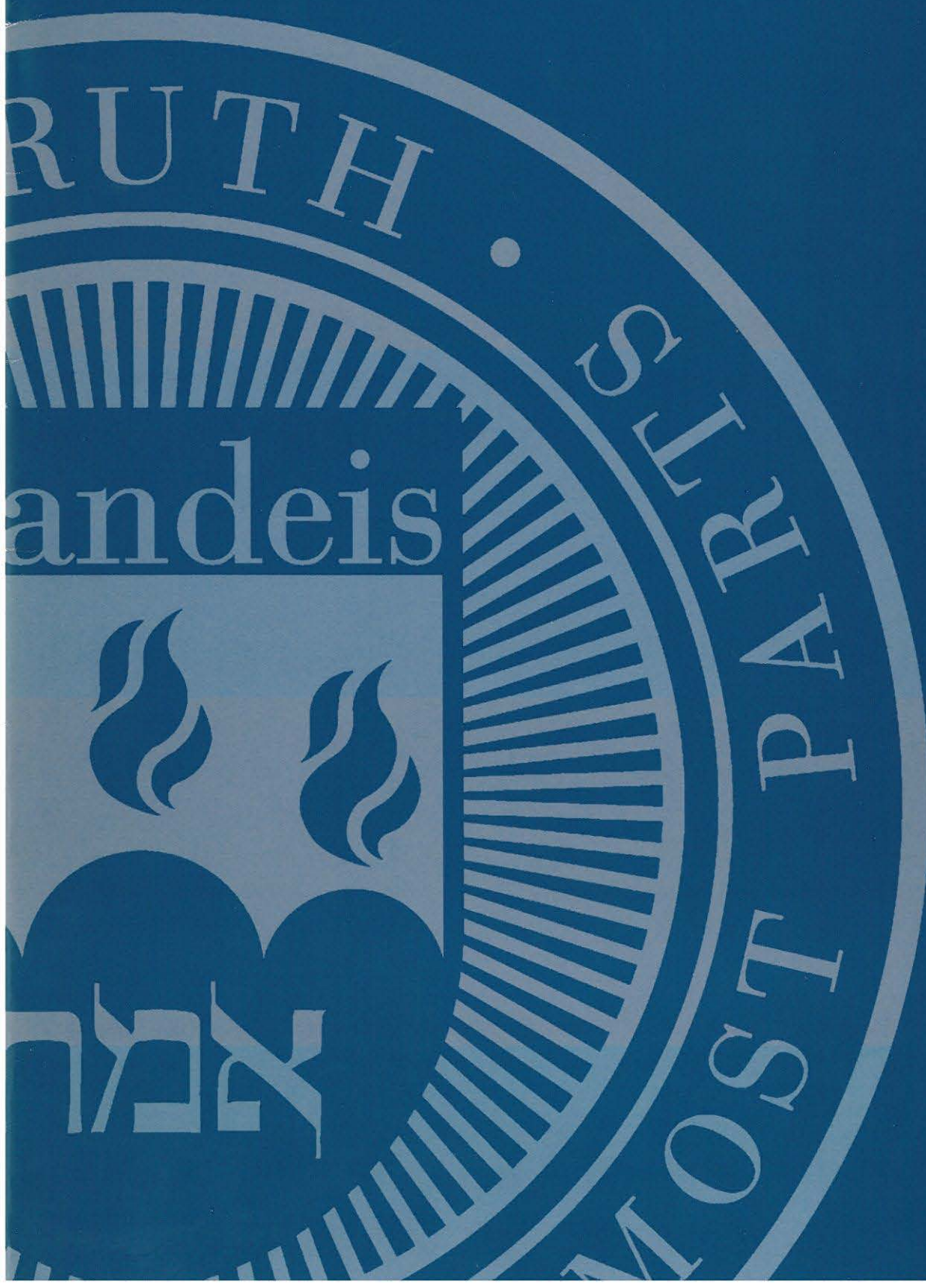

Brandeis University

Benjamin and Mae Volen National
Center for Complex Systems

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The M.R. Bauer Foundation
Colloquium Series,
Distinguished Lecturer Series,
and Scientific Retreat



The M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, and Scientific Retreat 2002-03 Summary

Brandeis University

**Benjamin and Mae Volen National
Center for Complex Systems**

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Introduction

The 2003 M.R. Bauer Foundation Colloquium Series, Retreat, and Distinguished Guest Lecturer Series: Introduction

I am pleased to present this year's proceedings of the M.R. Bauer Foundation Colloquium Series, Scientific Retreat, and Distinguished Guest Lecturer Series at Brandeis University's Volen National Center for Complex Systems. The generous support of the M.R. Bauer Foundation for these programs is now in its ninth year, and it has enabled the Volen Center to bring neuroscientists carrying out some of the most interesting work in the field to campus. The lectures and informal interactions that took place in the last year facilitated contacts among Brandeis's faculty and students with leading practitioners from the United States, Britain, Canada, Israel, and Switzerland—reflecting the international community of neuroscientists. The following proceedings describe, I believe, the excitement created by many of the new investigations in key areas of neuroscience. My colleagues at the Volen National Center join me in conveying our sincere thanks to the M.R. Bauer Foundation for its uninterrupted support, which has made these visits possible.

The M.R. Bauer Colloquium Series hosted seven speakers in 2002-03. Many of the talks focused on movement, spatial orientation, and decision-making. **Michael Graziano**, Ph.D., from Princeton University's

Department of Psychology proposed that the motor cortex does not contain a map of the muscles, as had been previously believed, but rather a "map" of the space towards which movements are directed. He has found that different regions in the brain, especially the primary motor and premotor cortex, control different types of actions in different spatial regions. **Paul Glimcher**, Ph.D., from New York University's Center for Neural Science, reviewed recent findings on the computational architecture for decision-making, and suggested that a mathematical framework based in current economic theory offers the "critical computational tool" for understanding the neural basis of human and animal decision-making. Using robotic modeling, **Arthur Prochazka**, M.D., a member of the University of Alberta's Division of Neuroscience, addressed one of the big unresolved questions in motor control physiology—do simple reflex pathways, such as the pathway underlying the tendon jerk, make a significant contribution to the control of movement? His answer is that reflexes can rescue a collapsing gait pattern, if the underlying activity is weak, but they are not likely to do more than change the body's attitude during movement—for example, in stretching to tip-toe—if the underlying activity is strong. Efforts to understand the neurobiology of movement bring together work that spans molecules to behavior. That important theme was taken up by the two Bauer Distinguished Guest Lecturers: **Rüdiger Wehner**, Ph.D., and **Michael Bate**, Ph.D., as described below.

