Experimental and Theoretical Approaches

Natural and Accelerated Recovery from Brain Damage

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The goal of the Caltech group is to gain insight into the processes that occur within the primate nervous system during dexterous reaching and grasping and to see whether natural recovery from local brain damage can be accelerated by artificial means. We will create computational models of the nervous system embodying this insight and explain a variety of clinically observed neurological deficits in human subjects using these models.

The Caltech group of the Defense Advanced Research Projects Agency (DARPA) Reorganization and Plasticity to Accelerate Injury Recovery (REPAIR) program consists of a close collaboration among four laboratories: the Andersen laboratory at the California Institute of Technology, the Schieber laboratory at the University of Rochester, the Thakor laboratory at Johns Hopkins University, and the Loeb laboratory at the University of Southern California. The overall effort examines natural recovery from brain damage to develop techniques that can accelerate recovery. In the future, these approaches may be applied to help soldiers and civilians with brain injury.

We will use the sensorimotor system of nonhuman primates as a model system because it shares common features with the human nervous system. In particular, we will focus on the parts of the brain that plan dexterous reaching and grasping. Activity from the various brain circuits involved in forming and executing these plans will be monitored while parts of the circuits are

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temporarily inactivated by applying pharmacological agents that produce local inhibition. The advantages of this technique, besides not producing any harm to the animals, include being able to produce highly localized inactivations of neural circuits that allow the fine functional dissection of neural networks. We will use these and other data to inform and validate computational models of the healthy and injured nervous system. A unique feature of our program is our focus on four distinct neurological deficits that occur frequently in humans: neglect, apraxia, hemianesthesia, and optic ataxia. We will use our computational models to account for the appearance of these deficits in our animal models and to suggest clinical strategies to recover function.

Figure 1 shows the basic circuit for sensory to motor processing in the primate brain. Sensory information for dexterous movements is derived in large part from vision and somatic sensation including touch and the sense of limb position. Visual inputs into the cortical circuits for reaching and grasping first arrive in large part in the parietal reach region (PRR) and the anterior intraparietal area (AIP), both within the posterior parietal cortex (PPC). Somatosensory signals enter the circuit a bit more directly as projections from the somatosensory thalamus (VPL) to the primary somatosensory cortex (S1) and later the PRR and AIP. Reaching and grasping are processed, to a large extent, separately in the cortex with reaching encoded by the PRR and the dorsal premotor cortex and grasping encoded by the AIP and ventral premotor cortex (PMv). These areas converge onto the primary motor cortex (M1) that issues commands for movements to the spinal cord, which in turn drives the muscles. In broad terms, the Andersen laboratory will be studying the neurophysiology of reaching and the Schieber laboratory will study the neurophysiology of grasping. The Thakor laboratory will be modeling the network of cortical areas and the Loeb laboratory will model the spinal cord and skeletal motor system.

Repairing Neglect and Optic Ataxia

The Caltech laboratory (http://vis.caltech.edu) will focus on two deficits that are caused by lesions to the PPC. One is referred to as *neglect*, in which patients can see and move but are not consciously aware of the side space opposite to the lesioned hemisphere and do not make voluntary movements into that half of the space. The second deficit is referred to as *optic ataxia*, in which patients cannot connect the perceived location of visual stimuli with the planning of accurate movements, as if vision has been disconnected from movement. One remarkable problem for optic ataxia patients is their grossly inaccurate reaches to seen objects.

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Neglect

We have developed an animal model of neglect by inactivating the PPC and pulvinar, the region of the thalamus that has direct connections with the PPC. In a free choice task, we find that the animals are biased and generally do not choose targets in the neglected visual field. We record activity using two methods. One method is functional magnetic resonance imaging (fMRI), in which the changes in blood flow related to changes in neural activity are measured. A great power of this technique is that it can image brain activity in the whole brain in a matter of seconds.

Figure 2 shows the eye movement activity in the cerebral cortex of a nonhuman primate for leftward eye movements, which activates the eye movement circuit in the right hemisphere, and rightward eye movements, which activates the left hemisphere.

