A Multi-Dimensional Approach to Molecular Recognition in Chemistry and Biology: Towards New Therapies Against Infectious Diseases

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We pursue since the early 1990s a molecular recognition-based approach to medicinal chemistry. Starting from the observation of an unfamiliar intermolecular contact seen in the X-ray crystal structures of protein-ligand complexes obtained in our medicinal chemistry programs, which target malaria and other important diseases, we undertake database mining in the Cambridge Crystallographic Database (CSD) and the Protein Data Bank (PDB) to explore the statistical relevance of the contact. If this contact is of a more general nature, we quantify it - depending on its energetic magnitude - in protein-ligand binding studies, molecular recognition studies with synthetic receptors or, if very weak, by studying intramolecular dynamic processes in designed model systems. Examples for this multi-dimensional approach are the elucidation of phosphate recognition in structural biology, the quantification of orthogonal multipolar interactions, discovered during a fluorine scan to map the fluorophilicity/fluorophobicity of the thrombin active site and the exploration of cation-π interactions in aromatic molecular boxes at enzyme active sites such as the S4 pocket of Factor Xa, another serine protease of the blood coagulation cascade. The application of the insight gained into biological molecular recognition phenomena to structure-based drug design will be illustrated by recent lead developments in our antimalarials program. Targets are IspE (4-diphosphocytidyl-2-C-methyl-D-erythritol kinase) and IspF (2-C-D-erythritol-2,4-cyclodiphosphate synthase), two enzymes from the non-mevalonate pathway to isoprenoid biosynthesis, exclusively used by plasmodium parasites, and the aspartic proteases plasmepsins I-IV used by the parasite to degrade hemoglobin.
Challenges in Organometallic Chemistry: From Bond Activation to Catalytic Design

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The insertion of transition metal complexes into strong chemical bonds can activate these bonds towards uncommon transformations and form the basis for the design of new catalytic reactions and new synthetic methodology. Studies on selective activation of strong bonds by specifically designed late transition metal complexes, and homogeneous catalysis involving these bonds, will be described. Emphasis will be placed on C-X (X= C, H, F, Cl) and O-H bonds. Among the ligands designed for these studies are pincer-type tridentate mono-anionic frameworks which can impart on metal centers both stability and unusual modes of reactivity. Facile de-aromatization processes have led to uncommon structures and have provided insight regarding the interactions of metals with aromatics. The role of pincer hemilability and reversible de-aromatization in catalysis will be illustrated.
The Resonance Phenomenon: From First Principles to Technology

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Resonances appear in different fields of physics and chemistry, and in many cases it is very hard (and often impossible) to calculate their properties of interest by standard methods. In chemistry resonances appear as metastable (i.e., finite lifetime) autionization states of atoms and molecules and as metastable predissociaion states which are often associated with activated complexes in chemical reactions. The understanding of the resonance phenomena helps to control the dynamics of the system of interest.

Complex scaling transformations make it possible to perform calculations in such cases. The main idea behind the complex scaling transformations will be explained in a visual way.

By using the formalism we derived, which enables the use of the complex scaling method in quantum mechanical (QM) calculations which are similar in their nature to electronic structure calculations of bound states in the conventional QM, I will explain experimental results that can not be explained by conventional (Hermitian) QM, will show how theoretical studies guide new type of experiments, and will describe new types of optical and electrical devices that have been invented on the basis of insights gained by using this method in the studying of photo-induced dynamics in simple chemical reactions.

For a review see: N. Moiseyev, "Quantum theory of resonances: calculating energies, widths and cross-sections by complex scaling", Physics Reports 302(5-6), 211-293 (1998); [Read online]
Weak alignment offers new opportunities in NMR of biomolecules

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Spectral simplicity of solution NMR spectra results from the Brownian rotational diffusion of solutes, which rapidly averages the strong dipolar interactions between different spins to exactly zero. Much valuable structural information, contained in these dipolar interactions, is lost in this averaging process. It has long been known that alignment of solutes in a magnetically oriented liquid crystalline medium restores the dipolar interactions, albeit at the cost of dramatically increased spectral complexity, limiting this approach to only very simple systems. However, by decreasing the degree of solute alignment, it is possible to retain the valuable structural information contained in the dipolar couplings, without considerably increasing spectral complexity.

With the rapidly increasing number of previously solved macromolecular structures, the alignment approach can take advantage of this structural database by revealing which fragments are compatible with experimental dipolar couplings. This approach can provide considerable shortcuts in macromolecular structural studies, while providing a very sensitive measure to identify subtle structural changes. Examples will be shown for both proteins and nucleic acids.
Bioelectrochemistry in the Management of Diabetes: The Science and Technology of TheraSense

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About 6 billion glucose assays are performed each year by self-monitoring diabetic people. These assays were painful until TheraSense, the venture founded by my son Ephraim and me, made them painless. We removed the pain by introducing FreeStyle™, an accurate, 300 nL volume, thin-layer micro-coulometer. The small blood volume made the assay painless and rapid. The assay is also accurate, because the outcome does not vary with kinetic parameters, like temperature or viscosity. The strip of FreeStyle™ comprises the smallest volume mass-manufactured fluidic device.

Our large scale clinical trials of an amperometric, continuous glucose monitor were also successful. We designed the monitor to remove the worry of diabetes: in managing their blood glucose concentration, diabetic people had to perpetually balance the risk of rare coma or even death causing hypoglycemia, against the risk of persistent hyperglycemia, a cause of blindness, amputations, kidney failure and vascular disease. The core component of the continuous glucose monitor is a subcutaneously implanted, glucose-specific, amperometric sensor, painlessly replaced by the user every 5-days. Through the catalytic electrooxidation of glucose, the sensor transduces its concentration-dependent flux to the electrode to an electrical current. Its unique electrocatalyst is a crosslinked electrostatic adduct of a polycationic redox-conducting polymer and polyanionic glucose oxidase. The polymer swells in water to form an electron conducting redox hydrogel, electrically connecting the enzyme’s redox centers to the electrode, irrespective of its orientation. Electrons diffuse in the hydrogel by electron-exchanging collision of redox-segments of the polymer.

TheraSense Inc. was acquired in 2004 by Abbott Laboratories for $1.26 billion and is now part of Abbott Diabetes Care. Its sales were of $500 million in 2005. The company employs about 1,500 people and is located near the site where Ephraim and I founded it in 1996.
Active Thermochemical Tables: Thermochemistry for the 21st Century

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Active Thermochemical Tables (ATcT) are a new paradigm of how to derive accurate, reliable, and internally consistent thermochemical values for stable, reactive, and transient chemical species. Availability of high-quality thermochemical values, accompanied by properly quantified uncertainties, is central to chemistry and critical in many areas of physical chemistry. As opposed to traditional sequential thermochemistry, ATcT is based on the Thermochemical Network (TN) approach, which involves the construction, manipulation, statistical evaluation, and optimization of the TN Graph. The TN Graph incorporates available experimental and theoretical knowledge on the target species and explicitly exposes to analysis the maze of inherent thermochemical interdependencies across various species, which is ignored by the conventional treatment. The approach allows, inter alia, a statistical analysis of the individual experimental and theoretical measurements that define the TN. The end result is a simultaneous extraction of best possible thermochemical values for all species in the TN, based on optimal use of all the available knowledge. In addition, ATcT introduces a number of additional features that are neither present nor possible in the traditional approach. With ATcT, new thermochemically-relevant determinations can be instantly introduced as they become available, and painlessly propagated through all affected thermochemical values, thus maintaining an updated and internally consistent set of thermochemical values that always reflects the latest knowledge. Not less importantly, ATcT also allows hypothesis testing and evaluation, as well as discovery of “weak links” in the TN. The latter provide pointers to new experimental or theoretical determinations that can most efficiently improve the underlying thermochemical body of knowledge. The capabilities of ATcT will be illustrated on several recent examples. This work was supported by the U.S. Department of Energy, Division of Chemical Sciences, Geosciences, and Biosciences of the Office of Basic Energy Sciences, under Contract No. DE-AC02-06CH11357.
Base-Induced Solvent Switches in Acid-Base Reactions

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We expand on the classic diffusion reaction model for aqueous acid-base neutralization reactions by Eigen and Weller to interpret experimental results obtained on the proton transfer dynamics between pyranine and trichloroacetate. We conclude that upon mutual diffusion of the acid and base to form an encounter reaction complex, solvent switches, consisting of one or several water molecules, between acid and base mediate the proton transfer, and provide a general framework for all observed dynamical features. We applied the kinetic scheme of Fig. 1 assuming reversible first order unimolecular or reversible second order bimolecular kinetics, depending on the specific reaction steps. Detailed balancing kinetics have been imposed on all reaction rates.
Coherent Control of Multiphoton Excitations and Information Processing

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The present experimental research is in the field of coherent control using shaped femtosecond pulses. It is along two inter-connected directions. One direction is extending the capabilities of coherent control with a-priori designed pulses (as opposed to the "black-box" feedback control methodology) beyond the weak-field regime. The other direction is photo-induced coherent information processing, where the coherent control capabilities are applied for problem-specific computation.

