A magazine highlighting research at the University of Oregon

Spring 2001, Volume VII, Number 1

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Science as a Tool for Medicine

UO biologist explores the cell to understand health and disease

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The Sound Around Us

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Using advanced technology in primitive settings, linguists race to save some of the world's dying languages

- **Molecules of Life**

With the recent human genome breakthrough, science is positioned to race ahead toward medical advances, new drugs, and greater understanding of the body, health, and disease

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INQUIRY

Summer 2001

A Message About Research From

Rich Linton
Vice Provost for Research and Graduate Studies
Dean of the Graduate School

More than 30 years ago, the film 2001: A Space Odyssey created an imaginary vision of a then-faraway future. Although the film anticipated advances such as talking computers and artificial intelligence, its scope was mostly limited to space science. It gave only a glimpse of the wide range of remarkable advances to come. University of Oregon researchers featured in these pages illustrate a broader odyssey in today's science and scholarship.

Roderick Capaldi and Brian Matthews are exploring biological molecules and functions at a level of detail that only a few decades ago was nearly beyond imagination. While these biologists are expanding our knowledge of life at the cellular and molecular levels, psychologist Michael Anderson is adding to our understanding of the human brain and behavior. An international group of scholars, including Gary Ferrington, is creating a promising new field called acoustic ecology. High-tech innovation also has applications for humanists such as Spike Gildea, who is using modern technology in his work to save endangered languages. Jim Mohr's meticulous research shows that although dazzling technological advances attract much of the spotlight, fundamental research and scholarship remain central to the core mission of the institution.

In short, these Inquiry articles illustrate the university's growing impact on scientific and technological innovation and on their applications to serve society--an impressive odyssey indeed!

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Spring 2001

Science as a Tool for Medicine

UO biologist explores the cell to understand health and disease

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.Treatments or cures for debilitating illnesses such as Parkinson's disease and Alzheimer's disease would help millions of individual sufferers. But the challenges associated with making these advances are enormous, says University of Oregon Biology Professor Roderick Capaldi, and they will require the combined efforts of researchers working in hundreds of laboratories around the world.


Roderick Capaldi

.Capaldi's own laboratory is at the forefront of one promising and rapidly advancing frontier in this global research effort.

."Our work is focused on basic questions of how cells work--specifically, how they make energy and use it," he says. "For 25 years, my colleagues and I have worked to understand how cells can provide enough energy to do all the tasks they need to do to survive."

.The energy production powerhouses in cells are called mitochondria. Mutations of the DNA inside mitochondria are believed to cause a variety of severe ailments, such as neurodegenerative disease, Parkinson's, and Alzheimer's.

."We want to know what goes wrong with DNA in the mitochondria because by doing so we also learn what is happening when they are functioning properly," he says.

.The events that started Capaldi on this path began in the early 1980s, when he got a call from a physician in Portland. One of the physician's patients appeared to have muscular dystrophy, but something about the diagnosis seemed inconclusive. Capaldi obtained a sample of the patient's mitochondrial DNA, analyzed it and discovered a mutation. This explained the patient's situation, but techniques were not advanced enough 20 years ago to turn the discovery of the mutation into a useful diagnostic tool.

.But times--and technological capabilities--have changed. For the past three years Capaldi and his

research group have been applying their basic knowledge of cell functions to develop diagnostic tools for a number of diseases of energy metabolism. These extremely rare diseases have names such as Leigh's disease, MELPS disease, and MERRF disease.

."These rare genetic diseases hold the key to understanding how energy metabolism is controlled in humans," Capaldi explains. "The diseases are brought about in most cases by a single mutation in the mitochondrial DNA. By learning about these odd and unusual diseases, we learn a great deal about the much more common diseases--Alzheimer's, for example--that are believed to be the result of accumulations of many mutations over a lifetime."

.This work has led to the development of a number of diagnostic tools now being applied in clinical settings. These tools have resulted from collaborations with private companies such as Molecular Probes, Inc, a Eugene-based biotechnology corporation. Capaldi used some of the revenues generated from these collaborations to fund further research in his laboratory.

."This collaboration is a textbook example of how intellectual capital of the university can be matched with the expertise of private industry to produce useful products and at the same time advance important basic research," says Don Gerhart, director of the UO Office of Technology Transfer.

.Capaldi and his laboratory colleagues are collaborating not only with the private sector but also with members of other university departments and researchers from around the world.

."The days of an academic intellectual working alone in a lab are over. Finding answers to the big questions in medicine today require many people, big grants, big machines," Capaldi says.

.His many on-campus collaborators come from the UO's Monoclonal Antibody Facility as well as the chemistry and physics departments.

."The talented researchers from around campus are attracted to the interesting biological questions that we're seeking to answer. It's a very healthy scientific environment," Capaldi says.

.On-campus colleagues aren't the only ones attracted to this area. So are researchers worldwide.

."The effort to solve these diseases is truly international," Capaldi says. "Here at Oregon, we attract scientific visitors from all over the world. Right now we have visiting researchers from Russia, Japan, Romania, Germany, Switzerland, England, France, and Sweden."

.Running a research laboratory at a university requires Capaldi to be a teacher both inside and outside his lab. In classrooms he teaches courses in human genetics and mitochondria. In the lab he helps undergraduates, graduate students, and postdoctoral researchers advance their knowledge of the process of science. His laboratory crew typically numbers between 12 and 15.

."I try to model not only the techniques, but also the excitement of doing science. This is especially important, I think, for the undergrad students. I want to help them see beyond the immediate task at hand and catch a glimpse of the larger picture of what they are doing or learning about. That's the best

instruction I can pass along to the next generation of scientists."

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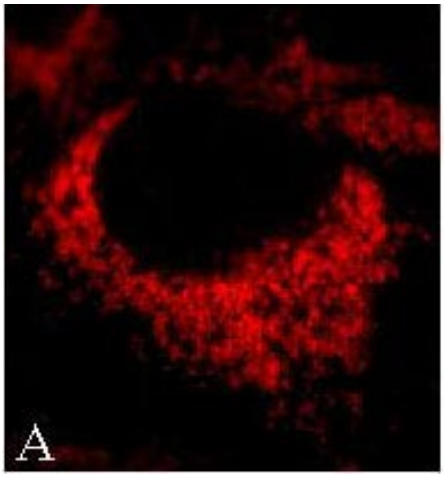
THE MITOCHONDRION PROJECT

The mitochondrial research project at the University of Oregon involves several laboratories and encompasses studies of structure, function and pathology of this organelle. The MORPHOLOGY AND CELLULAR ARRANGEMENT of mitochondria in several human cell lines is being studied using fluorescence microscopy. Mitochondria are "labeled" with Mitotraker, or by genetically-targeted GFP. Cell cycle dependent changes in mitochondrial morphology have been identified.



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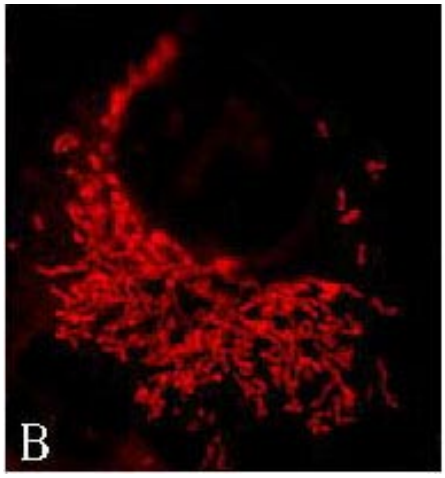

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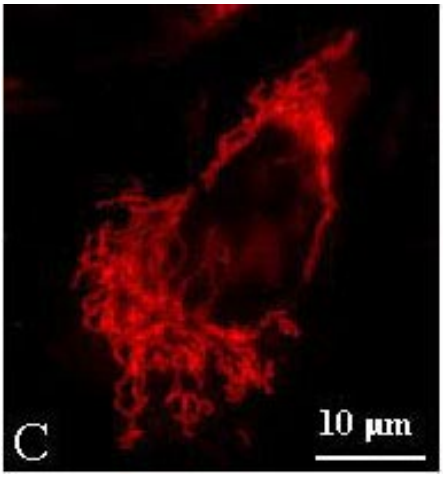

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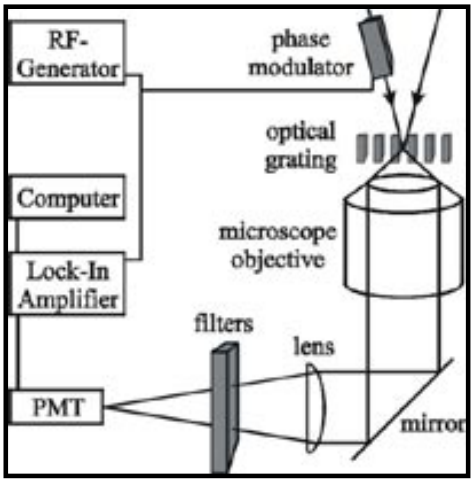
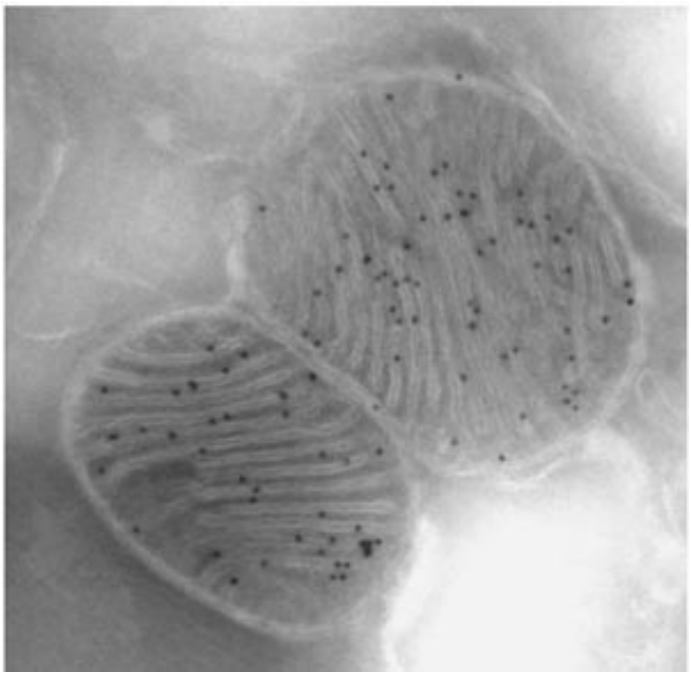


Movements of the organelle within the cell in response to extracellular and intracellular signals are being examined by digital fluorescence microscopy and by a novel technique of fourier imaging correlation spectroscopy (FICS) that has been developed recently in the laboratory of Dr. Andrew Marcus (Chemistry).

