Brandeis University

The Volen National Center for Complex Systems

The M.R. Bauer Foundation Colloquium Series and Scientific Retreat

August 1997

Introduction

The 1997 M.R. Bauer Foundation Colloquium Series and Scientific Retreat

Brandeis University

Benjamin and Mae Volen National Center for Complex Systems

Through the continued generous support of the M.R. Bauer Foundation, the M.R. Bauer Colloquium Series at the Volen National Center for Complex Systems has completed its third year. The 1996-97 Colloquium Series included presentations on topics ranging from the role of potassium channels in the nervous system to the way the brain directs physical resources in the function of working memory. Guest lecturers came from New York, Maryland, Virginia, and California to speak at the Volen Center.

The Bauer Foundation also supported the 1997 Volen Center Annual Retreat, which was held in Woods Hole, Massachusetts, for the second time. Approximately 125 faculty, staff, researchers, and graduate students came together for discussions, lectures, and informal talks. This year, the focus was on a blend of activities within the Center. Dr. Marilyn Albert from the Massachusetts General Hospital's Department of Psychiatry/ Gerontology was our guest keynote speaker. I was pleased to have the opportunity to make a presentation as well, the first time I have spoken at a Volen Center Retreat.

The value of the Bauer Colloquium Series and Annual Retreat is considerable; these opportunities for scientists from different disciplines to come together to discuss their work, as well as to hear presentations by their colleagues from other institutions, create an enriching atmosphere, especially for younger scientists—the students, postdoctoral trainees, and junior faculty. These activities challenge participants to reconsider what they know from new perspectives.

In closing, I would like to mention that I am stepping down as director of the Volen National Center for Complex Systems, a position I have held in conjunction with my teaching and research since the Center was established in 1989. It is my pleasure to introduce Professor of Biology Laurence F. Abbott as the next director. Professor Abbott received his Ph.D. from Brandeis in 1977, and has taught at the University since 1979. His primary research area is the mathematical modeling and analysis of neurons and neural networks.

It has been a privilege to lead the Volen Center and watch it grow into a flourishing research and training environment. It is time for a new director, from a different discipline, to lead this interdisciplinary community of scientists. I look forward to concentrating more fully on my own research and to seeing what new horizons the Volen Center approaches under Larry Abbott's leadership.

Irwin B. Levitan
Nancy Lurie Marks Professor of Developmental Neuroscience
Director, Volen National Center for Complex Systems

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Dana H. Ballard, Ph.D.

Professor
Department of Computer Science
University of Rochester
Rochester, New York
September 26, 1996

Biographical Information

Dana Ballard obtained his Ph.D. degree from the University of California at Irvine in 1974. During 1974-75 he had a post-doctoral appointment at the Laboratorio Tecnologie Biomediche in Rome, Italy. Since 1975 he has been at the University of Rochester in the computer science department, where he has the rank of professor. He is the coauthor with Professor Brown of *Computer Vision*, a standard text. His new text, *An Introduction to Natural Computation*, will be published by MIT Press in 1997.

Ballard's current research focus is in computational theories of the brain that account for its real-time performance. In 1985 with Chris Brown, he led a team that designed and built a high speed binocular camera control system capable of simulating human eye movements. Recently he has extended his interests to the use of Virtual Reality equipment, both for robot modeling and human behavioral studies.

The Role of Working Memory in Behaviors

Computational theories of the brain necessarily must have hierarchies, wherein the brain can be seen as using different instruction sets at different spatio-temporal scales. A central time scale is that of one-third of a second. At this time scale, the brain's neural instructions direct the physical resources of its body. An example of these kinds of instructions are those used to direct discrete eye-movements. Interpreting experimental data from this perspective implies that subjects select eye-movements in a special strategy to avoid loading working memory. Keeping working memory load at a minimum may reflect the structure of natural tasks. Studies of task learning show that the amount of state information needed at any instant is highly variable. This constraint has important implications for the computational theories of high-level behavior.