The studies investigated weak-field and intermediate-field coherent phase control over two- and three-photon absorptions in a system of coupled multiphoton excitations in Na. In the weak-field regime the absorptions are induced, respectively, by non-resonant two-photon and resonance-mediated (2+1) three-photon transitions, and are fully described within 2nd- and 3rd-order (i.e., lowest order) time-dependent perturbation theory. In the intermediate-field regime the valid perturbative description also includes the next perturbative order. Then, for example, the two-photon absorption also involves four-photon transitions. The results demonstrate high degree of control over the different multiphoton absorptions and the ratio between them. By comparison with numerical calculations, we precisely identified the intensities of 4th-order perturbative regime. This allowed us to keep analyzing the photo-excitations in the frequency domain also at intermediate intensities, differently from the commonly used time-domain analysis. This is very powerful since the frequency domain is the domain of experimental pulse shaping. Indeed, it led us to identify special families of pulse shapes, which at intermediate fields enhance the two-photon absorption and exceed the absorption induced by the transform-limited pulse (see figure). This is not possible in the weak-field regime. Based on all these studies, we implemented the computational task of identifying the anti-symmetry character of a given arbitrary numerical function: anti-symmetric, constant, or neither. The multiphoton absorptions in Na were used to efficiently characterize an unknown driving shaped pulse, into which the function is optically encoded in the spectral phases.
Long-Range Hydrodynamic Response of Particulate Liquids and Liquid-Laden Solids

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In viscous particulate liquids, such as suspensions and polymer solutions, the large-distance steady-state flow due to a local disturbance is commonly described in terms of hydrodynamic screening -- beyond a correlation length $\xi$ the response drops from that of the pure solvent, characterized by its viscosity $\eta_0$, to that of the macroscopic liquid with viscosity $\eta > \eta_0$. For cases where $\eta >> \eta_0$ we show that this screening picture, while being asymptotically correct, should be refined in an essential way. The crossover between the microscopic and macroscopic behaviors occurs gradually over a wide range of distances, $\xi < r < (\eta/\eta_0)^{1/2} \xi$. In liquid-laden solids, such as colloidal glasses, gels and liquid-filled porous media, where $\eta$ diverges, this intermediate behavior takes over the entire large-distance response. The intermediate flow field has several unique characteristics: (i) It has a dipolar shape with a $1/r^3$ spatial decay, negative transverse components, and vanishing angular average. (ii) Its amplitude depends on the liquid properties through $\eta_0$ and $\xi$ alone; thus, in cases where $\xi$ is fixed by geometry (e.g., for particulate liquids tightly confined in solid matrices), the large-distance response is independent of particle concentration. (iii) The intermediate field builds up non-diffusively, with a distance-independent relaxation rate, making it dominant at large distances before steady state has been reached. These general properties are demonstrated in several model systems.
Site-Directed Electronic Tunneling Through a Molecular Network

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Electronic tunneling in a molecular network of donor-acceptor sites, connected by molecular bridges is analyzed. A network of N donor-acceptor sites is mapped onto an N-level system using a recursive perturbation expansion, valid for the "deep tunneling" regime. The formulation is applied to a linear arrangement of three sites corresponding to a donor and two acceptors. It is shown that the contact unit at the donor site can be tuned in order to control the tunneling dynamics and particularly to switch the tunneling pathway to either one of the two possible accepting sites. Numerical simulations demonstrate that this tunneling switching phenomenon can be controlled by various parameters including on-site energy, electronic hopping matrix elements and electronic coupling to nuclear vibrations at the donor-bridge contact.

The common behavior observed in different models for the specific nature of the donor-bridge contact suggests that the effect of tunneling switching is not sensitive to a particular model and is likely to be observed in realistic molecular systems. Moreover, the effect of electronic-nuclear coupling in controlling the electronic tunneling dynamics through the molecular network is emphasized, suggesting its importance for the design of controllable molecular electron transfer networks.

Keynote Lecture

New Methods for the Preparation of Enantiomerically Pure Quaternary Carbon Centers

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Recent strategies and advances in the design and development of new asymmetric transformations will be presented. Specifically, the preparation of chiral quaternary carbon centers in the carbonyl allylation and aldolization reactions will be discussed in detail. The key features in these reactions are the high degree of stereocontrol, the level of predictability and the ease of execution.
Ion-Coupled Electron Transfer in Green Chemistry and Catalysis

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Energies and rates of electron-transfer processes are frequently controlled by seemingly innocent ions (alkali-metal cations or H⁺). This is true for electron-transfer reactions in molecular catalysis, as well as between the nanoscale domains of electronic devices and within biological macromolecules. Examples include Li⁺ intercalation upon electron injection into nanoporous TiO₂ in dye-sensitized photochemical energy-conversion devices, protonation of Pt-bound O₂ at the anodes of H₂ and MeOH fuel cells, H⁺-bonding between bound water molecules and superoxide anion (O₂⁻) during electron transfer from Fe(II) to O₂ in the active site of methane monooxygenase (MMO), and Na⁺-gated electron “hopping” in DNA. In numerous such cases, no simple mathematical models (e.g., the Marcus model) are applicable, and very little quantitative data are available. Fundamental studies of model reactions relevant to the above processes are one focus of research in our laboratory. In these investigations, redox-active Keggin heteropolytungstate cluster–anions are deployed as well-defined kinetic and mechanistic probes. In the present lecture, conclusions and insights drawn from several of these studies will be presented, along with new, unpublished, findings. Issues addressed include: (1) the mechanism by which alkali-metal cations, M⁺, accelerate electron transfer to electron acceptors within dynamic [(M⁺)(Acceptor)] ion pairs, and (2) the validity of conventional notions regarding the innocence of the “solvent cage” within which aqueous electron-transfer processes occur.
Two New Applications of Sol-Gel Technology to Organic Synthesis: Catalysis
with Hydrophobic Substrates in Aqueous Microemulsions and
Hydrodenitrogenation of Carcinogenic Polycyclic Nitroarenes

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Sol-gel technology has been shown to be of great asset to organic synthesis: it facilitates separation and recycling of organometallic catalysts, it protects vulnerable reactants from destructive environmental pollutants and it enables performing one-pot multi-step reactions with opposing chemicals [1]. We now report on the utilization of sol-gel entrapped catalysts in two additional areas (i) the performance of catalyses with hydrophobic reactants in aqueous media, and (ii) the hydrodenitrogenation of carcinogenic nitro compounds under mild conditions. Selective hydrogenation, hydroformylation, Suzuki, Stille and Heck coupling reactions with hydrophobic substrates and catalysts can be carried out by transforming the water insoluble reactants into microemulsions by suitable surfactants. The reactants are then adsorbed/desorbed by the porous sol-gel matrix in which the reaction takes place and the products are returned by the empty surfactant to the emulsion from which the product can be separated. Carcinogenic 2-nitronaphthalene, 9-nitroanthracene, 1-nitropyrene and 6-nitrochrysene are hydrogenated at 80-140°C by sol-gel entrapped catalysts composed of nanoparticles of Pd and [Rh(cod)Cl]2 to give initially the corresponding amino-arenes that are converted into a mixture of primary and secondary amines. While the primary amines lose NH3 to directly give benign alicyclic compounds, the secondary amines add in the closed system NH3 to give degradable primary amines.

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**Synthesis of Silicon Peptide Analogs via Novel α-Aminosilyllithiums**

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Although silicon is the second most abundant element, (after oxygen), in the earth's crust its participation in the life forms on Earth is rather small and life on Earth is carbon-based. This fact is interesting because silicon is the closest analog of carbon in the Periodic Table of elements. Can one envision biological-type behavior based on silicon? To answer this question we embarked on a program to synthesize silicon based peptides, i.e., peptides having silicon in the most important α-carbon position. In the lecture we report the preparation and structural characterization of the novel α-aminosilyllithium reagents of type 1 and their reactions with carbamoyl chlorides and chloroformates; the key step in the synthesis of 2 - a Si- analog of C-terminal protected amino acids and dipeptides, e.g., 3, which is a dipeptide of 2 with glycine (eq. 1). In addition initial experiments to test the biological activity of 4 that was prepared by a similar reaction (eq. 2), and in which a hypersilyl residue is connected by a peptide bond to a proline-ethyl-ester, will be reported.
The Chemistry of Cobaloximes

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We have synthesised and characterised 38 novel cobaloximes of the general type Co(dmgH)₂XL, where dmgH = dimethylglyoximato, X = NO₂, Cl and L = substituted pyridine or pyridine derivative. From the single crystal X-ray diffraction characterisation several trends in the packing patterns have been observed and will be discussed. From the IR and ¹H NMR data it has been seen that changes in the position of the substituent and the basicity of the substituent do not affect the observed trends, but rather they are limited to the subclass of substituent. These trends will be discussed and may be used as the basis for future identification of cobaloximes. In addition, a new synthetic route to chloro-cobaloximes has been devised and successfully tested, to produce a 5 new cobaloximes parallel to their nitro analogues.
Keynote Lecture

**Protein S-nitrosylation: Purview, Parameters, and Therapeutic Potential**

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S-nitrosylation, the covalent attachment of an NO group to the thiol side chain of cysteine, has emerged as an important mechanism for dynamic, posttranslational regulation of most or all classes of protein. S-nitrosylation thereby conveys a large part of the ubiquitous influence of NO on cellular signal transduction, and provides a prototypic example of redox-based physiological regulation. Accumulating evidence suggests that alterations in S-nitrosylation-regulated signaling contribute to human disease.
BL-1020: A Dopaminergic Antagonist with Agonistic GABAergic Activity as a Potential Novel Drug for the Treatment of Schizophrenia

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The clinical manifestations of schizophrenia are related to dopaminergic hyperactivity and dysfunction of the central nervous system inhibitory GABAergic neurons. BL-1020, a mutual prodrug of perphenazine and GABA, is an orally active dopaminergic antagonist with GABAergic activity that is being developed for the treatment of schizophrenia. In our studies the pharmacologic properties and therapeutic effectiveness of BL-1020 in animal models of schizophrenia were investigated. In radioligand binding studies, BL-1020 displayed strong interaction with dopamine receptors especially D2L and D2S (K_i of 0.27 nM and 0.17 nM respectively), the serotonin receptor 5-HY2a (K_i 0.25 nM) as well as moderate interaction with the GABAA receptor (K_i 3.29 microK). BL-1020, after oral administration, crosses the blood brain barrier intact and is metabolized to GABA and perphenazine. BL-1020 significantly increases the secretion of prolactin in rats confirming the in vivo dopamine antagonistic effects. BL-1029 reduces amphetamine-induced hyperlocomotion to the same degree as perphenazine when both are administered at equimolar doses. In comparison to perphenazine, the incidence of cataleptic manifestation was low. The effect is long-lasting as the anti-cataleptic effects of BL-1020 persisted for up to 17 days of daily administration. In contrast to other GABAergic drugs, BL-1020 did not have sedating effects when administered in therapeutic doses up to 20 mg/kg. The results of these studies indicate that BL-1020 possess both the characteristics of a first generation anti-psychotic and a GABAergic agonist, and has the potential to be a prototype for a new class of anti-psychotic agents.

