbations. These results thus showed the remarkable flexibility available within the nervous system to modify limb impedance presented to loads even during the execution of a movement. It was further shown that such flexibility is not limited to within a limb, but could extend bilaterally across limbs when the two arms cooperated to achieve the task goal,[105] a result that has since been confirmed by other studies.[106,107]

These studies lead to two major conclusions: (1) reflex modulation allows the nervous system to tune the impedance presented to predictable and unpredictable loads during posture or during movement, and (2) reflex modulation is highly sophisticated, accounts for a variety of task, body and environmental conditions, and is mediated via M1. Thus, reflex responses share many features of voluntary motor signals, including perhaps the underlying neural substrates. Such modulation of reflexes may provide a neurophysiological basis to the optimal feedback control theory of voluntary actions[108] in which motor commands for purposeful movement are derived by intelligent manipulation of sensory information.[109]

7 Summary and Conclusions

The study of reflex circuits and their modulation has come a long way since Sherrington's pioneering discovery of the "stretch reflex" in reduced animal preparations. Electrophysiological studies established that this response is mediated by a monosynaptic excitatory spinal circuit between afferent neurons from muscle spindles and motor neurons that innervate the same muscle. In humans, rapid stretch of a muscle results in a multi-compartment response rather than just a single burst of muscle activity. While the earliest component of this response is mediated by a monosynaptic spinal circuit (consistent with animal work), the longer latency components are mediated by spinal as well as supraspinal neural networks that traverse M1. A growing body of literature suggests that these reflex components are highly flexible, and can be remarkably tuned based on a variety of contingencies related to task goals and properties of the body and the environment. Such stunning modulation of feedback responses, similar to the modulation of motor output seen during voluntary motor control, along with the common neural substrates mediating the two, has begun to bring into question the traditionally held distinction between voluntary and reflexive actions.

Acknowledgements

Support from the Ramanujan Fellowship, the Health Sciences Committee and the Cognitive Science Research Initiative of the Department of Science and Technology (all of the Government of India) is deeply acknowledged.

Received: 22 September 2017 Accepted: 24 October 2017
Published online: 21 November 2017

References

1. Whytt R (1765) Observations on the nature, causes and cure of those disorders which are commonly called nervous, hypochondriac, or hysteric to which are prefixed some remarks on the sympathy of the nerves. Edinburgh, UK: Balfour
2. Eadie MJ (2000) Robert Whytt and the pupils. J Clin Neurosci 7:295–297
3. Zehr EP, Stein RB (1999) What functions do reflexes serve during human locomotion? Prog Neurobiol 58:185–205
4. Hall M (1833) On the reflex function of the medulla oblongata and medulla spinalis. Philos Trans R Soc Lond 123:635–665
5. Pfluger E (1853) Die sensorischen Functionen des Ruckenmarks der Wirbelthiere nebst einer neuen Lehre uber die Leitungsgesetze der Reflexionen. Hirschwald, Berlin
6. Exner S (1894) Entwurf zu einer physiologischen Erklarung der psychischen Erscheinungen. Deiticke, Wien
7. Levine DN (2007) Sherrington's "The Integrative action of the nervous system": a centennial appraisal. J Neurol Sci 253:1–6
8. Sherrington CS (1906) The integrative action of the nervous system. Yale University Press, New Haven, CT
9. Sherrington CS (1910) Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. J Physiol 40:28–121
10. Ijspeert AJ (2008) Central pattern generators for locomotion control in animals and robots: a review. Neural Netw 21:642–653
11. Liddell EGT, Sherrington CS (1924) Reflexes in response to stretch (myotatic reflexes). Proc R Soc Lond 96:212–242
12. Renshaw B (1940) Activity in the simplest spinal reflex pathways. J Neurophysiol 3:373–387
13. Lloyd DP (1946) Facilitation and inhibition of spinal motoneurons. J Physiol 9:421–438

