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PROSTHETICS

A guiding light for stimulating paralyzed muscles

Jordan Williams[1,2]*

Improving the performance of closed-loop optogenetic nerve stimulation can reproduce desired muscle activation patterns.

For injuries such as spinal cord injury (SCI) that compromise the ability to move, reanimating paralyzed muscles is a much-desired goal because it can greatly improve independence and quality of life. A common approach to restoring muscle control in such cases is to reroute movement commands from the brain around a damaged connection (i.e., the injured spinal cord) and use those commands to artificially drive muscle activity. A new study by Herrera-Arcos and colleagues (*1*) looks at advancing alternative optogenetic strategies for stimulating muscle activity in these cases.

Among the options for stimulating muscle activity, direct functional electrical stimulation (FES) of muscles or nerves has long been a traditional target. Although FES has shown some success in restoring control of paralyzed muscles in patients with SCI (*2*), it faces drawbacks such as the order in which it recruits muscle activity, traditionally thought of as nonphysiologically recruiting large motor units before small motor units (*3*, *4*). As a result, sustained periods of FES can often cause muscles to fatigue quickly.

With the introduction of optogenetics, a technology that genetically modifies neurons with light-sensitive ion channels ["opsins," e.g., channelrhodopsin-2 (ChR2)] to make them responsive to light, a new approach to restoring paralyzed muscle activity has emerged. First examined by Llewellyn *et al.* (*5*) in opsin-labeled nerves of transgenic mice bred to express ChR2 throughout their nervous system, functional optogenetic stimulation (FOS) of peripheral motor nerves has shown promise in alleviating drawbacks of FES while offering attractive benefits, including the possibility to genetically specify what targets are responsive to light. Specifically contrasting with FES, FOS of an opsin-labeled motor nerve has demonstrated graded recruitment of muscle activity closer to the body's normal physiological mechanisms (Fig. 1 Ai) also allowing target muscles to reside in a moderate activation range for longer periods without fatiguing.

Despite these advantages, an important consideration for FOS is the channel dynamics of a given opsin. Just as opening and closing rates for voltage-gated sodium and potassium channels govern a neuron's excitability and action potential shape, the opening/closing rates for ChR2 dictate how an opsin-labeled nerve responds to light, how frequently it can be stimulated, and so on. When an opsin-labeled nerve is subjected to a continuous train of light pulses, its response decays (Fig. 1 Aii) at a rate related to its opsin dynamics and stimulation rate. At elevated frequencies (>30 Hz), this nonlinear response can be pronounced and make producing desired activation patterns difficult.

The current study focused on addressing this challenge. The group had previously demonstrated closed-loop FOS control of muscle activity in rats injected with a virus for nerve ChR2 expression, scaling light intensity on the basis of differences between desired muscle activity and actual responses (*6*). The authors built on this demonstration by explicitly incorporating models of the optical recruitment properties and opsin dynamics described above into their control scheme. The authors first characterized optical muscle recruitment properties in transgenic mice and described two advantages of FOS over electrical stimulation: a more graded recruitment of muscle activity similar to Fig. 1 Ai (as expected from prior studies) and a wider total dynamic range of muscle activations including greater maximum force, suggesting that FOS can activate motor nerve axons that are inaccessible to electrical stimulation. These results imply that FOS not only can smoothly recruit fine changes in muscle force but may also be able to recruit stronger maximum contractions.

The researchers then modeled the nonlinear decay of force with sustained FOS by exposing the nerve to a library of light stimuli with random pulse widths and interpulse intervals. The resulting exponential decay model (Fig. 1 Aii) was combined with the above optical recruitment model and a standard muscle dynamics model to predict time-varying muscle forces resulting from optical nerve stimulation.

As the primary innovation of this study, these opsin models were incorporated into a closed-loop control scheme for optically stimulating a goal muscle force pattern. Expanding on their previous study, the authors used these models to add an initial "feedforward" estimate of optical stimuli needed to produce a desired force. This estimate was then modified by real-time force error feedback to generate the output light stimulus (Fig. 1A). The authors compared this closed-loop FOS scheme including opsin dynamics with a similar FES scheme and an FOS version without opsin dynamics. By forming a better initial estimate of appropriate light stimuli, the FOS model including opsin dynamics improved in several performance metrics over the other two approaches (only comparisons versus FES are shown; Fig. 1B). These included more accurate reproductions of desired force patterns and improved transient responses (i.e., rise/settling times and percent overshoot). However, perhaps most notable, the authors' highlighted approach dramatically increased the time over which a muscle could tolerate stimulation before fatiguing, showing relatively accurate force tracking throughout an entire 1-hour session with minimal fatigue. By comparison, fatigue from FES was so pronounced that it was unable to modulate force after only 15 min of periodic stimulation.

These results present compelling steps toward translating FOS for rehabilitation purposes. FOS's ability to recruit muscle activity in a graded manner could facilitate the restoration of fine, precise movements such as those used for dexterous tasks (e.g., picking up an egg

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[1] Joint Department of Biomedical Engineering, Marquette University and Medical College of Wisconsin, Milwaukee, WI, USA. [2] Department of Neurosurgery, Medical College of Wisconsin, Milwaukee, WI, USA.
*Corresponding author. Email: jordan.j.williams@marquette.edu

without breaking it). This result further leads to the observation of reduced stimulation-induced fatigue with FOS because it can better use the range of motor units. Thus, FOS could enable stimulation of sustained, periodic muscle activations such as those during walking. Last, the authors demonstrate that closed-loop FOS incorporating feedforward opsin dynamics improves both the accuracy of force production as well as transient responses. Importantly, this improvement is seen not only over FES but also over FOS using only feedback to modulate light stimuli, highlighting the utility of this approach in fully realizing FOS's potential benefits.