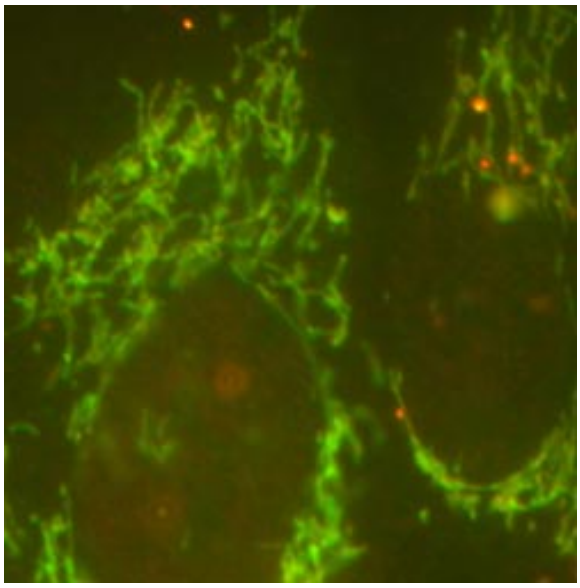
The INTERNAL STRUCTURE of mitochondria is being studied by Dr. Jeanne Selker and colleagues using a variety of electron microscopy techniques. In particular, the distribution of proteins to different compartments in the cell e.g. outer membrane, inner membrane, cristal membrane, inter-membrane space and matrix space is being examined by

immunological approaches employing gold labeled monoclonal antibodies.



Distribution of the cytochrome bc1 complex revealed by immunogold labeling of bovine heart ultrathin cryosections

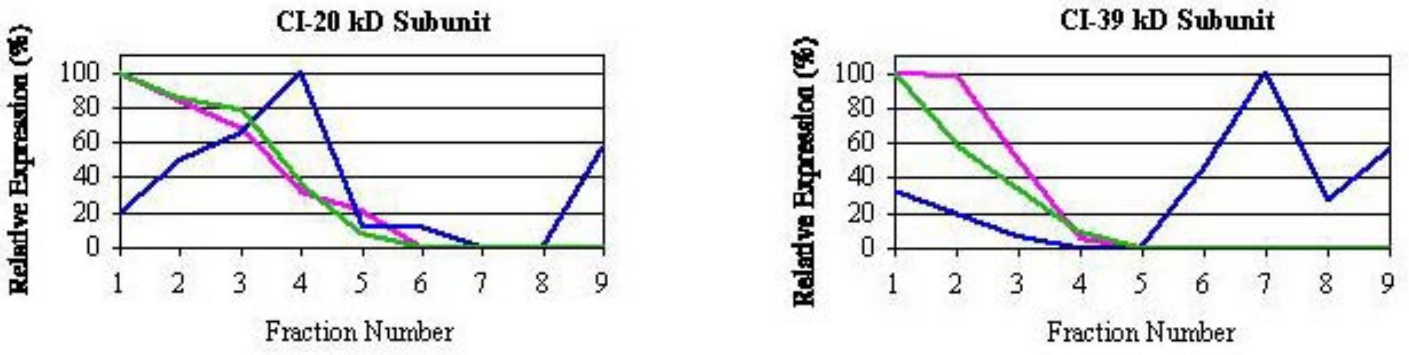
It is becoming clear that there is only limited diffusion of proteins, DNA and RNA's within the organelle. FICS is now being used along with video microscopy to determine movements within mitochondria when in the reticulum form.



As yet the TOTAL PROTEIN COMPOSITION of mitochondria is poorly defined. More than 150 proteins of the mitochondrion are known, but estimates suggest that the organelle includes in excess of 1000 different polypeptides, of which 13 are coded on mtDNA with the rest of nuclear/cytosolic origin. We have begun an effort to identify all components in human heart and human fibroblast mitochondria. This proteomics effort is a collaboration with Molecular Probes (Eugene). As novel proteins are identified, they are being overexpressed, purified and monoclonal antibodies made to each to aid in the structural studies described above.

Mitochondria labeled with a mAb against pyruvate dehydrogenase E2 subunit that has been conjugated directly with Alexa 488.

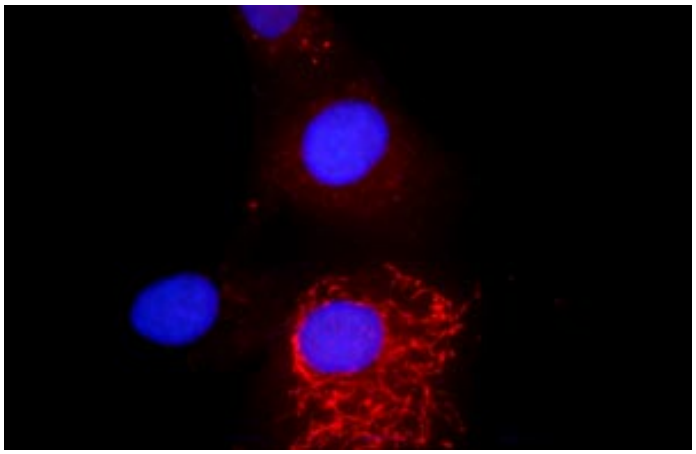
The monoclonal antibodies produced by Dr. Michael Marusich and colleagues are an important tool in examining the PATHOLOGY OF MITOCHONDRIA. There are a number of diseases caused by a primary defect in a component of mitochondria.



Mitochondria from a control cell line (green) and two cell lines from patients with Complex I (CI) deficiencies (blue and pink) were separated on a sucrose gradients. The positions in the gradient of a CI-20kD subunit and a CI-39kD subunit were determined by Western blotting and plotted. While CI assembly appears to unaffected in one patient (pink), it is clearly altered in the other patient (blue).

Additionally, many medical conditions cause altered energy metabolism by secondarily altering mitochondrial function. Also, this organelle is a critical player in programmed cell death or apoptosis. Diagnosis of mitochondrial diseases, and characterization of the changes in mitochondrial structure and functions as a secondary consequence of other diseases, remains difficult. Our collection of monoclonal antibodies listed below are useful in such studies.

In vivo tests of MITOCHONDRIAL FUNCTIONING are few. We have available through a collaboration with Dr. J Remington (Physics), two GFP mutants engineered to measure redox state and proton concentration respectively. These have been successfully targeted to mitochondria in normal and patient cell lines. Both reporters are ratiometric so that there is no concentration dependence of the signal. Free radical production and pH changes as a function of respiration and ATP synthesis in normal and altered cells are now being examined.



Immunohistochemical cellular mosaicism of mtDNA-encoded proteins is a diagnostic characteristic of mtDNA-depletion sydrome. Red = cytochrome *c* oxidase subunit I. Blue = nuclei. Some cells express apparently normal levels of mitochondrial COX-I, while other cells lack detectable COX-I.
For details, see Marusich, et al., (1997) *Biochem. Biophys. Acta*, 1362, 145-159.

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RECENT PUBLICATIONS

Margineantu, D.H., R.A. Capaldi, and A.H. Marcus. (2000) Dynamics of the mitochondrial reticulum in live cellls using patterned fluorescence correlation spectroscopy and digital video microscopy. *Biophys. J.* 79, 1833.

Gilkerson, R.W., D.H. Margineantu, R.A. Capaldi, and J.M.L. Selker. (2000) MtDNA depletion causes morphological changes in the mitochonrial reticulum of cultured human cells. *FEBS Lett.* 474, 1.

Capaldi, R.A. (2000) The changing face of mitochondrial research. *Trends in Biochem Sci.* 25, 212.

Garcia, J.J., I. Ogilvie, B.H. Robinson, and R.A. Capaldi. (2000) Structure functioning and assembly of the ATP syntase in cells from patients with the T8993G mitochondrial DNA mutation. Comparison with the enzyme in Rho cell completely lacking mtDNA. *J. Biol. Chem.* 275, 11075.

Rahman, S. J.W. Taanman, J.M. Cooper, I. Nelson, I. Hargreaves, B. Meunier, MG. Hanna, J.J. Garcia, R. A. Capaldi, B.D. Lake, J.V. Leonard, and H.V. Schapira. (1999) A missense mutation of cytochrome oxidase subunit II causes defective assembly and myopathy. *Am J. Human Genetics* 65, 1030-1039.

Taanman, J.W., M.D. Burton, M.F. Marusich, N.G. Kennaway, and R.A. Capaldi. (1996) Subunit specific monoclonal antibodies show different steady-state levels of various cytchrome *c* oxidase subunits in chronic progressive opthalmoplegia. *Biochem. Biophys. Acta* 1315, 199-207.

ANTIBODY LIST

Antigen	MAb	MW on SDS-Page	Antibody Isotype	Human XR	Rat XR	Bovine XR
C-I						
C-I-08	RAC#24-17C8E4E11	08 kD	IgG1,k	+	+	+
C-I-14 NDUFS5	RAC#24-21A6BE1BA3AD1	15 kD	IgG1,k	+	-	+
C-I-15	RAC#24-17G3D9E12	15 kD	IgG1,k	+	+/-	+
C-I-18	RAC#24A-22B8BE8H5	18 kD	IgG1,k	+	nd	+
C-I-20	RAC#24A-20E9DH10C12	20 kD	IgG1,k	+	nd	+
C-I-30 NDUFS3	RAC#24A-17D950C9H11	30 kD	IgG2a,k	+	nd	+
C-I-39 NDUFS2L	*RAC#24-20C11B11B11	39 kD	IgG1,k	+	+	+
C-II						
C-II-30 (FeS)	*RAC#23-21A11AE7	30 kD	IgG2a,k	+	+	+
C-II-70 (FL)	*RAC-#23-2E3GC12FB2AE2	70 kD	IgG1,k	+	+	+
C-III						