In recently completed Phase I clinical studies with healthy volunteers, BL-1020 was shown to elicit an improved toxicity profile to that of equimolar amounts of perphenazine.
Synthetic Probes for the Elucidation of Molecular Mechanisms in Bacterial Quorum Sensing

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Quorum sensing has evolved as a means for bacterial communities to rapidly and coordinatively adjust gene expression patterns in response to environmental cues. Each cell in a population not only produces signaling molecules, called autoinducers, but also responds to these molecules which serve to indicate population density. Quorum sensing (QS) is one mechanism through which bacteria can control many important functions including motility, sporulation, virulence and biofilm formation. QS systems exist in both gram-positive and -negative bacteria and a variety of oligopeptides and N-acyl-homoserine lactones have been identified as autoinducing molecules. One autoinducer distinct from all other signaling molecules identified to date is a small molecule termed AI-2 (derived from the precursor molecule (S)-DPD). This compound is unique as it appears to be utilized by both Gram-positive and -negative bacteria. However, AI-2’s apparent function and global importance in QS is still not fully understood. More than 60 bacteria produce AI-2, including many clinically relevant pathogens. Important questions regarding the mechanisms that bacteria use to communicate are still unanswered, and the effects of chemical interference with QS have barely been studied. An important question is: can we attenuate bacterial group behavior effectively using chemical means? In other words, can we trick bacteria into ‘thinking’ they are continuously at low cell density, thereby turning off their defense mechanisms and minimizing their pathogenicity? We have started to probe the AI-2 signaling machinery as a model system, and several synthetic analogs of AI-2 and DPD and metal complexes with this molecule have been synthesized and evaluated.
**Shiftides: LEDGF/p75-derived Peptides that Inhibit HIV-1 Replication by Shifting the Oligomerization Equilibrium of the Viral Integrase**

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The interaction of the HIV-1 integrase (IN) with LEDGF/p75 is an emerging therapeutic target for anti-HIV drugs. Here we show that LEDGF/p75-derived peptides inhibit IN in a non-competitive mechanism. We present a new concept for inhibition of proteins by "shiftides": inhibitory peptides that act by specifically binding to an inactive oligomeric state of a disease-related protein and shifting the oligomerization equilibrium of the protein towards it. Using biophysical, biochemical and cellular studies, we show that LEDGF/p75-derived peptides are shiftides that inhibit the DNA-binding of IN by shifting its oligomerization equilibrium towards the tetramer that is unable to catalyze the first integration step of 3'-end processing. The LEDGF/p75-derived peptides inhibit the enzymatic activity of IN in vitro and consequently block HIV-1 replication in cells. These peptides are promising anti-HIV lead compounds. We propose the shiftide approach as a new general methodology for drug design.
Enzyme Isoselective Inhibition Trend Analysis: A New Method for Drug Design

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Common methodologies of computer assisted drug design focus on enzyme-ligand non-covalent interactions. We introduce enzyme isoselective inhibition trend analysis as a methodology for analysis of covalent, reversible inhibitors. Such inhibitors can be formally treated as comprised of two parts: the chemical site, CS, which interacts covalently with the enzyme, and the non-covalent recognition site, RS. We have experimentally and theoretically characterized the dependence of the binding affinity trend in series of isoselective inhibitors (with identical RS and different CS fragments) on their CS fragments. Thus, very good correlation between experimentally determined and theoretically calculated Ki values was demonstrated. The methodology was applied to predict binding affinities of series of isoselective transition-state analog inhibitors of medicinally important enzymes. The methodology could be applied for virtual screening of inhibitor libraries and for drug design.
This lecture will focus on the role of nanotubes of several types in the composites area. Indeed, carbon nanotubes hold great promises as a possible reinforcing phase in composite materials of a new kind. Recent experimental and theoretical results regarding materials mechanics at the nanoscale will be reviewed. The main theme includes carbon and tungsten sulfide nanotubes, and nanotube-based composite materials. Such developments still present enormous practical challenges, in particular: (1) when attempting to probe the properties of individual nanotubes, for which most — but not all — studies consist of computer simulations, and (2) when attempting to optimize the mechanical properties of nanocomposites. We report in this lecture our most recent laboratory results regarding polymer-nanotube composite mechanics, including interfacial adhesion issues. The principle and potential use of nanotubes as sensors in composite structures is also briefly outlined.

Silicon Nanowire-based Electrical Devices in Biomedical Applications: ‘Nanotechnology Meets Biology’

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The lecture will focus on large-scale, label-free, real-time multiplexed electrical detection of proteins and viruses by silicon nanowire field-effect transistor arrays. Receptor-functionalized nanowire device arrays show discrete conductance changes characteristic of highly selective binding and unbinding of multiple target biomolecules, thus providing a general and powerful tool for parallel real-time detection and screening of libraries of biomolecules. Arrays of both p-type and n-type silicon nanowire devices enable discrimination against false positive signals, and fluorescence labeling was also used to verify electrical responses down to the single particle level. Tens of toxins/proteins have been simultaneously detected in arrays with femtomolar sensitivity, while studies of viruses have demonstrated simultaneous and selective detection of influenza-A and adenovirus at the single virus level. The integrated nanowire sensor arrays open up substantial opportunities for diagnosis and treatment of complex diseases, such as cancer, detection of biological threats, and fundamental biophysical studies.

In addition, I will discuss about arrays of n- and p-channel nanowire devices that can interact with mammalian neurons grown in vitro. Our nanowires can be configured to behave as (a) locally gated field-effect transistors (FETs) that are capable of measuring extracellular neuronal signals, and (b) stimulator electrodes that can be used to stimulate neurons, hence eliciting action potentials. These data suggest that our nanowire recorders are good electronic probes of local neuronal activity.
Supramolecular Assembly of Cytoskeleton Proteins

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At present there is a surge in interest in biophysical research in elucidating collective interactions between cellular proteins and associated biomolecules leading to supramolecular structures, with the ultimate goal of relating structure to function. The nerve cell cytoskeleton, provides a rich example of highly ordered bundles and networks of interacting neurofilaments, microtubules (MT) and filamentous actin, where the nature of the interactions, structures and structure-function correlations remain poorly understood. We present synchrotron x-ray diffraction, electron microscopy, and optical imaging data, in reconstituted protein systems from the bovine central nervous system, which reveal unexpected structures not predicted by current theories of polyelectrolyte bundling, including 3D MT bundles and 2D MT necklaces and bionanotubes with open or closed ends.
On-Chip Integration of Cell-Free Gene Expression

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We present a synthetic approach for the study of gene networks in vitro which is complementary to traditional in vivo methodologies. We have developed a technology for submicron integration of functional genes and on-chip protein synthesis using a cell-free transcription/translation system. The interaction between genes is facilitated by diffusion of on-chip gene expression products from ‘source’ genes towards ‘acceptor’ genes. We examine cooperative effects of transcription from dense DNA brushes. Our technology is simple and inexpensive and can serve as an improved platform for a wide variety of protein and DNA biochip applications.
Nanoparticles Formed by Polymer-Surfactant Interactions

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Nano- and microparticles formed by interactions between a polycation and an anionic surfactant in an aqueous solution were evaluated. The polymer-surfactant interaction is based on electrostatic attraction, which usually leads to phase separation. However, we found that at certain concentrations, nanoparticles are formed without precipitation. The interaction between the polymer and surfactant was studied by light scattering and ζ-potential measurements. The nature of the resulting nanoparticles was revealed by direct-imaging-cryogenic temperature transmission electron microscopy (cryo-TEM), showing nanometric details of the complexes formed around the point of neutralization. The images also reveal how those aggregates are solubilized by excess surfactant into different structures, and finally into spheroidal micelles. The nanostructure of the particles strongly suggests they are made of hexagonal liquid crystalline phase. This was further supported by small-angle X-ray scattering (SAXS).

Since the nanoparticles may be used as a powder, the external morphology of the dried polymer-surfactant nanoparticles was observed using AFM and SEM. The particles were shown to be spherical in shape, having a diameter of less than 100nm. The particles capability to solubilize hydrophobic molecules was examined using two probes, Pyrene, a fluorescence probe, and Nile Red, a solvatochromic probe. The probes yielded information regarding the solubilization process, and other parameters such as CAC and micropolarity.
Bohmian Mechanics with Complex Action: A New Trajectory Based Formulation of Quantum Mechanics

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Ever since the advent of Quantum Mechanics, there has been a quest for a trajectory based formulation of quantum theory that is exact. In the 1950’s, David Bohm, building on earlier work of Madelung and de Broglie, developed an exact formulation of quantum mechanics in which trajectories evolve in the presence of the usual Newtonian force plus an additional quantum force. In recent years, there has been a resurgence of interest in Bohmian Mechanics (BM) as a numerical tool because of its apparently local dynamics, which could lead to significant computational advantages for the simulation of large quantum systems. However, closer inspection of the Bohmian formulation reveals that the nonlocality of quantum mechanics has not disappeared — it has simply been swept under the rug into the quantum force. In this work, we present a new formulation of Bohmian mechanics in which the quantum action, $S$, is taken to be complex. This requires the propagation of complex trajectories, but with the reward of a significantly higher degree of localization. The method is particularly well-suited for tunneling processes, where even a small number of strictly localized trajectories (i.e. no communication with their neighbors) is sufficient to obtain virtually exact quantum mechanical tunneling probabilities down to $10^{-7}$. The method is applied to one- and two-dimensional tunneling, thermal rate constants in one and two dimensions, and the calculation of eigenvalues. On the formal side, the approach is shown to be a rigorous extension of semiclassical Gaussian wavepacket methods to give exact quantum mechanics and has intriguing implications for fundamental quantum mechanics.
Confinement effects on the Stimulated Dissociation of Molecular Bose-Einstein condensates

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We show that a molecular Bose-Einstein condensate in a trap is stabilized against stimulated dissociation if the trap size is smaller than the resonance healing length. The condensate shape determines the critical atom-molecule coupling frequency. We discuss an experiment for triggering dissociation by a sudden change of coupling or trap parameters. This effect demonstrates one of the unique collective features of 'superchemistry' in that the yield of a chemical reaction depends critically on the size and shape of the 'reaction vessel'.
A Density Functional that Works Across the Board

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We describe some serious deficiencies in standard density functional theories and their time-dependent extensions. We then describe the theory for constructing a new functional having 2 parameters. We semi-empirically tune these parameters using atomization energies and ground-state bond lengths. The resulting functional is shown to be very accurate for many types of properties of molecules, including excited states and even Rydberg excitations.
Selective Optical Addressing of Close Molecular Species: The Cases of N$_2$ Molecular Isotopologues and Para/Ortho Spin Isomers

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We experimentally demonstrate a new approach to selective excitation of close molecular species in a mixture. Following excitation by an ultrashort, strong laser pulse, the molecules are repetitively aligned (depending on their rotational constants, ~8 psec for nitrogen). In our double-pulse scheme, the first pulse excites both components in a binary mixture, and the second one de-excites one while enhancing the excitation of the other. The application of another strong, linearly polarized pulse, will preferentially dissociate/ionize the selected molecular component, thereby enrichment of the sample becomes feasible. This process is nonresonant and does not require any special conditions like temperature etc. this approach is general and can be applied to most linear molecules.