Saul Sternberg, Ph.D.

Professor of Psychology
University of Pennsylvania
Philadelphia, Pennsylvania
November 7, 1996

Parallel and Serial Operations in Character Identification

Collaborative work by
Teresa Pantzer and Saul Sternberg
University of Pennsylvania
Philadelphia

What operations are used to identify the characters in a visual display, and how are these operations arranged in time? These questions have attracted experimental psychologists since their field began, and different answers have been offered, based on the data from various paradigms. To investigate these issues, we used a task in which subjects under time pressure had to recite the names of all the items (numerals) in a briefly presented visual array. We manipulated the number of items in the array and their legibility.

We found that degrading one or more items produces dramatically different timing patterns, depending on the type of degradation. Superimposition of a grid influences primarily a parallel component (alpha; contour formation?) of the encoding process, whereas disorientation influences primarily a serial component (gamma; memory interrogation?). Data patterns that result when the two forms of degradation are combined within and across items also require us to postulate a third component (beta; feature extraction?) that occurs between the alpha and gamma components. The betas for different items occur serially, probably in the same order as the reciting order. Within an item, alpha, beta, and gamma appear to be arranged in series. Across items, alpha and beta can overlap: The beta operation for one item can start before the alpha operations for other items have been completed. This overlap property permits the parallel alpha process to reveal the seriality of the beta process.

Lilly Jan, Ph.D.

Professor of Physiology and Biochemistry
University of California
San Francisco, California
March 20, 1997

Transmitter Regulation of Inwardly Rectifying Potassium Channels

Our studies of potassium channels aim at learning about their functions at the level of the protein and at the level of the physiological contribution of these proteins to the control of excitability and signaling in the nervous system.

At the moment, one focus of our studies is the way neurotransmitter actions are mediated via modulation of inwardly rectifying potassium channels. We have shown that GIRK channels are directly activated by $G_{\beta\gamma}$ subunits, so as to mediate the effect of inhibitory transmitters such as acetylcholine in the heart and GABA in the brain. At the level of the channel protein, we are pursuing questions concerning the mechanism of G protein gating. At the level of the mammalian central nervous system, we hope to define the molecular composition of the channels that are effectors of various transmitter receptors in various neurons. A more challenging question concerns how only a subset of G protein coupled receptors of a neuron activate these channels as $G_{\beta\gamma}$ effectors. In contrast to inhibitory transmitters that can activate GIRK channels, some of the excitatory transmitters activate Gq/11 coupled receptors and suppress inwardly rectifying potassium channel activities. The mechanism for this modulation is under investigation.

Christof Koch, Ph.D.

Professor of Computation and
Neural Systems
California Institute of Technology
Pasadena, California
March 26, 1997

Biographical Information

Christof Koch was born in Kansas City, Missouri, in 1956 and studied physics and philosophy at the University of Tübingen in West Germany. He was awarded his Ph.D. in biophysics from the Max Planck Institute for Biological Cybernetics in Tübingen in 1982 (under Professors Valentin Braitenberg and Tomaso Poggio). He worked until 1986 at MIT's Artificial Intelligence Laboratory before joining the Computation and Neural Systems Program at the California Institute of Technology where he is now a full professor of computation and neural systems.

Koch's research focuses on understanding the biophysical mechanisms underlying information storage and processing in single neurons, in particular, the computations underlying motion and visual attention in cortical networks in the mammalian visual system. His laboratory builds neuromorphic, analog, smart vision chips to solve a host of applied vision problems. Together with Dr. Francis Crick, he works on the neuronal basis of visual awareness and consciousness.

Koch has published three books, well over 100 technical articles, and has numerous patents in the area of analog VLSI vision chips (smart vision chips).

