Create Hybrid Prostheses that Exploit Activity-Dependent Processes

TASK GROUP DESCRIPTION

Background

It is clear that a number of cellular processes within the nervous system are linked strongly to electrical activity within nerve cells. These processes include gene expression (West et al., 2002) and neuronal growth (Salimi and Martin, 2004), and patterned neuronal activity is also critical to neuronal cell birth (Diesseroth et al., 2004) and survival (Salthun-Lassalle et al., 2004). The link between neuronal activity and these activity-dependent processes may be through the magnitude and time course of intracellular calcium concentrations and subsequent activation of second-messenger pathways, as well as the dependence of release of neural signaling molecules on the pattern of neural activity. The release of neurotrophins (Lessmann et al., 2003), which contribute to neuronal plasticity and growth, is strongly linked to neuronal activity (Balkowiec and Katz, 2002).

In parallel with these scientific discoveries, engineers have developed methods to interface with and thereby control the electrical activity within populations of neurons. Fully implantable devices are available to stimulate reliably neurons in the brain, within the spinal cord, and in the peripheral nervous system. Electrical stimulation provides the ability to control electrical activity within neurons and therefore provides a means to enhance and control these activity-dependent processes.

Initial Challenges to Consider

Therefore, it should be feasible to bring together science and engineering to create hybrid prosthetic devices that employ regulated patterns of neuronal activity to harness the activity-dependent processes in neurons. In contrast to current implementations electrical stimulation of the nervous system as a modality to restore function (Peckham and Knutson, 2005), electrical stimulation becomes a modality to augment regeneration, repair, and plasticity in the nervous system (Grill et al., 2001). The prosthesis is the means to an end rather than the end itself.

This task group will examine the potential of and challenges associated with the use of electrical activation of the nervous system to provide a means to regulate activity-dependent biological processes in the nervous system, and thereby to create a hybrid prosthesis to exploit these processes.

Initial References

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TASK GROUP SUMMARY

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Summary

Challenged to design a radically new type of prosthesis, the group members chose to target the needs of a stroke victim. Stroke is the leading cause of adult disability in the United States. More than 700,000 people in this country suffer strokes each year, and many are unable to recover the range of movement they enjoyed before the stroke. The group recognized a clear need for better treatments for stroke victims, especially treatments that could better address neurological symptoms.

When a person has a stroke that disables the motor system, therapies are available to help him recover function, so long as the damage is not too severe. Recent work has suggested that massed practice—focused, deliberate practice of a variety of tasks—can help restore function by building on the bit of mobility the person retains after the stroke. However, the group identified two problems with current therapies. First, in the case of moderate to severe motor disability, patients are taught to use their remaining function to take care of themselves rather than to recover the full function they knew before the stroke. For example, a writer who suffers this type of disability may recover the ability to feed himself but not the ability to type. Second, when the patient has no voluntary movement around a particular joint, there are no known restorative therapies.

If the person is too disabled to practice moving, therapists may be left struggling to find functional areas and abilities upon which to work. Unable to help him practice movements, they might wish to work directly with the motor circuitry of his brain. Here we have a problem of not knowing what is activated in the brain when the stroke victim tries to move. This lack of knowledge of the nervous system’s internal state represents a serious impediment to designing a strategy that would bridge the gap between intention and action. The group realized this leads to the old, deep question of “knowing the internal state”—in other words, completely understanding the brain, a question unlikely to be solved in the near future. To avoid having to decode the entire brain, they recognized the need to identify the minimum amount of information about the internal state that might be sufficient for a useful prosthetic. The hope was to replace the current trial and error method of restoring function with a more focused approach based on knowledge of how neural processing is affected by brain lesions.

The prosthetic the group imagined would work differently from both traditional stroke therapies and other prosthetics. Where traditional stroke therapies might leave the patient dependent, this prosthetic would assist the patient not only with daily activity but also with fully recovering lost function, eventually making itself obsolete. Where traditional prosthetics try to replace missing parts, this prosthetic would serve to link existing parts, effectively connecting damaged brain and body to functional ability in order to restore independence.

To imagine the device clearly the group considered how it would address the *internal state*, how it would be *hybrid*, and how it would exploit activity-dependent processes to assist *plasticity*. With an outline for this device in place the group hoped similar techniques could be applied to facilitate the healing process for multiple types of neurological injury and disease.