14. Eccles JC, Eccles RM, Lundberg A (1957) The convergence of monosynaptic excitatory afferents on to many different species of alpha motoneurones. J Physiol 137:22–50
15. Eccles JC, Araki T, Ito M (1960) Correlation of the inhibitory postsynaptic potential of motoneurones with the latency and time course of inhibition of monosynaptic reflexes. J Physiol 154:354–377
16. Eccles JC, Fatt P, Landgren S (1956) Central pathway for direct inhibitory action of impulses in largest afferent nerve fibres to muscle. J Neurophysiol 19:75–98
17. Jankowska E, Roberts WJ (1972) An electrophysiological demonstration of the axonal projections of single spinal interneurones in the cat. J Physiol 222:597–622
18. Jankowska E, Roberts WJ (1972) Synaptic actions of single interneurones mediating reciprocal Ia inhibition of motoneurones. J Physiol 222:623–642
19. Eccles JC, Eccles RM, Lundberg A (1957) Synaptic actions on motoneurones caused by impulses in Golgi tendon organ afferents. J Physiol 138:227–252
20. Bradley K, Eccles JC (1953) Analysis of the fast afferent impulses from thigh muscles. J Physiol 122:462–473
21. Baldissera F, Hultborn H, Illert M (1981) Integration in spinal neuronal systems. In: Brooks VB (ed) Handbook of Physiology, The Nervous System, Motor Control part 1 II. Am Physiol Soc, Bethesda, MD, pp 509–595
22. Jankowska E (1992) Interneuronal relay in spinal pathways from proprioceptors. Prog Neurobiol 38:335–378
23. Houk JC (1979) Regulation of stiffness by skeletomotor reflexes. Annu Rev Physiol 41:99–114
24. Frank K, Fuortes MGF (1957) Presynaptic and postsynaptic inhibition of monosynaptic reflexes. Fed Proc 16:39–40
25. Carpenter D, Engberg I, Lundberg A (1966) Primary afferent depolarization evoked from the brain stem and the cerebellum. Arch Ital Biol 104:73–85
26. Carpenter D, Lundberg A, Norrsell U (1963) Primary afferent depolarization evoked from the sensorimotor cortex. Acta Physiol Scand 59:126–142
27. Eccles JC (1964) Presynaptic inhibition in the spinal cord. Prog Brain Res 12:65–91
28. Eccles JC, Kostyuk PG, Schmidt RF (1962) Central pathways responsible for depolarization of primary afferent fibres. J Physiol 161:237–257
29. Eccles JC, Kostyuk PG, Schmidt RF (1962) Presynaptic inhibition of the central actions of flexor reflex afferents. J Physiol 161:258–281
30. Eccles JC, Schmidt RF, Willis WD (1962) Presynaptic inhibition of the spinal monosynaptic reflex pathway. J Physiol 161:282–297
31. Hultborn H, Meunier S, Morin C, Pierrot-Deseilligny E (1987) Assessing changes in presynaptic inhibition of I a fibres: a study in man and the cat. J Physiol 389:729–756
