

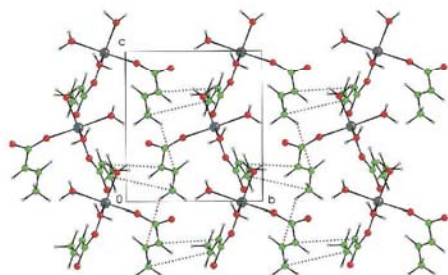
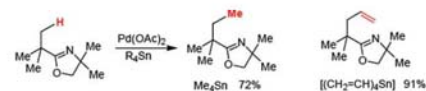
Brandeis University



Graduate Studies in Chemistry



New Shapiro Science Center



How to Apply

Graduate applications should be submitted to the Brandeis University Graduate School of Arts and Sciences (<http://www.brandeis.edu/gsas/apply/>).

Contact information for the Graduate School:

GSAS
Kutz Hall, MS 031
Brandeis University
Waltham, MA 02454-9110
Phone: 781-736-3410
gradschool@brandeis.edu

Contact information for the Chemistry Department:

Address for Chemistry personnel:

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You may also contact any of the faculty members directly. See the faculty pages in this brochure or <http://www.brandeis.edu/departments/chemistry/> for contact information.

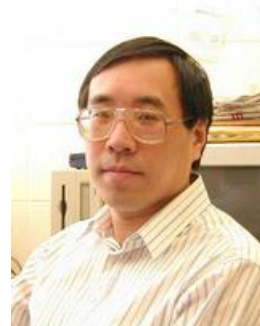
This brochure can be found online at:

<http://www.brandeis.edu/departments/chemistry/gradstudents/docs/chemistrygrad.pdf>.

We look forward to hearing from you!

Welcome from the Chair

Located in a small yet nurturing setting similar to that of a liberal arts college, the Brandeis chemistry department strives to provide a graduate education to rival those of the best large universities in quality. In a data-based analysis recently conducted by the National Research Council, our Ph.D. program was ranked among the top fifteen in the US. We offer a balanced portfolio of exciting research programs between established and emerging areas in chemistry. Our faculty members are widely recognized leaders in major traditional divisions of chemistry, as well as in the increasingly important interdisciplinary areas of chemical biology, complex systems, materials chemistry and catalysis. Our faculty has been honored with membership in the National Academy of Sciences, the American Academy of Arts and Sciences, an American Chemical Society division chairmanship, a Howard Hughes professorship, fellowships in major scientific societies, Guggenheim Fellowships, Teacher-Scholar awards and Young Faculty awards from the Camille and Henry Dreyfus Foundation, Research Corporation Innovation Awards, Humboldt Fellowships, Sloan Fellowships, named lectureships and memberships on editorial boards of major scientific journals. The strength of our faculty is also reflected by their numerous publications in leading journals such as *Science*, *Nature*, *Journal of the American Chemical Society*, *Angewandte Chemie* and others, and consistent success in securing highly competitive grants from federal agencies such as the National Institutes of Health, the National Science Foundation and the Department of Energy.



Individual faculty members typically direct a group of 4-6 graduate students. Close contact between faculty and students has thus become a hallmark of our graduate training. These research groups are supported by an excellent staff and have ready access to state of the art instrumentation. Our most recent infrastructure additions are a modern proteomics lab with 4 complementary high-resolution instruments, a high throughput X-ray diffractometer and an 800 MHz NMR spectrometer in a dedicated building, complementing 4 other departmental NMR instruments. Located in the Boston area, we belong to one of the strongest and most dynamic scientific communities in the world. Students enjoy exposure to exciting scientific development through numerous seminar programs and engage in productive collaborations, both within and outside of Brandeis University. In addition to providing rigorous scientific training, our graduate program is designed to enhance personal skills in communication, teaching and collaboration. The effectiveness of our graduate education is reflected by the outstanding productivity of our graduate students and, most importantly, their remarkable success in establishing thriving professional careers in both academia and industry.

Brandeis is an international university, where talented faculty and students come from all parts of the globe to form a vibrant, ethnically diverse community. In addition to the many musical, political, dramatic, athletic and artistic events occurring on campus, students have easy access via a short train- or car-ride to the unparalleled cultural activities in Boston. The proximity to the mountains and beaches of New England makes a wide range of outdoor recreational activities within easy reach in all seasons.


Browse this brochure and our website (<http://www.brandeis.edu/departments/chemistry/>) to peruse the research opportunities in chemistry and to learn more about the department, Brandeis University and the greater Boston area.

Li Deng

Orrie Friedman Distinguished Professor of Chemistry and Chair

National Ranking of Brandeis Chemistry Department by National Research Council (NRC)

The National Research Council (NRC) recently released its report “A Data-Based Assessment of Research-Doctorate Programs in the United States”. The Data-Based approach by the NRC is in contrast to the perception-based one employed by various popular magazines issuing annual ranking reports. Based on a wide variety of performance measures normalized for faculty size, the NRC report ranks the chemistry Ph.D. program at Brandeis as high as 13th among the more than 150 similar programs in the US. The Brandeis chemistry department stands out for its recognized excellence when compared with much larger institutions. Our strength comes from an award-winning faculty of devoted teacher-scholars, who are widely recognized leaders in the major traditional divisions of chemistry, as well as in the increasingly important interdisciplinary areas of chemical biology, complex systems, materials chemistry and catalysis. Our success reflects the effectiveness of our graduate education, which features close contact between faculty and students to ensure a rigorous yet supportive scientific training, a collaborative environment to nurture personal skills in communication, teaching and teamwork, and state of the art instrumentation to facilitate cutting-edge research.



