

PHYS 701 [750297]: Combining chemistry, molecular and structural biology in search of the elusive mechanism of Orotidine Monophosphate Decarboxylase

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Abstract

Orotidine 5'-monophosphate decarboxylase (ODCase) catalyzes the last step of de novo pyrimidine synthesis. It decarboxylates orotidine monophosphate (OMP) to synthesize uridine monophosphate. Most decarboxylases use either pyridoxalphosphate, metal ions or delocalization into aromatic systems to stabilize the charge developing in the transition state for reaction acceleration. ODCase, however, does not employ any cofactors or metal ions and the orotidine base of its substrate OMP is unable to delocalize the charge of the carbanion created upon the release of CO₂. Nevertheless, the enzyme accelerates the decarboxylation reaction by 17 orders of magnitude over the corresponding reaction in water of neutral pH making ODCase the most proficient enzyme known today. This remarkable property has caused the enzyme's mechanism to become the subject of major scientific interest. Recently, the structures of ODCase isolated from four different microorganisms (*Bacillus subtilis*, yeast, *E. coli* and *Methanobacterium thermoautotrophicum*) and complexed to various ligands have been determined by x-ray crystallography. The results of those experiments have ruled out some of the previously proposed mechanisms but were still not sufficient to settle all open mechanistic questions. In an effort to provide further structural clues about ODCase's mechanism, we have determined crystal structures of wildtype and mutant ODCase with various substrate analogues. As an example, we have determined the structure of *M. thermoautotrophicum* ODCase with a methyl ester of OMP. The ester part of this substrate is rotated over 50 degrees from the plane of the pyrimidine ring. The structure with the related ethyl ester is quite similar, suggesting that disruption of the conjugation might contribute to catalysis. Quite unexpectedly, 6-Cyano-UMP was identified not as an inhibitor but as a very slow substrate of ODCase. The novel reaction has a half-life of about 24 hours, allowing us to find the structure of an intermediate by flash-freezing.

PHYS 702 [744194]: Dynamic opening of normal base pairs in the enzymatic search for a damaged base

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Abstract

The enzymatic search for damaged bases in DNA requires extrahelical recognition of the aberrant base. Despite this well-documented structural transformation, it is unknown whether normal base pairs are inspected for their integrity by a similar extrahelical mechanism. Using nuclear magnetic resonance imino proton exchange measurements we find that the enzyme uracil DNA glycosylase (UDG) dynamically and selectively opens T:A base pairs. UDG acts by

increasing the equilibrium constant and lifetime of the open state by over 10^3 -fold as compared to unbound DNA. These findings provide the first evidence for extrahelical inspection of normal bases during the search for DNA damage.

PHYS 703 [753890]: Mechanism of phosphoryl transfer in a phosphomutase

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Abstract

Crystallization of β -phosphoglucomutase (β -PGM) in the presence of Mg(II) and the substrates glucose 1-phosphate or glucose 6-phosphate produced crystals of the enzyme-Mg(II)-glucose 1,6-bisphosphate (G-1,6-P) complex which diffracted to 1.2 Å. This structure reveals a stabilized pentacovalent reaction intermediate with the G-1,6-P and Asp8 nucleophile pressed together to form the phosphorane and is visual proof that the phosphoryl transfer proceeds via a nonconcerted, associative pathway. The alternate structural interpretation (bound MgF_3 offered by Blackburn and) coworkers in Science, was invalidated by phosphorus analysis of the crystalline complex, and structure determination of the enzyme- Mg(II)- α -galactose-1-phosphate complex. Single turnover reaction of [¹⁴C] β -glucose-1-phosphate with excess β -PGM and limiting or excess G-1,6-P shows that label exchanges into the G-1,6-P pool consistent with a model wherein G-1,6-P dissociates from the active site and rebinds. As opposed to substrate, G-1,6-P can efficiently phosphorylate the enzyme at physiological concentrations suggesting a moonlighting activity for fructose-6-phosphate kinase in producing G-1,6-P in the cell (NIH grant GM16099).