Other speakers in the Colloquium Series addressed the most recent important findings on synaptic plasticity, or the brain's ability to reshape and rewire itself, for learning and memory. **Neal Waxham**, Ph.D., from the University of Texas Medical School's Department of Neurobiology and Anatomy, used three-dimensional structural analysis and live cell imaging to investigate the role of a key enzyme, CaM-kinase II, in synaptic plasticity. He is seeking to pinpoint the temporal and spatial changes that occur when this enzyme is locked into the synapse, as new information is stored. **Catherine Dulac**, Ph.D., from Harvard University's Department of Molecular and Cellular Biology, described her work on pheromone detection, linking genes with behavior. Pheromones, which are detected by a structure in the nose called the vomeronasal organ, signal the sex and dominance of animals. Dulac estimated that the receptor gene families contain as many as 400 to 500 pheromone receptors, which are divided into distinct subgroups, far exceeding earlier estimates. Her work suggests that pheromone detection involves a remarkable molecular and cellular complexity. **Haim Sompolinsky**, Ph.D., from the Racah Institute of Physics at the Hebrew University of Jerusalem, spoke about the balance that neural networks in the cortex achieve between excitation and inhibition. Using statistical physics to look at the way in which network architecture, neural dynamics, and computation interact, Sompolinsky examined the cooperative aspects of information processing in the brain.

Now in its fifth year, the M.R. Bauer Distinguished Guest Lecturer Series brought two outstanding scientists to campus in 2002-03. **Rüdiger Wehner**, Ph.D., is professor and chair of the Department of Zoology and director of the Institute of Zoology at the University of Zürich in Switzerland. In his major work on ants, Wehner is trying to answer a general question: How can a tiny brain weighing about one-tenth of a milligram solve complex computational tasks such as navigating in a featureless desert? Wehner discovered that special photoreceptor cells along the top of the ant's eye are tuned to the polarized ultraviolet light of the sun. The pattern of polarized sunlight changes in color and geometry throughout the day as the sun changes position, giving the ants a "map" by which they can navigate. Furthermore, Wehner found that only three neurons integrate information from the photoreceptor cells, and these neurons do not react to light intensity, only to the vector orientation of light. Each point of the compass is defined for the ant by a particular response ratio of the three neurons (analogous to the human response to the three basic colors). Therefore, the neural network underlying the ant's navigation system may be similar to the human neural network for color. The study of the ant's navigation system shows that its brain is organized in modules or systems, a principle that has been conserved by evolution in creatures ranging from ants to humans. Neuroscientists refer to the notion of "modularity" when they talk about how the brain is organized into

distinct but interacting systems. In the case of ants, "modularity" is seen in high-level tasks that can be accomplished by lower-level solutions built into separate parts or modules of the brain.

The year's second M.R. Bauer Distinguished Guest Lecturer was **Michael Bate**, Ph.D., the Royal Society Professor of Developmental Neurobiology at the University of Cambridge in England. Bate's work focuses on the neuromuscular juncture during early development. He is especially concerned with the way in which the machinery underlying coordinated movement is assembled in the embryo. In part, this interest involves understanding how neuron motor circuits are generated and then begin to function. In the earliest developmental stages, how do nerve cells know how to make the right connections with the appropriate muscles? One of the important findings of Bate's work is that the motor system in the fruit fly is constructed without the need for sensory input. Bate also addresses how the cells of the motoneuron system are organized. The dendrites of these cells, or the branches of neurons that receive synaptic inputs in the central nervous system, are organized in a highly predictable spatial array that corresponds to the pattern of muscles on the periphery. Scientists call this a "myotopic map," which suggests evidence of an active process that causes dendrites of

nerve cells to grow into or target specialized areas during early development. Again, through a series of experiments, Bate shows that the map forms even without input from muscles. It therefore appears to be an autonomous property of motoneurons and has nothing to do with the periphery. This evidence provides just fragmentary glimpses of the way that the motor system is built, but these insights allow us to make a reasonable estimate of the process for the first time.

The 2003 Volen Center Retreat, sponsored by the M.R. Bauer Foundation, examined "Interesting Systems." For the first time, the Retreat, which took place on March 3, 2003, was held at the New England Aquarium in Boston. **Eve Marder**, Ph.D., the Victor and Gwendolyn Beinfeld Professor of Neuroscience at Brandeis, took up a question later addressed by Sompolinsky in the Colloquium Series—how the stability of complex neural circuits is maintained during developmental growth. Her work, based on experimental and computational approaches, is designed to explain how cellular and circuit homeostasis occurs in the presence of cellular plasticity. Using experimental results from the crustacean stomatogastric nervous system, Marder demonstrated that the long-term maintenance of stable neural circuit behavior requires the coordinated tuning of both intrinsic membrane properties (the number and kind of ion channels that provide electrical excitability) and inhibitory synapses (the connections between neurons

involved in cellular plasticity). **Tim Hickey**, Ph.D., professor of computer science at Brandeis, presented a new approach to studying nonlinear systems. By using interval arithmetic constraints, he is seeking to make "provably correct" inferences about the parameters of complex mathematical systems. Hickey is currently testing the technique on hybrid systems in which a digital controller interacts with the physical environment. Complex neural assemblies may offer, in Hickey's words, interesting non-linear case studies for the solver. **Robert Malenka**, Ph.D., from Stanford University's Department of Psychiatry and Behavioral Sciences, provided an overview of synaptic plasticity, which he defined as the ability of experience to modify the organization and behavior of neural circuits in the brain. Malenka described synaptic plasticity as a complex system, in which its two best understood forms, long-term potentiation (a long-lasting strengthening of a synapse) and long-term depression (a corresponding weakening of a synapse), are caused by different patterns of neural activity. He suggested that synaptic plasticity might also play an important role in the development of pathological behaviors, such as addiction. **Michael Kahana**, Ph.D., associate professor of psychology at Brandeis, described experiments in spatial navigational memory he conducted with epileptic patients who were undergoing invasive monitoring to identify seizure