Chemistry

Institution Name	S Rankings: 5th Percentile	Institution Name	S Rankings: 95th Percentile
HARVARD UNIVERSITY	1	HARVARD UNIVERSITY	2
HARVARD UNIVERSITY	2	HARVARD UNIVERSITY	4
CALIFORNIA INSTITUTE OF TECHNOLOGY	2	CALIFORNIA INSTITUTE OF TECHNOLOGY	5
UNIVERSITY OF CALIFORNIA-BERKELEY	3	UNIVERSITY OF CALIFORNIA-BERKELEY	8
NORTHWESTERN UNIVERSITY	3	NORTHWESTERN UNIVERSITY	9
COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK	4	COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK	13
STANFORD UNIVERSITY	5	STANFORD UNIVERSITY	13
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN	5	UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN	15
YALE UNIVERSITY	5	YALE UNIVERSITY	15
MASSACHUSETTS INSTITUTE OF TECHNOLOGY	6	MASSACHUSETTS INSTITUTE OF TECHNOLOGY	16
UNIVERSITY OF CALIFORNIA-SAN FRANCISCO	6	UNIVERSITY OF CALIFORNIA-SAN FRANCISCO	20
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL	8	UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL	23
PRINCETON UNIVERSITY	8	PRINCETON UNIVERSITY	25
UNIVERSITY OF CALIFORNIA-LOS ANGELES	8	UNIVERSITY OF CALIFORNIA-LOS ANGELES	28
GEORGIA INSTITUTE OF TECHNOLOGY	9	GEORGIA INSTITUTE OF TECHNOLOGY	29
RICE UNIVERSITY	9	PENN STATE UNIVERSITY	32
PENN STATE UNIVERSITY	10	RICE UNIVERSITY	32
UNIVERSITY OF CALIFORNIA-SAN DIEGO	12	UNIVERSITY OF CALIFORNIA-SAN DIEGO	35
BRANDEIS UNIVERSITY	13	UNIVERSITY OF CHICAGO	41
UNIVERSITY OF CHICAGO	14	IOWA STATE UNIVERSITY	44
IOWA STATE UNIVERSITY	14	BRANDEIS UNIVERSITY	46
UNIVERSITY OF CALIFORNIA-SANTA BARBARA	14	UNIVERSITY OF CALIFORNIA-SANTA BARBARA	48
CORNELL UNIVERSITY	15	MICHIGAN STATE UNIVERSITY	50
UNIVERSITY OF CALIFORNIA-IRVINE	15	UNIVERSITY OF WISCONSIN-MADISON	50

Department Facilities

X-Ray Structure Determination Facilities

The X-Ray Small Molecule Structure Facility consists of a Nonius CAD-4 linear diffractometer and a Bruker-Nonius Kappa Apex II CCD instrument, equipped with Mo and Cu radiation sources. The Kappa Apex II CCD machine, acquired recently with NSF funding, is a workhorse, ultimate state-of-the-art instrument that serves faculty and students at Brandeis and nearby institutions. The instrument can collect data at temperatures between 90 and 500K, and is capable of establishing stereochemistry, absolute configuration, composition, phase transitions as well as fine details of crystal and molecular structure for organic, inorganic and organometallic compounds. In addition, the same services are available for macromolecular crystal structure determination in the Laboratory for Structural Enzymology and Neurology, which houses two high-end protein crystallography systems: a Rigaku RU 300 with an R-Axis imaging plate detector, and a new Bruker UltraStar system (table-top synchrotron), which combines an X-ray source of very high brightness with novel optics and a new generation CCD detector. The system is capable of collecting data on very small protein crystals (0.1 mm or less) with very large unit cells (500 Angstroms). Small molecule facility:

<http://people.brandeis.edu/~foxman1/-xraywebpage.htm>

BUMS

The Brandeis University Mass Spectrometry Facility (BUMS) is home to the highest field Fourier transform mass spectrometer in New England, and is one of the only facilities in the world offering comprehensive analysis of intact proteins (so called "top-down" analysis) and MALDI-TOF and MALDI-FT mass spectrometry imaging of tissues.

<https://wiki.brandeis.edu/twiki/bin/view/Chem/BUMS>



BrUNMR

The Brandeis University Nuclear Magnetic Resonance Facility (BrUNMR) is open to all members of the Brandeis research community who require solution state NMR for their work. It is comprised of four well-equipped spectrometers ranging in magnetic fields from 400 to 800 MHz.

<http://www.bio.brandeis.edu/nmr/>

- Varian Inova 400 is primarily used by the chemistry department as a walk-up instrument for small molecule analysis.
- Varian Inova 500 and 600 are heavily used by the chemistry and biochemistry departments for multidimensional structural and dynamic studies of biomolecules.
- Bruker Avance 800 (located in the Landsman Research Facility) is a state-of-the-art regional facility instrument available to all NIH-funded researchers.



Instrumentation

Other instrumentation available, in the department facility and in individual faculty members' laboratories, includes LC-MS, ESR, CD, mass and GC/mass spectrometers, and computerized UV-visible and a Fourier-Transform IR spectrometers. Controlled atmosphere dry boxes, continuous flow stirred tank reactors, gas and liquid chromatography equipment, and a variety of laser sources are also available to students for their research.