Neuronal Correlates of Consciousness

What is the relationship between visual perception and the underlying neuronal activity in the visual cortical system? We (Crick and Koch, 1995) base our framework on the plausible hypothesis that the function of visual awareness is to produce the best current interpretation of the visual scene, in the light of past experience, and to make it available, for a sufficient time, to the parts of the brain that contemplate, plan, and execute voluntary motor outputs (of one sort or another). This suggests that the neurons that express the neural correlate of consciousness (NCC) must project from visual cortices to the frontal lobe. This hypothesis, combined with the neuroanatomy of the macaque monkey, suggests that primates are not directly aware of neural activity in primary visual cortex, although they may be aware of such activity in extrastriate cortical areas (Crick & Koch, 1995). In this lecture, I will discuss electrophysiological, clinical as well as psychophysical evidence that directly supports this hypothesis. I will argue that the neuronal correlate of consciousness is very likely to be found in a subpopulation of unique cells (characterized by their location, connectivity, morphology, and biophysics) in different cortical areas.

Michael Menaker, Ph.D.
Department of Biology and NSF
Center for Biological Timing
University of Virginia
Charlottesville, Virginia
April 17, 1997

The Mammalian Circadian Axis and Its Roots

Not only do circadian rhythms modulate virtually all sensory systems that interpret environmental changes for their owners, they also provide a temporal framework that supports much of the physiological adaptation to such changes. Work over the past 40 years has established firmly that circadian rhythmicity is pervasive: it is found (and displays the same general characteristics) in prokaryotic blue-green "algae" (bacteria), in human beings and, with rare exceptions, everywhere in between; within individual organisms multiple circadian rhythms have been described at many levels of organization. Work over the past 20 years has made it clear that the circadian system is tractable: pacemaking oscillators have been identified in many organisms, mutations affecting the timing process have been found and, in some cases, the genes involved have been cloned, promising work has begun on the biochemistry and molecular biology that underlies the generation of rhythmicity, and in complex organisms great progress has been made in understanding the ways in which the central nervous system (and its endocrine partners) generates and controls the many behavioral and physiological rhythms that are essential to life in the real world.

In the vertebrates we can already see the outlines of a complete first level explanation of circadian organization that will include answers to such questions as: where are circadian oscillators located? How do they interact with each other? How are they influenced by the environment? How do they control the downstream processes whose rhythmicity depends on their influence?

Furthermore, in the vertebrates, we can begin to define the evolutionary relationships between the circadian systems of non-mammalian and mammalian vertebrates. Investigation of the comparative physiology underlying these relationships has led to the hypothesis that all vertebrates share a common "circadian axis," the main components of which are the pineal gland, the retina, and the suprachiasmatic nucleus. This hypothetical axis (like the adrenal axis) contains both neural and humoral components and functions as a unit. Individual components of the axis can be studied in vitro and (with greater difficulty) the workings of the axis can be studied in intact, behaving organisms. Surprisingly, the circadian axis is simpler in mammals than in other vertebrates. I will briefly describe what is known about the circadian axes of non-mammalian vertebrates, contrast this with what we have learned about the mammalian axis, speculate about the selection pressures that have shaped the latter, and indicate the areas that I consider most promising for future work.

The 1997 Volen National Center for Complex Systems Scientific Retreat

The Center for Complex Systems: "Aging Brains"

Marine Biological Laboratory
Woods Hole, Massachusetts
March 27-28, 1997

The Center for Complex Systems: "Aging Brains"

On March 27 and 28, 1997, the Volen National Center for Complex Systems held its annual scientific retreat. This year the retreat, titled "Aging Brains," returned to the Marine Biological Laboratory (MBL), in Woods Hole, Massachusetts. The MBL facility includes lecture halls, function rooms, cafeteria-style dining, and overnight dorm room accommodations. Bringing the researchers together off-campus for a 24-hour retreat was tremendously successful. The MBL provided a stimulating environment for interactions between the faculty, post-docs, and graduate students, as well as a scenic site for walking and relaxing.