C-III-Core 2	*RAC-#23-13G12AF12BB11	45 kD	IgG1,k	+	+	+
C-IV						
C-IV-1	*RAC#18-1D6E1A8	40 kD	IgG2a,k	+	+	+
C-IV-2	*RAC#21-12C4F12	24 kD	IgG2a,k	+	-	+/-
C-IV-2	RAC#21-15B4C1	24 kD	IgG	+/-	-	+
C-IV-4	*RAC#11-20E8C12	17 kD	IgG2a,k	+	+	+
C-IV-4	*RAC#4-10G8D12C12	17 kD	IgG2a,k	+	-	+
C-IV-5a	RAC#1-6E9B12D5	08 kD	IgG2a,k	+	+/-	+
C-IV-5b	*RAC#7-16H12H9	08 kD	IgG2b,k	+	+	+
C-IV-6aH	*RAC#7-4H2A5	06 kD	IgG2a,k	+/-	-	+
C-IV-6aL	*RAC#15-14A3AD2BH4	06 kD	IgG1,k	+/-	+/-	+
C-IV-6b	RAC#10-8F2E3G10	06 kD	IgG2a	-	-	+
C-IV-6c	*RAC#10-3G5F7G3	06 kD	IgG2b,k	+	+	+
C-IV-7aHL	RAC#10-6D7G8E5	05 kD	IgG2a	+	+	+
C-IV-7b-VIIb	RAC#3-2G7H8R	05 kD		+/-	-	+
C-V						
C-V-Alpha	*MM#1-7H10BD4	53 kD	IgG2b,k	+	+	+
C-V-Alpha (plant XR)	MM#1B-15H4C4	53 kD		+	nd	nd
C-V-Beta	RAC#5-7E3F2	52 kD	IgG2a	+	+	+
C-V-IF1	RAC#25A-5E2D7	8 kD	IgG1,k	+	+	+
C-V-d	*MM#1-7F9BG1	29 kD	IgG2b,k	+	nd	+
PDH						
PDH-E1-B	MM#3-17A5E2H8	35 kD	IgG1,k	+	+	nd
PDH-E2	MM#3-15D3G9C11	72 kD	IgG1,k	+	-	nd
PDH-E2/E3bp	MM#3-13G2AE2BH5	72/55	IgG2a,k	+	nd	nd

NOTE: "Heat" for immunocytochemistry indicates that paraformaldehyde-fixed target cells must be treated for 20 min at 90 C in 0.1M Tris/HCl pH 9.5 with 5% urea before acetone permeabilization.
***Available through Molecular Probes Inc.**

POSITION OPENINGS

A post-doctoral position is available to work on structural aspects of mitochondria, using fluorescence microscopy of GFP-tagged mitochondrae proteins.

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Updated: January 2000
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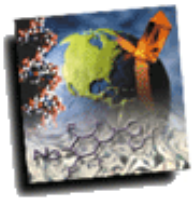

Office of Technology Transfer

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- To ***diversify*** and increase corporate support of faculty research
- To ***protect*** and manage the intellectual property assets of the University

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- Administer the transfer of materials (e.g., cell lines, clones) between the University and others to protect intellectual property rights
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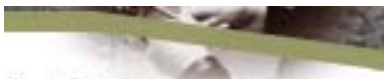

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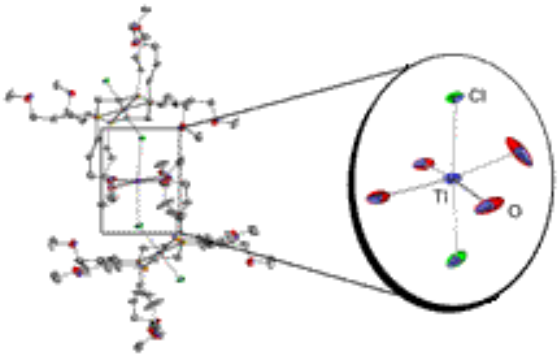

UO Lab Discovers Method to Assemble 1-D Coordination Polymers

Researchers in the Tyler lab recently demonstrated how "arrested" chloride abstraction reactions can be used to assemble 1-D coordination polymers.
PDF: Arrested chloride abstraction from trans-$RuCl_2(DMeOPrPE)_2$ with $TlPF_6$; formation of a 1-D coordination polymer having unusual octahedral coordination around Thallium(I). Nathaniel K. Szymczak, Fusen Han and David R. Tyler, Dalton Transactions, 2004, 3941 - 3942.
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Photo of Mt. Hood by Bernd Mohr.
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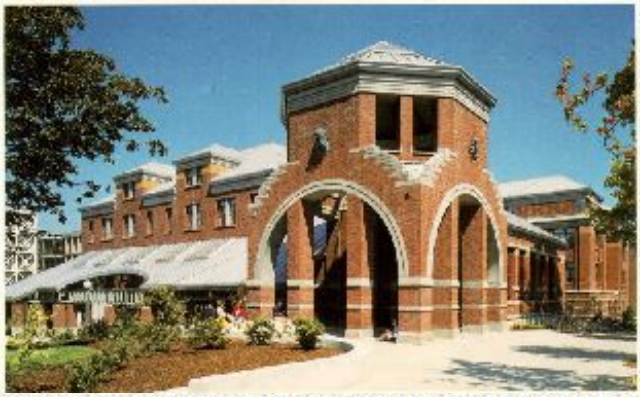

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INQUIRY

Spring 2001

Forget About It

New research shows how the mind gets rid of unwanted memories

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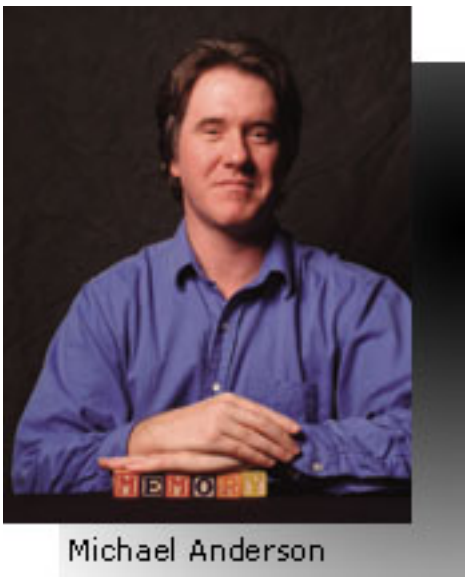

Michael Anderson

.More than 100 years after Sigmund Freud posited the existence of a repression mechanism that pushes unwanted memories into the unconscious, a researcher at the University of Oregon has found hard evidence to explain how that mechanism works. The research, conducted by UO assistant professor of psychology Michael Anderson, was published in a recent issue of the top science journal Nature.

."Our findings are consistent with Freud's ideas about voluntary repression but go a long way toward demystifying the process," says Anderson. "This work allows Freud's ideas to be understood in terms of widely accepted mechanisms of cognitive control that apply in a broader range of circumstances."

.The publication put Anderson in the spotlight of media attention. U.S. News & World Report, Science News and the Associated Press carried feature stories on the research. News outlets in Canada, Germany, Chile, Australia, Brazil, and England reported the story.

.Using rigorous laboratory techniques, Anderson's work shows that trying to keep an unwanted memory out of consciousness makes it harder for a person to recall that memory later, when he or she wants to recall it. The amount of forgetting increases with the number of attempts to exclude the unwanted memory from awareness--showing that the effects of inhibitory control accumulate with practice.

."Amazingly, this type of forgetting is more likely to occur when people are continuously confronted with reminders to the very memory they are trying to avoid. This is quite contrary to intuition, which says that seeing reminders a lot ought to make your memory better," Anderson says. " Under these circumstances--when reminders are inescapable--people must learn to adapt their internal thought patterns whenever they confront the reminders if they are to have any hope of avoiding the unwanted memory."

.An everyday example illustrates this mechanism at work. After having an argument with a friend, a person might want--or need--to continue interacting with the friend, even though the bad memory is brought to mind each time the friend or other reminders of the incident (for example, the place where the disagreement took place) are seen. For future interactions to remain pleasant or functional, the powerful associations set off by these reminders must be set aside.

.Anderson coauthored the paper with one of his undergraduate students, Collin Green, who is now enrolled in a prestigious Ph.D. program in psychology at UCLA.

."I really like working with undergraduates and mentoring students who show promise in scientific research. I currently have 10 undergraduate students in my lab," Anderson says.

.Some media reports suggested that the mechanism Anderson described could explain traumatic amnesia such as that seen in cases of posttraumatic stress disorder (PTSD) or in some cases of child sexual abuse. But there is a wide gap between the current findings and real-life clinical cases of traumatic amnesia, Anderson notes. In his research program, investigators test subjects' memories using simple pairs of words that are not emotionally significant. Amnesia associated with trauma involves many more distinctive, emotionally significant experiences that could stem from very different mental functions.

.Nevertheless, his findings may be useful in studying a number of clinical problems.

."It might be used as a measure of the effectiveness of attention control in various populations that are of great concern," he says.

.For instance, many current theorists have suggested the increase in distractibility and decrease in memory that is often associated with advancing age might be understood as a decline in controlled inhibition processes. Schizophrenia has also been attributed to inhibitory deficits. Understanding the mechanisms that may contribute to these conditions could lead to better treatments.

."The new paradigm developed in this work draws a direct link between people's efforts to regulate awareness and an objectively measured behavioral consequence of that internal act: forgetting. They thus provide a window into the mechanisms by which we regulate conscious awareness," Anderson says.

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INQUIRY

Summer 2001

The Way We Were

Historian sheds light on tough issues by discovering where they came from and how they developed

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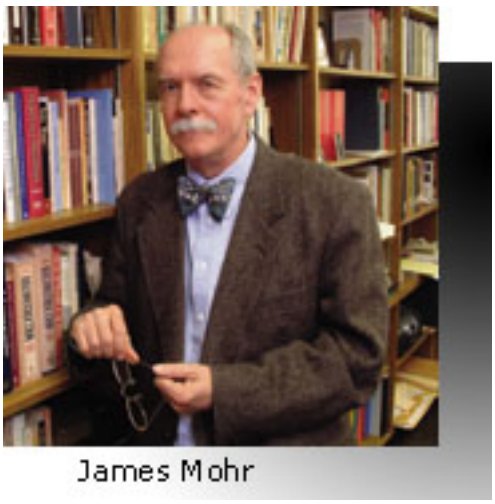
James Mohr

Abortion. The word brings to mind the acrimonious debate that has raged across America in the decades since the Supreme Court's landmark 1973 Roe v. Wade decision. And yet, for all the demonstrating and protesting and speech making on all sides of this contentious issue, precious little attention is paid to understanding the history of abortion in America. Anyone wanting to do so, however, would do well to begin the research effort with Abortion in America: The Origins and Evolution of National Policy, a book by University of Oregon history Professor James Mohr.

The book established Mohr as the preeminent scholar on this topic and led to his testifying twice before the U.S. Senate.

"In 1800 no jurisdiction in the United States had enacted any statutes whatsoever on the subject of abortion . . . . Yet by 1900 virtually every jurisdiction in the United States had laws on the books that proscribed the practice sharply and declared most abortions to be criminal offenses," Mohr notes in the preface of his book.

Mohr says he wrote the 1978 book not out of partisan feelings about this particular subject but as an attempt to understand how such a dramatic shift in social policy came about.

"We're the product of policy decisions made mostly at the state level and mostly in the nineteenth century," Mohr explains.

His studies have led him to the idea that professions, especially the medical profession, have played an important role in shaping American social policies and thus in shaping America.