Faculty Research Areas

<i>Professor</i>	<i>Inorganic</i>	<i>Physical</i>	<i>Biophysical</i>	<i>Organic</i>	<i>Chemical Biology</i>	<i>Materials Science</i>
<i>Agar, J. N.</i>	✓	✓	✓			
<i>Deng, L.</i>				✓	✓	
<i>Epstein, I. R.</i>		✓	✓			✓
<i>Foxman, B. M.</i>	✓	✓		✓		✓
<i>Hedstrom, L.</i>			✓		✓	
<i>Herzfeld, J.</i>		✓	✓			
<i>Krauss, I.</i>	✓			✓	✓	
<i>Petsko, G. A</i>	✓	✓	✓		✓	
<i>Pochapsky, T.C.</i>	✓	✓	✓	✓	✓	
<i>Ringe, D.</i>	✓		✓	✓	✓	
<i>Snider, B. B.</i>				✓	✓	
<i>Thomas, C</i>	✓					✓
<i>Xu, Bing</i>	✓		✓	✓	✓	✓



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High resolution mass spectrometry studies of protein post-translational modification

Protein post-translational modification underlies most biological processes. Moreover, the dysregulation of protein modification plays a causative role in a number of disease states, including the disease our group studies, ALS (Lou Gehrig's disease). Our laboratory studies protein modifications that occur during neurodegeneration, and tries to understand the role of modification in disease progression. We are also interested in the role of protein modification in the process of memory, which can involve modifications as subtle as conformational change. We use high resolution, Fourier Transform Mass Spectrometry (FTMS), and are equipped for electrospray and MALDI ionization, including MALDI imaging of tissues. Our research requires

considerable methods development, including the development of our own hardware and software. We are combining the techniques of optical laser spectroscopy, fluorescence microscopy, and mass spectrometry, to create high resolution, multimodal imaging platforms. We are also using high powered lasers to probe the structure of ions in the gas phase. Our laboratory is equipped with FT-, ion-trap, and MALDI-TOF mass spectrometers, sample handling robots, Class II biosafety tissue culture equipment, microfabrication and microinjection facilities, tunable YAG and excimer lasers, CO₂ and argon lasers, and formidable informatics software and hardware.



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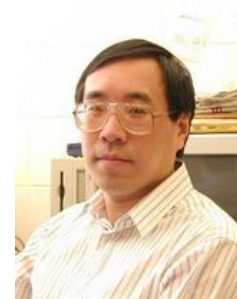
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Chan Memorial Award in Organic Chemistry, 2008; Japan Society for the Promotion of Science (JSPS) Fellow (2007) Alfred P. Sloan Research Fellow (2003); Research Corporation Research Innovation Award (1999); Medical Foundation New Investigator Award (1999)

Asymmetric Catalysis and Total Synthesis

To fulfill the promises and to meet the challenges of chemistry in the 21st century, chemists must develop new methods to manipulate and create substances of increasing complexity and diversity with dramatically enhanced efficiency and practicality. Our program focuses on the invention and development of new catalytic and selective reactions because of their fundamental importance to molecular science. Our approach involves the discovery and design of accessible catalysts for highly enantioselective asymmetric organic reactions of broad synthetic importance, the elucidation of the reaction mechanism and molecular recognition events underlying the catalytic activity and selectivity, and the applications in the synthesis of chiral compounds of varying complexity.

Our studies following the approach outlined above have led us to the discovery of powerful chiral organic catalysts promoting highly enantioselective reactions by general base catalysis. We also established that the general base catalysis could be coupled with electrophile-activating catalysis such general acid catalysis and iminium catalysis to form powerful bifunctional catalysis for asymmetric reaction development. These concepts have been successfully applied to the development of a wide range of novel and highly efficient asymmetric reactions of general scopes. Many of these reactions have already found wide applications in target- and diversity-oriented synthesis. Our reactions have also been developed into viable tools for industrial manufacturing of chiral compounds.

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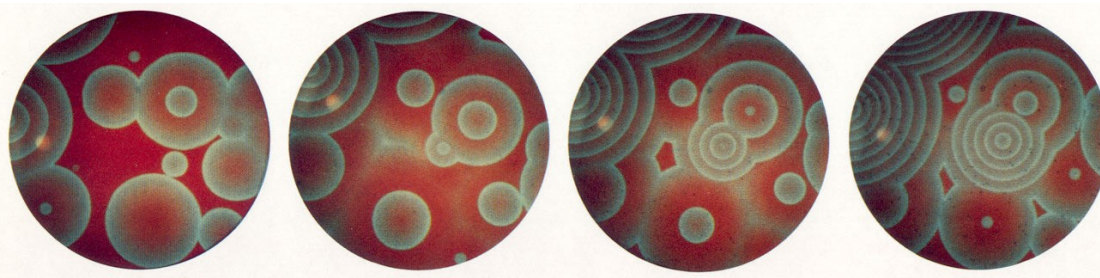
Oscillatory chemical reactions, spatial pattern formation, dynamical systems and neurobiology

Many phenomena in living systems involve periodic changes. In the past decade, oscillating chemical reactions have blossomed from a curiosity studied by an obscure group of Russians to a major area of scientific research. We study these systems both experimentally and theoretically, from several points of view. We have achieved the first successful design of a new chemical oscillator. We have used our systematic design algorithm to expand the family of chemical oscillators from two accidentally discovered reactions to some two dozen deliberately constructed systems. While we continue the search for new types of oscillators, we probe by a variety of techniques, including spectrophotometry, potentiometry, rapid mixing and computer simulation, the mechanisms of those that have already been discovered.

Chemical oscillators can be "tweaked" to give a variety of related phenomena, some with suggestive connections to biological systems. We study spatial pattern formation, in which an initially homogeneous medium spontaneously gives rise to concentric rings, or spiral color patterns resembling those seen in embryonic development or the aggregation of slime molds, and chemical chaos, in which concentrations oscillate deterministically, but in an aperiodic and apparently irreproducible fashion that

depends very sensitively on the initial conditions. We investigate, both experimentally and theoretically, Turing structures, patterns that arise from the interaction of reaction and diffusion, which have been suggested as the mechanism of spatial pattern formation in phenomena ranging from biological morphogenesis to geological stratification.

We are interested in the phenomena that can occur when two or more oscillators are coupled together, either physically, i.e., by diffusion or an electrical connection, or chemically, by having two oscillators share a common chemical species. Such systems can give rise to surprising phenomena, such as "oscillator death," the cessation of oscillation in two coupled oscillating systems, or the converse, "rhythmogenesis," in which coupling two systems at steady state causes them to start oscillating. Coupled chemical oscillators provide simple models for networks of oscillatory neurons. We have begun to apply some of the insights gained in our studies of coupled chemical oscillators to the modeling of small neural networks in conjunction with colleagues in the Biology Department, to develop chemical analogs of neural oscillators and to coupling chemical and neural oscillators.