A disadvantage of fMRI is that the temporal and spatial resolution is not as great as recording the electrical activity of single neurons. Thus, we will also be implanting around 500 electrodes throughout the cortical circuit, shown in Figure 1, to obtain added information from single neurons. From experiments over the

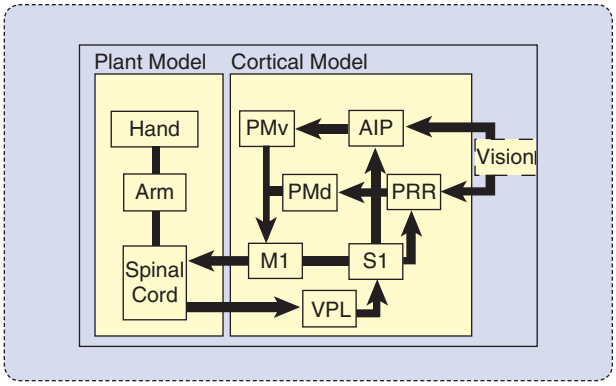


FIGURE 1 The schematic of the sensorimotor system in primates, including humans.

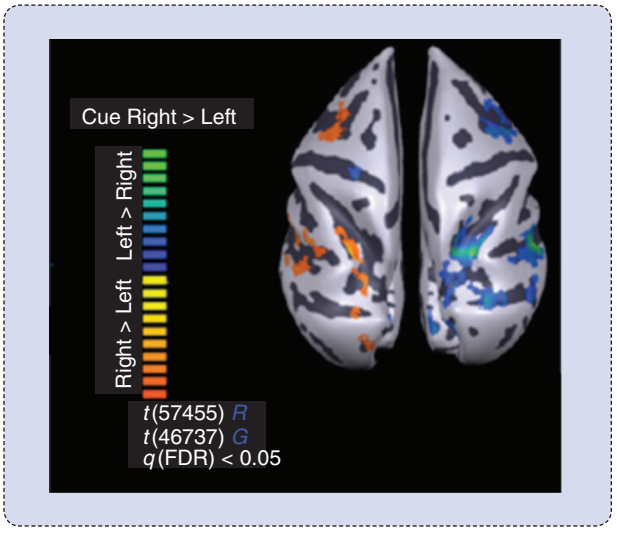


FIGURE 2 A view from above of an fMRI image of the cerebral hemispheres of a nonhuman primate. Left eye movements produce greater activity in the right hemisphere (shown in blue to green), and right eye movements produce greater activity in the left hemisphere (shown in yellow to red). (From Kagan et al. [1].)