In our work we implemented this approach to molecular isotopologues and spin isomers. The case of molecular isotopes is easy to understand since it is based on the slight difference in the masses of the molecular components, and based on the periodic process of repetitive alignment, one can distinguish between the isotopic components and selectively affect them. The case of spin isomers is more complicated since there are no differences in the mechanical or electrical properties of the spin isomers to be selectively controlled. Here we utilize the symmetry and statistics of the specific molecular wavefunction and demonstrate selective excitation of ortho/para nitrogen using non resonant laser pulse and at room temperature.
Tight Binding-Configuration Interaction (TBCI): A Non-Iterative Method to Incorporating Charges into Tight Binding

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The study of reactions and other processes in large molecules, clusters, solids and other condensed-phase materials, especially those including metal atoms, poses many unique quandaries. As one considers larger and more complex systems, the systems become too large to model with Density Functional Theory (DFT) or other reliable quantum chemical methods. Therefore, a different approach is required. One approach that is gaining popularity in recent years is to apply the semi-empirical Tight Binding (TB) method. We have developed a series of TB methods to study aluminium nanoparticles.¹ One disadvantage of these TB methods is that they do not take charges into consideration. One consequence of this is that they do not predict, in contrast to experiment, neutral dissociations of aluminium clusters. Herein, a novel form of TB, coined Configuration Interaction-Tight Binding (TBCI), will be presented. This method blends the concepts of TB with the accurate Configuration Interaction (CI) method. In contrast to other schemes used to incorporate charges, such as the self-consistent charge (SCC) model,² this method is non-iterative. This method will be presented along with the results obtained for aluminium and aluminium-hydrogen nanoclusters.


**Keynote Lecture**

**Chiral Lanthanide Clusters with Unique Luminescent and Magnetic Properties**

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Despite two decades of intensive study, lanthanide coordination chemistry continues to attract great attention and continues to surprise chemists by its fascinating structures, as well as rare combinations of optical, catalytic and magnetic properties. Nevertheless, the kinetic labiality and large ionic radii of the lanthanide ions along with weak, largely ionic coordinative preferences presents a major challenge in utilizing lanthanide luminescence to its full potential. A conceptually new approach in ligand design, to improve the inherent instability observed in lanthanide complexes, will be introduced.

Recent results regarding structure of tri- and seven-lanthanide complexes (see Figure), their chirality, as well as luminescent and magnetic properties will be presented and future potential applications outlined.
Synthesis and Study of First Highly Conductive Polyselenophenes: Poly(3,4-ethylenedioxyseleuno(phene)

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Owing to its excellent electronic properties (electrical conductivity, electrochromic properties, relatively low band gap, etc.) and high stability, poly(3,4-ethylenedioxythiophene) (PEDOT) is the most studied and the most industrially important conjugated polymer. We have developed a new, general and efficient synthetic strategy for the selenium analog of PEDOT, namely, poly(3,4-ethylenedioxyseleuno(phene) (PEDOS: 1) (Scheme 1). A selenophene core has been constructed for the first time by reaction of 2,3-dimethoxy-1,3-butadiene with SeCl2. PEDOS has been prepared using four different polymerization techniques: oxidative chemical polymerization, solid-state polymerization, transition metal-mediated polymerization and electrochemical polymerization. Our synthetic strategy has also been extended to the synthesis of PEDOS analogs (2-4). PEDOS is stable, completely insoluble in all common organic solvents, shows a π-π* transition on-setting at around 900 nm and has a conductivity of about 10 S cm⁻¹ (measured by the two probe method) after doping. The spectroelectrochemically measured band gap of PEDOS is ca. 1.3-1.4 eV, which is in excellent agreement with our calculated (PBC-B3LYP/6-31G(d)) value.

Scheme 1. Synthesis of 3,4-ethylenedioxyseleuno(phene and its subsequent polymerization to produce PEDOS.
Ionic Liquid Stabilized Metallic Nanoparticles Microencapsulated in Polyurea Matrix as Novel Hydrogenation Catalysts

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The entrapment of palladium acetate in polyurea microcapsules was described and patented by Ley and coworkers in 2002. The product was commercialized under the trademark Pd(II)EnCatTM. In recent two independent studies Jones and McQuade have unequivocally established that the Pd(II)EnCatTM, allegedly heterogeneous catalysts, are merely a reservoir of active metal released to the reaction solution and act as soluble homogeneous catalyst. Evidently, the encapsulated Pd itself had no catalytic activity whatsoever. To overcome the above leaching problem we have now changed the concept and encapsulated reduced Pd(II) and Ru(II) nanoparticles, stabilized in liquid tricaprylmethylammonium chloride medium, in a linear polyurea matrix. The latter was achieved via catalytic interfacial polymerization of 4,4’ diphenylmethane diisocyanate (MDI) in water-toluene interphase. The obtained hybrid catalyst was characterized and demonstrated to function as a highly robust, recycleable and active heterogeneous catalyst in several hydrogenation and hydrogenolyis processes.
Catalytic Addition of Si-H and N-H Bonds to Unsaturated Hydrocarbons Mediated by Early Transition Metal Complexes

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Addition of O-H and X-H (X = halogen) bonds to unsaturated carbon–carbon bond are classified as basic reactions in organic chemistry and appear probably in any introductory organic textbook. Carbon-heteroatom bonds formation reactions, involving olefins and alkynes, are important synthetic transformations in organic chemistry. That makes the catalytic addition of amine or silicon hydride to such bonds a highly desirable process.

A simple catalytic N-H bond addition to unsaturated carbon-carbon multiple bond, the hydroamination reaction, offers an efficient synthetic route to amines, enamines and imines which are important bulks and fine chemical building blocks in organic chemistry. Over the years, a great deal of effort has gone into finding the most efficient catalysts that will promote this process. Among the different catalysts for the hydroamination, group IV metal catalysts have proved widespread interest, due to their general reactivity and ubiquitous availability compared to toxic metals (such as Hg, Tl, U, and Th), or more expensive lanthanides and late transition metal complexes (Ru, Pd, Rh, Pt and Ag).

Catalytic addition of a Si-H bond to unsaturated carbon-carbon multiple bonds, the hydrosilylation reaction, is a widely used synthesis of organosilicons and has many advantages over the classical organic methods. Organosilicon compounds are used as building blocks in the manufacture of adhesives, binders and as coupling agents. Organosilicons are also used in research laboratories as starting materials in a synthesis of polymeric and dendrimeric materials.

Here we present new group-IV based catalysts that already are commercially available complexes that can perform these two transformations in high efficiency and chemo- and regio- selectivity. The scope and mechanisms of the reactions will be presented.
Radiolytic and Electrocatalytic Dehalogenation Processes in Aqueous Solutions

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The halo-aromatic compounds are hazardous pollutants due to their persistence in the environment. The electrocatalytic and radiocatalytic reduction of several bromo and chloro-alkanes and aromatics by \textit{NiI}-tetraazamacrocyclic complexes were studied.

Furthermore it is shown that formate radicals (produced radiolytically) catalyze the dehalogenation of bromo-alkanes by formate via a hydrogen atom transfer mechanism. Detailed mechanistic studies will be presented.
Keynote Lecture

Molecular Engineering of Cellular Environments: Cell Adhesion to Nano-Digital Surfaces

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Engineering of cellular environments has become a valuable tool for guiding cellular activity such as differentiation, spreading, motility, proliferation or apoptosis which altogether regulates tissue development in a complex manner. The adhesion of cells to its environment is involved in nearly every cellular decision in vivo and in vitro. Our approach to engineer cellular environments is based on self-organizing spatial positioning of single signaling molecules attached to inorganic or polymeric supports, which offers the highest spatial resolution with respect to the position of single signaling molecules. This approach allows tuning cellular material with respect to its most relevant properties, i.e., viscoelasticity, peptide composition, nanotopography and spatial nanopatterning of signaling molecule. Such materials are defined as “nano-digital materials” since they enable the counting of individual signaling molecules, separated by a biologically inert background. Within these materials, the regulation of cellular responses is based on a biologically inert background which does not trigger any cell activation, which is then patterned with specific signaling molecules such as peptide ligands in well defined nanoscopic geometries. This approach is very powerful, since it enables the testing of cellular responses to individual, specific signaling molecules and their spatial ordering. Detailed consideration is also given to the fact that protein clusters such as those found at focal adhesion sites represent, to a large extent, hierarchically-organized cooperativity among various proteins. Moreover, “nano-digital supports” are capable of involvement in such dynamic cellular processes as protein ordering at the cell’s periphery which in turn leads to programming cell responses.
Membrane Shape Driven by Actin and Myosin: Waves and Quantized Division

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We present a model which couples the membrane with the protrusive forces of actin polymerization and contractile forces of molecular motors, such as myosin. The actin polymerization at the membrane is activated by freely diffusing membrane proteins, that may have a distinct spontaneous curvature. Molecular motors are recruited to the polymerizing actin filaments, from a constant reservoir, and produce a contractile force. All the forces and variables are treated in the linear limit, which allows us to derive analytic solutions. Our results show that for convex membrane proteins the myosin activity gives rise to propagating membrane waves similar to those observed on different cells. For concave membrane proteins the myosin activity gives rise to an unstable contraction, which yields a length-quantization of the mitosis process.
Sticky Matter: Algal Adhesives and Their Bio-mimetic Analogs

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Tissue repair following surgery or trauma has been dominated by sutures, staples and wiring. Although these techniques are well established and widely used, their application often involves pain, unaesthetic results, or bleeding. These limitations emphasize the need for adhesive products to be available to surgeons.

A challenging aspect of developing new tissue adhesive is to create a material that can glue wet surfaces. The success of synthetic glues under such an environment is very limited. On the contrary, many marine sessile organisms produce adhesives that effectively stick to almost any wet surface. We have studied adhesive materials formulated from phenolic polymers extracted from the brown alga Fucus Serratus. Shear-lap tests demonstrated that the polyphenol forms contact point with the surface, however hardening with alginate and/or calcium is essential for high cohesive strength. Further insight into the mechanism of glue formation was obtained from scattering and electron microscopy experiments. These have shown that the phenolic polymer self-assembles and forms flexible chain-like objects. This structure does not change upon enzymatic cross-linking or addition of alginate. However, once the alginate is cross-linked with calcium ions, a rigid network is formed. Presumably, this network is responsible for the cohesive strength of the glue.