Mohr has recently weighed in on another hotly debated social issue. In April 5, 2000 he published an article in the Journal of the American Medical Association on the history of malpractice in the United

States (the article grew from research Mohr conducted for his 1993 book, Doctors and the Law: Medical Jurisprudence in Nineteenth-Century America).

."The article sparked a great deal of interest," Mohr says. "I've received more than 400 comments or requests for additional information since it appeared."

.The article explores two basic questions: Where did medical malpractice litigation begin in the U. S.? How did it develop? In one way or another the answers to these questions affect--often in the pocketbook--every American who is treated by a doctor.

."Currently we are rethinking what the U.S. health care system should be," he says. "My work tries to help us see what this system has been, where it has come from, and what forces have been at work shaping it."

.Of course, some people think that history doesn't apply to today's world, but Mohr disagrees.

."These debates about abortion or about how public health is administered don't come out of nowhere. We got ourselves into them through a series of historical processes. As a result, historical perspective adds to the quality and clarity of public discussion."

.The lack of a historical perspective can be a dangerous thing. And, Mohr warns, Americans are dangerously unaware of history.

."We don't operate in a vacuum. My profession tries to remind people that we're part of ongoing historical processes much larger than ourselves. History is one way you remain connected to human society," he says.

.These ideas run through a popular course Mohr teaches called American Identity. In it, he asks students to consider various theories about what factors have made America the country it is today. The nation's Puritan beginnings? That America is the product of the first anti-imperialist revolution? That we were a frontier society? That we are the embodiment of modern democracy?

."I try to get the students thinking about what our nation is--its strengths and weaknesses," he says. "How might each of these theories fit--or not fit--the historical evidence? What do they have to say about what holds us together? I want to help my students see their society in long-term historical perspective."

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INQUIRY

Spring 2001

The Sound Around Us

Noise pollution is only one concern of the new field of acoustic ecology

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.Chirping cell phones, beeping beepers, roaring leaf blowers, and screaming jet airplanes--many sounds are loud, unpleasant, and all too abundant. On the other hand, some of life's most enjoyable sensations are perceived through in the ear: twittering birds at dawn, the rumble of ocean waves, a string quartet, a cat's purr.


Gary Ferrington

.The way a person experiences the surrounding sonic environment is at the heart of a small but growing discipline called acoustic ecology.

."Acoustic ecology is an umbrella under which people in many fields find a common gathering place," says Gary Ferrington, who maintains the World Forum for Acoustic Ecology (WFAE) website at the University of Oregon.

.The website, receives about 12,000 hits a month from around the world. The principal purpose of the site is to function as a clearinghouse for information.

."I have created an article database to which various international scholars contribute. There are also many links to relevant articles on other websites," says Ferrington, who serves as WFAE secretary and on the editorial board for Soundscape: The Journal of Acoustic Ecology.

.The wide-ranging interests of acoustic ecologists include the scientific, aesthetic, philosophic, architectural, and sociological aspects of the soundscape environment. For example, some theorists are exploring the concept of a soundscape where the relationship between the human community and its sonic environment is balanced. Researchers are studying the significance of electroacoustic media (radio, TV, and other amplified sound) and their ever-increasing presence in the soundscape. Others are studying attitudes toward silence in different cultures. Since coming to the UO in 1967, Ferrington has taught classes in audio design and written about sound-rich classroom experiences, including some that involve sound-oriented virtual reality environments.

.The advent of the Internet has allowed the interdisciplinary array of individuals engaged in the study of acoustic ecology at universities around the globe to communicate easily with one another.

."Most of my colleagues in acoustic ecology live in Canada, Australia, Scandinavia, or Europe," says Ferrington. "The ability to collaborate using the tools of the Internet illustrates to me how interactive technologies can broaden one's access to knowledge and collaboration with others to solve issues that have no borders."

.Acoustic ecologists are sometimes asked if there are practical applications of ecoacoustic ideas.

.Architecture provides one good answer. Many architects are concerned about the acoustic design of spaces--office space, playgrounds, parks, and plazas.

."Some of our greatest cities have plazas and other areas where sound is a shared human experience," Ferrington notes. Thoughtful architects can consider sound in their designs much as they consider building materials and structural integrity.

.Some government officials, aware of increasingly noisy urban environments, are looking for solutions to noise issues. Other acoustic ecologists are working to preserve the few natural wilderness areas that remain largely free of human acoustic intrusion. Sound artists and composers are using the soundscape as source material from which to create their art.

.Failure to take steps toward improving the sound environment may have serious consequences.

."Noise pollution is an increasingly serious problem worldwide as we become more urbanized," Ferrington warns. "The use of headphones, boom boxes, and other amplified sound devices by youth is creating deafness at an early age. We first began to recognize this problem with the baby-boom generation. In recent years, the problem has become worse."

.But the world's acoustic future is not necessarily bleak, Ferrington believes. Increasing our understanding of the world of sound will have long-range benefits for society.

."Individuals and institutions need to recognize that the acoustic environment is as important as any other," he says. "It is a much healthier world when all living creatures can live in an acoustically balanced environment."

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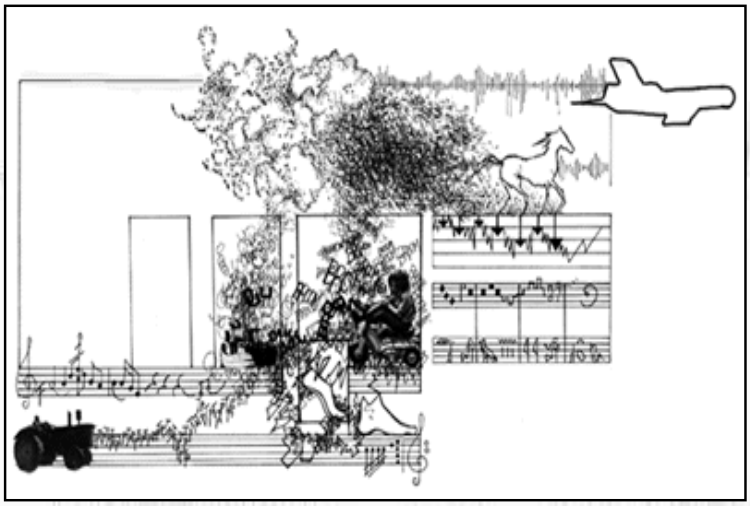
wfae

World Forum for Acoustic Ecology



Liliane Karnouk

WELCOME!

The World Forum for Acoustic Ecology (WFAE), founded in 1993, is an international association of affiliated organizations and individuals, who share a common concern with the state of the world's soundscapes. Our members represent a multi-disciplinary spectrum of individuals engaged in the study of the social, cultural and ecological aspects of the sonic environment.

Read: We offer a free online WFAE Newsletter as a monthly supplement to our print publication, *Soundscape: The Journal of Acoustic Ecology*. It includes news, events, workshops, and other activities related to the ecology of sound. The Journal is available to all paid members and is published twice a year.

Converse: We encourage you to participate in on-going discussions through the WFAE sponsored Acoustic-Ecology listserv. It is easy to join and participate with other ear-minded individuals regarding the soundscape environments in which we live.

Join: The World Forum for Acoustic Ecology encourages your participation in the growth and development of regional affiliate groups around the world. Learn more about becoming a member by downloading our WFAE 2005 membership form (PDF) or visiting the membership web page.

Participate: Join WFAE members and others at two WFAE endorsed events in 2005. Each will include special sessions and activities related to the field of acoustic-ecology.

- **Soundscape Conference**, April 22-24, 2005, Potsdam, Germany
  Contact: Forum Klanglandschaft Web:http://www.klanglandschaft.org/
- **Convegno sul Paesaggio Sonoro Soundscape Conference**,
  April 28-30, 2005, Palermo, Italy
- **International Congress on Sound and Vibration,** July 10-14, 2005 Lisbon,

Portugal. Web Info: http://www.icsv12.ist.utl.pt/

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Audio Design: Creating Multi-Sensory Images For The Mind

By Gary Ferrington
E-Mail: garywf@oregon.uoregon.edu

Abstract

When television, in the 1950's, replaced radio as the principle medium of home entertainment, the listener no longer had to use his or her imagination. Favorite characters and their actions became visually detailed. Society has increasingly relied on images created by others to give form and definition to the world in which all live.

Passive viewing has become the routine of both the family at home, and the students in the classroom. Creating images within the mind has become a skill no longer taught as an important aspect of the school curriculum.

Fortunately, there are many individuals who are rediscovering the role that audio can play in stimulating the imagination. Working in an audio medium provides the producer with the opportunity to rediscover the power of human imagination. This article explores the concept of the "theater of the mind", and the design factors which need to be considered in the creation of audio works for the ear.

Introduction

Given the amount of talk, rock, and western music, emanating from the nation's airwaves there would seem to be little room for imaginative informational, documentary, dramatic, and experimental audio. But that is not the situation. Producers in Europe, Canada, and the United States, are designing audio works which are not only broadcast on national radio systems, but are also widely distributed on cassette and compact discs.

Audio design is the process of creating meaning through the use of aural imagery. The sound designer recognizes the uniqueness of the medium and works with its symbolic language to effectively communicate ideas, concepts, and emotions (Zaza, 1991). Understanding the storytelling nature of audio and the power of the human imagination to generate mental images, is critical to effective audio design.

The nature of audio

Audio is a participatory medium which actively engages the listener in the on-going processing of aural information. This requires that the listener be able to discriminate between audio stimuli, employ aural decoding skills, and generate meaning for a perceived message.

The symbolic language of audio is purely auditory. It includes the spoken word, music, noise, and silence. Given that there are no other channels of information except sound, there is the potential risk of ambiguity in message design and interpretation (Crisell, 1986).

The audio designer recognizes the limits of the medium and strives to engage interaction between the sound stimulus and the listener's interpretive ability (Zaza, 1991). Frequently, the perception of a message is greatly influenced by the listener's ability to create multi-sensory imagery within the mind. These mental images are formed in response to an analysis of the signal received, and the personal experiential background the listener has with the subject or content. In effect, each individual fills-in details beyond the limited audio information provided (Crisell, 1986).

Sound and imagination.

The ability to form mental images of objects and events not immediately available to the senses is the essence of human imagination. This unique attribute of the mind makes possible the ability to seemingly see, smell, hear, and feel things which do not exist in the present tense.

Through imagination we experience a personal world created from our emotionally charged remembrances, dreams, and fantasies. The sound of a Christmas carol, for an example, may bring a flood of images to mind. The smell of fir boughs, the taste of rich holiday foods, the sparkle of colored lights, are but a few of the multi-sensory memories a holiday melody may stimulate within the mind.

Theater of the mind.