Approximately 120 people attended the retreat, which consisted of a poster session, a keynote speaker, and talks by four of the Center's senior faculty. The keynote speaker was Dr. Marilyn Albert from the Department of Psychiatry and Gerontology at Massachusetts General Hospital in Boston. She gave a thought provoking talk on "The Aging Brain: Normal and Abnormal Memory."

Thursday, March 27, 1997

2:00 pm
Arrival and check-in

4:30 pm
Poster session and refreshments

6:00 pm
Dinner

7:15 pm
"The Aging Brain: Normal and Abnormal Memory"
Keynote Speaker
Marilyn Albert, Ph.D.
Department of Psychiatry/ Gerontology
Massachusetts General Hospital
Boston, Massachusetts

8:30 pm
Music and dancing

Friday, March 28, 1997

7:00-8:30 am
Breakfast

8:30 am
"Optimal Implementation of Functional Programming Languages: Complexity, Linear Logic, and the Geometry of Interaction"
Harry Mairson
Associate Professor of Computer Science
Volen Center for Complex Systems
Brandeis University
Waltham, Massachusetts

9:15 am
"Co-evolutionary Learning Systems"
Jordan Pollack
Associate Professor of Computer Science
Volen Center for Complex Systems
Brandeis University
Waltham, Massachusetts

10:00 am
Break

10:30 am
"Molecular Mechanisms that Underlie the Circadian Pacemaker in *Drosophila*"
Michael Rosbash
Professor of Biology
Investigator, Howard Hughes Medical Institute
Volen Center for Complex Systems
Brandeis University
Waltham, Massachusetts

11:15 am
"How the Brain Works—Modulation of Ion Channels by Protein Phosphorylation"
Irwin Levitan
Professor of Neuroscience
Director, Volen Center for Complex Systems
Brandeis University
Waltham, Massachusetts

12:15 pm
Lunch

1:00 pm
Departure

Marilyn S. Albert, Ph.D.
Professor of Psychiatry and
Neurology
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

The Aging Brain: Normal and Abnormal Memory

Changes in memory occur with age but memory changes are also the earliest cognitive change seen in Alzheimer's disease (AD). Recent studies indicate that there is a considerable difference between the nature of the memory changes in aging and in AD and the underlying neurobiology responsible for those changes.

There are substantial changes with age in explicit secondary memory, in contrast to the minimal age changes in sensory and primary memory. The age at which changes in secondary memory occur depends upon the methods that are used to test the memory store. Difficult explicit memory tasks (e.g., delayed recall) demonstrate statistically significant differences by subjects in their fifties, in comparison to younger individuals. Non-human primates demonstrate age-related differences on difficult memory tasks at an equivalent point in their life span (i.e., 16-23 years).

A close examination of the human data indicates that the older individuals do not forget what they learn more rapidly; they take longer to learn the new information. For example, if one compares the difference between immediate and delayed recall over the life span, several studies demonstrate no statistically significant age differences.

The alterations in memory associated with early Alzheimer's disease (AD) differ in important ways from those associated with age-related changes in memory. Difficulty with delayed recall is generally the first and most salient symptom to emerge in patients with Alzheimer's disease (AD). Moreover, when compared with a variety of patient groups with amnesiac and dementing disorders, AD patients retain less information over a brief delay than any groups tested to date.

These findings suggest that selected, and differing, alterations in the brain are responsible for the differing pattern of memory loss seen in normal aging and in AD. The most likely explanation for the abnormalities in memory that characterize the early stage of AD pertains to the damage to the hippocampal formation seen in these patients. In the hippocampal formation, neuronal loss and abnormal formations with the cells (e.g., neurofibrillary tangles and neuritic plaques) are seen primarily in the entorhinal cortex and subiculum, the primary pathways that convey information into and out of the hippocampus. The entorhinal cortex appears to undergo the most profound changes in the early stages of AD, with a 32 percent loss of neurons overall, even among very mildly impaired patients.