Inspired by these findings we have developed a bio-mimetic analog composed of a synthetic phenol, alginate and calcium ions. The adhesion properties of the bio mimetic glue are comparable to these of the natural adhesive.
Biomimetic Organic-inorganic nanocomposite Coatings for Artificial Implants. Preparation and Characterization

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Biomimetic coating of the surfaces of bioinert materials (metals, polymers) with calcium phosphate crystals has been used to improve bioactivity and facilitate osteointegration of artificial bone implants. A novel approach consists in first laying down a matrix consisting of polyelectrolyte multilayers (PE MLs) alternating with layers of amorphous calcium phosphate (ACP) particles and subsequently growing calcium phosphate crystals upon/within this matrix. This attractive approach leads to the formation of a new class of true organic-inorganic nanocomposite coatings.

The coatings were prepared on titanium plates by alternate adsorption of PE MLs [poly-L-lysine (PLL) and poly-L-glutamic acid (PGA)] and layers of ACP particles, adsorbed from freshly prepared suspensions. The thus obtained materials were immersed into a metastable calcifying solution to initiate and sustain “in situ” crystal growth of nano-crystalline apatite. Multilayer build-up was followed by optical waveguide lightmode spectroscopy (OWLS), while the nanocomposites were visualized by SEM and characterized by EDX and thin layer XRD.

The general formula of the nanocomposite is (PLL/PGA)_n CaP [(PLL/PGA)_(n-m) CaP]_(n-m+1) (PLL/PGA)_(n-m). Addition of ACP particles during build-up of PE multilayers significantly changed their growth regime, indicating mutual PE-ACP interactions. Good cellular response was obtained from coatings containing a final PLL-PGA multilayer, rather than a final calcium phosphate layer. Such coatings have relatively smooth surfaces. EDX spectra show peaks characteristic of Ca, P, O, C and N and Ti with average atomic ratios C/Ti = 208.8 ± 46.4 and Ca/P = 1.46 ± 0.09, while thin layer XRD spectra show characteristic peaks of apatite. The adhesive tape test (ASTM D 3359-92a) showed good adherence of the material to the substrate surface. The procedure is largely independent of type and topology of the substrate, thus the coatings can be applied to a wide variety of implant materials.
Chemical and Mechanical Probing of the Structural Organization of Hyaluronan in the Pericellular Matrix

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The pericellular coat, a layer of cell-surface anchored glycosaminoglycans (GAG), proteoglycans, and proteins is the first to be involved in cell-substrate or cell-cell interaction in developing adhesions. Understanding this process requires detailed information on the architecture of the coat. Our approach to this challenge is threefold: by the synthesis of in vitro model systems, by electron microscopy of chemically induced transitions on fixed cells, and by direct mechanical probing of the coat on live cells using laser tweezers.

We demonstrate here that a lanthanide cation induced temperature-dependent transition in conjunction with variable temperature “wet mode” ESEM as an imaging technique is a promising tool for the investigation of complex, highly hydrated matrices both in model systems and in situ, i.e. on the cell. We provide a semi-quantitative analysis for structural differences of pericellular coat organization on two different cell types, i.e. chondrocytes and A6 epithelial cells, where the principal component is the GAG hyaluronan. These findings are complemented by mechanical probing of of the pericellular coat using laser tweezers. This allows us to directly investigate the native coat on live cells, and adds critical information with regard to the elastic and viscous properties of this complex material. We interpret the combined data as indicating a dense, possibly endgrafted, brushlike arrangement of hyaluronan on A6 as opposed to a less dense, entangled, and elastic network on chondrocytes.
Materials and Nano II

Keynote Lecture

Plasmonics: Optical Properties of Nanostructured Metals and its Applications

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Materials structured on the nanometer scale can lead to improved and sometimes surprising properties. Metals are no exception to this rule. Metal particles for instance display colours which vary with their size. The colour results from the coupling of light with the free electrons of the metal particle to form surface plasmons. On a broader level, with modern nanofabrication techniques it is possible to tailor the structure of metals and thereby to control the properties of surface plasmons opening many new possibilities.

The potential of nanostructured metals will be illustrated in some detail by our own work on the extraordinary optical properties acquired by metal films if they are simply structured with one or more voids and periodic corrugations. Metallic films perforated with sub-wavelength holes (~150 nm) can transmit the light with an efficiency hundred times larger than what classical theory predicts for single holes. The efficiency can even be larger than the fractional area of the holes, which means that even the light falling beside the holes emerges on the other side of the sample. This extraordinary transmission is due to the coupling of the incident light with the surface plasmons of the film. Such results raise fundamental issues and have practical implications in many areas including chemistry where it can be used to strongly enhance spectroscopic signals.
Individual single walled nanotubes (SWNT) are characterized by excellent mechanical electrical and thermal properties. While of great potential, a major obstacle for CNT (carbon nanotube) utilization is their tendency to aggregate. SWNT pack into bundles or "ropes" that typically contain 100-500 SWNT arranged in a close packed triangular lattice held by dispersion forces. The over-micron long ropes and MWNT further entangle into networks, rendering the tubes insoluble in aqueous and organic liquids, and thus almost un-processable. Development of efficient pathways for de-agglomeration and formation of stable dispersions of individual tubes in liquid media and polymeric matrices has been identified as one of the major challenges in the field of SWNT based material science and engineering. Strategies developed for exfoliating bundled SWNT and dispersing the tubes include approaches that rely on (severe to mild) modification of the extended graphene π-system (the origin of the strong dispersion attraction) leading to modification of the electronic structure and consequently the physical properties of the dispersed tubes. An alternative more tender approach is offered by physically adsorbed block-copolymers. We present a non-wrapping approach leading to the formation of stable dispersions of SWNT and multi walled carbon nanotubes (MWNT) in solutions of block-copolymers. Theoretical modeling and simulations, carried out by I. Szleifer et al., suggest that the adsorption energy and the consequential conformation of the adsorbed layer results in a steric barrier that prevents aggregation of the nanotubes, and coagulation of the dispersions. Our studies offer a generic scheme for optimization of the structure and composition of block copolymers used for dispersion of CNT in different media.
Co-Electrospinning of Core-Shell Polymer Nanofibers and Nanotubes

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Advanced techniques, such as electrospinning and co-electrospinning, have recently been established to yield nanofibers and core-shell fibers from natural and synthetic polymers with diameters as small as a few nanometers. In co-electrospinning, a syringe with two compartments containing different polymer solutions or a polymer solution (shell) and a non-polymeric liquid or powder (core) is used to initiate a core-shell jet (Fig. 1). At the exit of the core-shell needle attached to the two-compartment syringe appears a core-shell droplet. Being subjected to sufficiently strong electric field, it issues a compound jet, which undergoes the electrically-driven bending instability characteristic of the ordinary electrospinning process. Strong jet stretching resulting from the bending instability is accompanied by enormous jet thinning and rapid solvent evaporation, with core-shell nanofibers depositing on a counter-electrode. The experiments showed that for a stable co-electrospinning process both fluids should be electrified as shown in Fig. 1. Only then the electrical pulling forces create compound jets. Purely viscousentrainment of one of the fluids by another one appears to be difficult for stabilizing the process. The core-shell structure transformation into hollow fibers (nano-tubes) is primarily based on evaporation of the core solvent, or during post-processing such as solvent extraction or calcination with the shell of the fiber remaining intact (Fig 2). These as-spun core-shell nanofibers and nanotubes are of potential interest in the development of novel polymer-based structures and microfluidics. In particular, co-electrospinning of core-shell nanofibers allows encapsulation of catalytic and magnetic nanoparticles, chromophores, enzymes, proteins, cell growth factors, and living cells, directly during the electrospinning process.
The anti-corrosive properties of lead, its low melting temperature and good ductility have made it a much-used material since antiquity — for pipes, for example, but the metal does degrade, if only very slowly. We have exploited that characteristic to propose a new dating method for lead archaeological artifacts.

**Hypothesis:** The mass of corrosion per unit area of a lead artifact is correlated to its "archaeological age".

**Method:** We use the Meissner effect, i.e., total expulsion of a weak magnetic field from the interior of the lead metal in the superconducting state. This state is obtained for lead at temperatures below 7.2K. This ideal diamagnetic response serves to establish the volume of the uncorroded lead; knowing the density of lead, its mass is obtained. The diamagnetic contribution of the corrosion products is more than 10,000 times smaller than that of lead metal as the corrosion products of lead are not superconductors and thus can be ignored. Weighting the artifact - mass of corrosion + mass of lead metal - and knowing its surface area, the mass of corrosion per unit area is established.

Well-dated untreated lead samples from Tel-Dor, the Persian period, Caesarea, the Byzantine and the Crusader periods as well as contemporary data were used to establish the dating correlation over a time span ~2500 years. This new chemical dating method is apparently applicable to lead artifacts buried in soils with pH > 6.5. In such soils the corrosion process is very slow and the corrosion products, mainly PbO and PbCO3, accumulate over hundreds of years. The method is in principle non-destructive.

Large Area Smooth Gold and Surface Force Measurements

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For the past 30 years of Surface Force Balance (SFB) studies, mica has been considered optimal for surface force measurements due to its atomic smoothness over cm² areas. This property enabled force measurements across sub-nm separations, providing a better understanding of the properties of confined matter, such as the preservation of (bulk) water viscosity or the lubricating effect of hydrated ions confined to a few nanometers. Despite its advantages, mica has two major limitations: its surface potential cannot be directly controlled (mica is dielectric) and its surface is very difficult to modify chemically.

Motivated by the new possibilities offered by replacing mica with a metal, we have developed a method to produce large-area molecularly-smooth gold surfaces (rms roughness ca. 0.2 nm over areas larger than 10x10 µm²) that are compatible with surface force measurements. These provide not only a very different surface, but also one whose potential can be directly modified and which is amenable to thiol chemistry.

In this lecture I will present this method, explain its applicability to SFB measurements and compare the results with mica-mica to those between gold-mica.
Keynote Lecture

Energy Resources: What Is The Problem?

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Why do we (most of the scientific community) think that there is a problem of supply of sustainable energy resources to provide the world's power needs? What do we mean when we say that there is an energy problem and how can scientific research help us approach and solve it?

I will try to explain this issue, provide both sobering and optimistic information, and consider approaches to tackle the problem especially on solar energy, with some emphasis on what basic chemical research can contribute.
Sorption of Organic Compounds by Natural Organic Matter (NOM): What Insights Can We Gain about Mechanisms by Varying NOM Hydration Status?