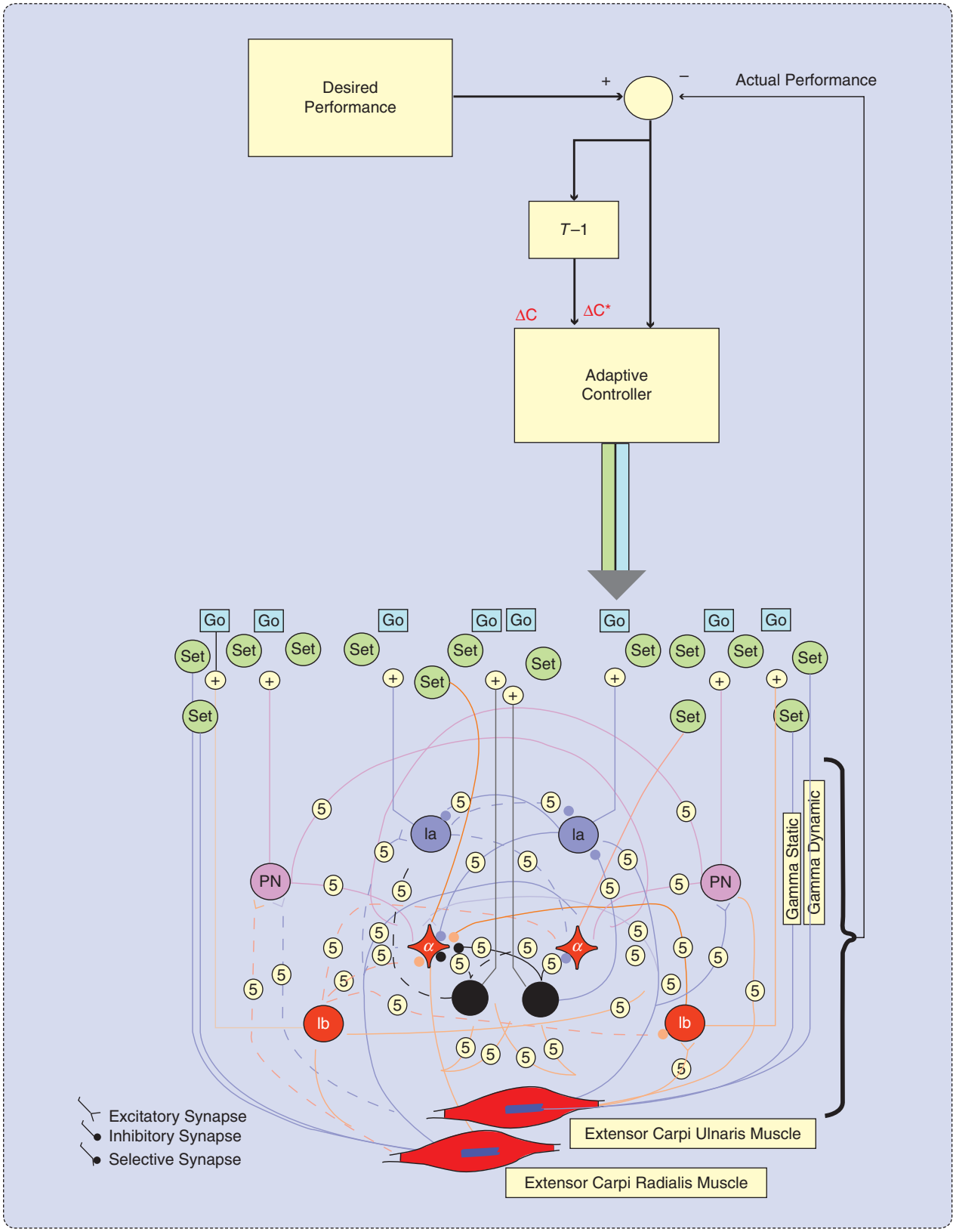
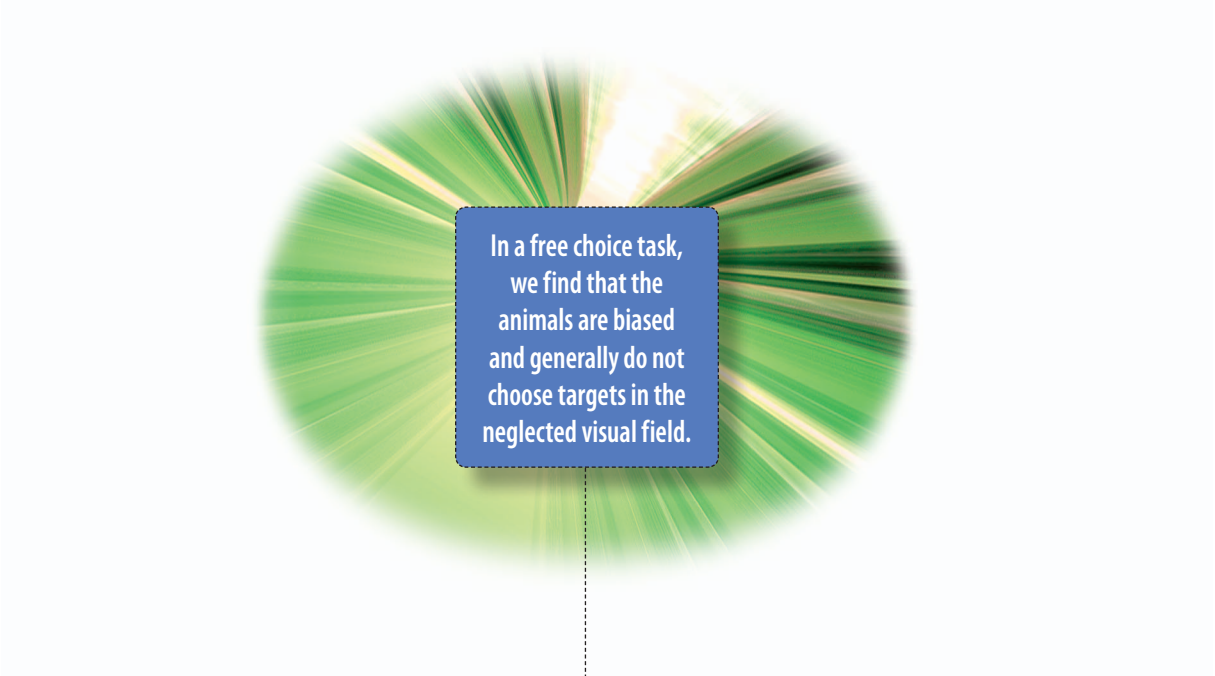