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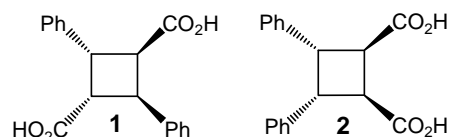


Member, Editorial Advisory Board, *Crystal Growth and Design*, *Journal of Chemical Crystallography*, Visiting Professor, Max-Planck-Institut für Polymerforschung (1995-96); Honorary Professor, University of Birmingham (2001); Professeur Invité, Université Louis Pasteur, Strasbourg (2002).

Solid-State Reactions and Polymorphism

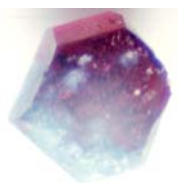
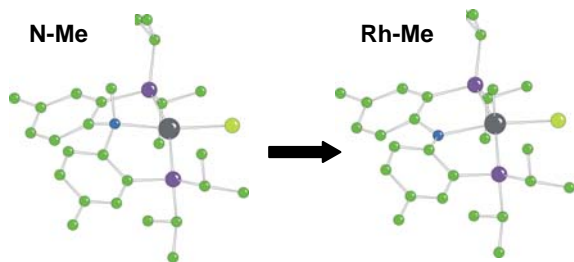
“Ein Kristall ist ein chemischer Friedhof!” This gripping phrase, literally, “A crystal is a chemical graveyard!” was spoken to Professor Jack Dunitz at the ETH, Zurich, by Leopold Ružička. Ružička (1887-1976) received the 1939 Nobel Prize in Chemistry (shared with Adolf Friedrich Johann Butenandt, KWI, Berlin) for his work on polymethylenes and higher terpenes. Apparently, Ružička’s thought was that, once a molecule reached the crystalline state, it was “all over”: nothing interesting would ever happen again to this *frozen, static* species. There was much work in the early chemical literature to disprove this thought, but general appreciation for what could be done in the solid state did not “arrive” until 1964, when the classic work of Schmidt and Cohen showed that there were two *polymorphs* (different crystal forms) of cinnamic acid, $C_6H_5CH=CHCOOH$. In the α -form the molecules were arranged in a head-to-tail fashion about a center of symmetry, while in the β -form, the molecules repeat along a 4 Å axis, effectively with mirror symmetry. When the *solids* are exposed to UV light, each undergoes a different stereospecific [2+2] photocycloaddition. The α polymorph produces only the head-to-tail dimer (1), and the β polymorph produces only the head-to-head dimer (2). This exceptional result clearly demonstrates the potential of solid-state

reactions. Our work focuses on the solid-state assembly – in arrangements designed to promote solid-state reactions – of polymorphic molecular crystals. We study



reactions and phase changes in crystals, and capitalize

on the opportunity of using a “crystal container” to synthesize molecules difficult or impossible to make in solution. Lack of solvent also holds the promise of environmentally benign chemistry. In recent work we have focused on metal-centered solid-state reactions and polymorphism. The reactions include solid-state polymerization of metal complexes using polyfunctional ligands (coordination chemistry), crystal-to-crystal oxidative addition reactions (organometallic chemistry), and very high density metal complexes (polymorphism). At the present time there are no openings for graduate students in our laboratory, but we welcome joint students (e.g., in collaboration with Prof. Chris Thomas) interested in X-ray crystallography and structural problems in their research programs.



Polymerization Reactions in Single Crystals



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Molecular mechanisms of cellular biochemistry and physiology

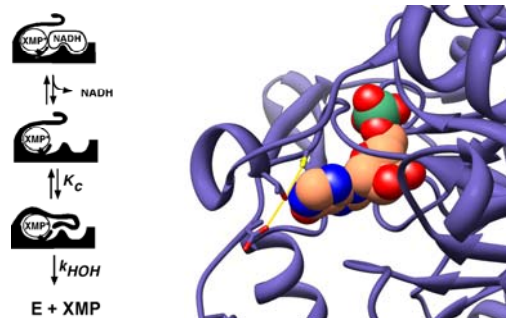
My laboratory uses approaches derived from both chemistry and biology to investigate molecular mechanisms of cellular biochemistry and physiology. Projects are organized around the themes of purine/pyrimidine metabolism and protease action and include problems in inhibitor design, protein engineering and cellular metabolism. Most projects have clinical relevance. Techniques vary with the particular project, and can entail organic synthesis and protein crystallography as well as protein purification, enzyme kinetics and mutagenesis. Some current projects are described below.

Mechanistic enzymology. One current system of interest is inosine monophosphate dehydrogenase (IMPDH). This enzyme offers a unique opportunity to investigate how proteins efficiently maneuver between conformations to accommodate multiple transition states. IMPDH controls the entry of purines into the guanine nucleotide pool and is therefore an important immunosuppressive, antiviral and anticancer target. IMPDH displays several remarkable mechanistic features, including a large conformational change in mid-catalytic stream, an Arg residue that acts as a general base catalyst and a K⁺ that serves as a ball and socket joint.

Drug Targets in *Cryptosporidium parvum*. The "vicious cycle of diarrhea and malnutrition" in developing countries could be broken with the advent of effective chemotherapy against *Cryptosporidium parvum*. Mining the sequence of the *C. parvum* genome revealed that the only route to guanine nucleotides is via IMPDH. Moreover, *C. parvum* obtained its IMPDH gene from bacteria by lateral gene transfer. We exploited this unexpected evolutionary divergence of parasite and host enzymes to identify parasite-selective IMPDH inhibitors. Importantly, these compounds also display antibacterial activity. This work could lead to novel treatments for a

wide variety of bacterial infections, including some of the most devastating and troubling human pathogens: *Mycobacterium tuberculosis*, drug-resistant *Staphylococcus aureus* (e.g. MRSA and VRSA), drug resistant *Streptococcus pneumoniae* and select agents such as *Bacillus anthracis*, *Burkholderia mallei/pseudomallei* and *Francisella tularensis*. The research team includes [Boris Striepen](#) (UGA), [Greg Cuny](#) (LDDN, Harvard U.), [Jan Mead](#) (Emory U.), [Wei Yang](#) (FSU) and [Barry Snider](#) (Brandeis U.).