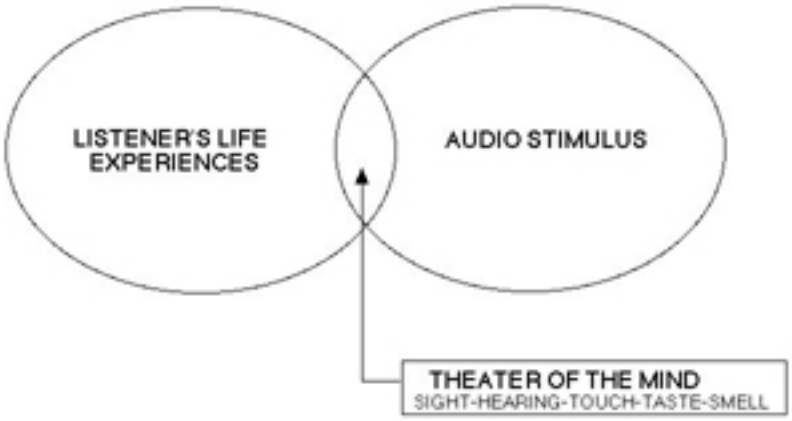
The power of the silent film, as a "mute" medium, was its ability to provoke human response through carefully composed images, the non-verbal action of actors, and the effective use of visual montage. Similarly, as Rudolf Arnhiem notes, audio is a "blind" medium. It lacks the multi-channel characteristics of other audiovisual media relying only on the elements of sound and silence to communicate information or emotional content. This "blindness" is both the weakness and strength of the medium (Arnhiem, 1986).

An effectively designed audio work may facilitate a listener's integration of life-based experiences into a 'movie' created within the 'theater of the mind'. Each individual becomes his or her own movie director with no two people having the same imaginary experience.

The following narrative illustrates the point.

Auditory Scene.
Heavy reverberating footsteps are heard as a person approaches from down a long hallway. The footsteps stop, a door opens and rapid gun fire is heard . The door is then slammed shut and the footsteps quickly retreat down the hallway.

Each listener will generate the missing "visual" details within this scene. For example, the gender and size of the person walking down the hallway, the style of clothing, the architectural space in which the event takes place, the smell of gun powder, or other information that may complete the scene, is all created within the mind of the listener as illustrated below.



The imagery generated by the listener comes from highly personal psychological resources. A dinosaur that a child creates while listening to a science fiction drama, for example, is not the same as one manufactured for him or her by Hollywood. It is a very personal dinosaur which comes from that child's joys, fears, and emotionally enriched experiences.

It must be noted that imagery, as discussed in this essay, is multi-sensory in nature. An individual who is congenitally blind will not have a pictorial memory upon which to create photographic-like mental images. All individuals give form and definition to the world through multiple senses. Aural cues give a blind person specific detailed information about the physical world to which a sighted individual may not attend as closely.

A blind individual, while listening to an audio work, will generate imagery based upon life's multi-sensory memories except that of sight. For example, the sound of thunder, wind and rain will give the listener an experienced sense of sky which is much different from that of a sighted person. Sound defines a sense of space for the sightless.

Good audio production design can expand human experience throughout the multi-sensory image building capability of the mind.

The elements of audio design

Storytelling is the art of oral communication and is integral to the design of effective audio. A good storyteller can relate for the listener the most recent developments in brain research as presented in an informational program; the complexity of a geological processes as found in a science broadcast; or the dramatization of life in the American colonies as explored through the use of a classroom audio tape. Good storytelling presents facts and concepts in a highly motivational manner which holds the attention of the listener.

Effective design begins with a well written script. It is through the use of words that ideas, concepts, and feelings are communicated. Understanding the power of language is imperative to the development of most effective audio products (Berger, 1990).

There are three narrative formats common to audio scripting (Thompson, 1969). The informational format presents content in a factual, news-like style. This is frequently used in instructional presentations which guide a student through a specific process. Sentences are purposefully direct and are void of superfluous color and texture.

The personal narrative strives to involve listener participation. This style is conversational, frequently acknowledges the presence of the listener, and directs attention to specific concepts or ideas.

The third style makes use of a dramatic or poetic presentation. Such narrative employs descriptive adjectives, use of analogies, imaginative rhythms, and other compositional elements which strive for maximum sensory response.

Though each of these narrative styles provides a conceptual framework within which to organize specific content, styles are frequently combined as needed. Scripting, regardless of the chosen format, begins with understanding the effective use of words.

Words, as used in audio, are written to be spoken and have paralinguistic characteristics which the designer must consider (Crisell, 1986) . The tone of voice, vocal emphasis, pacing, and regional accent, all have an effect on listener perception. In theatrical presentations, dialogue is accompanied by gesture and visually supported within the context of a stage setting. In an audio medium words are temporal and briefly exist in time. The listener must create continuity and meaning from the spoken narrative without the benefit of visual information.

Words can be vague. The word 'boat' for example tells us of a particular class of objects, but it in no way gives us detailed information about that object's characteristics. If one hears the dialogue line," Eric escaped from the prison using the old man's boat", the listener must imagine what that boat might look like, feel like to ride in, or perhaps even smell like in terms of age and mustiness.

The spoken word is more effective when it approximates that of daily speech compared to that of being read aloud from a printed page. Most all speech in audio is prescripted and then performed. This is true for informational, documentary, educational, as well as dramatic presentations. Prescripted speech may be elaborated upon to make the presentational flow seem more natural. Such phrasing as, "When you think of it..", "Let us consider for a minute...", or, " If we were to ..", all tend to personalize the written script. Such phrasing facilitates the illusion that the commentary is spontaneous in terms of

thought, and delivery was not premeditated (Crisell, 1986).

The delivery of words through narration or acting is an important consideration when both writing and producing an audio work. The listener should feel a sense of being situated within a given scene. The human voice should sound natural in an audio presentation. Unlike on a theatrical stage, the voice does not need to be projected. However, if characters are to create the illusion of movement and other activity, then physical emphasis must be given to the delivery of a particular line. For example the line, " Help me, I can't move this crate!", will need to have added physical stress in order to create the illusion that someone is actually struggling with an immovable object.

It is sometimes difficult to discriminate between the voices of characters who have similar tonal value. This is especially so when using young children. One might consider casting voices which reflect the uniqueness of the character as well as a distinct different voice from other characters on mike.

Music plays a significant role as a design element (Zaza, 1991). It can frame or establish the boundaries of an audio presentation. Music, used at the beginning, establishes a mood or sets the stage for the events which follow. Music is frequently used to link one scene to another. National Public Radio, for example, often uses a short musical bridge to segue between news features. And, of course, music is used to bring an event to a conclusion.

Music may be used to establish a setting, enhance action, or evoke a human response. In this context, the music can only be heard by the listener and not the characters within a scene. Such use plays upon human emotional response to musical forms with imagery generated by the rhythm, melody, and orchestration of the composition.

Music may originate from within the scene itself. A marching band, the loneliness of a saxophone played in a jazz club, or someone practicing the piano are all examples of in-scene use of music.

Music can be used to substitute for real world sounds. The audio designer may use music to represent battles at sea, thunderstorms, the wind, or other events. Again, the listener's experience with musical forms will facilitate the interpretation of the message.

Many audiovisual music libraries use descriptive labels such as industrial, travel, carnival, nature, sports and others, to classify musical compositions. Such classification suggest that we have developed a contextual perception of certain musical forms and visually associate them with specific places, things, and activities.

In addition to music, noise and silence are two ambient sound elements to consider. Noise includes all non-language and non-musical sound. Silence, as we will explore later, has

specific significance in that it can have either a positive or negative effect depending upon the designer's intentions.

An audio work's "soundscape environment" provides the context in which aural events happen (Schafer, 1977). The sound of an approaching car, footsteps on the gravel driveway, the echo of a river canyon, are all natural noises that provide the listener with a sense of place, or help define the attributes or actions of a character. Such sounds may take on other significance (Crisell, 1986). The sound of a train whistle may represent a melancholy mood. The crowing of a rooster might be used to symbolize the breaking of a new day.

Human sounds, other than those spoken, play an important role in aural communication. The sound of children at play, a baby's cry, laughter, the sadness of mourning, are all elements of the contextual soundscape which gives added depth and meaning to an audio production.

Silence is the opposite of noise. Silence, used as a void, creates the impression that something may have gone wrong. On the other hand it may facilitate a listener's ability to imagine completion of an action that, for one reason or another, cannot be represented through sound. For example, one character may ask of the other, " Pass me the hammer... (pause)...thank you." The silent pause will suggest that a transaction has taken place between the two individuals.

The challenge of creating acoustical space in an audio work is difficult. One is limited to the distance one can move from the microphone. There is no aural perception of up, down, left or right. The director working in a monaural medium, such as radio, must place the actor closer to, or further away from the microphone to create the illusion of depth and direction. Enhancement of relationships between characters is achieved with the use of narrative references such as, " What are you doing up there, John?", or " How can I get down to you from here?".

The director may also use selective focus to create an illusion of space. An individual, attending a typical office party, can easily isolate relevant conversations from the constant din of background sound. The creation of this same experience in an audio production is difficult and requires the director to focus the listener's attention.

Selective focus begins with prioritizing the sounds to which a listener's attention must be given (Zaza, 1991). The audio designer, replicating the office party, might mix one voice at a higher volume level than another so that it dominates the foreground. Or, the background volume might be lowered which would focus listener attention to selected conversations. It might be necessary to limit sound field to two or three representative elements of a party, thus allowing the listener to focus on specific dialogue. To create a

sense of movement within the party various voices can be slowly faded in or out to suggest movement away from or toward the listener.

The use of stereo recording technology provides the designer with a directional context for spatial sound referencing. The use of two microphones, one each for the left and right side of an acoustical stage, can simulate the effect of a passing automobile, or the moving of actors across a scene. The primary effect is that of a definite left, center, and right spatial orientation in front of the listener.

Stereo surround sound extends the stereo format by providing the listener with sound from the front, sides and rear. Such sound environments are more realistic than those created with monaural techniques - though not the true three dimensional effect as the word 'stereo' might suggest.

Binaural recording technology helps replicate the most life-like of acoustical spaces. Most binaural recordings are made using a dummy head in which a microphone has been implanted within each ear canal. The listener must wear headphones in order to hear the accurate reproduction of three-dimensional binaural sound. The listener's perspective is that of being on-site where the sound was recorded.

A critical difference between stereo and binaural playback is the aural effect each has on the listener when headphones are used. A stereo recording will sound as though it is originating within the listener's head. One seemingly becomes the soprano singing all the high notes. The sound from a binaural recording will seemingly exist in a spatial field outside the head forming a 360 degree sphere of acoustical space around the listener. A knock on the door, in a binaurally produced ghost story, is quite startling.