PHYS 704 [747723]: New paradigms of many-electron theory development

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Abstract

New paradigms have been put forward realizing efficient many-electron theory programs or calculations without incurring an excessive amount of manual work. They enable the pervasive application of these theories with an unprecedented level of complexity and accuracy. We review our general algebraic and symbolic manipulation program fully automating the derivation and parallel computer implementation of most any single-reference many-electron theories for electron correlation and other prior work leading to this development (automated formula derivation, automated program syntheses, determinantal and string-based general-order coupled-cluster methods, tensor formulation of many-electron theories, and general compiler optimizations of tensor expressions). We have demonstrated the viability of the automated approach by developing efficient parallel programs for high-order models of configuration-interaction theory, many-body perturbation theory, coupled-cluster theory, equation-of-motion coupled-cluster theory, coupled-cluster Lambda equation solvers, and their relativistic variants. We address the abstraction of theory and equations essential to such an automated scheme.

PHYS 705 [754399]: String-based implementation of quantum chemical methods

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Abstract

A comprehensive overview of the string-based formalism is presented. A comparison is provided between the string-based approach and other techniques such as the automatic program generation. The main advantage of using strings is that it enables us to implement quantum chemical methods in a general way without explicit reference to the number of indices of the wave function parameters and other quantities. The required contractions of many-index tensors can be computed by a couple of simple routines which may be ideally suited for methods of high complexity where evaluation of tens of thousands of contractions is necessary. The applicability of our algorithms is demonstrated for general coupled-cluster and configuration interaction methods including both single- and multi-reference-type models. The theory and implementation of analytic energy derivatives and computation of molecular properties for these wave function classes are discussed. A few selected chemical applications are presented.

PHYS 706 [754742]: Performance optimization issues in automatic synthesis of high-performance codes for correlated electronic structure methods

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Abstract

The Tensor Contraction Engine (TCE) is a software tool that can be used to automatically synthesize high-performance code for a class of correlated electronic structure methods. This talk will discuss a number of performance optimization approaches that have been incorporated in the TCE. The optimizations addressed by the TCE include operation minimization via algebraic transformation, memory optimization via loop fusion, disk I/O optimization via loop tiling, space-time trade-off optimization, and communication optimization. Data on experimental performance measurements will be provided, that demonstrate the benefits of using the implemented performance optimization techniques.

PHYS 707 [751098]: Parallelization of an electronic structure code

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Abstract

The strategy for parallelization of the GAMESS electronic structure code will be described. Such codes typically contain many different computational kernels, with data storage ranging from $O(N^2)$ to $O(N^4)$, and with computational costs of $O(N^3)$ to $O(N^7)$. The choices made reflect the nature of the constantly changing hardware, including the interconnection, and the available support software, in addition to the nature of the quantum chemistry calculation itself. Efforts to produce effective parallel code in GAMESS have been underway since 1993, when a parallel direct SCF program was introduced. Distributed memory programming was introduced in 1999 to support a parallel MP2 gradient code, through a library called the Distributed Data Interface. The latest enhancement of our DDI support software was introduced in 2004, to optimize distributed memory programming on the ubiquitous SMP nodes. The goal, of course, is to allow efficient, scalable computation of molecular wavefunctions, not only for large molecules, but also for more complex and accurate ansätze. A summary of the present capabilities and performance data of GAMESS will be included.

PHYS 708 [752791]: Parallel implementation of highly correlated electronic structure calculations

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Abstract

Highlights of an efficient parallelization strategy suitable for highly correlated electronic structure methods will be presented. As an example, we will use the recently developed parallel version of the symmetry-adapted perturbation theory (SAPT) - a well-established ab initio tool for accurate predictions of intermolecular interaction energies. A typical SAPT calculation involves SCF runs for the monomers followed by a specialized integral transformation, CCSD calculations, and computation of the interaction energy, currently at the intramonomer correlation level equivalent to MBPT4. The employed programming paradigm is to utilize sequential BLAS routines on portions of data assigned to each processor while minimizing the amount and frequency of interprocess communications. The key to the code's portability is the use of MPI as the only parallelization tool. Handling of files ensures scalability of I/O operations on platforms with various configurations of scratch disk space. Our code is one of very few implementations of electronic structure methods that show good time scaling characteristics on up to 32 processors on a variety of platforms, ranging from shared-memory SGI machines to IBM's SP systems to Beowulf clusters with slow ethernet-based connectivity.