Although FOS shows promise for reproducing useful movements, further investigation is warranted in several areas. This study used transgenic mice with robust nerve ChR2 expression. It is unclear how these results would extend to wild-type animals with more clinically relevant (but potentially incomplete or weak) viral-mediated opsin expression. By necessity, these experiments were performed in anesthetized animals with acute optical stimulation and muscle force measurements to develop the models described above. In addition, the template force profiles in this study followed stereotyped, periodic square or sinusoidal patterns on a relatively slow order of 0.5 Hz. Given these limitations, important milestones needed to translate this control system would therefore include the development of chronically implantable light sources [e.g., wireless LED nerve cuffs (*7*)] capable of similarly modulating light delivery, reproduction of dynamically rich muscle activation patterns analogous to those observed during natural locomotion or reaching, incorporation of chronic sensors or biological signals capable of providing appropriate feedback, and demonstration of such a control scheme in awake, behaving animals. Last, before any move toward clinical translation, optogenetic techniques must be scaled toward human proportions including virus delivery and expression in multiple muscle targets as well as optical stimulation of nerves an order of magnitude or larger than those examined here. We have previously demonstrated some success in nonhuman primates toward this goal (*8*), but much refinement is necessary before achieving control comparable to that in the current study.

In conclusion, the current study provides an important advancement in peripheral optogenetic neuromodulation technology. These results centered on closed-loop optical motor control will serve as an essential piece of a multifaceted approach needed before such technologies may be applied to restoring movements in devastating conditions such as SCI.

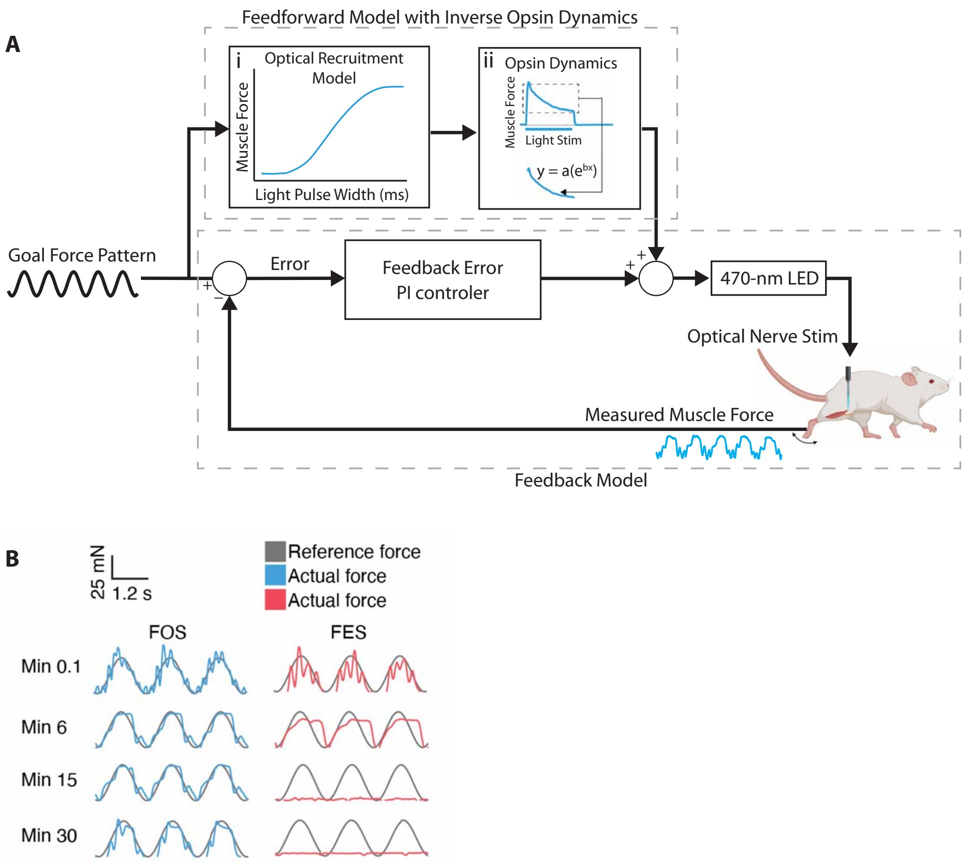

Fig. 1. Optogenetic nerve stimulation for real-time control of muscle force. (**A**) The optical stimulation control scheme used by the researchers combines a closed-loop feedback model (lower dashed box) and feedforward prediction model (upper dashed box) to modulate blue light delivered to an opsin-labeled mouse nerve to stimulate a target muscle tracking a desired force pattern. The feedback model modulates LED light output using a proportional-integral (PI) controller on the basis of current and recent errors between a goal force pattern (black sinusoid) and measured stimulus-induced muscle responses (noisy blue sinusoid). Unique to this study, the feedforward model generates an initial estimate of appropriate light stimuli to produce a desired force on the basis of an inverse model incorporating (i) an optical recruitment model relating light pulse duration to force output and (ii) a nonlinear opsin dynamics model detailing how muscle force output exponentially decays over time when exposed to a sustained light input. (**B**) Combining the unique opsin dynamics model in the feedforward loop with the force feedback control scheme results in improved tracking of desired muscle force with optical stimulation (blue traces) compared with functional electrical stimulation (red traces), both in terms of accuracy and the longevity of performance without fatigue.

CREDIT: ADAPTED FROM HERRERA-ARCOS *ET AL.* (*1*)

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