NEWSLETTER FROM THE DEPARTMENT OF
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Boston University School of Medicine · Division of Graduate Medical Sciences

Chairman's Report by Dr. Mark Moss

Anatomy & Neurobiology Department, 2005

Over the past year, the Department has continued on its course toward becoming one of the top tier Departments of Anatomy and Departments of Neurobiology/Neuroscience in the country. According to the 2004 rankings by the NIH, the Department has moved up to 13th of all Departments of Anatomy nationally with over 10 million dollars in NIH funding - a level that would place the Department 4th among all Departments of Neuroscience in U.S. Medical Schools. The Department has also attained national recognition by our continued leadership in the Carnegie Foundation's Initiative on the Doctorate, of which we are one of nine partner departments in Neuroscience.

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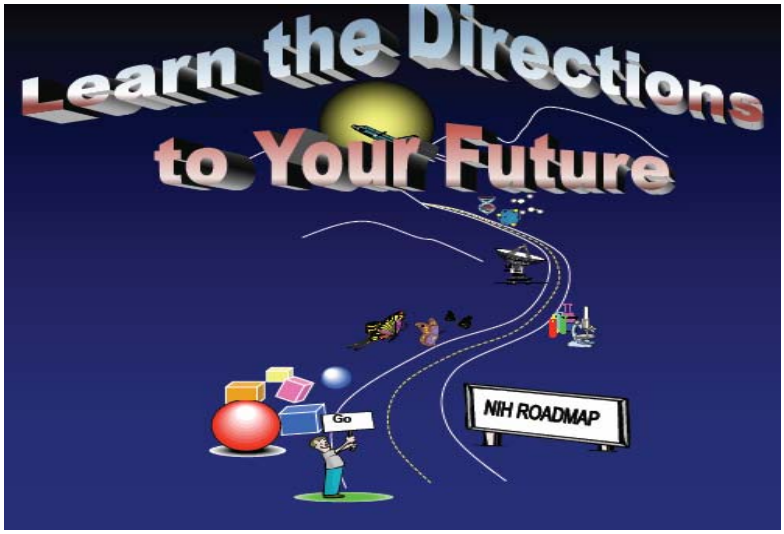
Learn to Speak the Language of Interdisciplinary Research: Dynamical Modeling by Dr. Peter Bergethon



Your work in the lab is complete for the day. You have been counting cells, washing blots, or recording spike patterns, intensively working to reduce some nervous system behavior to a countable number or parameter. The bright sun of the day (which you never saw) has given way to a clear crystal night and you look up at the starry sky. You notice the form of the Ursa Major (Big Dipper) and follow the line proscribed in the sky by its distal basin upward to the North Star at the end of the handle of Ursa Minor (the Little Dipper). Just briefly you wonder about the complex system that you have perceived and recognize a gnawing feeling that the study of a system such as star constellations (and more importantly the observer's nervous system identification of the same) might require a somewhat different scientific approach than our generally reductionist scientific process. After all, studying a single star would not ever get you to see or understand the constellations.

Welcome to the world of the systems science and thinking. These questions actually reveal the path to the NIH's Roadmap Initiative to reform the research enterprise (read here fundable research programs) in which systems science and theory will be part of the 21st century

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Blatt Laboratory of Autism Neuroscience Research: Perspectives and Goals

by Dr. Gene Blatt

The Blatt Lab: from left to right, Sandy Thevarkunnel, Claudia Persico, Dr. Jane Yip, Yuri Lawrence, Dr. Margaret Bauman, Dr. Thomas Kemper, Marissa Simms, Dr. Gene Blatt, Gillian VanSluytman

It began with a field biologist/ornithologist turned neuroscientist in the early 1980s when I teamed up with Dr. Leonard Eisenman at Jefferson Medical School in Philadelphia studying the organization of the olivocerebellar projection in spontaneous genetic mouse mutants when their main targets, GABAergic Purkinje cells, die postnatally. Despite this loss, olivocerebellar climbing distributed normally. Following a postdoctoral stint at the Salk Institute studying the physiology of the posterior parietal cortex in monkeys, I joined the Moss/Rosene lab and worked on the organization of limbic system projections in monkeys with Drs. Doug Rosene and Deepak Pandya until the mid 1990s when I learned about the neurological disorder autism from Dr. Tom Kemper when we teamed up to teach a department graduate course on the neuroanatomical basis of neurological disorders.

It turned out that right here in this Medical Center were *the* pioneers of neuropathology of autism research (Drs. Kemper and Bauman). Upon learning from Tom that the affected brain regions included the inferior olive, cerebellum and limbic system, it was amazing that all my training came together to now focus on the neuroanatomical and developmental etiology and timing of autism!