Pathophysiological mechanisms of retinal disease. Hereditary blindness is often caused by mutations in proteins of the visual cycle. However the RP10 form is caused by mutations in the widely expressed IMPDH1. We have recently discovered that IMPDH associates with polyribosomes, suggesting that this housekeeping enzyme has an unsuspected role in translation regulation. The disease-causing mutations block this interaction. We are now investigating how this defect causes apoptosis in photoreceptor cells with the aim of developing strategies for chemotherapy. This work is a collaboration with the [Stephen Daiger](#) (UTHSC).



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Physical and Biophysical Chemistry

Our current research, is primarily focused on

(a) solid state NMR studies of the structure and function of membrane proteins, with an emphasis on light-driven ion transport in bacteriorhodopsin, and protein folding and assembly in the floatation organelles of aquatic micro-organisms.

(b) the development of force fields for efficient simulations of chemical reactions, including proton transport in biological membranes and catalysis in enzymes.

(a) Because solid state NMR is unique in its ability to obtain high-resolution structural information from immobilized molecules that are not amenable to crystallization, it is being used to study detailed structure-function relationships in otherwise intractable systems.

For example, a wide variety of microorganisms produce retinal containing membrane proteins similar to the mammalian visual pigments. These "rhodopsins" include energy transducers that harvest light to drive ion transport, as well as signal transducers that use light to direct phototaxis. In the former, the photo-excited chromophore may be considered a useful analog of the high energy metabolites that power ion transport by other membrane proteins when light is not available. However, even in bacteriorhodopsin, the most accessible and thoroughly studied light-driven pump, the considerable information that has accumulated so far has not added up to a mechanism for vectorial action because large amounts of energy are stored in very small structural changes. Solid state NMR, at low temperatures and enhanced by dynamic nuclear polarization (DNP), has the great advantage of being able to clearly distinguish between the subtly different intermediates in the mixtures that occur during the photocycle, while also providing atomic level detail for each intermediate.

As another example, although ordinary proteins tend to denature at air/water interfaces, a variety of microorganisms produce resilient protein assemblies that stabilize air/water interfaces. Moreover, these gas vesicles and biofilms are amyloid-like and the means by which microorganisms control their formation may be instructive for approaching amyloid diseases. However, even for gas vesicles, the most accessible of these systems, ordinary structural studies have gotten stuck at the nanometer scale. In our studies we are using solid state NMR to obtain the detailed structural information necessary to model the assembly of gas vesicles.

(b) Conventional molecular mechanics simulations model molecules as clusters of partially charged atoms with empirical force fields that govern bond lengths, bond angles and dihedral angles. Since such constructs are unable to model the making and breaking of bonds, simulations of chemical reactions typically resort to highly time-consuming quantum mechanical calculations. To fill the need for greater efficiency, we are developing a reactive force field based on freely mobile and fully charged Lewis type particles. For example, whereas water is usually modeled as a fixed cluster of partial charges, we combine an oxygen core of charge +6, two protons of charge +1, and four valence electron pairs each of charge -2. This construct naturally and economically incorporates the polarizability and amphiproticity of water which are crucial to its ability to solvate molecules and to mediate proton transfer processes. To obtain the correct behavior with minimum computational effort, we have developed pair-wise pseudo-potentials between the particles that implicitly take quantum effects into account. Generalization from oxygen cores to include carbon and nitrogen cores extends the model to organic compounds. Simulations under way include proton transport in protein channels, alcohol dehydration to form ethers, and epoxide ring opening reactions.

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"Solid-State NMR Evidence for Inequivalent GvpA Subunits in Gas Vesicles," J. Mol. Biol. 2009, 387, 1032-1039; with AC Sivertsen, MJ Bayro, M Belenky, and RG Griffin.

"Energy transformations early in the bacteriorhodopsin photocycle revealed by DNP-enhanced solid-state NMR," Proc. Natl. Acad. Sci. USA 2008, 105, 883-888; with ML Mak-Jurkauskas, VS Bajaj, MK Hornstein, M Belenky, and RG Griffin.

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Organic Synthesis and Methodology, Chemical Biology

Why do research in organic synthesis? It is fascinating science, and this should be reason enough. However, this field also happens to have produced many direct societal benefits. Organic synthesis allows facile and economical preparation of various life-saving drugs, as well as materials which fill a wide range of technological needs. In the research realm, organic synthesis has allowed routine automated peptide and oligonucleotide synthesis, tools invaluable to biologists.

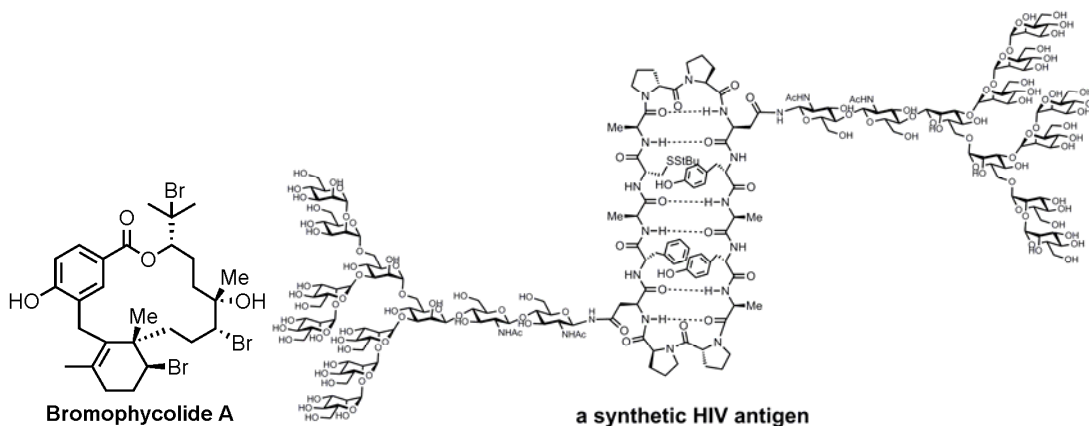
Our research program seeks to address needs unmet by the current state of the art. Research is divided into several areas:

1) Development of New Synthetic Methods. This part of our program is particularly focused on methods involving organometallic compounds, especially organoboron and organotitanium species. These methods are targeted at formation of asymmetric centers, particularly all-carbon quaternary stereocenters. Where

feasible, we seek to develop catalytic reactions that use cheap, non-toxic metals.

2) Total Synthesis of Natural Products. This effort is divided between projects which demonstrate the potential of the synthetic methods researched above, and the synthesis of complex targets using any available means. In the latter case, we are largely interested in cascade reactions and other strategies to simplify synthetic routes.

3) Chemical Biology. Whereas some small molecule natural products can inhibit enzymes, macromolecules such as glycopeptides can participate in critical biological recognition processes, such as the binding of the HIV envelope protein by neutralizing antibodies. One project in our lab involves synthesis of oligosaccharides and glycopeptides which will be of assistance in studying the HIV vaccine problem.



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Structural biology

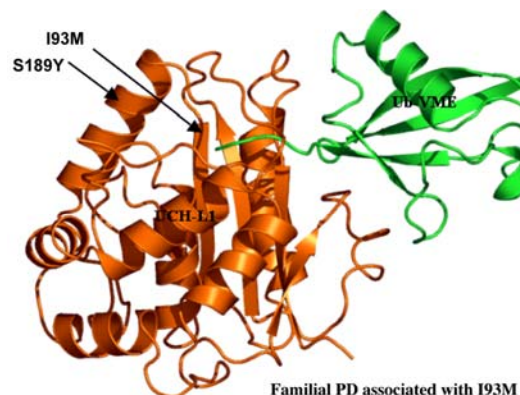
My research is concerned with the three-dimensional structures of proteins and their biochemical functions. Most of my work is done in collaboration with Prof. Dagmar Ringe; we share facilities, students, and a number of projects. The tools used by our groups are X-ray crystallography, molecular biology, yeast genetics, organic synthesis, enzyme kinetics and molecular dynamics calculations. These methods are being applied to several problems: the structural basis for enzymic catalysis of proton and hydride transfers; the role of the metal ions in bridged bimetalloenzymes; direct visualization of proteins in action by time-resolved protein crystallography; the evolution of new enzyme activities from old ones; the biochemistry of neurodegenerative diseases, and the biology of the quiescent state in eukaryotic cells.

We are trying to understand the structural basis for the catalytic power of enzymes such as aminopeptidase, mutarotase and ketosteroid isomerase. For all of them, structural information is being used to guide site-directed mutagenesis of the active site residues and combined quantum mechanics/molecular mechanics simulations of the catalytic reaction.

Protein crystallography is normally a static tool and cannot be used to follow biological reactions in real time. We have been involved in the development of new diffraction techniques, including Laue diffraction, that are capable of recording entire protein crystal data sets in a millisecond. When combined with low-temperature techniques, such methods can be used to determine the structures of catalytic intermediates.

A new area of research in the laboratory is the use of yeast genetics to study the quiescent state of eukaryotic cells. We have recently shown that yeast cells enter the G0 state when unfolded proteins accumulate in the

cytoplasm. We are interested in effect of misfolded, aggregated proteins on the quiescent state because neurons are quiescent cells and neurodegenerative diseases like Parkinson's Disease (PD) and Alzheimer's Disease (AD) involve the formation of toxic protein aggregates in such cells. Another project that uses genetics, structural biology and molecular biology is our attempt to design a new metabolic pathway that will allow yeast to grow on lactamide as sole carbon source. The enzymes in this new pathway are being engineered from enzymes of the mandelonitrile pathway in bacteria by a combination of structure-directed and random mutagenesis. This project represents an attempt to understand how cells react to the introduction of new enzyme activities and pathways. This process, horizontal gene transfer, was missing from Darwin's original view of evolution but accounts for a sizeable percentage of the genomes of most organisms.



Familial PD associated with I93M mutation ?
S18Y mutation confers decreased risk of PD

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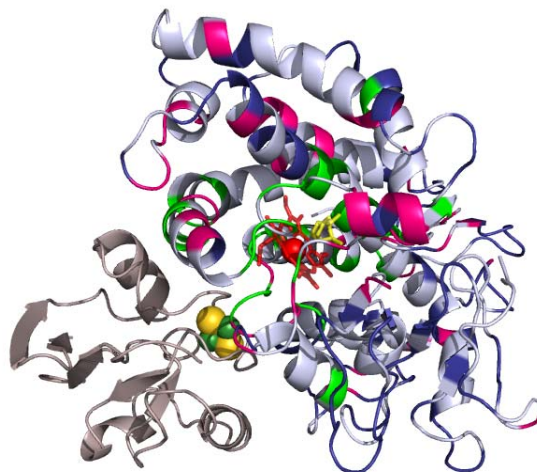
Camille and Henry Dreyfus Teacher-Scholar Award (1993 - 1995); National Science Foundation Young Investigator Award (1992 - 1997); Michael L. Walzer '56 Award for Teaching (1992); Metallobiochemistry NIH study section member (1998-2002)

Understanding of non-covalent interactions in chemical and biochemical systems

Our research is directed towards an understanding of non-covalent interactions in chemical and biochemical systems. We employ a variety of techniques in our work, including biophysical methods, protein engineering and organic synthesis, but nuclear magnetic resonance is our most important tool. NMR can be used to obtain structures of complex macromolecules and is sensitive to molecular dynamics over a wide range of time scales. Equally important is the ability of NMR to provide information concerning intermolecular interactions via nuclear Overhauser effects and residual dipolar

couplings. Combining NMR with other experimental and computational methods, we are actively investigating the following areas:

- Enzymes in the methionine salvage pathway: structure and function
- Monooxygenase enzyme systems: structure and dynamics
- We have access to NMRs at 400, 500 and 600 and 800 MHz.