Neuronal loss with age, however, appears to be minimal in the hippocampus, and recent positron emission tomography and functional magnetic resonance imaging studies demonstrate robust responses during memory tasks among elderly and young individuals. In addition, the brain regions examined to date show neuronal loss in the cortex is either not significant or not as extensive as earlier reports suggested. However, with advancing age, there is substantial neuronal loss in selected subcortical regions responsible for the production of neurotransmitters important for memory function, such as the basal forebrain and the locus coeruleus, and significant alterations in the composition and volume of the white matter.

Understanding the nature of these cognitive changes, and the brain alterations associated with them, is the first step in developing methods of changing them.

Harry Mairson, Ph.D.
Associate Professor of Computer Science
Volen Center for Complex Systems
Brandeis University
Waltham, Massachusetts

Optimal Implementation of Functional Programming Languages: Complexity, Linear Logic, and the Geometry of Interaction

This talk is a general survey of some issues at the branch points of logic, semantics, computation, and programming language design, rather than a report on particular research results of the speaker. It was felt that this more global outlook would be more informative to the researchers in the Volen Center, who are for the most part biological scientists. It is important, however, to remember that the Volen Center houses many different scientists with disparate research agendas. The point of this talk was to explain one such agenda.

Just as the world of freshman physics, with its massless beams and frictionless pulleys, describes the essence of the Newtonian world, and the Turing machine defines the essence of computer architecture, the lambda calculus, whose properties we will discuss in some detail, defines the essence of programming languages. In particular, it allows a fundamental insight into the design of procedure calling protocols—the mechanism that connects inputs and outputs in the functional style of programming.

In the "call-by-name" protocol, where arguments input to functions are not evaluated until they are needed, there is a fundamental and practical implementation problem where these arguments are recomputed each time they are needed. While a naive "caching" strategy works for base values, this naive approach fails when the argument is itself a function. We discuss an interpretative technology known as "optimal evaluation" to address this fundamental issue of sharing inputs in a functional computation.

In recent years, a type of logic has been invented that captures many of the computational issues involved in optimal evaluation. This logic is called "linear logic"—it is also referred to as a "resource-conscious logic," which addresses the problem of persistence of truth in time. This problem is particularly acute in computations that cannot be reversed. It turns out that building blocks in this logic correspond strongly to technology employed in implementation of programming languages, and that more can be learned about one from studying the other. The fundamental paradigm of "computational logic" unifies the two, where we can extract real computational information from the structure of proofs.

Finally, we discuss the "geometry of interaction," a beginning approach to understanding the semantics of proofs and of computer programs. Two entirely different proofs of the same theorem should have different denotational meanings, while simplifying a proof (through so-called "cut elimination") should preserve denotational meaning. We look at the basic idea of the geometry of interaction in the lambda calculus, showing how it models information flow in a computer program.

Jordan Pollack, Ph.D.
Associate Professor of Computer Science
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Waltham, Massachusetts
March 27, 1997

Co-evolutionary Learning

While in theory, machine learning techniques could achieve intelligence in artificial agents, in practice, the setup for learning has required enormous amounts of programming, as much or more than would be involved in producing a direct solution. If the sophistication of algorithms necessary for achieving cognition has been underestimated, then the critical basic research question becomes one of *automatic development and maintenance of very complex software structures.*

There are now many models of machine learning (ML), which are driven by metaphor and by performance criteria. These include models that are inspired by psychology, by neuroscience, or by evolution, and whose performance is measured by modeling experimental data or by competence on specific tasks.

Unfortunately, as each learning method has matured, we perceive two essential and self-limiting research dynamics:

1) The algorithms are "improved" through incremental modification based on performance over a set of tasks or benchmarks.