Internal State

The group quickly realized that building this dream device and using it would require finding a way for the machine to interface with the human brain, spinal cord, and peripheral structures. The device would need to read the brain's signals and return signals that the brain could read and interpret. It would need to cooperate with and enhance the brain's ability to compensate and adapt to the environment and environmental challenges. Finally, it would need to prevent the patient’s brain from forming potentially harmful adaptations in the process of recovering from the injury.

While the potential device might need to have a high degree of sophistication and bandwidth to interface with the brain's relevant processes, the group found examples of crude forms of that intimacy in current technology. One member described the integration he has seen between upper-extremity amputees and their prosthetic arms. Once people learn to use the arm consciously, he said, they begin to use it unconsciously, talking with their hands and gesturing casually.

This example gave the group hope that through the use of the cutting-edge technologies of today and the near future, it would be possible to build devices that link ever more closely to the humans they are meant to help.

Hybrid

The device the group imagined was hybrid in many ways. They imagined a prosthetic system that united the body's biological processes with the system's synthetic ones. The device could intervene on the body's behalf by applying electrical stimulation, activating engineered tissue, delivering gene therapy, or supporting and amplifying remaining mental or muscular function. At the same time it could record progress, receiving feedback from the body that would teach it which interventions were the most helpful and providing feedback to the brain that would fill in gaps left by neurological damage. Finally, the device would be a hybrid because it would serve a hybrid *purpose*. In one way it would work as a traditional prosthetic, assisting the body in carrying out necessary tasks. In another way it would be a prosthetic means to an end, helping to rehabilitate the body with the goal of reducing the body's need for the prosthetic's assistance.

To function as a means to an end the prosthesis would need to insert itself into existing circuites in the brain, so it could assist wounded neurological tissue. Since much of the brain's ability to control the body's systems and adapt to situations depends on neuronal activity, the prosthetic would stimulate that activity at the appropriate times or amplify the signals of a few intact neurons.

A hybrid prosthesis would be fundamentally different from a traditional prosthesis. Rather than allowing the device to remain in a static relationship to its user, the hybrid prosthesis would incorporate three elements: the user, the adaptable prosthetic device, and a training or therapeutic regime. In the course of the patient’s use of the device these three elements would adjust in relation to each other so that the patient would be gradually trained to function without the device.

Plasticity

Plasticity is the ability of the brain to change in response to learning or experience. Devices such as the cochlear implant have shown the power of this phenomenon. While the cochlear implant has been very successful at restoring lost hearing, that success is not achieved by replacing the damaged cochlea with an exact replica. Instead, the device takes advantage of the brain’s ability to reorganize itself to make good use of the auditory inputs the implant does provide. By harnessing the brain's inclination to adapt positively, a great deal of function can be restored in the face of hearing loss. Following this example group members hoped to make their device use the same helpful tendencies of the brain.

The mechanisms that control plasticity are activity-dependent processes; effects in the brain that have different consequences depending on whether the affected neurons have recently fired (see sidebar for more information). Group members intended the device to make use of these processes to increase positive brain plasticity at times when the patient is trying to learn to restore lost function.

Other suggestions for ways to increase the brain's receptivity to the device's interventions included inserting engineered tissue, stimulating the brain, and using rehabilitation techniques, such as focused, deliberate practice of a variety of tasks.

Questions and Recommended Research

While the concept of a new type of prosthesis seemed promising, the question of the internal state remained a major hurdle. The group tried to find ways to define the success of the device by measuring easily observable external signals. It would be necessary to know the internal state or some approximation of it in real time, in order to see what effect, positive or negative, an intervention was having.

The group's recommended areas of research and identified knowledge gaps focused on unlocking the mystery of these internal states and making use of them. They wanted to understand how plasticity works in an injured system, and to learn how to control, activate, and facilitate plasticity and recovery. The limits of plasticity also need to be discovered. Though much remains to be learned about the rules governing plasticity and its limits, the group agreed that taking advantage of the brain's plasticity mechanisms was desirable. To achieve that goal they suggested research into the following questions:

- How far is the brain able to adapt?
- Is there a limit to neuronal adaptation?
- Are there focal neural areas that need to be targeted for an intervention to be most effective?
- What are the critical factors, internal to the system, that enhance neural plasticity?

These questions are the beginning of the journey to solve the mystery of the brain, prosthesis, and function.

The connection of internal to external was also an area the group wanted to explore further. What would be an adequate way to represent the internal state in order for a device to interface with the neurological system? How could they drive a system toward a desired internal state and what might that desired state be? How could a feedback loop be set up between the brain and a prosthetic device?