32. Hultborn H, Meunier S, Pierrot-Deseilligny E, Shindo M (1987) Changes in presynaptic inhibition of Ia fibres at the onset of voluntary contraction in man. J Physiol 389:757–772
33. Matthews PB (1959) A study of certain factors influencing the stretch reflex of the decerebrate cat. J Physiol 147:547–564
34. Feldman AG, Orlovsky GN (1975) Activity of interneurons mediating reciprocal 1a inhibition during locomotion. Brain Res 84:181–194
35. Eccles JC, Magni F, Willis WD (1962) Depolarization of central terminals of Group I afferent fibres from muscle. J Physiol 160:62–93
36. Lundberg A, Voorhoeve P (1962) Effects from the pyramidal tract on spinal reflex arcs. Acta Physiol Scand 56:201–219
37. Illert M, Lundberg A, Tanaka R (1976) Integration in descending motor pathways controlling the forelimb in the cat. 2. Convergence on neurones mediating disynaptic cortico-motoneuronal excitation. Exp Brain Res Exp Hirnforsch 26:521–540
38. Illert M, Lundberg A, Tanaka R (1977) Integration in descending motor pathways controlling the forelimb in the cat. 3. Convergence on propriospinal neurones transmitting disynaptic excitation from the corticospinal tract and other descending tracts. Exp Brain Res Exp Hirnforsch 29:323–346
39. Lundberg A, Norrsell U, Voorhoeve P (1963) Effects from the sensorimotor cortex on ascending spinal pathways. Acta Physiol Scand 59:462–473
40. Sherrington CS (1894) On the anatomical constitution of nerves of skeletal muscles; with remarks on recurrent fibres in the ventral spinal nerve-root. J Physiol 17(210):212–258
41. Matthews BH (1933) Nerve endings in mammalian muscle. J Physiol 78:1–53
42. Boyd IA (1962) The structure and innervation of the nuclear bag muscle fibre system and the nuclear chain muscle fibre system in mammalian muscle spindles. Philos Trans R Soc Lond 245:81–136
43. Boyd IA (1956) The tenuissimus muscle of the cat. J Physiol 133:35–36
44. Hunt CC, Kuffler SW (1951) Further study of efferent small-nerve fibers to mammalian muscle spindles; multiple spindle innervation and activity during contraction. J Physiol 113:283–297
45. Kuffler SW, Hunt CC, Quilliam JP (1951) Function of medullated small-nerve fibers in mammalian ventral roots; efferent muscle spindle innervation. J Neurophysiol 14:29–54
46. Cooper S (1961) The responses of the primary and secondary endings of muscle spindles with intact motor innervation during applied stretch. Q J Exp Physiol Cogn Med Sci 46:389–398
47. Matthews PB (1981) Evolving views on the internal operation and functional role of the muscle spindle. J Physiol 320:1–30