The binaural production of audio plays has opened new production opportunities. In the ZBS presentation of Carlos Fuentes' Aura, the listener enters the dark landscape of the mind. A young man answers a newspaper ad and finds himself drawn into the lives of a reclusive old woman and her beautiful daughter who live in house devoid of daylight. The ambient sound was recorded on-site in Mexico City and the use of binaural technology enhances the listener's sense of presence's in each scene of the play.

Stephen King's The Mist, an audio production published by Simon & Schuster, effectively uses binaural sound to involve the listener. Closing one's eyes facilitates the participation in a macabre world that is so real that its hard not to believe that one is actively trying to survive the life threatening events in the story.

In the German radio play *Marianne from 7 to 7* , the listener becomes the principle character hearing the world from her own personal perspective. An especially effective scene is one in which the listener, as Marianne, puts on a shower cap and steps into the

shower. The sound of the water falling upon the plastic cap is so real, that it stimulates the tactile sense of the listener.

Summary

Hearing and listening are not the same. Hearing is a physical process by which sound pressure waves are turned into signals to the brain. Listening is a psychological process by which meaning is given to aural input.

The goal of good audio design is to effectively engage the listener in active and attentive listening. Such listener participation is critical to releasing the imaginative power of the mind. It is this "imaging" that is important when thinking of audio's relationship to visual literacy.

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INQUIRY

Spring 2001

So Many Languages, So Little Time

Using advanced technology in primitive settings, linguists race to save some of the world's dying languages

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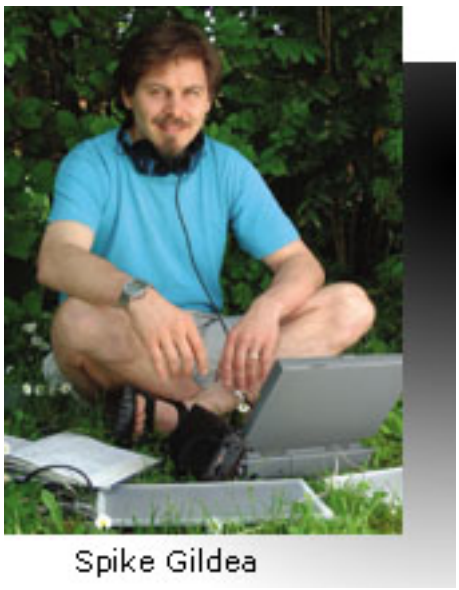

Spike Gildea

One of the greatest human cultural achievements is language, and languages are becoming extinct at an alarming rate.

"It has been estimated that half of the world's languages will die out when the generation now learning them dies, and that 90 percent will be gone in less than 100 years," says University of Oregon linguistics Professor Spike Gildea.

Not only are thousands of languages dying, but the number of field linguists who have the skills to study the languages with native speakers, learn, and preserve their linguistic idiosyncrasies is alarmingly small.

"Only a few hundred trained field linguists worldwide are doing this kind of work," Gildea says. "Once a language is gone, it's gone. So these researchers are in something of a race against time."

Gildea is himself one of the field linguists in this race. He spent four months in Venezuela conducting field research with the Panare and Yukpa Indians, both of the Cariban language family. The work with Panare became the basis of his master's degree in 1989. He continued his studies of Cariban languages in the library, finishing a companion volume of the grammar of known Cariban languages in his Ph.D. dissertation in 1992. Then a $270,000 grant from the National Science Foundation allowed him to spend two years in the Brazilian jungle north of the Amazon and to return for two additional summers of research.

"My time in the jungle was amazing--like something you'd see in a National Geographic article," Gildea recalls. "I was in heaven. One of the reasons I'm attracted to this kind of work is that I love being in the field. Not many disciplines allow you to do that."

The challenges Gildea faced as a field researcher in the Amazon were many and varied: food

poisoning, limited medical care, lack of such basics as gasoline, malfunctioning equipment.

.But the grueling work has its rewards.

."The Northern Amazon region used to be a black hole from a linguistic point of view. Virtually nothing was known about a whole group of languages, many of which were spoken by only a few hundred individuals. We didn't even know how many languages were there," Gildea explains. "Now we know that there are only 16 Cariban languages in this area, and we're writing grammars for four of them."

.The methods field linguists use to gather information about languages is changing fast. For example, Gildea and his colleagues take laptop computers into the jungle, using solar collectors to recharge the batteries. The linguists record extensive sessions of native speakers using their language and store the recordings in digitized form.

."We can then study and manipulate these recordings in sophisticated ways," he says. "In the past whole grammars were based on transcriptions of the utterances of native speakers and perhaps a small amount of recorded material. In 20 years a grammar will not be taken seriously without extensive recordings of natural speech to substantiate transcribed utterances."

.Gildea, a native Oregonian, got an early cross-cultural experience when he spent two years in the Peace Corps in Nepal following completion of his undergraduate degree at the UO.

."It was in Nepal that I realized how much I love languages. In my ensuing studies I've sometimes felt like a butterfly collector. Each thing I learn about linguistics or about a specific language is another beautiful example of what we can do with our endlessly diverse ability to make language."

.Gildea may soon have the opportunity to gather many more linguistic butterflies. He is seeking support from the National Science Foundation to venture next into the jungles along Guyana's border with Venezuela.

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S01, S02	Ling 452/552	Syntax and Semantics 2
F01	Ling 614	Theory of Phonology
W01	Ling 615	Theory of Syntax

This Year's Classes

F02	Ling 407/507	Seminar: Field Field Phonetics and Phonology (co-taught with Susan Guion)
W03	Ling 451/551	Syntax and Semantics 1
S03	Ling 426/526	Structure of the Cariban language Family

Selected Publications

Books

1998. *On Reconstructing Grammar: Comparative Cariban Morphosyntax*. Oxford: Oxford University Press.

2000 (ed). *Reconstructing Grammar: Comparative Linguistics and Grammaticalization.* Amsterdam: John Benjamins

Articles

1993a. The rigid postverbal subject in Panare: a historical explanation. *International Journal of American Linguistics (IJAL)* 59.44-63.

1993b. The development of tense markers from demonstrative pronouns in Panare (Cariban). *Studies in Language* 17-1.53-73.

1994. Semantic and pragmatic inverse - "inverse alignment" and "inverse voice" - in Carib of Surinam. *The Pragmatics of Voice: Active, Inverse, Passive* . ed. by T. Givón, Typological Studies in Language, vol 30, 187-230. Amsterdam: John Benjamins.

1995. A comparative description of syllable reduction in the Cariban language family. *International Journal of American Linguistics* 61.62-102.

1997a. Introducing ergative word order via reanalysis: Word order change in the Cariban language family. In *Essays on Language Function and Language Type,* ed. by Joan Bybee, John Haiman and Sandra Thompson, 145-61. Amsterdam: John Benjamins.

1997b. Evolution of grammatical relations: How functional motivation precedes structural change. In *Grammatical Relations: A Functionalist Perspective on Structure,* ed. by T. GivÛn, 155-198. Amsterdam: John Benjamins.

2000. On the genesis of the verb phrase in Cariban languages: Diversity through Reanalysis. In *Reconstructing Grammar: Comparative Linguistics and Grammaticalization*, ed. by Spike Gildea. Amsterdam: John Benjamins

Recent Presentations

1994. Towards a New Classification of the Cariban Languages of Northern Brazil. Presented at the *International Congress of Americanists*, Stockholm, Sweden.

1995. Functional versus syntactic evidence for reanalysis. Presented at the *Conference on Functional Approaches to Grammar*, Albuquerque, New Mexico.

1995. From biclausal coreference conditions to monoclausal alignment: the evolution of Cariban split ergativity. *Workshop on Diachronic Syntax, International Conference on Historical Linguistics*, Manchester, England.

1998. The Reconstruction of Imperfectives/Progressives in Proto-Cariban. *Seventh Workshop on Historical Reconstruction*, University of Pittsburgh.

1999. Two invited talks for the *Curs de tipologia de les llengües ameríndies*, Secció de Lingística General de la Universitat de Barcelona, Barcelona, Catalonia (Spain).

- Ergatividad bifurcada en panare (Carib)
- La evolucion de la grammática: la autonomía de sintaxe en un modelo funcional de lingística.

1999. Two invited talks at the *Centro Colombiano de Estudios de Lenguas Aborígenas (CCELA)*, Universidad de Los Andes, Bogotá, Colombia.

- Relaciones gramaticales e introducción a la ergatividad.
- Para explicar la ergatividad: bifurcaciones y sus orígenes.

2000. Invited discussant. Rencontre sur le grammaire des langues Tupi-Guarani, *Institut de Recherche pour le Developpement (IRD) et Centre Nacional de la Recherche Scientifique (CNRS)*, Cayenne, French Giuana.

2000. The Innovative Progressive in Akawaio (Cariban). *Workshop on American Indian Languages*, University of California, Santa Barbara.

2001. Pre-Proto-Tupí-Guaraní Main Clause grammar. *I Encontro Internacional do Grupo de Trabalho de Línguas Indígenas da Associação Nacional de Pós-Graduação e Pesquisa em Letras e Lingüística.* Belém, Brazil.

2002. An Unsuspected Asymmetry in the Evolution of Ergativity. Keynote talk, *Workshop on American Indian Languages,* University of California, Santa Barbara

Other Professional Activities:

Assistant Editor for the series *Typological Studies in Language,* Amsterdam: John Benjamins Press

Member, Comité Científico, *Centro Colombiano de Estudios de Lenguas Aborigenas (CCELA),*, Universidad de los Andes, Bogot·, Colombia.

Research Interests

- Descriptive linguistics, especially of indigenous languages of South America
- Historical linguistics, especially comparative studies of the Cariban language family
- Diachronic Syntax, especially reconstructing grammar

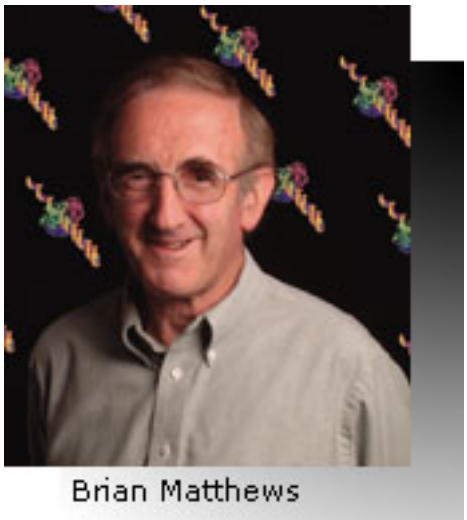
INQUIRY

Spring 2001

Molecules of Life

With the recent human genome breakthrough, science is positioned to race ahead toward medical advances, new drugs, and greater understanding of the body, health, and disease

A member of the National Academy of Sciences and the author of more than 250 scientific papers, biophysicist Brian Matthews is one of the University of Oregon's most distinguished professors. During his long career he's seen some of science's most impressive advances come to pass--including the recent large-scale effort to understand the human genome.