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Natural organic matter (NOM) is the sorbent that often controls distribution and environmental fate of organic compounds in diverse soil, aqueous and atmospheric environmental compartments. Due to the complexity of the chemically and physically heterogeneous NOM sorbent phase, sorption mechanisms in NOM are far from understood. Structure of the NOM sorbent can change drastically as its hydration status varies under different environmental conditions. Hence, comprehending the effect of hydration (or solvation, in a wider sense) on organic compound sorption by NOM is helpful in delineating sorption mechanisms in this complicated and important environmental sorbent. Based on a number of liquid-phase sorption studies with different organic compounds on model NOMs at varying hydration levels, and in active organic solvent systems under different extents of NOM solvation, we present a concept and model for elucidating the relationship between the hydration effect on organic compound sorption by NOM, the sorbent structure, and sorption mechanisms. The central point of this concept is based on the observation that for certain compounds, sorption strongly increases upon NOM hydration (or solvation by strongly interacting organic solvents). In this concept, NOM phase is represented by a set of distributions of various inter- and intra-molecular non-covalent links and contacts that can be disrupted by sorbate and solvent molecules. We demonstrate how this model can explain, both qualitatively and quantitatively, different scenarios in hydration-affected sorption of organic compounds by NOM, including hydration-assisted sorption, hydration-suppressed sorption, and cooperativity in organic compound-NOM interactions.
Development of Fuel Cells for Electric Vehicles and for Solar-Energy-Storage Applications

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Fuel cells based on proton-conducting membranes (PCM) are considered to be the best choice for transportation and for solar-energy-storage applications. At present, the cost of materials prohibits their commercialization. The cost of the platinum catalysts and the cost of the PCM have to be reduced. In order to achieve this goal, a lower-cost membrane that can operate at above 120°C as well as more active catalysts must be developed. Many fuels are being considered for various FC applications. Hydrogen has received the greatest attention for transportation and organic fuels including methanol, ethanol and ethylene glycol have been studied for small electric vehicles. Any organic fuel to be used in a fuel cell must be completely oxidized to CO2 with no accumulation of side products. Up to now, with current catalyst technology, methanol, ethylene glycol and DMO meet this requirement while ethanol does not. Better Pt-alloy nanosize catalysts for oxygen reduction will be presented. Here we also present progress in the development of four membranes, two based on PVDF and the other two on a Teflon matrix for high-temperature (over 100°C) FC applications. The properties and performance of FCs fed by methanol (DMFC), ethylene glycol (DEGFC), DMO (DDMOFC) will be addressed. In addition, the performance of a hydrogen/air FC and of a hydrogen/bromine FC, based on a nanoporous proton-conducting membrane (NP-PCM) will be presented. The hydrogen/bromine FC demonstrated a world record in power density (1.5W/cm²). Because of its low cost, the hydrogen/bromine regenerative fuel cell is considered to be an enable technology for solar- and wind-energy storage systems as well as for load leveling. The state-of-the-art solar electrical-energy-storage systems are too expensive as a result of the high cost of the chemicals used for storage.
New Developments in Photovoltaic Dye Cells

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Photovoltaic (PV) dye cells offer a new generation, low cost alternative to rival types of PV cells, such as silicon based systems. Not only are the raw materials and process equipment for dye cell technology cheaper, but the actual manufacturing is much simpler also. Till now, however, PV dye cells have not been successfully commercialized mainly because of scaleup and performance limitations. In the Orionsolar system for dye cells, a unique current collecting grid and titania based photoanode has been developed in collaboration with Bar Ilan University. This gives a stable chemistry while maximizing the available active area, enabling building of large cells and modules having a commercially viable solar-to-electric energy conversion efficiency. This paper will describe the latest developments.
Keynote Lecture

Laboratory Studies on the Properties of Complex Organic Aerosols

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Aerosol particles affect climate in several direct and indirect manners. The direct effect is via scattering and absorption of radiation and the indirect effect is mostly by affecting the properties of clouds and precipitation. Recent studies have shown that organic matter, natural and anthropogenic, is dominating the tropospheric aerosol mass and affects its properties. We will present laboratory studies that focus on studying the properties and processes of organic aerosols, especially their interaction with water, their optical properties and density. Focus will be given to organic aerosols from biogenic emissions. We will emphasize the experimental approaches and the increased complexity of the experiments.

[Organizers' Note: this lecture will be 35 minutes, and this session will end 10 minutes later than the others.]
Keynote Lecture

The Power of Forensic DNA Typing

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Forensic genetics (or DNA typing) is a subset of forensic science used primarily as a means to establish identity in situations such as paternity testing, inheritance matters, mass disasters, missing persons, bioterrorist events, and criminal cases. Genetic evidence can be derived from any biologic material, including blood, bone, hair, teeth, muscle tissue, saliva, etc. and can be used for characterization of humans, animals, plants, and microorganisms. There are three potential interpretations that can result from a comparison: inclusion, exclusion, and inconclusive.

With success, more demanding applications are beginning to be addressed, such as typing samples containing very minute amounts of degraded DNA. A class of genetic markers, known as single nucleotide polymorphisms (SNPs), can in theory enable analysis of DNA fragments as small as 50 nucleotides in length. SNPs will have a niche in forensic analyses particularly for typing degraded or small quantity human remains from missing persons and mass disasters, for determining the geographical origin of the donor of a sample, for lineage-based studies, and for typing physical attributes.

A new approach employing the mass spectrometer is well-suited as an analytical platform for SNP analysis. It is a highly automatable, highly accurate (over several orders of magnitude) instrument that does not require DNA to be fluorescently labeled for detection. An ESI-MS method called TIGER (Triangulation Identification for Genetic Evaluation of Risks), will be presented. It will prove useful for identifying DNA profiles from IEDs, human remains, and from microorganisms.

Lastly, a databank that contains DNA profiles of offenders, profiles derived from evidentiary samples from crime scenes, and profiles from missing persons and their relatives provides investigative leads for resolving certain crimes. One example is the U.S. databank, known as the COmBined DNA Index System (CODIS), which provides the tools to search and compare DNA profiles for cases with no known suspect and linking cases committed by the same individual. Thousands of cases have been aided using this powerful tool.
Detection and Characterization of the Improvised Explosive Urea Nitrate

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Urea nitrate (uronium nitrate) UN, is a powerful improvised explosive, frequently prepared and used by terrorists. In its pure form, UN is a white, crystalline powder, which, just by looking at it, cannot be distinguished from e.g., sugar. It is assumed that about half a ton of this material was used in the first World Trade Center bombing, in February 1993 (1). In Israel, urea nitrate is believed to be one of the most widespread explosives used by Palestinian terrorists, which is responsible for the loss of many lives.

A sensitive and specific color test for urea nitrate was developed. It is based on its reaction with p-dimethylaminocinnamaldehyde under neutral conditions. The pigment thus formed was characterized by X-ray crystallography. It is a mono-ureido-nitrate salt, with a pronounced quinoid character. Laboratory identification of unexploded UN involves a preliminary color test, followed by IR spectroscopy and LCMS.

It is much more difficult to identify urea nitrate in post explosion debris, since it is readily hydrolyzed by hot water to urea and nitrate ion. A method for its recovery and clean-up from debris, followed by LCMS analysis was developed. By applying this technique it was possible to successfully identify urea nitrate as an intact molecule in actual exhibits. It was found that UN can be formed also during the analytical procedure, by certain combinations of urea, a nitrate salt and a source of protons and hence, the presence of the characteristic adduct ion does not necessarily mean an "authentic" urea nitrate.

Urea nitrate was found to be also a powerful, regioselective aromatic nitration agent. It converts deactivated aromatic substances to their mono-nitro derivatives under very mild conditions. A plausible mechanism involving nitrourea as an intermediate was suggested.
The growing threat of terror by peroxide-based explosives

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The 2005 terrorist attacks in London had demonstrated the intolerable potential for a new kind of terrorism with peroxide-based explosives, such as TATP and HMTD. The threat arises primarily from the fact that these explosives are very easy to make by anyone, without any training or experience. Furthermore, these materials, which serve as both detonator and main charge, can be initiated by a spark, minor friction or impact. It is particularly alarming that these explosives, which are easily made from cheap raw materials that are available in the free market, are very difficult to detect.

This report covers several research projects on peroxide-based explosives in an effort to develop methods for their detection, characterization and prevention. For example, the thermal decomposition pathway of TATP was investigated by a series of calculations that identified transition states, intermediates, and final products. These studies predicted that the detonation of TATP is not a thermochemically highly favored event. It rather involves entropic explosion, which is the result of formation of one ozone and three acetone molecules from every molecule of TATP in the solid state. Experiments with a fast camera supported these predictions. TATP is different from most other explosives in that it forms at least three different polymorphic crystals, depends on the synthetic conditions and crystallization media. A useful Peroxide Explosives Tester (PET) was developed on the basis of an enzyme-catalyzed chemical reaction that produces a characteristic color in the presence of few nanograms of the explosive material. This small-size, disposable device is particularly designed for non-experts to allow fast identification of suspected materials in a variety of settings. The method underscores the utility of chemical methods in explosives detection and characterization.
Fingerprint Development by Vacuum Metal Deposition (VMD) Technique: The Relationship between Prints' Quality and Surface Properties

Michal Levin Elad¹, Pazit Papo², Myriam Azoury³, Joseph Almog⁴

¹Division of Identification and Forensic Science (DIFS), Israel Police, ²Shenkar Engineering college, Department of chemical Engineering, ³Division of Identification and Forensic Science (DIFS), Israel Police, ⁴Casali Institute of Applied Chemistry, The Hebrew University of Jerusalem

One of the most sensitive methods for fingerprint development on polymeric surfaces is Vacuum Metal Deposition (VMD). It is of particular importance on polyethylene items such as "supermarket bags." The process, which involves consecutive evaporation of gold and zinc metals on the item under examination, requires expensive equipment and long training. However, results are not always consistent and there is much debate over the use of the method in the normal sequence of fingerprint development techniques. The purpose of our study is to find out more about certain surface properties and how they affect the quality of VMD-developed fingerprints. Two properties were investigated: Surface free energy, calculated from measuring the contact angle between liquid drops and the surface and surface roughness, calculated from atomic force microscopy measurements. Experiments were conducted on polyethylene sheets, which are frequently encountered in high profile crimes such as drug trafficking. Initial experiments show no connection between free surface energy and fingerprint quality. However, there is a correlation between the surface roughness and the quality of the VMD prints; the higher the surface roughness, the better the quality of the developed fingerprints.
Detecting the Unexpected: Some Unique Aspects of Forensic Analytical Chemistry

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Analytical chemists, whether in academia, pharmaceutical, agricultural or industrial laboratories, usually deal with the identification of a defined set of materials or elements, within more or less defined matrices. Forensic analysts in contrast, frequently deal with "totally unknown" mixtures, within the most unusual matrices. In some cases the goal may not be the absolute analysis of a mixture, but rather its association with another sample. It is not uncommon that while expecting a certain group of materials, e.g. drugs, something absolutely unexpected pops up, such as poisons or explosives. In this presentation, examples from real case work will be presented and discussed.
Keynote Lecture

Mechanics and Electronics of Single Large Molecules at Surfaces and Interfaces

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Single crystalline substrates coated with physisorbed molecular adlayers have been employed to investigate mechanical and electronic properties of single large molecules. Nanostructure and molecular dynamics of the molecular adlayer, together with the forces exerted by scanning probes are employed in order to control structure and orientation of macromolecules, such as DNA [1] and dendronized polymers [2]. Nanoscopically thin liquid layers were employed to transmit forces in two dimensions in order to stretch, bend and break individual plasmid DNA [3]. Finally, the workbench is also used to correlate structure and electronic properties of molecular nanostructures such as in a single-molecule chemical field-effect transistor with nanosized gates [4].