48. Matthews PB (1962) The differentiation of two types of fusimotor fibre by their effects on the dynamic response of muscle spindle primary endings. Q J Exp Physiol Cogn Med Sci 47:324–333
49. Prochazka A (1981) Muscle spindle function during normal movement. Int Rev Physiol 25:47–90
50. Merton PA (1953) Speculations on the servo-control of movements. In: Malcolm JL, Gray JAB, Wolstenholm GEW (eds) The spinal cord. Little Brown, Boston, pp 183–198
51. Vallbo AB (1971) Muscle spindle response at the onset of isometric voluntary contractions in man. Time difference between fusimotor and skeletomotor effects. J Physiol 218:405–431
52. Houk JC, Rymer WZ (1981) Neural control of muscle length and tension. In: Brooks VB (ed) Handbook of physiology, the nervous system, motor control part 2 II. Am Physiol Soc, Bethesda, MD, pp 257–323
53. Cody FW, Harrison LM, Taylor A (1975) Analysis of activity of muscle spindles of the jaw-closing muscles during normal movements in the cat. J Physiol 253:565–582
54. Goodwin GM, Luschei ES (1975) Discharge of spindle afferents from jaw-closing muscles during chewing in alert monkeys. J Neurophysiol 38:560–571
55. Prochazka A, Westerman RA, Ziccone SP (1976) Discharges of single hindlimb afferents in the freely moving cat. J Neurophysiol 39:1090–1104
56. Prochazka A, Westerman RA, Ziccone SP (1977) Ia afferent activity during a variety of voluntary movements in the cat. J Physiol 268:423–448
57. Nichols TR, Houk JC (1976) Improvement in linearity and regulation of stiffness that results from actions of stretch reflex. J Neurophysiol 39:119–142
58. Nichols TR, Houk JC (1973) Reflex compensation for variations in the mechanical properties of a muscle. Science 181(182–184):1973
59. Feldman AG (1966) Functional tuning of the nervous system with control of movement or maintenance of a steady posture. II. Controllable parameters of the muscle. Biophysics 11:565–578
60. Houk JC (1976) An assessment of stretch reflex function. Prog Brain Res 44:303–314
61. Lee RG, Tatton WG (1978) Long loop reflexes in man: clinical applications. In: Desmedt JE (ed) Cerebral motor control in man: long loop mechanisms. Karger, Basel, pp 320–333
62. Matthews PB (1991) The human stretch reflex and the motor cortex. Trends Neurosci 14:87–91
63. Cheney PD, Fetz EE (1984) Corticomotoneuronal cells contribute to long-latency stretch reflexes in the rhesus monkey. J Physiol 349:249–272
64. Evarts EV, Tanji J (1976) Reflex and intended responses in motor cortex pyramidal tract neurons of monkey. J Neurophysiol 39:1069–1080
65. Marsden CD, Merton PA, Morton HB (1973) Latency measurements compatible with a cortical pathway for the stretch reflex in man. J Physiol 230:58P–59P
66. Pruszynski JA, Kurtzer I, Scott SH (2011) The long-latency reflex is composed of at least two functionally independent processes. J Neurophysiol 106:449–459
67. Shemmell J, An JH, Perreault EJ (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
68. Ghez C, Shinoda Y (1978) Spinal mechanisms of the functional stretch reflex. Exp Brain Res Exp Hirnforsch 32:55–68
69. Hammond PH (1960) An experimental study of servo action in human muscular control. In: Proceedings of III international conference on medical electronics, pp. 190–199
70. Hammond PH (1956) The influence of prior instruction to the subject on an apparently involuntary neuromuscular response. J Physiol 132:17–18P
71. Hammond PH (1955) Involuntary activity in biceps following the sudden application of velocity to the abducted forearm. J Physiol 127:23–25P
72. Colebatch JG, Gandevia SC, McCloskey DI, Potter EK (1979) Subject instruction and long latency reflex responses to muscle stretch. J Physiol 292:527–534
73. Rothwell JC, Traub MM, Marsden CD (1980) Influence of voluntary intent on the human long-latency stretch reflex. Nature 286:496–498
74. Hagbarth KE (1967) EMG studies of stretch reflexes in man. Electroencephalogr Clin Neurophysiol Suppl 25:74–79
75. Crago PE, Houk JC, Hasan Z (1976) Regulatory actions of human stretch reflex. J Neurophysiol 39:925–935
76. Ravichandran VJ, Shemmell JB, Perreault EJ (2009) Mechanical perturbations applied during impending movement evoke startle-like responses. Conf Proc IEEE Eng Med Biol Soc 2947–2950:2009
77. Pruszynski JA, Kurtzer I, Scott SH (2008) Rapid motor responses are appropriately tuned to the metrics of a visuospatial task. J Neurophysiol 100:224–238
78. Pruszynski JA, Omrani M, Scott SH (2014) Goal-dependent modulation of fast feedback responses in primary motor cortex. J Neurosci 34:4608–4617
79. Akazawa K, Milner TE, Stein RB (1983) Modulation of reflex EMG and stiffness in response to stretch of human finger muscle. J Neurophysiol 49:16–27
80. Colebatch JG, McCloskey DI (1987) Maintenance of constant arm position or force: reflex and volitional components in man. J Physiol 386:247–261
81. Doemges F, Rack PM (1992) Changes in the stretch reflex of the human first dorsal interosseous muscle during different tasks. J Physiol 447:563–573
82. Doemges F, Rack PM (1992) Task-dependent changes in the response of human wrist joints to mechanical disturbance. J Physiol 447:575–585