PHYS 709 [753625]: Forum discussion: Parallel and automated implementations of high accuracy quantum chemistry methods

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Abstract

A panel chaired by Prof. Mark Gordon will discuss the prospects of automatic code generation in

electronic structure theory and the challenges in designing high-performance parallel quantum chemistry software.

PHYS 710 [751755]: Single molecule studies of motors and DNA

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Abstract

Abstract text not available.

PHYS 711 [755522]: Single-molecule protein conformational dynamics in cell signaling

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Abstract

We have demonstrated the application of single-molecule imaging and ultrafast spectroscopy to probe protein conformational dynamics in solution and in lipid bilayers. Dynamic protein-protein interactions involve significant conformational motions that initiate chain reactions leading to specific cellular responses. We have carried out a single molecule study of dynamic protein-protein interactions in a GTPase intracellular signaling protein Cdc42 in complex with a downstream effector protein, WASP. We were able to probe hydrophobic interactions significant to Cdc42/WASP recognition. Single molecule fluorescence intensity and polarization measurements have revealed the dynamic and inhomogeneous nature of protein-protein interactions within the Cdc42/WASP complex that is characterized by structured distributions of conformational fluctuation rates. Conducting a single-molecule fluorescence anisotropy study of calmodulin (CaM), a regulatory protein for calcium-dependent cell signaling, we were able to probe CaM conformational dynamics at a wide time scale. In this study, CaM contains a site-specifically inserted tetra-cysteine motif that reacted with FIAsh, a biarsenic fluorescein derivative that can be rotationally locked to the host protein. The study provided direct characterization of the nanosecond motions of CaM tethered to a biologically compatible surface under physiological buffer solution. The unique technical approaches are applicable of studying single-molecule dynamics of protein conformational motions and protein-protein interactions at a wide time range without the signal convolution of probe-dye molecule motions.

PHYS 712 [767636]: Single-molecule enzymology of RNA: Essential functional groups impact catalysis from a distance

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Abstract

The hairpin ribozyme is a minimalist paradigm for studying RNA folding and function. In this enzyme, two domains dock by induced fit to form a catalytic core that mediates a specific

backbone cleavage reaction. Here, we have fully dissected its reversible reaction pathway, which comprises two structural transitions (docking/undocking) and a chemistry step (cleavage/ligation), by applying a combination of single-molecule fluorescence resonance energy transfer (FRET), ensemble assays, and kinetic simulations. This has allowed us to quantify the effects that modifications of essential functional groups remote from the site of catalysis have on the individual rate constants. We find that all ribozyme variants show similar fractionations into up to four non-interchanging molecule sub-populations of distinct undocking rate constants, leading to heterogeneous cleavage activity as commonly observed for RNA enzymes. A modification at the domain junction additionally leads to two distinct docking rate constants. Surprisingly, all modifications not only affect docking/undocking but also significantly impact the chemistry rate constants over a substantial distance from the site of catalysis. We propose that a network of coupled molecular motions connects distant parts of the RNA with its reaction site, which suggests a new analogy between RNA and protein enzymes. Our findings also have broad implications for applications such as the action of drugs and ligands distal to the active site or the engineering of allostery into RNA.

PHYS 713 [743509]: Single-molecule visualization of protein-DNA interactions

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Abstract

Individual molecules of the RecBCD helicase can be seen acting on single molecules of DNA (1). Detection involves optical trapping of fluorescently-tagged dsDNA attached to a polystyrene bead. Translocation is monitored by displacement of fluorescent dye from the DNA, using fluorescence microscopy. RecBCD is a bipolar helicase, containing two motor subunits that translocate with opposite polarities, but in the same direction, on opposing strands of the anti-parallel DNA duplex (2). The enzyme is regulated by the DNA sequence, Chi, which is recognized during translocation. We could see that RecBCD paused precisely at Chi (3). More unexpectedly, after pausing, the enzyme continued but at about half of its initial rate. We propose that interaction with Chi uncouples one of the two motor subunits from the enzyme to produce the slower translocase. Thus, Chi is a molecular throttle that controls translocation by RecBCD. (1) Bianco, P. R., et al. (2001) *Nature* 409, 374-378. (2) Dillingham, M. S., et al. (2003) *Nature* 423, 893-897. (3) Spies, M., et al. (2003) *Cell* 114, 647-654