Revisiting the Metal to Insulator Transitions in Clusters

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We critically review the issue of Metal to Insulator Transitions in metal clusters, in view of our new photoelectron spectroscopy (PES) studies on bivalent Zn\textsubscript{n} clusters. We show that zinc clusters in the size range of n=3-117 exhibit a distinct transition in their electronic structure characteristics as a function of their size. At small sizes up to n=18 the clusters follow the Bloch-Wilson picture of the development of a metal from closed-shell atoms, exhibiting a gradual decrease of the gap between the fully occupied s band and the empty p band. For large sizes (n>32) the band overlap allows the valence electrons to fully delocalize. This leads to an almost perfect free-electron density of states, as predicted by standard free-electron models and as supported by comparison to the PES obtained on sodium clusters. Based on those results, and measurements on Mg and Sr clusters, we suggest a refined criteria for the Metal to Insulator Transitions in clusters.

Finally, we will present ultrafast studies on electron thermalization dynamics in mercury clusters. We show that as channels of electron-electron scattering are blocked, thermalization of electrons is dramatically slower than in other metal clusters.
Electrical Transport, Polarizability, and Spectroscopic Measurements Through DNA Molecules and Derivatives Using Conductive AFM and STM

Hezy Cohen¹, Claude Nogues², Daniela Ullien¹, Tomer Sapir¹, Errez Shapir¹, Natalia Borovoka³, Tatyana Mototsky³, Ron Naaman², Alexander Kotlyar³, Danny Porath¹

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DNA is considered one of the attractive candidates for molecular electronics. It was studied in many ways including: electrical transport, atomic force microscopy (AFM) and scanning tunneling microscopy (STM). The results of various measurements of charge transport in DNA seem inconsistent. A deeper look into the experiments can offer a general understanding of the reports and ways to optimize the conductivity in DNA.

We have developed a method to attach short (26 bp) DNA molecules to a gold surface at one end and to a gold nanoparticle on the other end. Upon approaching and contacting the gold particle with a conductive AFM tip with a controlled applied force, we can measure current-voltage curves through the double-stranded DNA molecule. Our measurements show relatively high currents (200 nA@2 V). We report a comprehensive set of control experiments that support these results. Further, we compare the electrical conductivity of monolayers of: ssDNA, dsDNA and dsDNA with thiols in the upper end. The results call for faster conduction mechanism than those suggested to account for the solution chemistry experiments.

One of the attractive DNA derivatives for nanoelectronics is G4-DNA, a molecules composed of consecutive guanine tetrads. I will present clear polarizability measurements in this molecule. In addition, I will also report STM spectroscopy of single DNA molecules and universal scaling behavior observed in these spectra.

Novel Spray Technique for the Production of Semiconductor Nanocrystals

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We present a novel spray technique for the production of high quality semiconductor nanocrystals that offers an attractive alternative to conventional production methods, epitaxial growth and colloidal synthesis. According to this spray method, solutions of semiconductor salts are first sprayed into monodispersed droplets, which subsequently become solid nanoparticles by solvent evaporation. Each semiconductor nanocrystal is produced from a single spray droplet upon the full vaporization of the liquid. The average diameter and size distribution of the final nanocrystals can be controlled and determined by the solute concentration of the sprayed solution and the droplet size, hence by spray production parameters.

The method uniquely enables the production of free, uncoated semiconductor nanocrystals. This feature is of great fundamental scientific significance and practical importance as it enables the production of the densest possible assemblies (mechanically robust) due to the lack of organic capping. Electron transport properties as well as energy transfer mechanism, which drastically change with the semiconductor nanocrystals organization, can then be measured within new and more interesting range of inter-particle distances. Furthermore, the effect of the organic capping on the nanocrystals physical properties could be obtained and explored for the first time.

The potential of the novel method further include: (1) Production of core-shell or core-alloyed shell due to separate precipitation rates for different component within the droplet; (2) Dry collection on any desired solid support; (3) the introduction of extra carriers (i.e., electrons or holes) or spins into the nanocrystals by means of doping (since kinetic processes govern the nanocrystals generation).

Figures: Spray produced (A) 4nm spherical CdS nanocrystal; (B) 8nm cubic PbS nanocrystal; (C) Ordered clusters (50nm) of MnS nanocrystals with crystal size range of 1-2nm; and their assembly into micron-sized coral-shaped fractal aggregates (D).
Quasi-CW Spectroscopy of Multiexcitons in Colloidal Semiconductor Quantum Dots

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Following optical excitation, the exciton state in a semiconductor quantum dot (QD) radiatively relaxes on a typical time scale of tens to hundreds of nanoseconds. Further excitation of a previously excited QD results in the formation of multiexcitons. In colloidal QDs, where these are spatially confined to a region smaller than the exciton Bohr radius, these states are characterized by strong exciton-exciton interactions, reflected in rapid nonradiative relaxation via an Auger process, as well as in the emission spectrum via exciton-exciton binding and by state filling.

We present a new spectroscopy method, based on quasi-CW excitation, in which multiply excited states are generated via a ladder-climbing mechanism. This enables us to directly extract the exciton-exciton interaction energies as well as to follow the relaxation pathways. This is utilized to elucidate the mechanism of Auger ionization of CdSe QDs, which we attribute to two consecutive Auger events occurring in a single QD.

We proceed to show methods of controlling Auger relaxation rates and binding energies in CdTe/CdSe multicomponent QDs with type-II alignment, where the hole is localized in the CdTe core, and the electron in the CdSe shell. We develop a generalized scaling law for the Auger relaxation in these QDs, and show a transition from positive to negative biexciton binding energy, which has important consequences on optical gain dynamics.

Finally, we discuss the advantages and disadvantages of the quasi-CW approach vs. the more common time-resolved transient absorption and fluorescence upconversion methods.
Keynote Lecture

The Protein Folding Problem: Slow Progress by Studying Fast Kinetics Using Ultrafast Spectroscopy

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The Anfinsen experiment led to the thermodynamic hypothesis and launched the search for the mechanism that enables the extremely fast protein folding transition. Now, 50 years later the answer to the key question “can we read genes?” is still “in principle yes, but not yet”. Why? Probably because of the complex nature of the interactions that cooperate in the transition and the stochastic nature of the elementary steps of the mechanism.

In our research we focus on some aspects of the mechanism and ask some basic questions such as: Do non-local or local interactions (long loops formation versus secondary structure elements formation) dominate the critical initial phase of the folding transitions of globular proteins? Is the initial collapse a random condensation or programmed transitions? To what extent is the native state of a protein fully folded and the denatured state fully unfolded?

Answers to these and additional questions are being sought by determination of multiple distributions of intramolecular distances in site specifically labeled model protein molecules either at equilibrium, under folding, denaturing or partially unfolding conditions, or during the fast unfolding/refolding transitions. The main experimental approach is based on time resolved dynamic resonance transfer of electronic excitation energy (FRET) measurements monitored either by the time correlated single photon counting under equilibrium conditions or by the single pulse approach in the “double kinetics” experiments. Multiple transitions were observed in each of the model proteins studied, and non-local interactions appear to be effective long before the secondary structures are formed.

So far the results are compatible with the hypothesis that few very effective non-local interactions can be essential factor in stabilization of the early transient structures of folding of globular proteins and that the hydrophobic collapse of the molecule is probably not a random solvent exclusion process but rather a programmed transition. Experiments aimed at characterization of the native state of proteins show that there is a wide spectrum of the degree of order of globular protein structures in their functional states.
Mechanisms of Biomolecular Self-Recognitions

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Many cellular functions rely on interactions among proteins and between proteins and nucleic acids. In the recent years, we have come to understanding the assembly of the individual actors in this drama thanks to many cooperative experimental and theoretical efforts. We now better understand the main principles of the self-assembly of a single protein chain into its unique structure (i.e., protein folding). Furthermore, we can often predict monomeric protein structure and even design novel protein structures. However, knowing everything about monomeric proteins does not give a "full picture" of function. Function requires change of structure and specific recognition to form large assemblies. Understanding the principles of biomolecular self-assembly in quantitative detail constitutes the basis for the molecular theory of biological networks. In my presentation, I will discuss the dynamics and mechanisms of protein-protein assembly and of protein-DNA recognition that are studied using simplified computational models. Native topology based landscape models, which corresponds to a perfectly funneled energy landscape, reproduces many of the grosser and finer structural and kinetic aspects of various binding mechanisms found in the laboratory. Not only are our computational results consistent with experiments, they also demonstrate that protein plasticity, as envisioned by the fly-casting mechanism, is more fundamental in protein recognition than traditionally imagined. In protein-DNA recognition, both fly-casting effect and electrostatic forces contribute to an efficient binding. Finally, we propose resolutions of a few longstanding experimental puzzles and anomalous self-assembly behaviors.
Electron Spin Resonance Microscopy in Chemical Biophysics

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Fluorescence Microscopy is unfoundedly the single most important tool in modern Biochemical and Biophysical research. However, even with all its might, Fluorescence is still lacking several important capabilities that limit its use in several key problems. For example, fluorescence microscopy cannot penetrate into many samples of interest, it provides non-linear image intensity (due to unknown absorption and scattering), and it does not have a good capability to quantify the viscosity or to measure concentrations of O2, NO, and other reactive species. A possible complementary tool that can be used to acquire this data is Electron Spin Resonance (ESR) microscopy (ESRM). ESRM is an emerging technique, aimed at obtaining spatially-resolved information about samples containing paramagnetic species (instead of fluorophores) with micron resolution. ESRM enables one to obtain information such as the line shape, relaxation times, and diffusion coefficient of the relevant paramagnetic probes, as a function of the location. The potential applications of this technique range from examination of medical tissue to biochemistry and biophysics of living cells.