points in the brain for surgery. By playing a game in which the patients explored a virtual space, Kahana recorded from single neurons in various parts of the brain in order to show that the hippocampus is specialized for spatial position while the parahippocampus is specialized for spatial views. Kahana's work fits especially well with the research of Graziano and Wehner, who have demonstrated the modularity of the brain in spatial navigation. **Xiao-Jing Wang**, Ph.D., associate professor of physics at Brandeis, spoke about modeling studies he has conducted on the mechanisms of working memory and decision making. A major challenge for neuroscientists has been to understand the cellular and synaptic mechanisms of the circuits in the cortex of the brain. In order to maintain working memory, the brain has to convert a transient pulse-like impulse into an ongoing activity that can be self-sustained over a much longer time. Wang's computer modeling of this process shows a "slow reverberation" characteristic of the neural circuits that create human cognition.

Over the past nine years, the M.R. Bauer Foundation Colloquium and Scientific Retreat have helped to promote the exchange of ideas and new methodologies, and, in general, to advance the study of neuroscience. In the past five years, the M.R. Bauer Distinguished Guest Lecturer Series has brought some of the most accomplished neuroscientists in the world to the University. Both programs have created a strong sense of community among Brandeis's

scientists and the visitors from other institutions. Our faculty and students have benefited tremendously from their interactions with the Bauer Colloquium speakers and Distinguished Guest Lecturers, and these visitors in turn have taken away a strong sense of the exciting research and learning at the Volen Center. This booklet represents an important part of the Volen Center's effort to reach out to neuroscientists in the broader community in order to make this work more widely known and continue to facilitate scientific collaboration and discussions. It is with great pleasure that I recognize the support of the M.R. Bauer Foundation for making these activities possible through its foresight and generosity.

Arthur Wingfield, D.Phil.
Nancy Lurie Marks Professor of
Neuroscience and
Director, Volen National Center for
Complex Systems

Michael Graziano, Ph.D.

Department of Psychology
Princeton University
Princeton, New Jersey
September 23, 2002

The Cortical Control of Movement

Electrical microstimulation was used to study primary motor and premotor cortex in monkeys. Each stimulation train was 500 ms in duration, approximating the time scale of normal reaching and grasping movements and the time scale of the neuronal activity that normally accompanies movement. This stimulation on a behaviorally relevant time scale evoked coordinated, complex postures that involved many joints. For example, stimulation of one site caused the mouth to open and also caused the hand to shape into a grip posture and move to the mouth. Stimulation of this site always drove the joints toward this final posture, regardless of the direction of movement required to reach the posture. Stimulation of another site caused the left eye to close, the head to turn to the right, the left hand to move to the space on the left side of the head, and the hand to turn such that the palm faced outward, as if the monkey were protecting itself from a potential threat to the side of the head. Stimulation of other cortical sites evoked different postures. Postures that involved the arm were arranged across cortex to form a map of hand positions around the body. This stimulation-evoked map encompassed primary motor and the adjacent premotor cortex. Primary motor cortex appeared to represent

mainly postures of the arm that brought the hand into central space, and postures of the fingers that were consistent with manipulation of objects. These findings suggest that motor cortex does not contain a map of the muscles as was previously thought, but instead a map of locations in space to which movements are directed. They also suggest that the differences between primary motor and premotor cortex may be related to the control of different types of actions in different regions of space.

Neal Waxham, M.D.

Department of Neurobiology and Anatomy
University of Texas Medical School
Houston, Texas
November 11, 2002

Constraints on Neuronal Signaling through the Calmodulin and CaM-kinase II Pathways Based on Three-Dimensional Structural Analysis and Live Cell Imaging

Neuronal plasticity is governed in part by well-orchestrated intracellular signaling pathways. The orchestration involves the where and when individual molecules become activated. Ca^{2+} /calmodulin-dependent protein kinase II (CaM-kinase II) is the most abundant protein kinase in nerve cells and its role in regulating neuronal plasticity is well documented.

Inhibiting the kinase through either genetic knockout strategies or pharmacological treatments negatively impacts one of the widest-studied models of neuronal plasticity, long-term potentiation. A unique feature of CaM-kinase II is that the molecule catalyzes the covalent modification of itself through an autophosphorylation event and this autophosphorylation impacts the functionality of the enzyme. Each CaM-kinase II molecule can therefore exist in different stable states adding significant, but fascinating, complexity to the enzyme population within neurons.

CaM-kinase II is a complex of multiple subunits that forms an oligomeric structure and it is the interactions between subunits of a holoenzyme that is proposed to underlie the autophosphorylation mechanism. In addition, the multimeric structure of the kinase provides numerous opportunities for protein-protein interactions either between CaM-kinase II and other proteins, such as

the NMDA receptor, or possibly between CaM-kinase II holoenzymes. The hypothesis is put forth that the combined molecular features of CaM-kinase II subserve a Ca^{2+} /calmodulin regulated scaffolding function leading to the additional idea that CaM-kinase II is a structural protein.

The talk addressed several of these issues. First, work describing the solution of the three-dimensional structure of the kinase at a resolution of approximately 27 angstroms was presented. CaM-kinase II is a dodecameric (12-subunit) molecule that has dimensions of $\sim 20 \text{ nm} \times 20 \text{ nm}$. The 12 subunits are arranged in a tail-to-tail fashion producing a molecule with a dense central core and catalytic domains extending away from the core on short stalks. A comparison of the three-dimensional structure of each CaM-kinase II gene family member (a, b, g and d) reveals significant homology in overall architecture. Thus the differences in the biology ascribed to these different isoforms cannot be due to differences in their overall architecture. The distances between and rigidity of the catalytic domains suggested by these three-dimensional reconstructions leaves open the question, from a structural viewpoint, how two subunits within one holoenzyme can be brought into contact with each other to autophosphorylate.

