Topical Review

Learning from the spinal cord

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The graceful control of multiarticulated limbs equipped with slow, non-linear actuators (muscles) is a difficult problem for which robotic engineering affords no general solution. The vertebrate spinal cord provides an existence proof that such control is, indeed, possible. The biological solution is complex and incompletely known, despite a century of meticulous neurophysiological research, celebrated in part by this symposium. This is frustrating for those who would reanimate paralysed limbs either through promoting regeneration of the injured spinal cord or by functional electrical stimulation. The importance of and general role played by the spinal cord might be more easily recognized by analogy to marionette puppets, another system in which a brain (the puppeteer's) must cope with a large number of partially redundant actuators (strings) moving a mechanical linkage with complex intrinsic properties.

This symposium covered learning *about* the spinal cord (e.g. interneuronal systems, central pattern generators) and learning *in* the spinal cord (e.g. training, plasticity, regeneration). Attempts to reanimate paralysed limbs by functional electrical stimulation (FES) are concerned mostly with bypassing the spinal cord, so there is a tendency to think that it is largely irrelevant. In fact, the spinal cord is an important existence proof that sensorimotor control of limbs is possible despite their formidable 'design limitations'. The spinal cord circuitry enables the central nervous system to generate robust, graceful, effective and efficient behaviours that transcend the capabilities of conventional robots despite their much faster and more accurate sensors, actuators and servocontrollers. For this reason, we would do well to learn *from* the spinal cord, especially if we are trying to repair or replace it.

Therapeutic strategies

This paper considers four different strategies for treating spinal cord injury that interact very differently with spinal cord function.

(1) Regeneration, in which severed axons are induced to grow across the injury site and re-establish functional connections with distal spinal circuits.

(2) Spinal cord microstimulation, in which electrical pulses activate spatially localized spinal neural processes resulting in distributed state changes produced by the spinal circuits themselves.

(3) Quasirobotic FES, in which the muscles are treated as independently controlled actuators that are activated electrically to produce the computed joint torques required to produce the desired movement.

(4) Biomimetic FES, in which independent channels of stimulation and sensing in the muscles are co-ordinated by prosthetic regulator algorithms modelled on spinal interneurons.

The primary motivation behind research on FES starting in the 1960s was the generally accepted notion that CNS neurons were incapable of regenerating severed connections. Recent progress (discussed elsewhere in these reviews) has shown this to be untrue as an absolute, but the ultimate safety and efficacy of the methods involved remain much in doubt. Clinical and laboratory FES have been severely limited, however, by the practical problems of electroneural interfaces. The conventional approaches to instrumenting the body with multiple sensors and stimulating electrodes (transcutaneous, percutaneous, or fully implanted) have encumbered and distracted researchers, clinicians and patients from the real task at hand (Fig. 1, inset). For example, one of the main motivations behind quasirobotic control of individual muscles has been the lack of sensors required to implement more distributed control algorithms. One of the main motivations behind spinal microstimulation has been that it circumvents the technological and surgical problems of gaining access to large numbers of individual, widely distributed muscles.

We have been developing a new class of wireless, injectable microelectronic modules (called BIONs – BIOnic Neurons) that appears to overcome many of these logistical problems (Fig. 1; Cameron *et al.* 1997; Loeb &

Richmond, 2000; Richmond *et al.* 2000). Success in this endeavour will force us to confront the primitive state-of-the-art and limited applicability of robotic control theory and the lack of any generally accepted 'theory of computation' to describe biological sensorimotor control. These shortcomings have an impact on many endeavours in which biological and electronic systems must interact. For example, despite all the resources now going into computed animation, the motion picture industry still creates most action scenes by tediously capturing the natural movements of live actors wearing reflective markers, using the software only to add a virtual 'skin' and external props and scenery. Similarly, robots on assembly lines usually mimic the recorded movements of skilled humans rather than compute their own trajectories.

Conceptual problems

Even if the technical problems of establishing biological or prosthetic interfaces are solved, the control of multiarticulated limbs operated by real muscles remains a daunting task. The various strategies that have been suggested need to be considered in the light of how the intact spinal cord successfully performs this task. Some of the features that particularly should concern us are illustrated anatomically in Fig. 2 (adapted from Szentagothai & Rethelyi, 1973) but the functional implications must be updated in the light of more recent research.