PHYS 714 [741343]: Interaction of a nucleic acid chaperone protein and DNA hairpins: HIV-1 nucleocapsid protein reduces TAR DNA hairpin closing rate

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Abstract

Reverse transcription of the HIV-1 RNA genome involves several complex nucleic acid rearrangement steps that are catalyzed by the HIV-1 nucleocapsid protein (NC), including for example, the annealing of the transactivation response (TAR) region of the viral RNA to the complementary TAR region in minus-strand strong-stop DNA ((-) SSDNA. We report herein extensive fluorescence resonance energy transfer (SM-FRET) measurements on single immobilized TAR DNA hairpins and hairpin mutants complexed with NC (i.e TAR DNA/NC). Using this approach we have explored the conformational distribution and dynamics of the hairpins with and without complexed NC. The data demonstrate that NC shifts the equilibrium secondary structure of TAR DNA hairpins from a fully “closed” conformation to essentially one specific type of “partially-open” conformation. In this specific conformation, the two terminal stems are “open” or unwound and the other stems are closed. This partially-open conformation is arguably a key TAR DNA intermediate in the NC induced annealing mechanism of TAR DNA. The observed terminal stem closing rate constant is orders of magnitude slower than closing rates for analogous DNA structures with no NC. This clearly demonstrates that NC strongly stabilizes the “partially-open” conformation of TAR/DNA.

PHYS 715 [745446]: Analysis of molecular conformations with high time resolution by multi-parameter single-molecule fluorescence spectroscopy

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Abstract

Using a confocal fluorescence microscope the newly developed multiparameter fluorescence detection (MFD) enables us to simultaneously collect all fluorescence information such as intensity, lifetime, anisotropy in several spectral ranges). MFD is applied to perform single-molecule fluorescence-resonance-energy-transfer (FRET) studies on biological systems. These novel FRET-based detection and analysis methodologies allowed us to resolve structural subpopulations with sub-nanometer resolution. Furthermore, direct access to the time trajectories of the different fluorescence parameters is obtained revealing the dynamics of the system. Finally, the construction of more-dimensional frequency histograms of the fluorescence parameters found in the trajectories on the single molecule level and selective analysis of these species (e.g. selective correlation analysis) give detailed view on the molecular energy landscape and the associated molecular structures. Work on various nucleic-acid structures, HIV-1 Reverse Transcriptase:DNA/DNA complexes the SNARE-protein Syntaxin and FOF1-ATPase synthase will be presented.

PHYS 716 [744213]: Subkelvin cooling of molecules via a single collision with an atom

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Abstract

The preparation and trapping of molecules at microkelvin temperatures has been much desired, although not yet accomplished in a general way. Several methods for slowing or cooling have been demonstrated to accomplish this are being developed. Although successful, each approach has limitations in applicability or execution. We report progress on a technique we are developing for the cooling of molecules that relies upon a single collision between the molecule and an atom, in a crossed molecular beam. The method depends on the fact that in a collision between an atom and a molecule, one of the collision partners can have a final Center of Mass (COM)-frame velocity that is essentially equal in magnitude and opposite in direction to the velocity of the COM, thus yielding a molecule that is essentially standing still in the lab. This cooling process is general and realizable under easily accessible experimental conditions in crossed atomic and molecular beams.