With the three-dimensional structure in hand it is now possible to paint CaM-kinase II into electron micrographs of synaptic contacts as a means of providing a visual framework to constrain thinking about the molecules associated with the synaptic architecture.

The second half of the talk addressed the mechanism of CaM-kinase II self-association in living cells. The multimeric nature of the holoenzymes provides ample opportunities for interactions that lead to macromolecular assemblies of CaM-kinase II molecules. Live cell imaging indicates that enzyme clusters assemble and disassemble on the minute time scale in a stimulus-dependent manner. Binding of the activator Ca^{2+} /CaM is essential for the expression of this property as is the holoenzyme structure. One possibility is that self-assembly of CaM-kinase II holoenzymes may provide synaptic contacts with a previously unidentified Ca^{2+} /CaM-regulated structural element to help stabilize synaptic contacts. Another consequence of self-association would be to limit the diffusion of CaM-kinase II away from its point of activation, tagging that spot (i.e., a particular synapse) with activated CaM-kinase II molecules.

Overall, the hope of the presentation is to provide new data from CaM-kinase II structure-function studies that will stimulate novel hypotheses about the role of this enzyme in the regulation of neuronal function. Incorporating temporal and spatial changes in the kinase's localization and providing a spatial framework for possibly relating the enzyme's function at synaptic contacts is a further goal.

Paul Glimcher, Ph.D.

Center for Neural Science
New York University
New York, New York
December 2, 2002

Decision Uncertainty and the Brain

Recent studies of neuronal activity in awake-behaving primates have begun to reveal the computational architecture for primate decision-making. Perhaps unsurprisingly, these experimental studies indicate that neurons of the parietal cortex explicitly encode classical decision variables like Bayesian prior probability and expected utility. The most recent of these studies have even employed game theoretic methodologies to examine neuronal computation during volitional decision-making. Glimcher's presentation reviewed many of these findings and suggested that a mathematical framework rooted in modern economic theory will provide the critical computational tool required for understanding the neural basis of human and animal decision-making.

Arthur Prochazka, M.D.

Division of Neuroscience
University of Alberta
Edmonton, Alberta, Canada
March 10, 2003

Our Growing Appreciation of the Control Mechanism Underlying Animal Movement

The range of motor capabilities of animals is truly astonishing. Not surprisingly, the underlying neural control mechanisms are highly sophisticated and varied. It seems that each time robotic technology "discovers" a new control system, we later realize that evolution also "discovered" it in the distant past. Furthermore, we have come to realize that unorthodox control schemes that would be unstable in most robots work well in animals because of specific unorthodox properties of muscle actuators. In this talk I described some of the control mechanisms we have come to recognize in animals and the quirky conclusions they have sometimes led us to.

Summary of Presentation

1. Activity of ensembles of sensors in muscle and skin. It has become possible in the last few years to "intercept" the activity of individual axons signaling sensory activity during movement of limbs. Thanks to a new type of implantable "hairbrush" microelectrode array (the Utah array), we have recently even been able to record from up to 20 sensory axons simultaneously during locomotion. From all of the data gathered in this and other ways over the last three decades, it has been possible to compile "look-up-charts" of the sensory signals from various parts of the limb that enter the spinal cord and get transmitted to the brain during stereotyped motor tasks such as locomotion. These look-up-charts have also allowed us to identify mathematical models of sensory activity, which predict sensory input from known muscle length and force variations.

Most recently, our group has used a mathematical matrix inversion method to predict locomotor movements of the whole limb from ensemble sensory recordings obtained with the Utah array (coworkers: Doug Weber, Dick Stein, Dick Normann). This corroborates the recent hypothesis of Bosco and Poppele at the University of Minnesota that ensemble sensory activity is used by the nervous system to derive limb end point position. From a clinical point of view, it may be possible to use implanted devices such as the Utah array to control neuroprostheses in paralyzed people.

2. One of the big unresolved questions in motor control physiology is whether simple reflex pathways (such as that underlying the tendon jerk) make a significant contribution to the control of movement and, in particular, to limb loading (such as occurs when a leg bears the weight of an animal). It may seem strange that such a fundamental question hasn't yet been answered. The problem is that when muscles are activated, e.g., by direct electrical stimulation, they develop an intrinsic resistance to stretch, even in the absence of stretch reflexes. The intrinsic stiffness alone could be capable of providing weight-bearing during locomotion. Stretch reflexes mediated by the spinal cord would add to this intrinsic property, but the question remains, how much?

Alternatively, the more significant role of sensory input may be to mediate higher-level control, such as state-dependent switching between the stance and swing phases of the locomotor step cycle, and the control of global variables such as locomotor speed, stability, and adaptation to the environment.

One of the ways to assess the role of sensory input is to study motor control in people in whom sensory input has been destroyed by disease. Experimental abolition of sensory input is another method. However, because sensory loss is rarely complete, and the brain has astonishing ways of developing coping strategies, sensory abolition studies are often quite hard to interpret.

Biomechanical modeling is another option that is growing in importance, thanks to the development of powerful software tools such as two-dimensional models. In the talk, I showed movies of robocats and robohorses: dynamic models approximating "animals." The models, developed by my graduate student Sergiy Yakovenko, incorporate intrinsic muscle stiffness and viscosity, as well as reflexes based on the mathematical models of sensory input I referred to above. The models "walk" in an extraordinarily life-like manner. Because they are just mathematical constructs, it is of course possible suddenly and completely to remove all sensory input during locomotion. The answer to the question "are reflexes important" turns out to be "it depends." If the underlying, centrally generated

locomotor activity is weak, stretch reflexes can "rescue" a collapsing gait pattern. But if the underlying activity is strong, stretch reflexes merely alter the attitude of the body during locomotion, for example elevating the body such as in tip-toe walking or trotting.