First, the well-known segregation of the motor nuclei into narrow columns with rostrocaudal and mediolateral topography (Romanes, 1951) is misleading because the columns extend over two to three segments and their huge dendritic trees are distributed over the entire ventral and intermediate horns (Burke, 1979; Rose & Keirstead, 1988).

Second, the segmental interneurons that were originally associated with homonymous reflexes generated by a single sensory modality (e.g. Ia reciprocal interneurons, Ib inhibitory interneurons) are now known to receive descending and afferent inputs from many modalities and to project widely to many motor nuclei and to other interneurons (McCrea, 1986).
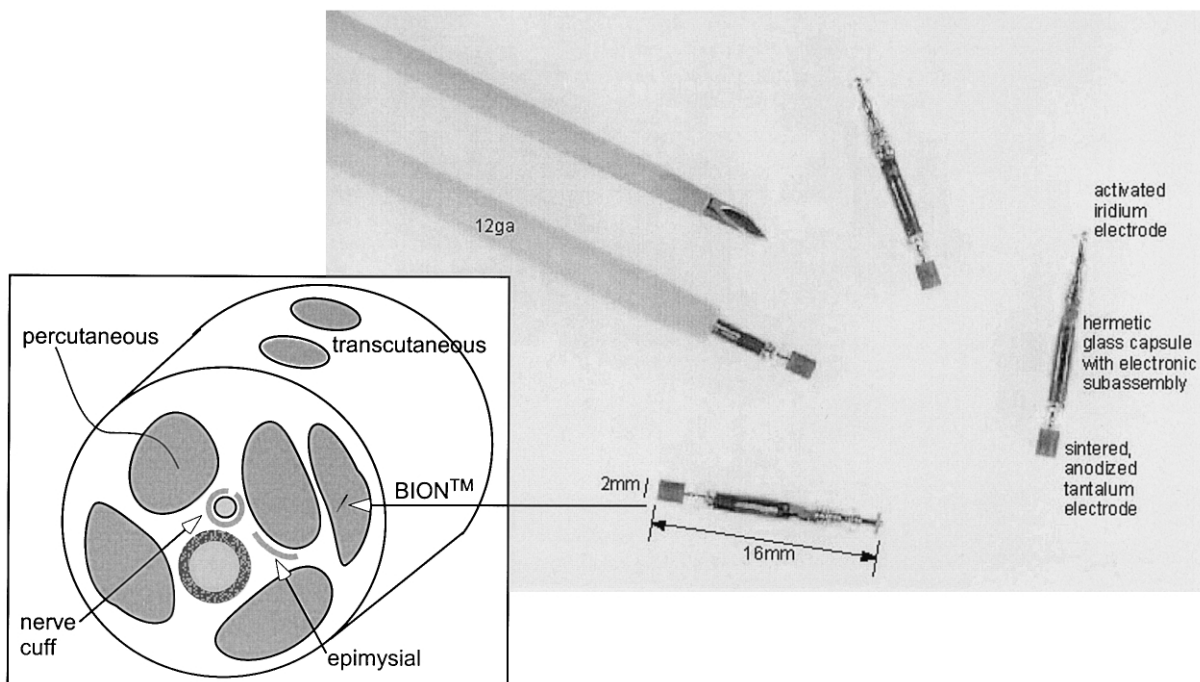
Figure 1

Various approaches to stimulating muscles include transcutaneous and percutaneous electrodes and surgically implanted multichannel stimulators with electrodes attached to nerves and muscles. BION implants are shown as they would be injected into muscles through a 12 gauge (ga) hypodermic needle. Each wireless implant receives power and digitally addressed and encoded commands from an external controller and transmission coil. This system is in clinical trials to prevent disuse atrophy and related complications of upper motor paralysis as a result of e.g. stroke and spinal cord injury. Work is underway to incorporate various modalities of sensors and back telemetry into such modules. In principle, co-ordinated stimulation of many muscles could reanimate a paralysed limb, but this will require substantial advances in the sensing of command and feedback signals from the patient and in emulating the complex and poorly understood control circuitry of the brain and spinal cord.

Third, most of the descending control terminates on spinal interneurons rather than projecting directly to moto-neurons, particularly for proximal limb muscles. The propriospinal circuits that appear to co-ordinate the muscles of an entire limb during finely controlled tasks tend to be clustered at the rostral end of the segmental representation of the limb (Lundberg, 1992; Pierrot-Deseilligny, 1996).