83. Hore J, McCloskey DI, Taylor JL (1990) Task-dependent changes in gain of the reflex response to imperceptible perturbations of joint position in man. J Physiol 429:309–321
84. Kanosue K, Akazawa K, Fujii K (1983) Modulation of reflex activity of motor units in response to stretch of a human finger muscle. Jpn J Physiol 33:995–1009
85. Perreault EJ, Chen K, Lewis GN (2006) Regulation of multijoint stretch reflexes during interactions with stiff and compliant environments. Conf Proc IEEE Eng Med Biol Soc 1:300–302
86. Nashed JY, Crevecoeur F, Scott SH (2014) Rapid online selection between multiple motor plans. J Neurosci 34:1769–1780
87. Selen LP, Shadlen MN, Wolpert DM (2012) Deliberation in the motor system: reflex gains track evolving evidence leading to a decision. J Neurosci 32:2276–2286
88. Lacquaniti F, Soechting JF (1986) EMG responses to load perturbations of the upper limb: effect of dynamic coupling between shoulder and elbow motion. Exp Brain Res Exp Hirnforsch 61:482–496
89. Soechting JF, Lacquaniti F (1988) Quantitative evaluation of the electromyographic responses to multidirectional load perturbations of the human arm. J Neurophysiol 59:1296–1313
90. Gielen CC, Ramaekers L, van Zuylen EJ (1988) Long-latency stretch reflexes as co-ordinated functional responses in man. J Physiol 407:275–292
91. Jongen HA, Denier van der Gon JJ, Gielen CC (1989) Inhomogeneous activation of motoneurone pools as revealed by co-contraction of antagonistic human arm muscles. Exp Brain Res Exp Hirnforsch 75:555–562
92. Koshland GF, Hasan Z, Gerilovsky L (1991) Activity of wrist muscles elicited during imposed or voluntary movements about the elbow joint. J Mot Behav 23:91–100
93. Kurtzer I, Crevecoeur F, Scott SH (2014) Fast feedback control involves two independent processes utilizing knowledge of limb dynamics. J Neurophysiol 111:1631–1645
94. Kurtzer I, Pruszynski JA, Scott SH (2009) Long-latency responses during reaching account for the mechanical interaction between the shoulder and elbow joints. J Neurophysiol 102:3004–3015
95. Kurtzer IL, Pruszynski JA, Scott SH (2008) Long-latency reflexes of the human arm reflect an internal model of limb dynamics. Curr Biol 18:449–453
96. Pruszynski JA, Kurtzer I, Nashed JY, Omrani M, Brouwer B, Scott SH (2011) Primary motor cortex underlies multi-joint integration for fast feedback control. Nature 478:387–390
97. Weiler J, Gribble PL, Pruszynski JA (2015) Goal-dependent modulation of the long-latency stretch response at the shoulder, elbow, and wrist. J Neurophysiol 114:3242–3254
98. Weiler J, Saravanamuttu J, Gribble PL, Pruszynski JA (2016) Coordinating long-latency stretch responses across the shoulder, elbow, and wrist during goal-directed reaching. J Neurophysiol 116:2236–2249
99. Krutky MA, Ravichandran VJ, Trumbower RD, Perreault EJ (2010) Interactions between limb and environmental mechanics influence stretch reflex sensitivity in the human arm. J Neurophysiol 103:429–440
100. Perreault EJ, Chen K, Trumbower RD, Lewis G (2008) Interactions with compliant loads alter stretch reflex gains but not intermuscular coordination. J Neurophysiol 99:2101–2113
101. Kimura T, Haggard P, Gomi H (2006) Transcranial magnetic stimulation over sensorimotor cortex disrupts anticipatory reflex gain modulation for skilled action. J Neurosci 26:9272–9281
102. Scott SH (2016) A functional taxonomy of bottom-up sensory feedback processing for motor actions. Trends Neurosci 39:512–526
103. Koshland GF, Hasan Z (2000) Electromyographic responses to a mechanical perturbation applied during impending arm movements in different directions: one-joint and two-joint conditions. Exp Brain Res Exp Hirnforsch 132:485–499
104. Mutha PK, Boulinguez P, Sainburg RL (2008) Visual modulation of proprioceptive reflexes during movement. Brain Res 1246:54–69
105. Mutha PK, Sainburg RL (2009) Shared bimanual tasks elicit bimanual reflexes during movement. J Neurophysiol 102:3142–3155
106. Dimitriou M, Franklin DW, Wolpert DM (2012) Task-dependent coordination of rapid bimanual motor responses. J Neurophysiol 107:890–901
107. Omrani M, Diedrichsen J, Scott SH (2013) Rapid feedback corrections during a bimanual postural task. J Neurophysiol 109:147–161
108. Todorov E, Jordan MI (2002) Optimal feedback control as a theory of motor coordination. NatNeurosci 5:1226–1235
109. Scott SH (2004) Optimal feedback control and the neural basis of volitional motor control. Nat Rev 5:532–546

Pratik Mutha is an Assistant Professor in Biological Engineering and the Center for Cognitive Science at the Indian Institute of Technology (IIT) Gandhinagar. He received his Bachelors in Engineering from the College of Engineering, Pune and his Masters and PhD from the Pennsylvania State University, USA. After a 4-year postdoctoral stint at the New Mexico Veterans Affair's Healthcare System, USA, he joined IIT Gandhinagar in late 2013. Dr. Mutha's research interests lie in understanding the neural control human movement, and disruption in this control in patients with neurological injury. This research informs the development of novel rehabilitation strategies for neurologically impaired patients, thereby creating impact outside the lab. Dr. Mutha has been the recipient of a number of awards including the prestigious Ramanujan Fellowship of the Government of India.