The main thing the models have taught us is the importance of sensory input in implementing higher-level control. For example, incorporating some simple if-then rules can strongly influence the "read-out" of centrally generated muscle activity patterns, which in turn adapts cadence to the external requirements and "rescues" gait over a wide range of circumstances. Hazard "rules" that generate prepackaged reactions (such as the tripping response when a foot encounters an obstacle during forward swing) provide the models with a life-like ability to negotiate uneven terrain. In the next few years I predict that we will see some truly astonishing examples of life-like behavior of such models and the anthropoid robots they spawn.

Does this modeling tell us anything about the way real nervous systems control movements such as locomotion? I think the answer is yes, and I gave various examples during my talk, including the control of backwards, forwards, and sideways gait in infants supported over a treadmill, exploratory movements in locusts, and locomotor control in stick insects.

Catherine Dulac, Ph.D.

Department of Molecular and Cellular
Biology
Harvard University
Cambridge, Massachusetts
April 7, 2003

Molecular Biology of Pheromone Detection in Mammals: From Genes to Behavior

Pheromones have evolved in all animal phyla, including mammals, to signal the sex and the dominance status of animals and to promote mating and social rituals among conspecifics. In mammals, pheromones are primarily detected in a distinct olfactory structure opposed to the ventral nasal septum, the vomeronasal organ (VNO). VNO-derived signals are directly targeted to discrete loci of the amygdale and hypothalamus that elicit innate behavioral and neuroendocrine programs. The ability to associate VNO chemosensory stimulation with specific behavioral arrays and defined hormone changes provides a unique opportunity to uncover the neural basis of mammalian behavior.

The identification of the pheromone receptors is essential for further investigation of VNO function. Work performed in my lab has been instrumental in identifying novel families of candidate pheromone receptors as well as molecules unique to the VNO that are likely to be associated with pheromone detection.

The isolation of the olfactory receptor genes in mammals and in *Caenorhabditis elegans* has led to breakthroughs in our understanding of olfactory sensory coding. Similarly, the molecular and functional characterization of VNO-specific receptors and signaling molecules is likely to provide insight into the logic of the pheromone-evoked responses in the mammalian brain (Dulac 2000).

Several years ago, as a postdoctoral fellow in Richard Axel's lab (HHMI, Columbia University), I developed a procedure to generate cDNA libraries from individual neurons (Dulac and Axel 1995). The construction of single-cell libraries is invaluable in the nervous system because neurons, even within the same neural structure, display heterogeneous molecular properties and neural connectivity. The ability to investigate specific gene expression in individual cells provides a powerful tool to analyze the molecular basis of neuronal identity. We have used this approach to discover different classes of VNO sensory neurons, to characterize their receptor properties, and to proceed with analysis of olfactory development and function.

Our cloning efforts have led to the identification of large and divergent families of candidate pheromone receptors in the VNO (Dulac and Axel 1995; Herrada and Dulac 1997; Pantages and Dulac 2000). We estimate that the receptor gene families contain as many as 400–500 putative pheromone receptors subdivided into distinct subgroups. This exceeds previous estimates and suggests that a remarkable molecular and cellular complexity is required for pheromone detection.

What is the molecular and functional significance of this organization? Our recording of the VNO neurons shows that large fractions of the VNO

neuronal population are activated by natural sources of pheromonal stimuli (Holy et al. 2000). The absence of any clustering of the neuronal response types, together with recent evidence of the narrow tuning of the VNO neuronal activation by defined compounds points to the activation of multiple receptor populations by large but distinct sets of pheromonal cues. Furthermore, we have uncovered a wiring diagram of the VNO fibers within the anterior accessory olfactory bulb (AOB) that appears perfectly suited to accomplish the integration of multiple receptor inputs (Belluscio et al. 1999).

We propose a model of pheromone information processing in which the VNO acts as a sensor for a variety of chemical cues and the AOB mitral cells function as coincidence detectors to ensure the pheromone response is specific to the species, the sex, and the individual.

Sensory transduction in the VNO appears unrelated to that in the vertebrate olfactory and visual systems: the putative pheromone receptors of the VNO are evolutionarily independent from the odorant receptors and, in contrast to vertebrate visual and olfactory transduction, vomeronasal transduction is unlikely to be mediated by cyclic nucleotide-gated channels. We hypothesized that sensory transduction in the VNO might involve an ion channel of the TRP (transient receptor potential) family, members of which mediate cyclic nucleotide-independent sensory responses in *Drosophila* and *C. elegans* (Liman et

al. 1999). We isolated a cDNA (rTRP2) from rat VNO encoding a protein of 885 amino acids that is equally distant from vertebrate and invertebrate TRP channels (10-30 percent amino acid identity). The rTRP2 mRNA is exclusively expressed in VNO neurons, and the protein is highly localized to VNO sensory microvilli, the proposed site of pheromone sensory transduction. The specific expression of TRP2 in the VNO, together with the absence of a cyclic nucleotide-mediated response, suggests parallels between vomeronasal sensory transduction and light-induced signaling in the *Drosophila* eye.

Genetic ablation of the TRP2 channel, a candidate-signaling molecule in the mouse VNO, allowed us to assess VNO-mediated sensory responses and behaviors directly. We found that TRP2 deficiency eliminates the sensory activation of VNO neurons by urine pheromones. Moreover, the absence of VNO function has striking behavioral effects. TRP2^{-/-} male mice appear unable to recognize the sexual identity of their conspecifics: they fail to display the pheromone-evoked aggression toward male intruders that is normally seen in wild-type males and, remarkably, they display courtship and mounting behavior indiscriminately toward males and females (Stowers et al. 2002). Our data contradict the established notion that VNO activity is required for the

initiation of male-female mating behavior in the mouse and suggest instead a critical role in ensuring sex discrimination.

The identification of a large number of putative pheromone receptor genes grouped into several divergent gene families, together with the collection of multiple receptor projections within individual glomeruli, suggests that the pheromone-evoked response is likely to involve patterns of activity across the receptor population. In collaboration with the lab of Markus Meister (Harvard University), we reasoned that such a distributed population code should be observed by simultaneously recording the activity of a large number of VNO neurons in response to natural stimuli. Using a flat array of 61 extracellular electrodes, we have obtained the simultaneous recording of action potentials from large subsets of VNO neurons (Holy et al. 2000). Our study revealed several features of VNO neuronal activation. First, VNO neurons respond to components of urine by increasing their firing rate. In accord with our proposed model of VNO signaling that parallels that of *Drosophila* phototransduction and involves a channel of the TRP family, we showed that the chemosensory activation requires phospholipase C function. Moreover, unlike most other sensory neurons, VNO neurons do not appear to adapt under prolonged stimuli. This surprising feature of the VNO response may be physiologically related to the necessity of detecting minute amounts of pheromonal cues and to the long-lasting impact of pheromone detection on the organism.