PHYS 717 [753710]: On the dynamics of rotationally broad wavepackets

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Abstract

Moderately intense laser fields can be used to excite rotationally broad, coherent superposition states with fascinating properties that may also be potentially useful. We illustrate the possibilities of forcing the three axes of an arbitrary polyatomic molecule to align along given three axes fixed in space, of preserving the field induced alignment after turn-off of the laser pulse, of forming superposition states that are perfectly aligned and fully isotropic periodically in time, and of focusing, collimating, steering, dispersing and reflecting molecular beams with light. Potential applications include a new opportunity for quantum storage, control of charge separation and charge recombination reactions, separation of racemic mixtures of chiral molecules into pure enantiomers, generation of high harmonics and of ultrashort (attosecond) pulses, enhancement of the sensitivity of time-resolved probes of polyatomic dynamics, and nanoscale processing of surfaces.

PHYS 718 [749273]: Photoassociation of cold calcium atoms through spin-orbit states: An ab initio nonadiabatic treatment

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Abstract

State-of-the-art ab initio techniques have been applied to compute the potential energy curves for the excited singlet and triplet states of the calcium dimer in the Born-Oppenheimer approximation. The potentials were computed using a combination of the equation-of-motion approach within the coupled-cluster singles and doubles framework for the valence-core electron correlation and of the full configuration interaction for the valence-valence correlation. The potentials were corrected for the scalar relativistic terms resulting from the many-electron Breit-Pauli theory. The spin-orbit coupling matrix elements and the nonadiabatic coupling terms were obtained from the multireference configuration interaction calculations. Finally, the electric

transition dipole moment governing the transitions from the ground X state was computed as the first residue of the polarization propagator with the coupled-cluster method restricted to a single and double excitations. The computed points have been analytically fitted and used in nearly exact fully nonadiabatic calculations of the rovibrational energy levels and photoassociation intensities. Our theoretical results will serve to interpret the measurements of the photoassociation spectra of colliding cold calcium atoms, as well as the conventional high-resolution spectra of the calcium dimer.

PHYS 719 [751080]: Dynamics of chemical reactions at cold and ultracold temperatures

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Abstract

Recent advances in cooling and trapping of molecules and the realization of Bose-Einstein condensation in molecular systems have opened up unique opportunities for the study of molecular collisions and possibly chemical reactions at ultracold temperatures. Over the past several years we have carried out quantum scattering calculations of molecular collisions at ultralow energies and demonstrated that chemical reactions may occur with significant rate coefficients at ultracold temperatures. The studies revealed that van der Waals interaction in the entrance channel of the reaction may significantly influence reactivity at ultracold temperatures. Here, we will give an overview of our recent research in this area with particular emphasis on atom-molecule systems involving polar molecules. We will discuss how reactivity is affected by isotope substitution and vibrational excitation of reagent molecules.

PHYS 720 [761843]: Intramolecular and guest-host dynamics of NO₂ in Helium clusters

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Abstract

The dynamics of NO₂ embedded in helium droplets is discussed, specifically, the guest-host interactions that shift and broaden resolved spectral features in the regime of vibronic chaos, and that affect unimolecular decomposition at energies above D₀. At energies above the / conical intersection, NO₂ is known to exhibit quantum chaos, as inferred for example from nearest-neighbor spacing distributions for levels having a common set of good quantum numbers. The helium host introduces two additional observables: shifts and broadenings. This presupposes that the spectrum changes in a manner such that the term "shift" is an appropriate metric. Spectra have been recorded in the region 17,700 – 18,300 cm⁻¹ by using the mass spectrometric depletion method. It is found that shifts are rather constant from one level to the next, with a single value of 7 cm⁻¹ providing an acceptable fit. Likewise, broadenings are rather constant from one level to the next, with a single value of 7 cm⁻¹ providing an acceptable fit. Dispersions about the central values are modest, and it is argued that these dispersions reflect the extent to which the

dynamics are chaotic. Above D_0 , it is shown that there is no net unimolecular decomposition in the range D_0 to $D_0 + 4300 \text{ cm}^{-1}$. At the highest energies, gas phase NO_2 decomposes with rate constants $\sim 5 \times 10^{12} \text{ s}^{-1}$.