Fourth, the central pattern generators of the spinal cord are also somewhat more localized than the motor nuclei that they control (Grillner & Zangger, 1979), while their outputs play a much broader role in setting the gains of widespread spinal reflexes by exciting or inhibiting spinal interneurons (Burke, 1999).

These considerations pose problems for each of the treatment strategies outlined above.

(1) Regenerating axons must not only form synaptic connections, but they must also have sufficient specificity to provide functionally useful and stable effects. Many, if not most, of the developmental cues that permit useful connections to form during embryogenesis are not present and probably cannot be recreated in the rather cluttered adult spinal cord.

(2) Spinal cord microstimulation is likely to activate a highly unnatural admixture of adjacent circuits subserving many different, potentially competing functions, resulting in
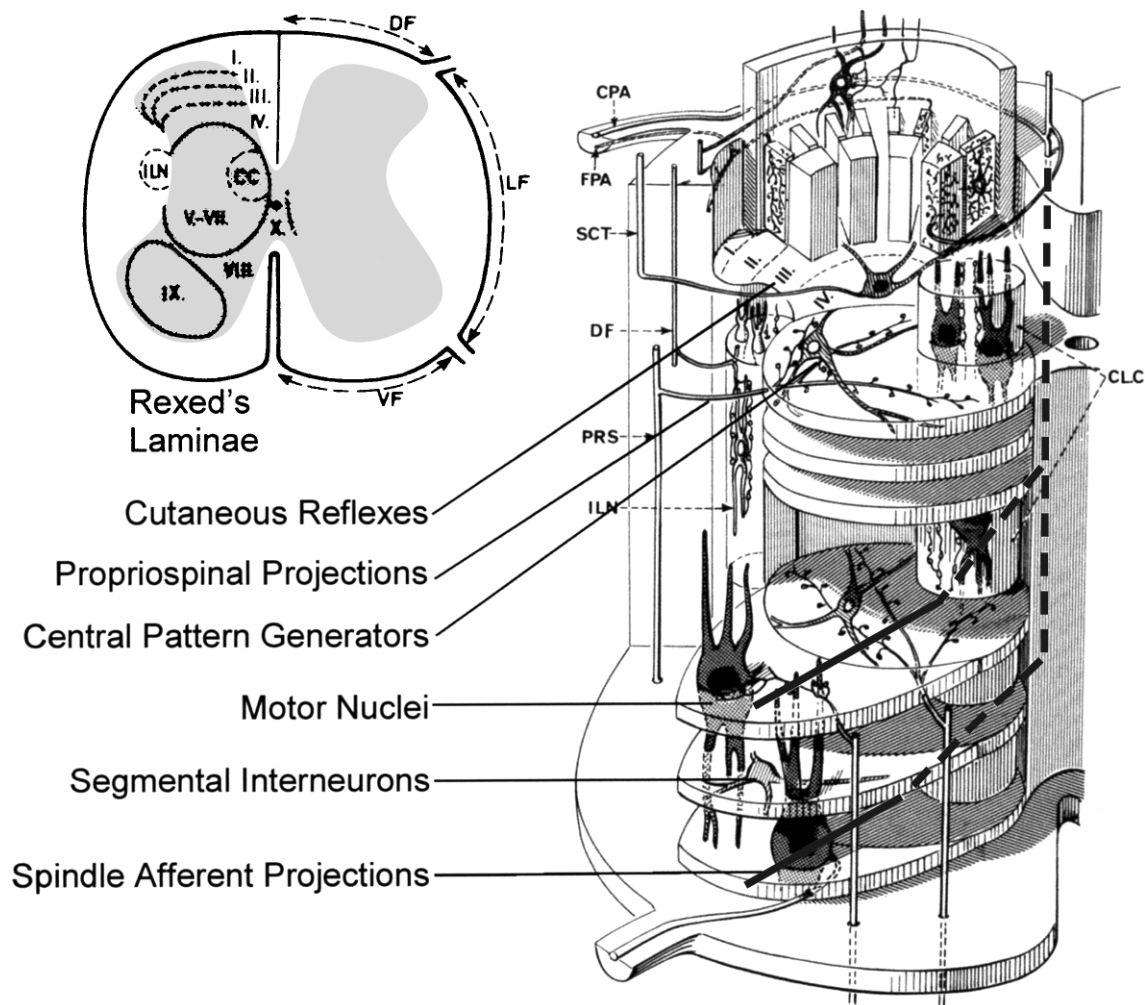
Figure 2. Anatomical arrangement of spinal circuits responsible for normal sensorimotor regulation in adult vertebrates