Remarkably, the full-time course of VNO spiking in response to the stimulus concentration can be captured by a first-order kinetic. By directly quantifying the neuronal response to a given chemical stimulus, we generated a simple quantitative model of the neuronal response. This enabled us to demonstrate that subsets of VNO neurons are strongly selective for either male or female urine, while other neurons appear to recognize pheromones that vary between individuals of the same sex. The population recording of VNO neurons provides a powerful tool to investigate the complex sensory recognition involved in the pheromone-evoked response: the discrimination of the species, the sex, the familial status, or the individual differences among animals.

Haim Sompolinsky

The Racah Institute of Physics
The Hebrew University
Jerusalem, Israel
April 28, 2003

Excitation-Inhibition Balance: The Search for Functional Principles of Cortical Networks

Neural circuits show a great deal of variability in their responses, even when identical stimuli are presented. The source of this variability has been an ongoing question in studies of neural dynamics. The large magnitude of the variability is especially puzzling in view of the fact that individual neurons integrate large numbers of inputs, and therefore would be expected to average out noise. However, model neural networks that are constructed with (1) large numbers of neurons, (2) sparse connections between neurons, and (3) an approximate balance between excitatory and inhibitory input can reproduce the high levels of variability seen in real neural circuits.

We have constructed such models and explored their properties in great detail using a combination of analytic techniques and computer simulation. In previous models, noise was always injected into models from an unknown external source. It did not arise naturally from the model itself as it does in this work. The general level of variability, the statistics of individual response, and the correlations between responses seen in the model networks match quite well with those measured in vivo. Furthermore, we have applied these ideas to models of primary visual cortex and accounted for a number of features of visual responses seen in recordings from anesthetized and awake animals. Thus, we feel we have a basic understanding of the sources and the consequences of high levels of variability in neural circuits.

Introduction

One of the highlights again this year has been the M.R. Bauer Distinguished Guest Lecturer Series. This program, now in its fifth year, brought to campus two outstanding people, both well-known neuroscientists—Rüdiger Wehner, professor of zoology at the University of Zürich, and Michael Bate, F.R.S., of the Department of Zoology at University of Cambridge in England.

Both guests spent a full week at Brandeis, giving public lectures, class sessions, and presentations at journal clubs, meeting with graduate students and postdoctoral fellows, and spending time in many neuroscience laboratories. Feedback from our students clearly indicates that it is a significant privilege to have these world-class scientists spending this amount of time on campus, getting to know the students, and providing invaluable advice to these younger scientists. Both weeks were very busy, informative, and enjoyable for all.

Ant Navigation: Mini Brains-Mega Tasks-Smart Solutions

Ants of the Sahara desert, *Cataglyphis* by name, are skillful navigators. While foraging and homing over distances of several thousand times their body lengths, they accomplish truly formidable tasks. They use a pattern in the sky that is invisible to man to steer their compass courses, and then they integrate all angles steered and all distances covered by remarkable acumen. This system of path integration works even in completely featureless terrain. In addition, *Cataglyphis* can use landmarks by employing photographic skyline memories. Finally, they rely on search strategies that are much more efficient than a random walk would let one assume.

This talk focused on the behavioral performances as well as on the sensory and neural mechanisms that are involved in mediating this behavior. How can a 0.1-mg brain equipped with a panoramic compound-eye system accomplish these awe-inspiring modes of behavior? The presentation focused on the general sensory stratagems employed by *Cataglyphis*, and showed that this small-brain navigator uses simpler tricks than meets the human designer's eye. Cataglyphoid robots are used to test the hypotheses derived from neurophysiological analyses.

The general message is that a high-level task can be solved by the cooperation of a number of low-level systems. These low-level systems are adapted to the particular ecological niche, within which the desert navigator operates.

Michael Bate, Ph.D.

Department of Zoology
University of Cambridge
Cambridge, England
March 17-22, 2003

The Development of Neural Circuits and Behavior in the Embryo of *Drosophila*

There have been great advances in our knowledge of the way in which the nervous system develops in the last few decades. We now begin to understand how nerve cells are made, how growing axons are guided, and how connections are formed. However, at least one great area of neuronal development remains relatively unexplored: the development of the circuitry underlying movement and the maturation of coordinated patterns of locomotion in embryos. We have chosen to work on the development of larval movement patterns in the embryo of the fruit fly *Drosophila* using this as a model for the development of motor circuitry and behavior. The overall goal is to be able to write down the principles for genetically specifying and assembling the elements of a motor system. A simple pattern of peristaltic contractions develops in the late *Drosophila* embryo and it is the posterior to anterior passage of a wave of such contractions that enables the newly hatched larva to move forwards over the substrate. An important point can be quickly established in the *Drosophila* embryo: mis-expression of toxins and a mutant ion channel in sensory neurons shows that the peristaltic motor system can be constructed without sensory input. This work demonstrates a fundamental point, namely that a motor pattern and the central pattern generator that produces it can develop without

sensory feedback. It is also a useful simplification: it shows that the development of the system is an autonomous property of the neurons that comprise the central pattern generator and allows us to focus our future analysis on these cells and their properties.