PHYS 721 [765281]: Dopant-induced infrared activity in HCl-doped solid hydrogen:

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Abstract

Atomic and molecular dopants embedded in solid hydrogen matrices induce infrared activity in the matrix through a mechanism much like that which generates collision-induced absorption in dense gases. For HCl dopants, this induced infrared activity is associated solely with the twelve H_2 molecules that are nearest neighbors to the dopant; studies of the infrared absorption spectrum of HCl-doped solid H_2 can thus provide detailed information about the coupled vibrational dynamics of these twelve molecules, and more generally about the physics of solvation in molecular quantum solids. We show that the high-resolution infrared absorption spectrum of HCl-doped solid H_2 provides clear evidence for three-body HCl- H_2 - H_2 interactions in the matrix, extract information about these interactions from the experimental spectra, and compare these results against high-level *ab initio* quantum chemical calculations.

PHYS 722 [753636]: Computations of reacting flow with detailed chemical kinetics

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Abstract

Detailed computations of reacting flow present both computational and analysis challenges due to chemical complexity and the large range of length and time scales involved. This talk will cover a range of issues pertaining to computations of multidimensional low Mach number reacting flow. We discuss numerical time integration algorithms necessary to deal with the high stiffness of detailed chemical models, using semi-implicit or operator-split constructions. We also discuss the utility of adaptive mesh refinement computational strategies, and associated challenges. We examine computational singular perturbation dynamical systems analysis techniques in the context of multidimensional reacting flow, and illustrate their utility for providing physical insight on coupled transport-chemistry processes and for automatic chemical model reduction. Finally, we discuss the quantification of uncertainty in reacting flow model predictions, highlighting spatiotemporal growth of uncertainty in modeling results, and consequences to predictability of reacting flow systems.

PHYS 723 [751068]: Detailed chemical mechanisms in turbulent flame calculations

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Abstract

Calculations of several turbulent nonpremixed flames are presented to illustrate the current state of the art in PDF modeling. For a lifted hydrogen flame in a vitiated coflow, calculations are performed using the 9-species mechanism of Li et al. (2003). For piloted methane flames a 19-species reduced mechanism based on the detailed GRI mechanism is employed. In both cases, the computational cost of implementing the chemistry is substantially reduced by using in situ adaptive tabulation (ISAT). These flame calculations demonstrate how detailed chemical kinetic mechanisms can be used in turbulent combustion modeling, and that the results are sensitive to specific reaction rates.

PHYS 724 [751682]: Chemical-Kinetic reduction in the presence of diffusion

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Abstract

The role of diffusion in dimension reduction for chemical-kinetic modeling is discussed. This work is an extension to reaction-diffusion systems of the reduction of complex chemical kinetics via low-dimensional manifolds. It is shown that there are three types of manifolds present under the conditions of reaction with diffusion: 1) standard chemical-kinetic manifolds, 2) diffusion manifolds, and 3) inertial manifolds. The first two types of manifolds reduce the number of partial differential equations and the third reduces the system to a finite-dimensional one (a few ordinary differential equations). Several examples are discussed, including model systems with exact manifolds, a chain-branching mechanism, and a model for ozone combustion.

PHYS 725 [755011]: PRISM: Piecewise reusable implementation of solution mapping to improve computational economy

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Abstract

PRISM (Piecewise Reusable Implementation of Solution Mapping) was developed to reduce the computational burden attributable to chemistry associated with implementing complex kinetics into high fidelity fluids codes. PRISM is an economical and accurate approach to mechanism reduction that draws upon factorial design, statistics and numerics, caching strategies, data structures, and long term reuse of chemical kinetic calculations. A solution-mapping technique is invoked, in which the result of time-integrating the chemical rate equations is parameterized by a set of algebraic polynomial response surfaces. Issues associated with the efficiency and accuracy of PRISM are discussed for several applications. Approaches to improving PRISM's efficiency: deferred polynomial construction, the trajectory velocity concept, and dynamic dimensional system reduction will be discussed. The impact of increasing turbulence intensity on the performance of PRISM and comparable methods deduced through measures of chemical composition space dimensionality also will be presented.