2) The field "selects" the tasks or benchmarks which best "fit" the method, therefore showing off its performance while not explicitly displaying its inductive bias. Thus, there is a fundamental problem in machine learning that was noticed first by Doug Lenat: a system can learn only what it almost already knows. A learner converts knowledge perceivable in its environment into knowledge expressible in its internal structure. The words "perceivable" and "expressible," when applied to a human or animal (even to invertebrates!), describe robust systems, but for computer programs, perceivable means "arranged in a precise syntactic form, parsed, and ready for input" and expressible means "within a small search space over constrained parameters of the model class."

Because of the need to carefully specify the input form and model class, every ML method converges before achieving the kind of autonomous learning necessary for embedding into agents who face a novel and changing world. There is a new opportunity for breaking through this inductive bias paradox—"Co-Evolution"—which involves adaptive learning agents within adaptive environments. In co-evolutionary learning, improvement by the agents on the current instance of a task provokes increased challenges in the task environment, leading to systems that can continuously develop. Our research is focused on the principles by which systems that can undergo a sustained growth in their abilities—rather than on systems that succeed at a given task due to the skill of the programmer who develops the inductive bias in the learning algorithm or in the careful representation of the learning environment.

There are several existing feasibility demonstrations of continuous development, which fall under the rubric of "arms races" and "co-evolutionary feedforward loops," but there are only a few key pieces of work to date to understand the potential of open-ended learning: Thomas Ray's TIERRA eco-system of artificial assembly language programs made the first strong claims, but is difficult to evaluate. Axelrod and Lindgren's work on adaptive Prisoner Dilemma ecologies show the right kinds of long-term dynamics, but there is not enough strategic content in the continuous Prisoner's Dilemma game in order to build complex programs. Hillis's work on co-evolving sorting networks and difficult sequences pointed out the idea of relative fitness providing diversity, as well as several interesting directions in the exploitation of SIMD machines. There is also another body of work on co-evolutionary learning, especially on pursuit-evade, or predator/prey games. However, the best exemplars to date are Tesauro's work on self-learning in backgammon

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March 28, 1997

A *Drosophila* Circadian Clock

(Tesauro, 1992), which we were able to replicate with simple hill-climbing (Pollack, Blair, & Land, 1996), and Sims's recent work on co-evolving the body and brains of simulated robots (Sims, 1994).

Karl Sims developed a computer graphics simulator of the physics of robots composed of rectangular solids and simple joints, and evolved complex behaving animated creatures. Sims's virtual robots are clear evidence that under the right simulated conditions, we can automatically develop complex functional forms from simple initial conditions. We are currently building on this work with a simulator for lego blocks, where the results of virtual evolutionary simulations can be converted into physical reality (Funes & Pollack, 1997).

Funes, P. & Pollack, J. (1997). Evolution of buildable objects. *European Conference on Artificial Life,* MIT Press.

Pollack, J., Blair, A., and Land, M. (1996). Co-evolutionary learning of backgammon. *Artificial Life V*, MIT Press.

Sims, K. (1994). Evolving 3d morphology and behavior by competition. In *Proceedings 4th Artificial Life Conference.* MIT Press.

Tesauro, G. (1992). Practical issues in temporal difference learning. *Machine Learning*, 8:257–77.