Brian Matthews

.You've spent the greater part of your career focused on proteins. What is a protein?

BM: A protein is a tiny machine that performs a biological function. We are largely made up of proteins. The way we breathe, eat, move; the way we fight infections--all these are controlled by proteins. They're absolutely vital.

.But sometimes they malfunction and cause medical problems?

BM: That's right. Very occasionally a protein can be defective and it can lead to disease. For example, a mutation in the protein hemoglobin leads to sickle cell anemia and defects in the protein insulin can lead to diabetes. Proteins control the division of cells--when this process breaks down it can lead to cancer.

.What about proteins is of special interest to you?

BM: Their structure--literally how they hang together. Technically this is called determining the three-dimensional, or 3-D, structure of a protein. We've determined a number of these structures in my laboratory.

.Why is it important to know the structure?

BM: The structure tells us a great deal about what these proteins do, how they act inside cells. Knowing the structure can also help us understand why a protein is defective. If the protein is defective, it can lead to a disease state. High blood pressure, for example, is often the result of an overly active

protein. Patients with hypertension are often treated with drugs that reduce the activity of this hyperactive protein.

.So treatments for many diseases could potentially improve as more and more is understood about proteins?

.BM: Definitely. A major application of this kind of research is in the area of medicine. If one knows the exact structure of a protein, one can possibly design a drug to control the activity of that protein. Similarly, some promising drug candidates have both desirable and undesirable properties or side effects. If one knows how the drug interacts with the target protein--and one knows this by its structure--it may be possible to design a new drug that keeps the desirable attributes and eliminates the negative side effects.

.What changes have you seen in your field during your career?

.BM: I began my work on simple structures in the 1960s. Only one protein structure had been determined at that time. During the sixties more were determined, and it became clear that this was going to be a powerful and productive field. I had the good fortune to be involved in one of the earliest determinations.

.For many years the field was very productive but limited to investigating the proteins that occur in nature. In the eighties it became possible to generate completely new proteins and to determine how mutations change the structure and activity of existing proteins. It also became possible to adapt or engineer existing proteins to improve their properties. This led to a real explosion in the field.

.Another watershed was when it became possible, through genetic engineering, to produce large quantities of proteins that occur in nature only in very small quantities.

.What kinds of advances do you expect to see in the next few decades?

.BM: One of the major areas of promise stems from the human genome research that has been in the news so much lately. Our DNA provides the codes for the structure of every one of our cells--including their proteins--but the structures of these proteins are mostly unknown. There is a great deal of interest in the next step, which will be to determine these protein structures. There are at least 30,000 proteins in humans; of these, only a few hundred structures have been determined. There's still lots of work to do.

.Where will human genome research take us?

.BM: The genome as we've come to understand it today is just the beginning. Understanding the structural biology of the proteins encoded in the genome--that's the next step. The National Institutes of Health is supporting a major new initiative in this area.

.Do you have any personal hopes or expectations about how science might change our world?

.BM: It is very pleasing to have chosen work in a field because of its inherent scientific interest and then, many years later, to find that this field can be very powerful in treating human disease.

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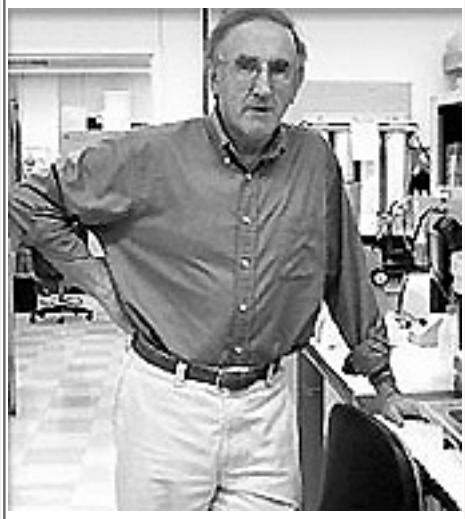
Faculty Profile | UNIVERSITY OF OREGON INSTITUTE OF MOLECULAR BIOLOGY

Brian Matthews



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Research Interests

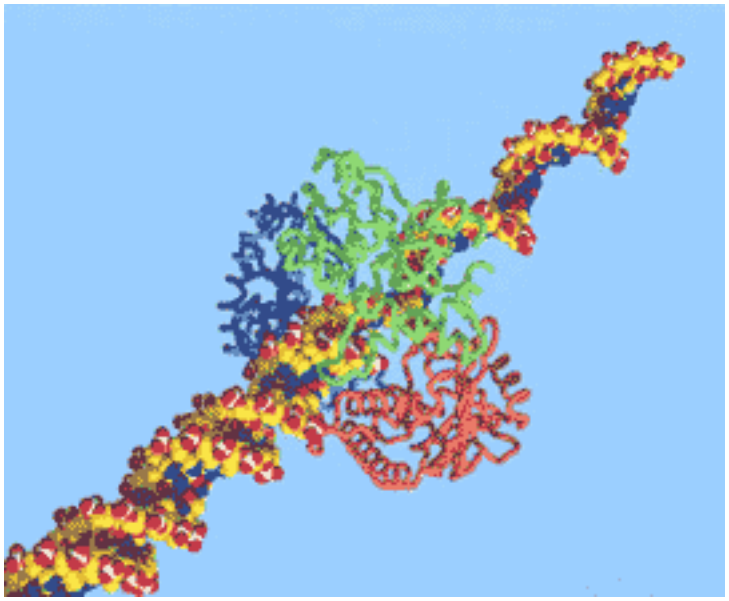
Our laboratory uses X-ray crystallography, in concert with other techniques, to address some of the fundamental problems in biology: How do proteins spontaneously fold into their biologically active three-dimensional configurations? What determines the stability of these folded proteins? Can stability be improved? How do proteins interact with each other? How do proteins interact with DNA? How do enzymes interact with their substrates and act as catalysts?

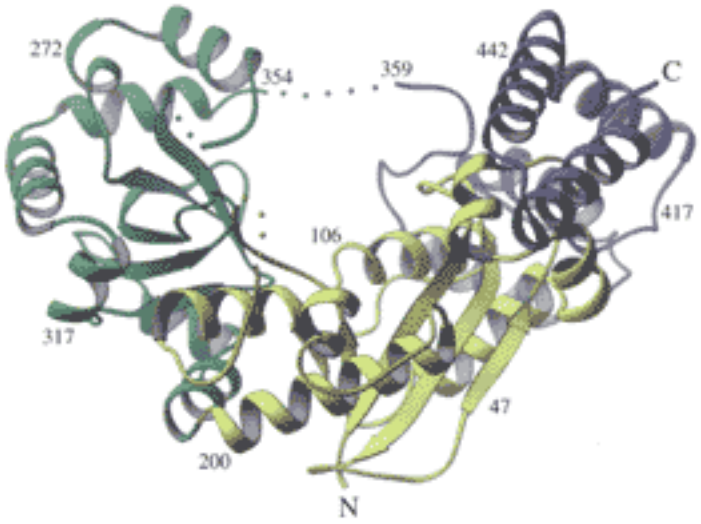
We have used the lysozyme from bacteriophage T4 to define the contributions that different types of interaction make to the stability of proteins. One of the key findings is that the protein is, in general, very tolerant of amino acid replacement. This has permitted more challenging experiments such as the insertion or deletion of longer segments of the polypeptide chain. Such changes can be used to address a variety of questions regarding protein folding. It has recently become possible to monitor the behavior, including folding and catalysis, of single molecules. The wealth of information already available for T4 lysozyme makes it a very attractive subject for such studies and we are actively pursuing this new area.

Lysozymes with designed cavities are being used to test and to improve the effectiveness of docking programs designed to predict the optimal small-molecule

that will bind to a given target site. Such sites are also being used to model the binding of general anesthetics.

We are also interested in the structural basis of DNA-protein interaction. Recent studies have focused on enzymes that are highly processive, i.e. they undergo multiple rounds of catalysis without dissociating from the substrate. In many, but not all cases, processivity can be achieved by having the enzyme completely enclose its substrate. In the case of lambda-exonuclease, for example, the enzyme forms a symmetrical toroid. For exonuclease I from *E. coli*, a toroid is also formed, but is by no means symmetrical (see figures).





Model (left) showing the presumed mode by which lambda-exonuclease encloses DNA and processively hydrolyzes one of the two strands. The figure on the right shows the structure of exonuclease I from *E. coli*. (Work of Rhett Kovall and Wendy Breyer in the Matthews laboratory).

Several years ago we determined the three-dimensional structure of *Escherichia coli* beta-galactosidase, one of the classic enzymes in molecular biology. As well as studies of the enzyme, *per se*, we are also using this system to try to understand, in detail, the response of protein crystals to flash-freezing, an increasingly common step in contemporary X-ray crystallography.

Other areas of interest include structure-function studies of the F- and V-type ATPases, as well as various peptidases including the thermostable zinc protease thermolysin, the cobalt-requiring methionine aminopeptidase from *E. coli* as well as the serine peptidases.

Selected Publications

Ostheimer G.J., H. Hadjivasiliou, D.P. Kloer, A. Barkan, and B.W. Matthews. (2005) Structural analysis of the group II intron splicing factor CRS2 yields insights into its protein and RNA interaction surfaces. J Mol Biol **345**:51-68.

Mooers B.H., and B.W. Matthews (2004) Use of an ion-binding site to bypass the 1000-atom limit to structure determination by direct methods. Acta Crystallogr D Biol Crystallogr **60**:1726-37.

Dyer C.M., M.L. Quillin, A. Campos, J. Lu, M.M. McEvoy, A.C. Hausrath, E.M. Westbrook, P. Matsumura, B.W. Matthews, and F.W. Dahlquist (2004) Structure of the constitutively active double mutant CheYD13K Y106W alone and in complex with a FliM peptide. J Mol Biol **342**:1325-35.

He M.M., Z.A. Wood, W.A. Baase, H. Xiao, and B.W. Matthews (2004) Alanine-scanning mutagenesis of the beta-sheet region of phage T4 lysozyme suggests that tertiary context has a dominant effect on beta-sheet formation. Protein Sci **13**:2716-24.

Yousef M.S., W.A. Baase, and B.W. Matthews (2004) Use of sequence duplication to engineer a ligand-triggered, long-distance molecular switch in T4 lysozyme. PNAS **101**:11583-6.