PHYS 726 [755002]: Reduction of comprehensive chemistry with constraint potentials and implementation with artificial neural networks

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Abstract

Comprehensive models of hydrocarbon combustion chemistry involve many species and hundreds of reactions, and their reduction is a problem of key importance for the efficient coupling of thermo-chemistry with fluid dynamics. According to the concept of Rate-Controlled Constrained Equilibrium (RCCE), combustion kinetics can be reduced into a set of constraints whose relaxation guides the evolution of the system towards equilibrium.

The RCCE concept is best formulated in terms of constraint potentials, a set of thermodynamically-derived variables that lead to a system of implicit ODEs. This formulation is employed here in conjunction with a comprehensive mechanism for CH₄ combustion comprising 63 species and 415 reactions, including N chemistry. The outcome is tested by means of homogeneous combustion and pairwise-mixed stirred reactor (PaMSR) calculations, and it is shown that sets of few variables are able to provide very accurate prediction of the major species, and moderately successful prediction of NO.

The direct integration of chemistry or RCCE ODEs in turbulent combustion CFD codes poses extreme computational demands. Artificial Neural Networks are non-linear algebraic models that can be “trained” to replace the direct integration of the ODEs. In conjunction with RCCE, ANNs provide an efficient means of implementing combustion chemistry, particularly suitable for use in practical combusting flow computations.

PHYS 727 [753152]: Predicting reacting flows with complex chemistry: Rigorous error control in adaptive chemistry calculations

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Abstract

Accurate prediction of performance and emissions is very important in the design of combustion systems. However, detailed description of complex chemical kinetics coupled with fluid dynamics is usually computationally expensive and often impractical. Since conditions vary drastically in a flame, not all reactions are always important everywhere in the computational domain. Adaptive chemistry has been proposed to enable efficient and accurate simulations of reacting flows by using several smaller locally-valid kinetic models over the computational domain. A method has been developed for determining the smallest sub-model of a given comprehensive model that satisfies user-specified tolerances at a set of reaction conditions. A new rigorous method for identifying valid ranges of the optimally-reduced models is introduced. Control of errors due to adaptive chemistry is discussed in the context of selecting appropriate tolerances for model reduction. Implementation of adaptive chemistry in CFD codes is also discussed.

PHYS 728 [750106]: Simulating phosphate hydrolysis in key biological reactions

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Abstract

Phosphate hydrolysis plays a pivotal role in many of life processes, including signal transduction, replication, and energy transduction. In many cases we now have detailed X-ray structures of the proteins involved in catalyzing the formation and breakage of phosphate oxygen bond and what is missing is a quantitative relationship between the structural information and the corresponding functional results. This lecture describes the progress in simulating the energetics of the hydrolysis of phosphate esters and anhydrides and/or the reverse reaction. The systems considered will include the Ras/GAP system, F1 ATP synthase, DNA polymerase, and hydrolysis reactions in aqueous solution.

PHYS 729 [746014]: Molecular basis of mRNA 3'-end formation

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Abstract

Formation of the mature 3'-end of an mRNA by cleavage and polyadenylation is required to produce a stable, translation-competent mRNA. It has recently been discovered that this nearly universal RNA processing event is also highly regulated, providing diversity to gene expression. We are dissecting the molecular basis of polyadenylation by studying components of the polyadenylation machinery and their interaction with pre-mRNA and with each other. We have determined the structure of the RNA-binding domain of human CstF-64 and described its interaction with G/U-rich sequences. This interaction occurs early during assembly of the polyadenylation complex. Increased levels of CstF-64 can switch the utilization of alternative poly(A) sites on the same mRNA, and is observed in differentiating immune system cells. We have also demonstrated that the C-terminal domain of CstF-64 folds into a novel helical fold. This domain is responsible for the interaction with PC4, normally a component of the transcriptional apparatus. Its interaction with CstF-64 couples transcription and RNA processing. The molecular description of RNA processing events and their coupling to transcription will be crucial to understand both basal polyadenylation and its regulation in response to developmental and exogenous signals.