In addition to addressing these questions group members also suggested more research into methods they hoped to incorporate in their hybrid prosthesis. For example, they suggested further research into the safety, efficacy, and reality of using gene therapy and tissue transplants. They also found promise in current approaches such as functional electrical stimulation and powered prostheses.

The Vision

If it is possible to extend current knowledge of the brain's processes to the necessary next level, people may be able to build the device the group imagined. One group member described what the device might look like for the person with the severe stroke.

The device he would wear would be a very “smart” hybrid prosthetic with many redundant systems. It would possess motors that could help move his limbs if necessary. It would be able to stimulate his muscles or his brain. It would be able to measure performance and adapt its function based on the measurements it made.

Maybe the stroke victim wants to reach for a glass of water. The system registers the initial signal from the brain that attempts to begin a movement in his arm. If he is successful and he reaches for the glass without any help from the device, it simply records the event. If, on the other hand, he is not able to do it alone, the device begins to assist, trying various strategies one after another. It would begin with the slightest interventions and if those were unsuccessful, would progress to the point that it used its motors (effectors) to move the man's arm for him if necessary. In the process it would observe which interventions worked and were most effective. Over time it could reduce the types of stimulation and intervention it used as the man recovered and gained better control of his arm. This long-term outcome would be considered analogous to skill learning of the very smart hybrid prosthetic.

The person suffering the debilitating neurological effects of a stroke represents one user who could benefit by exploiting activity-dependent processes to help the body help itself. But the work described above could be extended to improve neurorehabilitation for a variety of conditions. The more effectively the prosthetic can interface with the user, the more it could reach the seemingly unreachable cases that need the most assistance but are most difficult to help.

SIDEBAR

Activity Dependent Processes: What is Known

By George Wittenberg

We know a great deal about the rules governing CNS neuronal plasticity in animal models. The most familiar model is LTP in the hippocampus,[1] in which coordinated pre- and postsynaptic activity leads to increased synaptic strength. LTP occurs at a synapse, at least partly, by a mechanism in which presynaptic release of glutamate onto postsynaptic NMDA receptors leads to an increase in synaptic efficacy, if the postsynaptic neuron is active close to the time of that release of glutamate. But there exist other mechanisms for LTP, with other important transmitters and mediators.

Besides LTP there are *homeostatic* mechanisms that tend to maintain mean neuronal firing rates near a criterion. One might not think that homeostatic mechanisms as supporting recovery, but if the nervous system were in homeostasis prior to injury, the firing rates of neurons would be changed by injury and homeostatic mechanisms might restore function by changing a few, more global parameters. Homeostatic mechanisms may be useful in development, may be detrimental after injury (e.g., by causing spasticity), and may underlie recovery from diaschisis. Homeostatic mechanisms include synaptic scaling, a nonspecific change in synaptic strength, and changes in neuronal excitability. Synaptic scaling is partly mediated by activity-dependent release of brain-derived neurotrophic factor (BDNF). BDNF is released and transferred to postsynaptic neurons in an activity-dependent manner.[2] Neurons regulate intrinsic excitability to promote stability in firing.[3,4]

There are also other synapse-level kinds of plasticity. Synaptic *augmentation*, a longer-lasting form of facilitation could enhance the ability of a neuronal circuit to sustain persistent activity after a transient stimulus, and this has been demonstrated in a competitive model of sensory integration in spinal cord neurons.[5] Long-term synaptic depression (LTD) is an important complementary phenomenon to LTP, because it can prevent runaway increases in synaptic strength and because it can reduce activity in ineffective neuronal pathways. Endogenous cannabinoids may mediate LTD, with the timing of their breakdown influencing the time window for long-term plasticity.[6] Endocannabinoids are important to glutamate-dependent motor plasticity in mice[7] and deletion of an endocannabinoid receptor is associated with reduced exploratory behavior.

In summary, restoration of normal function in a damaged neuronal network depends on activity-dependent changes in excitability and synaptic strengths. Known activity-dependent mechanisms include synaptic scaling, changes in excitability, timing dependent mechanisms such as LTP and LTD, and shorter-term activity-dependent mechanisms such as synaptic augmentation. There are anterograde molecules—glutamate, BDNF, among others—and retrograde molecules such as endocannabinoids and nitric oxide. These processes and signaling molecules are targets for hybrid prosthetic interventions. Still, as Robert Froemke pointed out: Knowledge of how any of these factors influence actual neurorehabilitation in human patients is sorely lacking.

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