We are now a multidisciplinary research laboratory investigating the possible underlying substrates including neuropharmacology of specific transmitter systems in autism, a disorder characterized by impaired social interaction, delayed and disordered language, repetitive behavior, and an insistence on sameness in the environment. We currently have projects in the brainstem, cerebellum, cerebral cortex, fusiform gyrus, and the hippocampus. Techniques we use include immunocytochemistry, ligand binding, and *in situ* hybridization in collaboration with Dr. Soghomonian's laboratory. Since the genes for autism have not yet been discovered, there is much national and international attention on research labs investigating developmental, behavioral, and cognitive aspects of the disorder.

Dr. Beth Whitney recently defended her PhD thesis and found that about half of autistic cases have a reduced number of Purkinje cells by using calbindin in place of the standard Nissl stain which can show agonal changes and produce less reliable results. She further demonstrated that despite this decrease in target neurons, the GABAergic interneurons in the cerebellar molecular layer showed normal density. This research, coupled with our PhD student Sandy Thevarkunnel's finding of normal numbers of principal olive neurons that project to the part of the cerebellar cortex in Beth's study, gives us insight into the developmental timing of the Purkinje cell loss which is most likely beyond 32 weeks of gestation when these neurons are at their final location in the Purkinje cell layer.

Dr. Jane Yip joined our lab as a Research Associate about one year ago and has already made invaluable contributions. Working with Lin Nguyen and Dr. Soghomonian, Jane quantified GAD67 mRNA, a component of the main GABA synthesizing enzyme, in cerebellar Purkinje cells and found a 40% decrease in the posterior lobe. This means that there may be dysfunction of the output to the deep cerebellar nuclei and subsequently out to the thalamus and cortex.

Our limbic system efforts in autism involve Yuri Lawrence, a Master's student in our department investigating GABAergic interneurons in the hippocampus where there is increased packing density in select subfields; Claudia Persico investigating the serotonergic input to the hippocampus; Marissa Simms, a student on loan from Smith College quantifying GABAergic interneurons in the anterior cingulate cortex; and Eleni Antzoulatos who earned her Master's degree with us this year and is now at USC, found reduced 5-HT2a receptors in the anterior cingulate in collaboration with Dr. Terry Gibbs in the Pharmacology Department here at BUSM. Gillian VanSluytman and Rita Marcon, research technicians have also made significant contributions to our research efforts.

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Through the efforts of our Carnegie Leadership team, consisting of faculty, graduate and postdoctoral students, we have transformed our own graduate student program and have had a strong positive influence at our partner institutions. With the support of the Carnegie Foundation, we have also begun a series of interdisciplinary initiatives and projects that we believe will prepare the Department for the emerging research mission of the 21st century by the NIH as well as other government and private biomedical research organizations.

These efforts have already resulted in the funding of a Roadmap grant, one of the first in the country, to our Department. Key to this success has been the recruitment of Peter Bergethon by our Department jointly with the Department of Biochemistry. Dr. Bergethon, who is a neurologist, neuroscientist and physical biochemist, has emerged as one of the nation's leaders on interdisciplinary studies in the biomedical sciences. Together with Dr. Ted Woodcock of George Mason University, he recently organized the Medical School's first interdisciplinary biomedical course entitled "Introduction to Interdisciplinary Systems Science: Dynamical Modeling" that will be available to graduate students throughout the medical center next year as both a short and full-length course.

Also on the national level, the Autism Research Center at BUSM, directed by Helen Tager-Flusberg, Ph.D., Professor in our Department, has established our Medical School as one of the top ranking centers for autism in the world. Similarly, the Center for Biomedical Imaging under the direction of Dae-Shik Kim, an Associate Professor in the Department, has gained national recognition for the quality of its MR imaging. It has grown significantly since its opening in March of 2004 and has already attracted several new research grants for the Medical School.

Also seeing continued success is the Master's Program in Mental Health Counseling and Behavioral Medicine that we developed together with the Department of Psychiatry three years ago. The program has now expanded to over 50 students for the coming academic year. Not to lose momentum in programmatic development, the Department of Anatomy and Neurobiology, together with the Department of Radiology, has submitted a proposal for a new Master's program in Bioimaging through the Division of Graduate Medical Sciences. This program would be the first of its kind in the entire country, and we are optimistic that it will be approved and launched sometime next year.

Similarly, the Department has been working toward the development of a new Master's Program in Biomedical Forensics, the first of its kind in the country that would be affiliated with a Medical School. Under the direction of Tara Moore, Ph.D., Assistant Professor in Anatomy and Neurobiology, a new course in Biomedical Forensics was organized and run this past spring with the participation of members of local and federal law enforcement agencies. The course was a striking success, and we believe it will lay the groundwork for an exciting graduate program in the future.