The circadian clock (pacemaker, oscillator) is considered endogenous, as opposed to driven, because rhythmic oscillations persist with near 24-hour periodicity under constant conditions. It is, however, connected with the environment as the rhythm is usually entrained or synchronized by the 24-hour light-dark cycle, the major environmental zeitgeber or time cue. The clock is also connected to downstream outputs, namely, the biochemical and behavioral fluctuations that are generally observed as rhythmic phenomena. An impressive array of evidence now indicates that the per and tim genes encode bona fide components of the *Drosophila melanogaster* pacemaker (PER and TIM, respectively). Molecular characterization indicates that the clock mechanism includes the rhythmic accumulation and disappearance of these two gene products; protein cycling depends on transcriptional autoregulation, which is part of this intracellular clock mechanism. In this presentation, I will concentrate on recent studies from my laboratory that contribute to this *Drosophila* clock story. A new clock mutant predicts that there is at least one transcription factor dedicated to PER and TIM mRNA production. There is increasing evidence that a temporal post-transcriptional program—particularly phosphorylation of PER and TIM—also plays an important role in the time-keeping process. The characterization of the first TIM mutant with an altered period phenotype reinforces the importance of the phosphorylation program. Finally, our recent experiments provide insight into the way that light entrains and phase shifts the clock. They suggest that light has a primary post-transcriptional effect on TIM, which affects its phosphorylation status as well as its half-life. This light-induced change then has secondary effects on several aspects of the clock, which leads to phase advances and delays. These experiments underscore the fundamental role of the PER-TIM system in circadian time keeping and predict the existence of additional as yet unidentified clock components.

Irwin Levitan, Ph.D.
Nancy Lurie Marks Professor of
Developmental Neuroscience
Director, Volen National Center for
Complex Systems
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Waltham, Massachusetts
March 28, 1997

How the Brain Works—Modulation of Ion Channels by Protein Phosphorylation

Irwin Levitan's laboratory is interested in the regulation of the electrical activity of nerve cells. Such regulation of neuronal electrical activity is critical for long term changes in behavior. The specialized membrane proteins known as ion channels are responsible for all electrical signaling in neurons, and hence understanding how ion channel activity is modulated is of fundamental importance. The ion channel modulatory mechanism that has been most thoroughly studied and is best understood is modulation by protein phosphorylation. Ion channels, like many other proteins, are substrates for protein kinases and phosphoprotein phosphatases, and channel activity can be altered profoundly by phosphorylation.

Levitan began his lecture with a summary of the effects of phosphorylation on the properties of several different kinds of ion channels. He emphasized that modulation by phosphorylation is not confined to a particular class of ion channel, but is widespread, and suggested that modulatability by phosphorylation may be as intrinsic to ion channels as are such properties as voltage dependence, conductance, and selectivity. He then moved on to the major theme of his lecture, that ion channels do not exist alone in the plasma membrane, but often are bound tightly to the modulatory enzymes (such as protein kinases and phosphatases) that influence channel activity.

This theme was illustrated by two examples of work from Levitan's laboratory. The first example concerned the modulation of calcium-dependent potassium channels from rat brain, reconstituted in artificial phospholipid bilayers. Under these experimental conditions, proteins are effectively at infinite dilution in the vast ocean of bilayer lipid. Channel activity can be modulated in the bilayers by the addition of ATP to their cytoplasmic sides, and a variety of evidence demonstrates that this modulation results from protein phosphorylation. Because no exogenous protein kinase was added in these experiments, it could be inferred that the modulation must be mediated by an endogenous protein kinase activity that is tightly bound to the channel and accompanies it in the bilayer. Similar experiments demonstrated that a phosphoprotein phosphatase activity is also part of the modulatory complex.

In another set of experiments, biochemical methods were used to demonstrate directly that another kind of potassium channel, a human voltage-gated potassium channel, binds tightly to the Src protein tyrosine kinase. Specific antibodies that recognize the channel or the kinase were used in co-immunoprecipitation experiments. These experiments demonstrated that when channel is immunoprecipitated with its specific antibody, the kinase can be detected in the immunoprecipitate, and vice versa. Other experiments defined the specific amino acid sequences in both channel and kinase that are involved in the binding interaction. Because these sequences occur with high frequency in many other ion channels and signaling proteins, it is likely that such ion channel/signaling protein interactions are extremely common.

Levitan concluded by emphasizing that the traditional picture of ion channels as membrane loners is inappropriate. Their tight associations with protein kinases, phosphoprotein phosphatases, and other signaling and scaffolding proteins has fundamental implications for temporal features and specificity of neuronal signaling.