How are the cells of the motor system organized? We can label all of the motoneurons concerned and we find that their dendrites (the branches that receive synaptic input in the central nervous system) are organized in a highly predictable spatial array. This pattern of neuronal branches is a faithful replica in the brain of the pattern of innervated muscles in the periphery—we call this a myotopic map in comparison to the somatotopic maps of sensory endings that are also formed in the developing nervous system. Interestingly, the myotopic maps of the muscles are organized in register with the body segmentation, suggesting that they represent a fundamental way of partitioning neuronal connectivity comparable to the segmental body plan of the insect. Our experiments show that the development of the map is once again an autonomous property of the motor neurons and does not depend on the muscles. It is clearly essential to begin to understand how the pattern synaptic contacts on the motor neuron dendrites are organized as the system develops. Our experiments show that these synapses are made by neurons that use acetylcholine as a neurotransmitter but the identity of the cells concerned is still unclear. As a model for understanding presynaptic development in the central nervous

system we have looked at the endings of distinct subsets of sensory neurons within the developing brain. We find that termination sites are determined independently of target neurons and can be respecified by the expression of inappropriate transcription factors in the presynaptic cells. It appears that a system of signals within the embryonic nervous system provides a set of coordinates that guide growing axons to particular termination sites, independently of their targets, but depending on the particular constellation of receptors for signaling molecules that each neuron expresses. We propose that in this first phase of target independent termination and branching, pre- and postsynaptic partner neurons are delivered to a common region of neuropile. This is an economical mechanism for providing an initial platform from which actual patterns of connectivity are formed in a subsequent, putatively activity-dependent phase of development. It is these patterns of connectivity between pre- and postsynaptic neurons that are at the heart of the developing motor system that we seek to understand.

The 2003 Volen National Center for Complex Systems Scientific Retreat “Interesting Systems”

New England Aquarium
Boston, Massachusetts
March 3, 2003

On March 3, 2003, the Volen National Center for Complex Systems held its 15th annual scientific retreat. This year's retreat was titled “Interesting Systems.” The topics covered a wide range of approaches to studying neuroscience, and our speakers included Brandeis's well-known professors Eve Marder, Tim Hickey, Michael Kahana, and Xiao-Jing Wang. The day also included a guest speaker, Rob Malenka, a professor of neuroscience at Stanford University.

Approximately 80 people attended this year's retreat, which was held at the New England Aquarium in Boston, Massachusetts. This was our first retreat held at the aquarium and it was a true success. The aquarium's lecture room facilities are excellent, their food superb (including the fish-shaped ravioli), and the aquatic life provided wonderful entertainment throughout the evening.

11:00-11:30 am

Arrival and check-in

11:30-12:15 am

Eve Marder '69, Ph.D.

Victor and Gwendolyn Beinfeld
Professor of Neuroscience and
Volen National Center for Complex
Systems

Brandeis University

“The Balance between Stability and
Plasticity in The Neuromodulation
and Growth of Neural Circuits”

12:15-1:00 pm

Tim Hickey, Ph.D.

Professor of Computer Science
and Volen National Center for
Complex Systems
Brandeis University

“Exploring Complex Non-Linear
Systems Using Interval Arithmetic
Constraints”

1:00-2:30 pm

Lunch

2:30-3:30 pm

Rob Malenka, M.D., Ph.D.

Professor of Neuroscience
Stanford University

“Synaptic Plasticity—The Brain's
Response To Experience”

3:30-4:30 pm

Poster session and refreshments

4:30-5:15 pm

Michael Kahana, Ph.D.

Associate Professor of Psychology
and Volen National Center for
Complex Systems

“Neurophysiology of Navigational
Spatial Memory”

5:15-6:00 pm

Xiao-Jing Wang

Associate Professor of Physics and
Volen National Center for Complex
Systems

“Cortical Microcircuits of Working
Memory and Decision-Making”

6:00-7:00 pm

Dinner

6:00-9:00 pm

New England Aquarium Main Exhibit
Hall open

Eve Marder, Ph.D.

Victor and Gwendolyn Beinfeld
Professor of Neuroscience and Volen
National Center for Complex Systems
Brandeis University
Waltham, Massachusetts

The Balance between Stability and Plasticity in the Neuromodulation and Growth of Neural Circuits

Neuronal circuits must maintain stable function throughout the lifetime of the animal although all of the receptors and channels necessary for signaling are constantly turning over. Because the activity of single neurons depends not on the number of any single ion channel, but on the number and kinds of all its channels, stable electrical excitability requires the coordinate regulation of the conductance densities of all channels. Likewise, network activity requires the coordinate regulation of synaptic strength and intrinsic cellular excitability. I described a series of experimental and computational studies that address the problem of how cellular and circuit homeostasis occurs in the face of all of the mechanisms for cellular plasticity. The experimental system we use is the crustacean stomatogastric nervous system, which produces rhythmic motor patterns that depend on the presence of bursting neurons and a large number of inhibitory connections. Therefore, the self-assembly and maintenance of stable circuit behavior requires the coordinate tuning of intrinsic membrane properties and inhibitory synapses.

Tim Hickey, Ph.D.

Professor of Computer Science and
Volen National Center for Complex
Systems
Brandeis University
Waltham, Massachusetts

Exploring Complex Non-Linear Systems Using Interval Arithmetic Constraints

Complex systems often tend to exhibit non-linear effects and that non-linearity makes such systems difficult to study using standard techniques. In this talk I presented a new approach to studying non-linear systems that relies on interval arithmetic constraint solving to infer properties of these systems. This work grows out of seminal research by Moore in the 1960s on application of interval arithmetic as well as work in the 1980s and 1990s on high-level computer languages based on logic and constraints.

The key idea behind this work is to build a system that will use numerical techniques to automatically make “provably correct” inferences about the parameters that appear in mathematical systems. For example, one could specify an ordinary differential equation with some parameters (known only to lie in some specific intervals) together with values of the solution function at certain points (again known to lie in specific intervals). The constraint solver would then try to shrink these intervals without removing any possible solutions to the system. In this way the parameters could be constrained to fairly small intervals by giving a large set of measured values (with explicit error intervals).

The techniques we use to implement such a solver decompose the original complex constraint into a large number of primitive constraints by introducing additional variables representing intermediate quantities. These new variables are initially

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Ph.D.**

Professor of Neuroscience
Stanford University
Stanford, California
March 3, 2003

**Synaptic Plasticity—
The Brain's Response
to Experience**

assigned to the intervals $[-\infty, \infty]$ and the constraint solvers for each of the primitive constraints is repetitively called to narrow its variables intervals. This process continues until there is no longer any change. The beauty of this technique is its simplicity. It allows one to work with extremely general constraints. The downside is that the constraint solver may not be able to make any progress on some constraints. There are several approaches to making this technique more robust. One method we have investigated is building meta-level solvers on top of the underlying solver.