Kingston R.L., D.J. Hamel, L.S. Gay, F.W. Dahlquist, and B.W. Matthews (2004) Structural basis for the attachment of a paramyxoviral polymerase to its template. PNAS **101**:8301-6.

Wei B.Q., L.H. Weaver, A.M. Ferrari, B.W. Matthews, and B.K. Shoichet (2004) Testing a Flexible-receptor Docking Algorithm in a Model Binding Site. J Mol Biol **337**:1161-82.

Juers D.H. and B.W. Matthews (2004) The role of solvent transport in cryo-annealing of macromolecular crystals. Acta Crystallogr D Biol Crystallogr **60**:412-21.

Sagermann M., W.A. Baase, B.H. Mooers, L. Gay, and B.W. Matthews (2004) Relocation or duplication of the helix a sequence of T4 lysozyme causes only modest changes in structure but can increase or decrease the rate of folding. Biochemistry **43**:1296-301.

Carmel A.B. and B.W. Matthews (2004) Crystal structure of the BstDEAD N-terminal domain: a novel DEAD protein from Bacillus stearothermophilus. RNA **10**:66-74.

Juers D.H., S. Hakda, B.W. Matthews, and R.E. Huber (2003) Structural basis for the altered activity of Gly794 variants of Escherichia coli beta-galactosidase. Biochemistry **42**:13505-11.

Quillin M.L. and B.W. Matthews (2003) Selling candles in a post-Edison world: phasing with noble gases bound within engineered sites. Acta Crystallogr D Biol Crystallogr **59**:1930-4.

Carmel A.B. and B.W. Matthews (2003) Purification, crystallization and preliminary X-ray analysis of the novel DEAD protein BstDEAD from Bacillus stearothermophilus. Acta Crystallogr D Biol Crystallogr **59**:1869-70.

Mooers B.H., D. Datta, W.A. Baase, E.S. Zollars, S.L. Mayo,and B.W. Matthews (2003) Repacking the Core of T4 lysozyme by automated design. J Mol Biol **332**:741-56.

Sagermann M., L. Gay, and B.W. Matthews (2003) Long-distance conformational changes in a protein engineered by modulated sequence duplication. PNAS **100**:9191-5.

Copik A.J., S.I. Swierczek, W.T. Lowther, V.M. D'souza, B.W. Matthews, and R.C. Holz (2003) Kinetic and spectroscopic characterization of the H178A methionyl aminopeptidase from *Escherichia coli*. Biochem **42**:6283-92.

Gassner N.C., W.A. Baase, B.H. Mooers, R.D. Busam, L.H. Weaver, J.D. Lindstrom, M.L. Quillin, and B.W. Matthews (2003) Multiple methionine substitutions are tolerated in T4 lysozyme and have coupled effects on folding and stability. Biophys Chem **100**:325-40.

Peters R.J., O.A. Carter, Y. Zhang, B.W. Matthews, and R.B. Croteau (2003) Bifunctional abietadiene synthase: mutual structural dependence of the active sites for protonation-initiated and ionization-initiated cyclizations. Biochem **42**:2700-7.

Shoemaker G.K., D.H. Juers, J.M. Coombs, B.W. Matthews, and D.B. Craig (2003) Crystallization of beta-galactosidase does not reduce the range of activity of individual molecules. Biochem **42**:1707-10.

Zhang X.J., W.A. Baase, and B.W. Matthews (2002) A helix initiation signal in T4

lysozyme identified by polyalanine mutagenesis. Biophys Chem **101-02**:43-56.

Wei B.Q., W.A. Baase, L.H. Weaver, B.W. Matthews, and B.K. Shoichet (2002) A model binding site for testing scoring functions in molecular docking. J Mol Biol **322**:339-55.

Ostheimer G.J., A. Barkan, and B.W. Matthews (2002) Crystal structure of E. coli YhbY: a representative of a novel class of RNA binding proteins. Structure (Camb) **10**:1593-601.

Ryter J.M., C.Q. Doe, and B.W. Matthews (2002) Structure of the DNA binding region of prospero reveals a novel homeo-prospero domain. Structure (Camb) **10**:1541-9.

Hausrath, A.C. and B.W. Matthews (2002) Thermolysin in the absence of substrate has an open conformation. Acta Cryst **58**:1002-7.

Lowther, W.T., H. Weissbach, F. Etienne, N. Brot, and B.W. Matthews (2002) The mirrored methionine sulfoxide reductases of *Neisseria gonorrhoeae* pilB. Nat Struct Biol **9**:348-52.

Sagermann, M. and B.W. Matthews (2002) Crystal structures of a T4-lysozyme duplication-extension mutant demonstrate that the highly conserved beta-sheet region has low intrinsic folding propensity. J Mol Biol **316**:348-52.

Sagermann, M. L.G. Martensson, W.A. Baase, and B.W. Matthews (2002) A test of proposed rules for helix capping: implications for protein design. Protein Sci **11**:516-21.

Quillin, M.L. and B.W. Matthews (2002) Generation of noble-gas binding sites for crystallographic phasing using site-directed mutagenesis. Acta Cryst **58**:97-103.

Juers, D.H. T.D. Heightman, A. Vasella, J.D. McCarter, L. Mackenzie, S.G. Withers, and B.W. Matthews (2001) A structural view of the action of *Escherichia coli* (lacZ) beta-galactosidase. Biochemistry **40**:14781-94.

Weaver, L.H., K. Kwon, D. Beckett, and B.W. Matthews (2001) Competing protein: protein interactions are proposed to control the biological swich of the *E. coli* biotin repressor. Protein Sci **10**:2618-22.

Hausrath, A.C., R.A. Capaldi, and B.W. Matthews (2001) The conformation of the

epsilon- and gamma-subunits within the Escherichia coli F(1) ATPase. J Biol Chem **276**:47227-32.

Juers, D.H. and B.W. Matthews (2001) Reversible lattice repacking illustrates the temperature dependence of macromolecular interactions. J Mol Biol **311**:851-62.

Breyer, W.A. and B.W. Matthews (2001) A structural basis for processivity. Protein Sci **10**:1699-711.

Sagermann, M., T.H. Stevens, and B.W. Matthews (2001) Crystal structure of the regulatory subunit H of the V-type ATPase of *Saccharomyces cerevisiae*. PNAS **98**:7134-9.

Weaver L.H., K. Kwon, D. Beckett, and B.W. Matthews (2001) Corepressor-induced organization and assembly of the biotin repressor: a model for allosteric activation of a transcriptional regulator. PNAS **98**:6045-50.

Xu, J. W.A. Baase, M.L. Quillin, E.P. Baldwin, and B.W. Matthews (2001) Structural and thermodynamic analysis of the binding of solvent at internal sites in T4 lysozyme. Protein Sci **10**:1067-78.

Su, A.I., D.M. Lorber, G.S. Weston, W.A. Baase, B.W. Matthews, and B.K. Shoichet (2001) Docking molecules by families to increase the diversity of hits in database screens: Computational strategy and experimental evaluation. Proteins **42**:279-93.

Yang, G., C. Cecconi, W.A. Baase, I.R. Vetter, W.A. Breyer, J.A. Haack, B.W. Matthews, F.W. Dahlquist, and C. Bustamante. (2000) Solid-state synthesis and mechanical unfolding of polymers of T4 lysozyme. PNAS **97**:139-44.

Korndörfer, I.P., J. Salerno, D. Jing, and B.W. Matthews (2000) Crystallization and preliminary X-ray analysis of a bacteriophage T4 primase fragment. Acta Cryst **D56**:95-7.

Liu, R., W.A. Baase, and B.W. Matthews (2000) The introduction of strain and its effects on the structure and stability of T4 lysozyme. J Mol Biol **295**:127-45.

Matthews, B.W. (2000) Obituary: Paul Sigler. *Nature* **403**:848.

Sagermann, M. and B.W. Matthews (2000) Cloning, expression and crystallization of VMA13p, an essential subunit of the vacuolar H+-ATPase of *Saccharomyces cerevisiae*. Acta Cryst **D56**:475-7.

Rupert, P.B., A.K.M.M. Mollah, M.C. Mossing, and B.W. Matthews (2000) The structural basis for enhanced stability and reduced DNA binding seen in engineered second-generation Cro monomers and dimers. J Mol Biol **296**:1079-90.

Lowther, W.T. and B.W. Matthews (2000) Structure and function of the methionine aminopeptidases. Biochem Biophys Acta **1477**:157-67.

Wray, J.W., W.A. Baase, G.J. Ostheimer, and B.W. Matthews (2000) Use of a non-rigid region in T4 lysozyme to design an adaptable metal-binding site. Prot Engin **13**:313-21.

Quillin, M.L. and B.W. Matthews (2000) Accurate calculation of the density of proteins. Acta Cryst **56**:791-4.

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Korndoerfer, I.P., W-D. Fessner, and B.W. Matthews (2000) The structure of rhamnose isomerase from *Escherichia coli* and its relation with xylose isomerase illustrates a change between inter- and intra-subunit complementation during evolution. J Mol Biol **300**:917-33.

He, M.H., S.L. Clugston, J.F. Honek, and B.W. Matthews (2000) Determination of the structure of *Escherichia coli* glyoxalase I suggests a structural basis for differential metal activation. Biochemistry **39**:8719-27.

Juers, D.H., R.H. Jacobson, D. Wigley, X-J. Zhang, R.E. Huber, D.E. Tronrud, and B. W. Matthews (2000) High resolution refinement of ß-galactosidase in a new crystal form reveals multiple metal-binding sites and provides a structural basis for a-complementation. Prot Sci **9**:1685-99.

Quillin, M.L., W.A. Breyer, I.J. Griswold, and B.W. Matthews (2000) Size versus polarizability in protein-ligand interactions: Binding of noble gases within engineered cavities in phage T4 lysozyme. J Mol Biol **302**:955-77.

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in protein folding. PNAS **96**:6078-83.

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Kuroki, R., Weaver, L.H. and B.W. Matthews (1999) Structural basis of the conversion of T4 lysozyme into a transglycosidase by re-engineering the active site. PNAS **96**:8949-54.

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Gassner, N.C., W.A. Baase, A.C. Hausrath, and B.W. Matthews (1999) Substitution with selenomethionine can enhance the stability of methionine-rich proteins. J Mol Biol **294**:17-20.

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Baase, W.A., N.C. Gassner, X-J. Zhang, R. Kuroki, L.H. Weaver, D.E. Tronrud, and B. W. Matthews (1999) How much sequence variation can the functions of biological molecules tolerate? In *Simplicity and Complexity in Proteins and Nucleic Acids*, Dahlem Workshop (H. Frauenfelder, J. Deisenhofer & P.G. Wolynes, eds.), Dahlem University Press, Berlin, pp. 297-311.

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