FIGURE 3 The adaptive controller in the brain controls most muscles indirectly, via spinal interneuronal circuitry to motoneurons (α) that includes feedback from muscle force sensors (Ib) and length sensors (Ia) whose sensitivity is controlled by fusimotor neurons (gamma static and dynamic). Other important interneurons include Renshaw (R) and propriospinal (PN). We hypothesize that the difference between desired and actual performances constitutes a cost function (ΔC^*) and a rate of progress toward the goal (ΔC) that is used to determine the range of trial-and-error explorations of this high-dimensional control space.



last year, we have determined, using fMRI, how inactivation of the PPC leads to decreased activity in cortical circuits. Next, we plan to implant stimulating electrodes for electrical stimulation in these sites in an attempt to repair neglect. We will be particularly interested in whether short periods of stimulation can lead to long lasting effects.

Optic Ataxia

A second accomplishment in the last year on the REPAIR project has been the development of an animal model of optic ataxia. To our knowledge, this is the first animal model of this deficit. We find that inactivation of PRR produces misreaching of the animals in the space opposite the inactivated hemisphere. Next, we will image and record from the network and plan subsequent electrical stimulation therapies similar to our studies of neglect.

Repairing Apraxia and Hemianesthesia

The simple act of reaching out to grasp your coffee cup is not as simple as it seems. Your brain has to assess the size and shape of the cup and plan how your fingers will shape to grasp the cup. Although your hand shapes to match the cup even as you reach, once your hand touches the cup, sensation from your fingertips also contributes to controlling how your hand grasps, lifts, and handles the cup so that you can drink.

Information about the shape of objects you see is processed by an area in the parietal lobe of the cerebral cortex called *AIP* (see Figure 1). When objects are to be grasped with the hand, AIP sends relevant shape information to another cortical area in the frontal lobe referred to as *PMv*. Here, the shape information is translated into the necessary conformation of the fingers, and this information is sent to the primary motor cortex (M1), which executes the appropriate grasp. Once the fingers contact the object, sensory information from the fingers ascends from the spinal cord through deeper parts of the brain arriving in a region called *VPL* and then in the somatosensory cortex (S1). Sensory information from S1 can then guide M1 in handling the object without dropping it.

Injuries to the parietal lobe of the cerebral cortex that damage AIP can cause a movement abnormality referred to as *apraxia* in which the patient is unable to handle objects appropriately, while still being able to recognize the object and know its use, having no loss of strength or dexterity in the hand. In some cases, the subject may be unable to pantomime use of the object, but once it is grasped, the subject may perform movements appropriate for its use.

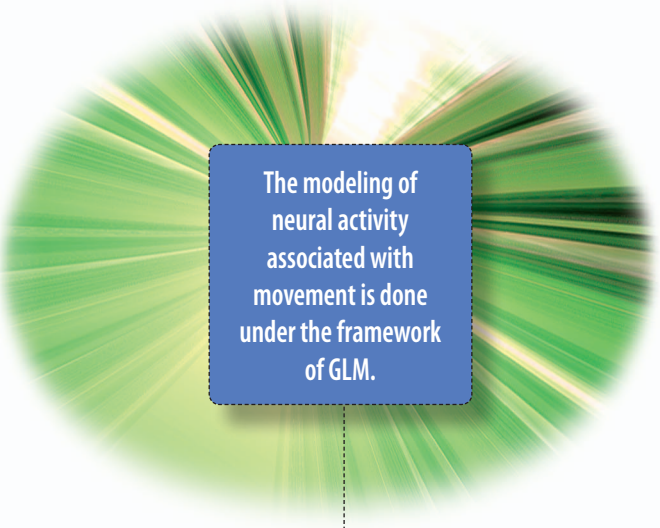
We are studying an experimental model of apraxia to see whether such a cortical deficit can be ameliorated by multichannel biomimetic intracortical microstimulation. Using neural signals recorded painlessly from the AIP, F5, M1, and S1 in nonhuman primates as they reach and grasp various objects, we will build a computer model of how the brain identifies the shape of objects visually and adjusts the shape of the hand to match. Then, by reversibly inactivating AIP, we will induce a temporary apraxia. While the apraxia is present, we will deliver biomimetic microstimulation in PMv to determine whether such stimulation can effectively repair the apraxia. At other times, we will reversibly inactivate VPL and deliver biomimetic stimulation in S1 to repair the deficit resulting from the loss of hand sensation, known as *hemianesthesia*. These studies will advance our understanding of how biomimetic microstimulation can be used to deliver missing information into the brain to repair apraxia as well as other neurological deficits that result from injuries to the nervous system (University of Rochester, http://www.urmc.rochester.edu/labs/Schieberlab/).