This year also saw the development of a new graduate course on ethics and grant writing, organized and run by Julie Sandell, Vice-Chair of the Department. This course entitled "Professional Skills for Students in the Biomedical Sciences" will be offered through the graduate division and will be offered every spring semester in the future.

In addition to our success in completing several long-term goals in the Department, ongoing activities include successful recruitment of two postdoctoral candidates for our training grant from the NIA entitled "Training in the Neurobiology and Neuropsychology of Aging". This is our multi-institutional training grant that includes 20 faculty from BUSM and the Massachusetts General Hospital that was cited by the NIA as a "model for training grants in the field of aging." The department sponsored Clinical Neuroscience Society, an organization that provides mentoring, research opportunities and exposure to the clinical neurosciences for medical and graduate students at BUSM, has completed its fourth year of existence and is flourishing with over 40 active members.

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Congratulations

John Pugh
Natalie Zahr
Laura Welke

For completing your thesis defense!

Congratulations

Tulay Tankir Cushman
Rahul Desikan
Kelli Dominick
Maureen Estevez
Steve Schettler

For passing your qualifying exam!

Grants and Awards

Dr. **Todd Hoagland** was awarded BUSM's Stanley L. Robbins Award for Excellence in Teaching.

Tulay Tankir Cushman has been awarded a one year fellowship from the NSF to pursue a formal mentored program in K-12 education.

Dr. **Robert Joseph** has been awarded a K01 Research Scientist Development Award by the National Institute of Mental Health to investigate *The Neural Substrates of Gaze and Face Processing in Autism*. Dr. Dae-Shik Kim will mentor him on the award, and Dr. Tom Kemper is among several consultants to the project.

The Lab of Developmental Cognitive Neuroscience has received two fellowships from the National Alliance for Autism Research. **Kristen Lindgren** has received a predoctoral award. In addition, Dr. Ruth Grossman, a new addition to the lab, has received a postdoctoral fellowship. Drs. Helen Tager-Flusberg and Robert Joseph will mentor on the awards.

Learning Interdisciplinary Research

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scientist's toolkit. And whether you know it or not, systems thinking and its operational process, dynamical modeling, is close to the heart and mind of the Department of Anatomy and Neurobiology. Just take a look at our mission statement:

- Our unique Research Mission is to investigate the structure and function of Cerebral Circuits and Systems in health and disease, and a successful research future lies in a community of curiosity, intellectual creativity, and research productivity embodied by the Department's faculty.
- Our Teaching Mission is to educate graduate students in the discipline of Systems Neurobiology, from molecule to behavior. Education in this discipline is not limited to the evolving body of factual knowledge, but as importantly includes education in its integral art and cognitive skills.
- The systematic thinking processes applied in the mastery of the neurobiological sciences are the same processes crucial for successful research and teaching.

Talking about "systems" research is all the rage. But talking about it is not enough. Systems thinking and dynamical modeling methods are at the heart of interdisciplinary science and the NIH is serious about funding them. Our department has one of the first Interdisciplinary Roadmap Initiative grants to do just this kind of training and our participation in the Carnegie Initiative on the Doctorate has been instrumental in our success in acquiring that grant. In addition, we have taken a leadership role in the development of a center for Biomedical Interdisciplinary Research and Development by submission in the last several months of three grants to the NIH and to the Howard Hughes Medical Institute that incorporate systems science and dynamical modeling as the foundational language of an interdisciplinary research process.

The NIH Roadmap's initiative in Interdisciplinary Research argues strongly that successful interdisciplinary preparation for research, teaching, and public policy is not currently occurring in our institutions of biomedical education. Why is this the case? The overall enterprise of science is properly viewed as a way of looking at, discovering, and understanding the world around us. All scientists generally pay homage to the value of "the scientific method" but would rapidly be divided, usually along disciplinary boundaries, as to how this "universal" method would be best employed in each of many disciplines. The scientific disciplines themselves are characterized by their own intellectual history, vocabulary, assumptions, and accepted research protocols and paradigms, as well as a common agreement on theoretical contexts and controversies that provide a unique way for exploring a particular aspect of the "world around us." The knowledge represented by these elements and their inter-relationships comprise the structure of disciplinary knowledge. The pedagogy of training in a discipline typically

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Dr. Larry Zoller at a going away celebration thrown in his honor by the Goldman School of Dental Medicine

Chairman's Message

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Stemming from the Departments' commitment to the belief that teaching as well as research form the foundation for excellence in a basic science department, the department was again recognized for its excellence in teaching. Dr. Todd Hoagland was this year's recipient of the Stanley L. Robbins Award for Excellence in Teaching. Indeed, the faculty from the Department have received all four of the Robbins awards for the preclinical sciences spanning the last eight years. Dr. Lawrence Zoller was again acknowledged for his teaching acumen with the Proctor & Gamble Award for Excellence in Teaching from the Goldman School of Dental Medicine, and one of our graduate students, Tulay Tankir Cushman, was awarded a one year fellowship from the NSF to pursue a formal mentored program in K-12 education.