PHYS 730 [746037]: Fidelity mechanisms of DNA polymerase beta

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Abstract

Capturing long-time, large-scale conformational rearrangements in biomolecules remains a challenge, open to many inventive techniques that exploit advanced software and hardware technologies. I will describe work in our group to develop and further apply the Transition Path

Sampling (TPS) method of Chandler and coworkers and the stochastic pathway approach (SPA) of Elber and coworkers to a large nucleoprotein complex whose conformational transition occurs on the millisecond time frame. Combined simulations suggest five major transition states in the reaction profile of DNA polymerase beta's closing motion, which precedes, and is essential for, the chemical reaction of nucleotide incorporation. The associated free energy barriers describe the cooperative dynamics associated with the conformational transition of pol beta, highlight key residues that play a critical role in the enzyme's function, and begin to yield clues into the relation between conformational and chemical barriers as well as correct versus incorrect nucleotide incorporation. Significantly, the rate-limiting conformational change is close to the overall experimentally determined reaction barrier, underscoring the importance of subtle local motions on reaction efficiency and fidelity.

PHYS 731 [744973]: Structural mechanism for T7 RNA polymerase translocation

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Abstract

During gene expression, RNA polymerases catalyze template dependent RNA synthesis. The polymerases are capable of converting the chemical reaction energy into the mechanical movement along the template, thereby, belongs to a class of molecules named molecular motors. To study the mechanism of translocation, we determined crystal structures of T7 bacteriophage RNA polymerase at each step of a single nucleotide addition cycle: a substrate complex with a non-hydrolyzable nucleotide analogue alpha,beta-methylene-ATP, a product complex captured at the pre-translocation conformation and a post-translocation elongation complex. These structures revealed that during translocation the fingers domain acts like a lever-arm to move the polymerase in the direction along the RNA:DNA heteroduplex axis at the step size of one base pair, 3.4 Å. An active site loop connected to the lever-arm moves in and out of the nucleotide binding site and functions like a pawl on a ratchet device during translocation, structurally links nucleotide selection with frameshift prevention. From these structural results we demonstrate that pyrophosphate product release triggers a power stroke movement of the polymerase along DNA during translocation.

PHYS 732 [753669]: Single-molecule fluorescence assay of T7 DNA polymerase with single nucleotide resolution

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Abstract

The study of individual DNA polymerases has been made possible by the advent of novel techniques allowing to mechanically manipulate individual DNA molecules. However, the limited spatial resolution of these single-molecule assays prevents the observation of individual turnovers of a DNA polymerase corresponding to the incorporation of a single nucleotide. Here we utilize single-molecule fluorescence technique to study the DNA polymerase from the bacteriophage T7. Short DNA duplexes with a receded 3' terminus were labeled with Cy3,

immobilized on a glass surface, and imaged with a total-internal-reflection fluorescence microscope. The association of individual DNA polymerases with the duplex could be observed in real-time utilizing the change in photophysics of the fluorophore in the presence of the protein. By presenting the enzyme with Cy5 labeled nucleotides, fluorescence-resonance energy transfer was used to observe individual incorporation events. This novel single-molecule assay provides detailed information regarding the mechanism of DNA synthesis.

PHYS 733 [753630]: Nucleic acid conformational flexibility and function:

Molecular dynamics and normal mode analyses of the hammerhead ribozyme

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Abstract

The conformational flexibility of the hammerhead ribozyme has been systematically investigated using several computational methods to test the applicability of Normal Mode Analysis (NMA) to nucleic acids. NMA is used to study large scale motions in macromolecular systems and has been shown to be a useful and appropriate tool when applied to proteins. For nucleic acid systems, which have very different structural features and interactions than proteins, it has not been conclusively determined if NMA reliably predicts collective motions or how sensitive the results are to the details of the computational model. In this work, we investigate these questions by comparing the motions of the hammerhead ribozyme calculated with NMA using the all-atom Hessian but diagonalized at different levels of spatial resolutions, the Elastic Network Model, and principal component analysis of nanosecond molecular dynamics simulations with explicit treatment of the solvent and counter ions and Particle Mesh Ewald summation for the electrostatic interactions. The implication of the results on the functional mechanism of the hammerhead ribozyme is discussed.