Modeling Cortical Networks

Figure 1 describes, from a systems engineer's perspective, a block diagram of the cortical organization of movement as first described from its anatomical and physiological basis. This schematic makes it clear that there is a great deal of complex connectivity, including both feedback and feedforward paths, involved in initiating and executing movements of the upper limb. A quantitative understanding of the neural activity and its origins from each of the cortical regions and further quantitative analysis of the connectivity among different regions will allow us to build what we will call in silico models of the cortex (John Hopkins University http://web1.johnshopkins.edu/nthakor/).

Modeling Neural Signals

The modeling of neural activity associated with movement is done under the framework of generalized linear modeling (GLM). The basic idea is to encode the spiking activity for each



neuron to its external covariates. These may be the neurons' own prior history, activity of other neurons, and even the motion of the limb and its parameters. The GLM framework allows, essentially, a regression on the general framework of the extrinsic model parameters to model and estimate a neuron's activity associated with movement. The most common and robust framework for estimation is to calculate the maximum likelihood estimate (MLE). The MLE of the model parameters allows, in a statistically robust manner, the estimation of a neuron's activity from various relevant parameters (including the neuron's own past activity and movement kinematics).

Modeling Connectivity

As seen in Figure 1, a major challenge is understanding the network properties of the neurons in the cortex, i.e., how neurons in different cortical regions come together to produce coordinated limb movement. At a practical level, recordings are obtained from different regions of the brain by inserting microelectrode arrays. The neural activities in each of these areas vary with time throughout the movement. Therefore, we need tools to describe the time-varying connectivity (When are neurons in one area functionally connected with those in another?) and causality (Does activity in one area cause activity in another?). We will apply a variety of signal processing and modeling tools to answer these questions.

Predicting Limb Movement

Once the generalized model of the neuronal activity is created, the next step is to understand its relationship to the movement of the limb, including arm, hand, and finger movements. Each neuron's tuning parameters will be used to estimate the kinematic parameters of the hand, including individuated finger movements, grasp types, and their kinematics or dynamics.

Modeling the Lower Sensorimotor System

The control problem that the brain must solve is strongly influenced by the complex circuitry of the spinal cord and the nonlinear mechanical properties of the musculoskeletal system. A great deal of information is available about these individual elements, but this is the first time that a comprehensive and quantitative model of the entire system has been assembled (Figure 3). At first glance, the very large number of elements to be controlled would seem to make it difficult to learn new tasks. However, this would be surprising, given that survival often depends on acquiring skills quickly. When we used trial-and-error methods to program our models to perform specific tasks, they converged reliably and rapidly on performance that appeared similar to that of normal humans (Raphael et al., 2010, http://bme.usc.edu/assets/007/73098.pdf).

The design of the lower sensorimotor system has apparently evolved to provide large numbers of easily discovered solutions that are good enough, rather than optimal, in the usual engineering sense. We are developing general software tools for modeling the various musculoskeletal systems used for experimental studies by our collaborators in the REPAIR program (Davoodi et al., in press, http://mddf.usc.edu/software.html). Models of all levels of the nervous system must be integrated to understand emergent properties such as motor habits, coaching strategies, and the effects of injuries and recovery processes (University of Southern California, http://mddf.usc.edu/).

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Reference

[1] I. Kagan, A. Iyer, A. Lindner, and R. A. Andersen, "Space representation for eye movements is more contralateral in monkeys than in humans," *Proc. Nat. Acad. Sci.*, vol. 107, pp. 7933–7938, 2010.