Regenerating axons from many different sources will have to find their way to the appropriate neurons in this cluttered space. Many of these circuits are likely to be stimulated directly or indirectly by intraspinal microstimulation. If these circuits are bypassed by peripheral FES, at least some of their functionality must be incorporated into the algorithms for controlling the FES. DF, dorsal funiculus; LF, lateral funiculus; VF, ventral funiculus; ILN, intermediolateral funiculus; CC, CLC, Clarke's column; CPA, coarse primary afferents (thick dashed line denotes longitudinal and transverse projections of proprioceptive afferents to various motor nuclei); FPA, fine primary afferents; SCT, spinocervical tract; PRS, pontorubrospinal. (Modified from Szentagothai & Rethelyi, 1973.)

poorly controlled and inefficient patterns of muscle activation.

(3) Quasirobotic FES control bears little similarity to natural spinal cord function, suggesting that it may lack features that are essential for the stable control of muscles (as opposed to torque motors) and that the operator may have difficulty in learning how to control this foreign system.

(4) Biomimetic regulators have to make decisions about which subsets to include from the extremely rich set of naturally occurring spinal circuits.

Understanding the task

The severity of and possible remedies for each of the above problems are difficult to appreciate in the absence of an overall theory of computation for spinal cord functions. Theories of computation are often expressed as analogies to other, more familiar machines. In order to describe the function of the spinal cord, we have previously used the analogy of the regulator, a multi-input, multi-output system of distributed interconnections with adjustable gains (He *et al.* 1991). Engineering control theory has provided an elegant set of mathematical tools to design and program regulators for complex functions, at least if one is willing to accept certain constraints on system properties and performance criteria (Athans & Falb, 1969; Stein & Athans, 1987). The CNS would not be expected to embody such tools, but it seems likely to arrive at similar solutions and to be able to handle less-constrained problems by employing adaptive neural networks. Nevertheless, complex regulators are not familiar to most laypersons or neuroscientists. They have generally been used by engineers to solve non-motor problems such as process control in oil refineries. A more accessible and intuitive analogy that captured spinal cord function at least qualitatively might be helpful.

Some deceptively simple mechanical structures that present many of the problems and solutions of biomechanical control are illustrated in Fig. 3. Marionettes represent the elite of puppetry, the art of creating and operating animated figures to perform as surrogate actors. They are an elite specifically because they require a high level of knowledge and skill. The audience usually assumes that most of that expertise resides in the operator during the performance. The real craft, however, is in the design of the marionette and its control apparatus so that together they naturally tend to produce realistic movements without placing excessive demands on the operator (Coad & Coad, 1993).

The obvious analogy is that the marionette puppet represents the musculoskeletal system and the operator represents the brain, leaving the deceptively simple handheld pieces on which the strings are attached to represent the spinal cord (Fig. 4). To a puppeteer, however, the design of the handheld control is neither simple nor obvious; it requires a thorough integration of the intrinsic mechanical properties of the puppet with the range of movements and tasks it must perform. The mechanics of the puppet account for the nominal trajectory of motion in response to a particular pattern of tugs from the strings. The handheld control causes simple movements of the operator's hand to result in simultaneous tugs and relaxations on many strings. Reactive forces from the puppet and any external obstacles propagate backward to the control, where they
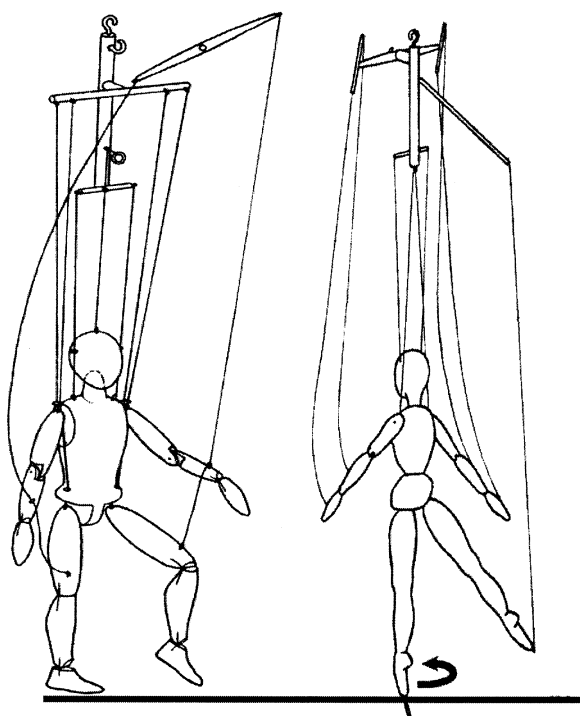
Figure 3