Transitions: Dr. Larry Zoller has accepted a position at the University of Nevada Las Vegas School of Dentistry where he will bring his teaching talents to help build their basic science program. We wish Larry the best of luck in this challenging endeavor. He will be missed by all.

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involves instruction and apprenticeship in both its physical or operational skills, such as impaling a cell with an intracellular electrode or using a microscope, and also its modes of presentation and argumentation, such as population studies in clinical epidemiology and proof of an axiom in mathematics. From a broader perspective, various disciplines can have an interest in deriving explanations and understanding of the same piece of the world. Yet as each scientist brings their own unique tools and perspectives to bear on a common piece of the reality, often the descriptions and understanding gained will be unavailable to practitioners of other disciplines engaged in study of the "same piece of the world." This cognitive relativity does not suggest that the contributions made by each discipline may not be valuable and important, but they may be unknowable. The "unknowability" is a result of the overriding truth of all science practice, "if it cannot be interacted with (and measured), it cannot be known." Thus, interdisciplinary progress is frustrated because of an inability to speak to one another in anything approaching a universal language of science.

Thus, interdisciplinary research actually proceeds by the comparison of one "system" of investigation to another. The language that is required to overcome unknowability is that of systems science. And here is some good news: Starting this summer you can take a short course in systems science and dynamical modeling and start on the road to interdisciplinary thinking.

The course, which was offered in the Summer Session II term, is

GMS AN 820S Introduction to Interdisciplinary Systems Science: Dynamical Modeling

The course provides participants with unique hands-on experience in the development and use of computer-based models to study biological systems. The first seminar introduces the principles of systems dynamics and identifies challenges in biomedical science that are addressed during the course. In the next few seminars, students learn to use the STELLA computer modeling software under the guidance of Dr. Bergethon and his colleague, Dr. Alexander Woodcock who is a visiting faculty member from George Mason University. Two case studies are undertaken to demonstrate how systems dynamics modeling can facilitate a new level of understanding in biomedical research areas such as neurobiology, cardio-vascular physiology, and pathobiology. During those case studies the participants will use, modify, and enhance the software models already developed by the course faculty. Finally, each student will choose a project in a biomedical application of his or her interest. The project will involve developing a systems dynamics model in that area and using those models in a series of computer-based experiments.

The course includes 9 seminars (9-12 in the morning MWF) with access to the computer laboratory during the remainder of the day. The course ran from July 6 to July 22, 2005 (3 weeks) this summer. We expect to run the short course at least once a year but may offer it summer and winter as is necessary to accommodate interest.

For information please contact Dr. Bergethon (8-4108) or prberget@bu.edu.

The Blatt Laboratory

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We have been very privileged to be able to look at many brain areas to pursue clues in an attempt to solve the enigmas of autism. Being part of a multidisciplinary group headed by Dr. Helen Tager-Flusberg as part of the NIH Autism Center of Excellence has also broadened our horizons and helped provide us with insights and direction toward future studies. We hope that our small but significant contributions will aid in the better understanding of the neuroanatomical and neuropharmacological basis of autism and ultimately provide clues regarding the etiology of the disorder.

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The Blatt Laboratory of Autism Neuroscience Research currently receives funding from NIH NICHD HD39459-04 "Olivocerebellar Circuitry in Autism"; NIH STAART Center Grant U54 MH66398-03: Project III: "The Neuroanatomical Basis of Social Affective Deficits in Autism" and from The Institute for Brain Potential "Glutamatergic Receptors in the Cerebellar Cortex in Autism." We receive post-mortem brain tissue from the Harvard Brain Tissue Resource Center (HBTRC) and The Autism Tissue Program (ATP).

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Recent Publications

Chang, Y. M., Rosene, D. L., Killiany, R. J., Mangiamele, L. A., & Luebke, J. I. (2005). Increased action potential firing rates of layer 2/3 pyramidal cells in the prefrontal cortex are significantly related to cognitive performance in aged monkeys. *Cereb Cortex, 15*, 409-418.

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