Model for the complex between putidaredoxin and cytochrome P450 determined by NMR

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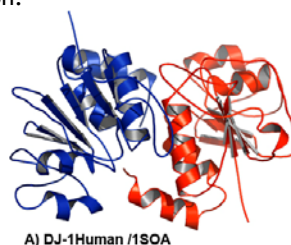
Fellow, American Association for the Advancement of Science; Abram L. Sachar Medallion, Science for Life Award, Brandeis University; Alexander von Humboldt Forschungspreis; Board of Trustees, Gordon Research Conferences (2000-); Associate Editor, *Biophysical Journal* (1999-); Guggenheim Fellowship (1997); Program Officer, Biophysics Program, National Science Foundation (1997, 2000-01); Co-Chair, Gordon Conference on Enzymes, Coenzymes and Metabolic Pathways (1994).

Structural enzymology

My work is aimed at the relationship between three-dimensional structure and function. Much of the work is done in collaboration with Prof. Gregory Petsko, in that we share facilities, students and collaborate on some projects. The tools we use include X-ray crystallography, molecular biology, kinetics, organic synthesis, genetics, and computational approaches. There are a number of problems to which these methods are being applied, and they include: the structural basis for efficient enzymic catalysis of proton and hydride transfer; the role of the metal ions in bridged bimetalloenzyme active sites; direct visualization of proteins in action by time-resolved protein crystallography; the structural basis for reaction selectivity in enzymes; the evolution of new enzyme activities from old ones and the development of new pathways; and the study of neurodegenerative diseases with a view toward drug design.

The approaches include site-directed mutagenesis followed by binding and structural studies; computational prediction and validation of the electrostatic properties of residues in the active site; design of specific inhibitors as potential drugs using multiple drug design methods.

These tools are being applied to the identification and characterization of gene products of unknown function that are associated with neurodegenerative diseases, with a view to the design of ligands that could be used for intervention.



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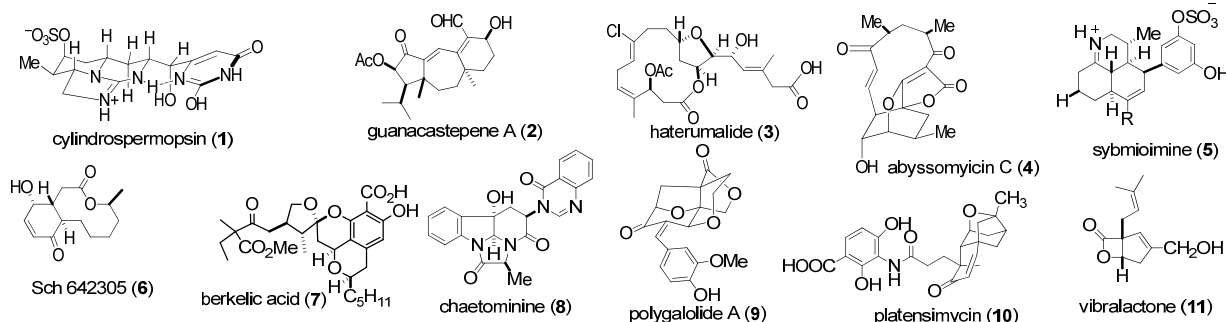
Chair of the Organic Division, ACS, 2007; Honorary Professor East China University of Science and Technology (2006); Boehringer Ingelheim Distinguished Lecturer at the Université de Sherbrooke (2003); Fellowship, Japan Society for the Promotion of Science (1999); Arthur C. Cope Scholar Award, American Chemical Society (1995); Dreyfus Teacher-Scholar Grant (1982 - 1987); Sloan Fellow (1979 - 1983); Dupont Young Faculty Grant (1977); Upjohn Young Faculty Grant (1976 - 1977).

Total synthesis and synthetic methodology

Our research is centered in two distinct areas: (1) the total synthesis of biologically active natural products and (2) the development of new free-radical based synthetic methods. In optimal cases new methods are developed and applied to the synthesis of biologically active natural products.

Total Synthesis. Targets are chosen based the biological activity of the target and the structural novelty of the ring system or functionality. Our research program includes a wide variety of structural types with numerous different types of biological activity. In the past few years we have completed syntheses of the structurally novel potent liver toxin cylindrospermopsin (1),¹ the antibiotic guanacastepene A (2),² haterumalide (3),³ abyssomicin C (4),⁴ symbioimine (5),⁵ Sch-642305 (6),⁶ berkelic acid (7),⁷ chaetominine (8),⁸ polygalolide A (9),⁹ platensimycin (10),¹⁰ and vibrallactone (11).¹¹

Methods Development. Oxidative free-radical cyclizations, in which the initial radical is generated oxidatively, and/or the cyclic radical is oxidized to terminate the reaction, have considerable synthetic potential since more highly functionalized products can be prepared from simpler precursors than with standard tin hydride reductive radical cyclizations. Over the past 15 years we have developed the use of Mn(OAc)₃, often in conjunction with Cu(OAc)₂, for the oxidative cyclization of unsaturated ketones and 1,3-dicarbonyl compounds. A highlight of recent studies is the discovery that these cyclizations can be terminated by trapping with azide ion to introduce nitrogen into the product.¹² Current studies involve asymmetric induction, extending the scope of the oxidizable substrate, and applications to natural product synthesis.