Two marionette puppets (analogous to musculoskeletal systems) with their handheld controls (each analogous to the spinal cord when given a particular functional set by descending commands from the brain). While there are similarities in general form between the puppets and the controls, there are many differences that reflect the performances for which they are specialized. Changes in the mechanics of the linkage require complementary but non-obvious changes in the stringing of the control. Adapted from Fraser (1971).

result in additional, complexly distributed movements of the strings that occur more rapidly than the voluntary reaction time of the operator. The operator can change the nature of these reactions by adjusting the orientation and stiffness of his/her grip on the control and by modifying the linkage itself by repositioning moveable parts of the control during the performance. Thus, the marionette would seem to be endowed with all of the fundamental properties of hierarchical sensorimotor control (Loeb *et al.* 1999): a descending voluntary control system (operator) that acts indirectly on the musculo-skeletal plant (puppet) via an intermediary (handheld control) that distributes both nominal commands and conditional reflex responses to a wide range of actuators (strings).

In principle, a marionette operator could forego the handheld control by tying each of the puppet's strings to a separate finger of each hand. The intrinsic mechanics of the puppet (nature of the articulations, weight of the segments, attachment points for the strings) would still be important in producing the emergent behaviour, but the degrees of freedom would not be constrained by the rigid mechanical linkage of the handheld control. The burden of creating the co-ordinated pattern of string movements and of responding to reactive forces would then fall entirely on the manual dexterity of the operator. Alternatively, the marionette operator could simplify the

problem by gathering the loose strings together into bundles based on some simple factor such as the physical proximity of their origin on the puppet. Early marionette designs using both these schemes can be found, but they have not survived the evolution of the art.

Unfortunately, current strategies for FES control of limbs seem to be analogous to some of the naive strategies embodied in primitive marionettes. Designers of FES systems to stimulate peripheral nerves and muscles tend to focus on the selective stimulation and control of individual muscles (analogous to the distal termination of the strings) rather than their natural co-ordination (analogous to the design of the handheld control and the origin of the strings attached to it). Explicit, direct control of individual muscles, using either feedforward or feedback servocontrol, represents an attempt to ignore entirely the natural function of the spinal cord (e.g. Crago *et al.* 1996). Intraspinal microstimulation represents an attempt to simplify spinal cord functionality on the basis of gross anatomical proximity (Mushahwar & Horch, 2000; Tai *et al.* 2000). Microstimulation necessarily depends on the weak topography of the spinal cord, overlooking the complex but highly specific circuitry that lies within. Note that what is important in a marionette is not where the strings attach to the skeleton (i.e. what muscles do when they contract) or where they are attached to the control (i.e. segmental and mediolateral