There is much work to be done in this area. We are currently using these techniques to study hybrid systems. These are systems in which a digital controller interacts with a physical environment. The environment is generally modeled as a non-linear ODE or PDE and the constraint solvers we consider are well suited to this type of problem. We are also looking for examples of complex systems that arise when studying neural assemblies as they may provide interesting non-linear case studies for the solver.

One of the most fascinating and important properties of the mammalian brain is its plasticity. Plasticity refers to the ability of experience, whether it be learning in a classroom, a stressful event, or ingestion of a drug, to modify the organization and behavior of neural circuits in the brain. Experience-dependent brain plasticity is in large part due to long-lasting, activity-dependent changes in the strength of communication at excitatory synapses, that is synaptic plasticity.

The most well-understood forms of synaptic plasticity are termed long-term potentiation (LTP) and long-term depression (LTD) and these have been studied most extensively in the hippocampus, a region of the brain known to be important for a number of different forms of learning and memory. LTP, which refers to a long-lasting increase in synaptic strength, and LTD, which refers to a long-lasting decrease in synaptic strength, are triggered by different patterns of neural activity that lead to the activation of a specific subtype of receptor for the neurotransmitter glutamate, termed an NMDA receptor. When activated, the NMDA receptor lets calcium enter the cell and depending on the detailed characteristics of this calcium signal, different intracellular signaling cascades are activated leading to LTP or LTD. Specifically LTP involves activation of specialized enzymes (termed protein kinases) while LTD involves activation of enzymes (termed protein phosphatases). These enzymes then modify a different family of glutamate receptors (termed

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Neurophysiology of Navigational Spatial Memory

AMPA receptors) and it is this modification of AMPA receptors that directly leads to LTP or LTD. Indeed, LTP and LTD may be the first steps leading to structural changes in the brain, specifically the formation of new synaptic connections (LTP) or the elimination of pre-existing synaptic contacts (LTD).

How do we know LTP and LTD are really important for brain plasticity? Work from a number of laboratories has shown that drugs or genetic manipulations that prevent LTP and/or LTD also routinely impair many different forms of learning and memory. Indeed, these forms of synaptic plasticity may also play an important role in certain disease states. For example, drugs of abuse such as cocaine modify the strength of excitatory synapses in certain key brain regions known to be involved in addiction. Thus in addition to being important for adaptive forms of experience-dependent plasticity, synaptic plasticity may also play an important role in the etiology of pathological behaviors such as addiction.

The place cells of the rodent hippocampus constitute one of the most striking examples of a correlation between neuronal activity and complex behavior in mammals. These cells increase their firing rates when the animal traverses specific regions of its surroundings, thus providing a contextually dependent map of the environment. Because humans rely heavily on visual cues in exploring their environment, it is unclear whether the place-coding mechanisms in rodents also are sufficient to characterize human spatial navigation. Indeed, the human hippocampus and parahippocampal region receive extensive projections from visual areas and respond selectively to visual stimuli. Whereas neuroimaging studies implicate the hippocampus and parahippocampal region in human navigation, the underlying cellular networks remain unknown.

Responses of single neurons were recorded in six subjects who were patients with pharmacologically intractable epilepsy undergoing invasive monitoring with intracranial electrodes to identify seizure focus for potential surgical treatment. Subjects played a taxi driver game in which they explored a virtual town, searching for passengers who appeared in random spatial locations and delivering them to fixed target locations (stores).

Xiao-Jing Wang, Ph.D.

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Cortical Microcircuits of Working Memory and Decision-Making

We directly recorded from 287 neurons in the temporal and frontal lobes as subjects actively explored the virtual town. We present evidence for a neural code of human spatial navigation that includes cells, primarily in the hippocampus, that respond at specific spatial locations and cells, primarily in parahippocampal region, that respond to views of landmarks. These data provide a neuroanatomical dissociation between human hippocampal and parahippocampal function during navigation, suggesting that the hippocampus is specialized for spatial position while the parahippocampal region is specialized for spatial views. Cells throughout the hippocampus, parahippocampal region, and frontal lobes also responded to subjects' navigational goals and to conjunctions of place, goal, and view during our virtual spatial exploration task.

Working memory is the ability to maintain and manipulate information "on-line" in the absence of external stimulus. For example, when there is a delay between stimulus and response, an animal's behavior relies on the active short-term memory of the sensory stimulus across the delay time. Perceptual decision-making is a very general process through which the brain evaluates and discriminates sensory inputs and makes a categorical choice of perception or action. Interestingly, neural correlates of working memory and perceptual decision making have been found in the same association cortical areas, such as posterior parietal cortex and prefrontal cortex. A major challenge is to understand the cellular and synaptic mechanisms of such "cognitive" cortical circuits.

Over the last eight years, we have used biophysically realistic modeling to investigate cortical mechanisms of working memory and decision-making. Our models are based on new advances in cortical neurophysiology and are sufficiently quantitative so that comparison between the models and physiological data becomes possible. Our work gave rise to testable hypotheses about the cellular mechanisms of working memory, such as the critical role of NMDA receptors at recurrent synapses and differential functions of diverse subtypes of inhibitory neurons. Conceptually, our work supports the idea that working memory and decision-making can be

conceptualized in terms of time integration by attractor network dynamics. In order to maintain the memory of a stimulus, neural activity in the brain has to convert a pulse-like transient input into a persistent activity that is self-sustained for many seconds. Thus, the output activity is like the time integral of the input. Similarly, to subserve a decision-making process, neural activity has to integrate the stimulus over time, so that the brain can accumulate and weigh evidence for choice alternatives. Our work suggests that such attractor dynamics should be implemented by slow, not fast, synaptic or cellular mechanisms. Slow reverberation may be a characteristic of "cognitive" cortical microcircuits.

The text of this summary of the Bauer Foundation series, along with summaries from previous years, can be found at: www.bio.brandeis.edu/bauer/previous.html.

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