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Synthetic Inorganic and Organometallic

The underlying theme of our research is the investigation and utilization of cooperation between the components of transition metal complexes. This pertains to bimetallic complexes, and metal complexes featuring redox active ligands, as well as metal complexes that are strongly influenced by their secondary coordination sphere. We are particularly interested in utilizing these unique complexes for the catalytic activation and functionalization of small molecule substrates. These types of processes are critical for the development of sustainable energy technology, for furthering our understanding of the function of metalloenzymes, and for the catalysis of organic transformations. While synthesis and characterization of new transition metal complexes is an essential aspect of our research, we also utilize electrochemical techniques to evaluate new catalysts and computational chemistry (DFT) to better understand the electronic structure of our molecules.

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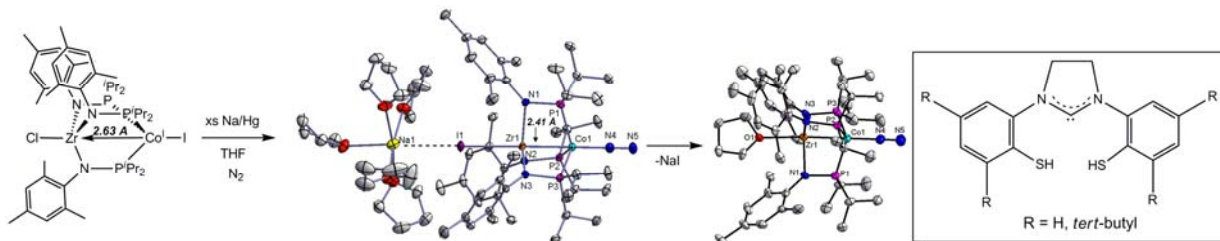
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Heterobimetallic complexes. Inspired by the extensive studies and multi-faceted reactivity of iron tris(phosphines) and molybdenum tris(amides), our group plans to examine heterobimetallic complexes that incorporate these two platforms into a single bimetallic framework. Our approach is to link the two metal centers together into a C_2 -symmetric framework using bifunctional phosphinoamide ligands, $[R^1_2PNR^2]$. We are particularly interested in the extent of electronic communication between these two metal centers, and

how this affects their reactivity. We expect that the presence of two transition metal centers will facilitate redox reactions and the catalysis of small molecule activation reactions by (1) providing different catalytic sites per molecule, (2) the presence of electronic communication between the two metal centers, and (3) the avoidance of high oxidation state intermediates during small molecule activation processes.

Phosphenium cations. While N-heterocyclic carbenes (NHCs) have become ubiquitous in many areas of coordination chemistry and catalysis, their isolobal analogues, N-heterocyclic phosphenium cations (NHP⁺s), are far less studied. While NHCs are known to be strong σ -donors and poor π -acceptors, NHP⁺s are weak σ -donors and strong π -acceptors. We are interested in whether this extreme contrast in bonding properties can lead to vastly different applications in catalysis. In addition to monodentate NHP⁺s, we have incorporated these ligands in a rigid pincer ligand framework to impart stability.

Redox-active ligands. Another line of research the Thomas group is pursuing is the synthesis and transition metal chemistry of NHC-dithiolate pincer ligands. These previously unreported ligands have electronic properties amenable to stabilizing a wide variety of transition metals in various oxidation states - an important characteristic catalytically viable transition metal complexes. We are particularly interested in examining ligand-centered or cooperative metal-ligand redox activity in these complexes.



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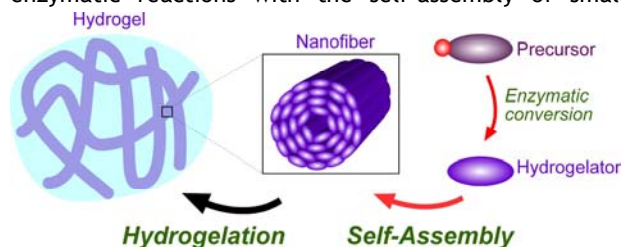
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Supramolecular & Biofunctional Nanomaterials

Supramolecular Materials We are interested in the fundamental processes like self-assembly and enzymatic reaction. Self-assembly, a process prevalent in nature, plays important roles in biology, from maintaining the integrity of cells to performing cellular functions, and inducing abnormalities that cause disease. Subcellular nanostructures such as actin filaments, microtubules, vesicles, and micelles are the microscopic presentations of molecular self-assembly in biology. Enzymes, as a class of highly efficient and specific catalysts, dictate a myriad of reactions that constitute various cascades in biological systems. The expression and distribution of enzymes differ by the types and states of cells, tissues, and organs, thus leading to diverse extracellular and intracellular environments. Specifically, we integrate enzymatic reactions with the self-assembly of small



molecules to form a variety of nanostructures and/or trigger the formation of hydrogels (Figure). The use of enzymes to trigger and control the self-assembly of small molecules for hydrogelation, which takes place *in vitro* or *in vivo*, extra- or intracellularly, offers a new strategy for detecting the activity of enzymes, screening for enzyme inhibitors, promoting biomineralization, typing bacteria, drug delivery systems, enhancing the activity and stability of enzymes, and controlling the fate of cells. This approach is emerging as a unique means for scientists to integrate molecular self-assembly with enzymatic reactions inside cells for developing new biomaterials and therapeutics at the supramolecular level.

Biofunctional Nanomaterials Since 2001, we have been working to build a research program focusing on the interdisciplinary frontier of materials chemistry-biofunctional nanomaterials. We are integrating the knowledge and techniques in organic chemistry, surface chemistry, biochemistry, materials science, and nanotechnology to design new biofunctional materials for exploration in molecular drug delivery, biomedical diagnostics, biomimetics, and other important problems.

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