Figure 4

The marionette operator (analogous to the brain) creates most of the puppet's movements through the handheld control (analogous to a spinal cord controlled largely by corticospinal projections to propriospinal and other interneurons). Certain individuated movements of the puppet's hands are facilitated by positioning the strings to these structures (as seen more clearly in the inset view from above) so that they can be manipulated individually (analogous to corticomotoneuronal projections). Adapted from Frascone & Frascone (1998).
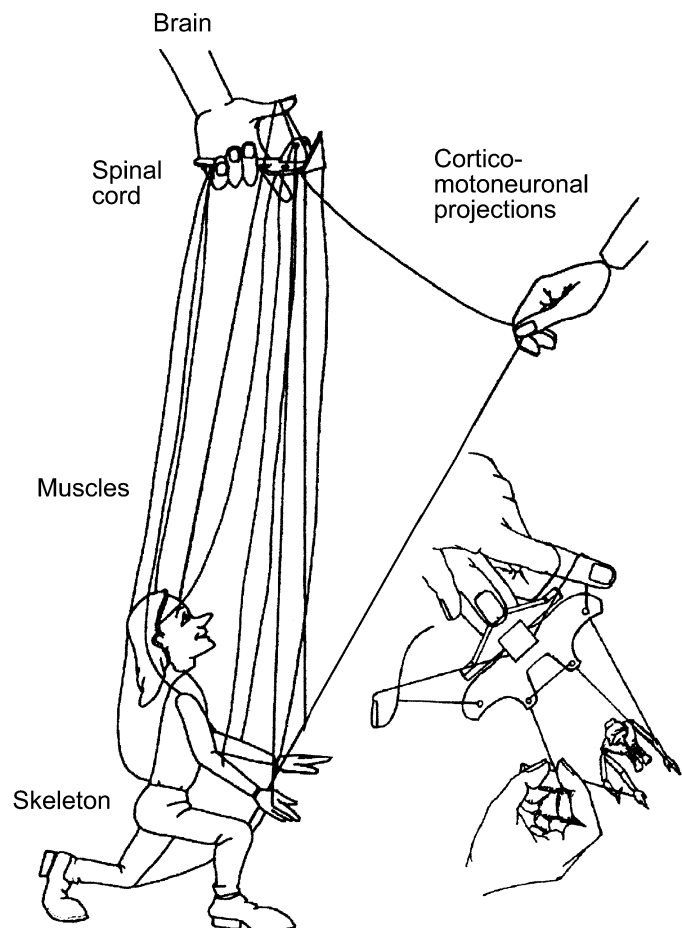
arrangements of the motor nuclei) but how they are functionally linked by the mechanics of the handheld control (i.e. interneuronal circuits).

Using our knowledge base

This symposium celebrates the meticulous electrophysiological and microanatomical methods pioneered by Sherrington, Eccles, Lundberg, Jankowska, Burke, Rudomin and many others. This approach has provided a detailed but still incomplete representation of the sensorimotor connectivity of the spinal cord and the manner in which it may be controlled by the brain. If the spinal cord is the existence proof that FES is possible, then we ignore this knowledge at our peril. The trick is to distill the myriad details now available from interneuronal circuits identified in various limbs and species into a manageably simplified theory of computation for the spinal cord. Ironically, the broad framework of such a theory has existed from the early days of spinal cord research. It arises naturally from clinical observations of natural and pathological behaviours and reflexes and from the related concepts of reciprocal and non-reciprocal inhibition, flexor and extensor synergies, and half-cycle oscillators and reflex gating. We now know that these concepts represent a limited and simplified subset of spinal cord functions and circuits, but they are also broadly and generally correct and therefore useful. They are certainly better than conceptual organizations like 'force-field primitives' (e.g. Giszter *et al.* 1993) that have no discernible link with the cellular organization and connectivity so meticulously characterized over the past century of spinal cord physiology. It is better to have a coarse but accurate map that leaves out many side streets than to have a map of a fictional city.

The analogy to marionettes can provide us with at least one further insight into how to bend the body of spinal cord data to the problems of sensorimotor rehabilitation. If we look at a large number of different handheld controls for marionettes, we can easily note broad similarities as well as individual differences. Some of the differences are inconsequential accidents of their evolution by differing schools of puppetry, each of which has discovered a physically different but functionally equivalent machine. Most of the differences can be related to differences in the mechanics of the puppet or specializations in their repertoires (e.g. puppets that ride bicycles, tumble like clowns or even hang by their heels).

The designer of a new marionette will start with a general control template that is known to work in most circumstances, modify it based on experience with the desired movements in similar puppets, and then fine-tune it by trial-and-error adjustments of the strings and control pieces. The eventual performance of the marionette will depend as well on how effectively the operator learns to adjust his/her motor control strategies to eliminate residual errors. A biomimetic strategy for

rehabilitation needs to identify and respect the general principles of spinal circuitry, to design therapies that are tailored to the biomechanical and behavioural requirements of the patient, and then to enable the adaptive controller of the patient's brain to develop its own strategies for eliminating residual errors. In both situations, the operator would seem to have the best chance of adapting to a system if it were engineered to behave like a real spinal cord and musculoskeletal system, i.e. something with which the operator's brain is already familiar. The difference is that a marionette operator usually works alone to build the puppet, design and perfect the controls, and learn the performance, all on the basis of subjective experience and intuition. Larger problems like reanimating paralysed patients require teams of experts and a common, objective knowledge base that can be applied with quantitative analytical tools. The sheer complexity of the spinal cord and the clinical applications is daunting and may tempt us to abandon what knowledge we have in favour of magic bullets. Society has been well rewarded, however, by investing in science and engineering rather than magic.

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