Our recent efforts were devoted to the development of this technique. Currently our pulsed ESR microscope, operating at a frequency of 16 GHz, can acquire 3D images of 128*128*128 voxels with a resolution of ~5 microns in typically 30 minutes. Although these figures represent an advance over previous efforts in the field, there is still much room for improvement in resolution, acquisition time, imaging algorithms, and sample preparation. Such improvements would be realized by employing elevated microwave frequencies, along with further technological optimization. Achievement of true micron scale imaging at a few minutes of acquisition time is vital for most bio-science applications, and would indeed enable ESR to adequately complement the information gained by fluorescence microscopy.
NMR Structural Studies of the Interferon-α Signaling Complex

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Type I interferons (IFNs) are a family of homologous helical cytokines which elicit strong anti-viral and anti-cancer activity and provide the first line of defense of the human body against pathogens long before the adaptive immune response. Consequently, IFNs are the human proteins most widely used in the treatment of several diseases (e.g. several kinds of cancer, hepatitis C, MS). All type I IFNs bind to a cell surface receptor consisting of two subunits, ifnar1 and ifnar2, associating upon binding of interferon.

Here I describe our ongoing studies on the structure and dynamics of the 44 kDa complex of IFN-α-2 with the extracellular domain of IFNAR2 (R2-EC) and of the binding site of the 70 kDa complex between IFN-α-2 with IFNAR1 (R1-EC) by multidimensional NMR techniques. These two complexes are very challenging projects for NMR studies and require the use of all available state of the art techniques. We derived a model of the IFN-α-2/R2-EC complex based on NMR and Double Mutant Cycle (DMC) data. NMR data suggests that tertiary complex formation occurs via an allosteric mechanism.
DNA Charge Transport as a Signaling Mechanism for DNA Repair Enzymes

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Many base excision repair (BER) enzymes contain an [4Fe4S] cofactor yet a biological role for these ubiquitous cofactors has been unclear. We have proposed a model in which the redox chemistry of these cofactors plays an essential role in scanning the genome for chemically modified bases by a DNA-mediated electron transfer process.

I will describe this model and provide evidence in support. First, I will show that an electron originating from the [4Fe4S] cluster of a BER enzyme is trapped on the DNA duplex via a DNA-mediated charge transfer reaction. Next, I will present evidence that the redox activation of these cofactors may be triggered in DNA in situ by guanine radicals, which are the first DNA products generated under oxidative stress.
Design and assembly of functional soft materials in the form of electrochemical, chemical or photochemical responsive organic mono- and multilayers offers a great challenge that promises new device properties, enhanced performance, and eventually affordable production costs. We recently demonstrated that charge storage in well-defined metal complexes covalently attached to silicon-based surfaces result in a reversible change in the optical properties of the system. The chemical sensitivity and the stability of these films over a number of redox cycles may make these systems suitable candidates for a new generation of non-volatile memory elements and sensors.

Incorporation of Carbonaceous Nanomaterials into Proteins: Preparation and Characterization

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For decades chemical industry has been manufactured different kinds of carbonaceous materials in high volumes. For example, nano-scale size carbon blacks have been in production for more than a century and are used for fabrication of rubber products and pigments. Also, recently developed chemical technologies for production of other carbonaceous nanomaterials, such as fullerenes and carbon nanotubes, are reaching a multi-ton per year level, and may reach hundreds of tons in the future. As a result, the human and environmental exposure to the carbonaceous nanomaterials will be undoubtedly increased. This issue became lately of great public concern. Although current knowledge of the toxicology of carbonaceous nanomaterials just began to be accumulated, most of the current nanotoxicology research is focused on examination of the nanomaterials influence at the tissue and cellular levels.

Our project is aimed to study interactions between carbonaceous nanomaterials and various transport proteins. Also, we made an effort to understand how carbonaceous materials could be transported from one biochemical system to another. We believe that this research is important as it lays a solid foundation for better understanding of nanomaterials interaction with living organisms. In addition to understanding of how carbonaceous materials are interacting with living cells and tissues, more basic questions are related to these compounds transport and interactions on molecular level. Thus, a study of protein-promoted dissolution and transport of carbonaceous materials in biological systems is very important, as it should provide valuable information that toxicologists need for better evaluation of these nanomaterials usability or threat.
Protein-Protein Association in Polymer Solutions: A Tale of Three Regimes

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The crowded cellular environment may be simulated in vitro using synthetic polymers. Here, we followed the association and diffusion rates of TEM1-β-lactamase (TEM) and the β-lactamase inhibitor protein (BLIP) in the presence of crowding agents of varying molecular weight, from monomers (ethylene glycol, glycerol or sucrose) to polymeric agents such as different polyethylene glycols (PEGs, 0.2-8 kDa) and Ficoll. An inverse linear relation was found between translational diffusion of the proteins and viscosity in all solutions tested, in accordance with the Stokes-Einstein (SE) relation. Conversely, no simple relation was found either between rotational diffusion rates or association rates (kon) and viscosity. To study the translational diffusion independent steps along the association pathway, we introduced a new factor, \(\alpha\), which corrects the relative change in kon by the relative change in solution viscosity, thus measuring the deviations of the association rates from SE behavior. We found that these deviations were related to the three regimes of polymer solutions: dilute, semidilute and concentrated. In the dilute regime PEGs interfere with TEM-BLIP association by introducing a repulsive force due to solvophobic preferential hydration, which results in slower association than predicted by the SE relation. Crossing over from the dilute to the semidilute regime results in a positive deviations from SE behavior, i.e. relative faster association rates. These can be attributed to the depletion interaction, which results in an effective attraction between the two proteins, winning over the repulsive force. In the concentrated regime, PEGs again dramatically slow down the association between TEM and BLIP, an effect that does not depend on the physical dimensions of PEGs, but rather on their mass concentration. This is probably a manifestation of the monomer-like repulsive depletion effect known to occur in concentrated polymer solutions.
High-Resolution Solution State NMR Chromatography

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Until now NMR spectroscopy has been a poor method of choice for analyzing mixtures. Here we show that with NMR chromatography, mixtures can be usefully analyzed by high-resolution NMR for the first time. Self-diffusion NMR in the DOSY representation can be used to separate a mixture of molecules in an NMR spectrum. But, unless there is a very wide variation in molecular size, this separation is not sufficient to be workable. When a conventional chromatographic medium is added and the experiment is acquired under CP-MAS conditions, greater separation is achieved. We show that it is possible to enhance 'chromatic' separation in a high-resolution solution-state experiment by one of two methods: 1) Using a solid chromatographic medium that is susceptibility matched to the solution 2) Using a dissolved polymer or large molecule that differentially binds the molecules under study. (R. E. Hoffman, A. Aserin and N. Garti, Provisional US patent application)
Rethinking charge transport through alkyl chain monolayer

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The field of molecular electronics is flooded with theoretical models, which often do not coincide with experimental results. That is, there is no theoretical model with a proven predictive power. As a result, this field lacks guidelines for designing molecular electronic devices.

In this lecture I will show new experimental results of charge transport through Si-C bound alkyl chains monolayer that fit to an established theoretical model of conduction through an insulating layer. The reproducibility of our experimental transport results, together with spectroscopic measurements followed by theoretical calculations, enables us to answer the following questions:

- Is the molecule/electrode interfacial chemical bond relevant for charge transport through molecular junctions?
- Can we define "THE" energy barrier for charge transport through molecules?
- Is there anything molecular in the charge transport process?
- What are the possible transport mechanisms in these molecular junctions?

Hopefully this study can serve as a building block for further work with complex molecules in molecular electronics field.
The Rationale and Implementation of the New Chemistry Curriculum for High-School Students

Nitza Barnea

Ministry of Education, Jerusalem, Israel

The new chemistry curriculum for high-school students in Israel was implemented in 1986. The curriculum was developed to replace the previous one and to enhance the teaching of chemistry in high schools.

The curriculum emphasized practical hands-on learning, and the laboratory component was increased. The new curriculum also introduced new topics such as environmental chemistry, biochemistry, and analytical chemistry.

The curriculum was designed to encourage critical thinking, problem-solving skills, and the ability to interpret and analyze scientific data. The curriculum was evaluated in terms of its impact on student learning and performance in national exams.

In order to ensure the implementation of the new curriculum, professional development programs were conducted for teachers, with a focus on improving their understanding of the new topics and teaching methods.

The new curriculum was designed to prepare students for higher education and to enhance their critical thinking skills. It was also intended to increase their understanding of the role of chemistry in modern society.
Chemical Bonding: A New Unit

Tami Levy Nahum*

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The new unit of 'Chemical Bonding' was developed in the Department of Science Teaching at the Weizmann Institute of Science, under the guidance of Professor Avi Hopshtein. The team consisted of: Dina Ror, Rachel Rabin-Roth, and Tami Levy Nahum. The development team included: Tami Levy Nahum, Dina Ror, and Rachel Rabin-Roth. The project was supervised by Professor Avi Hopshtein and was supported by the Ministry of Education and the Weizmann Institute of Science. The new unit of 'Chemical Bonding' was developed in response to the need for a new unit that would provide a comprehensive and coherent framework for teaching chemical bonding. The unit includes a series of modules that cover the basic concepts of chemical bonding, including the nature of chemical bonds, the types of chemical bonds, and the properties of chemical compounds. The unit is designed to be used in conjunction with other modules in the science curriculum, and provides teachers with a range of resources and activities to help students understand and engage with the material.
Stoichiometry & The Gaseous State - A New Module

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Innovative ways of teaching chemistry and their effects, considering the various fields of study and the relationships between them.

The second section "Substances - Quantities and Relationships" deals with the quantitative aspects of chemical reactions, which are crucial for understanding the particulate level of thinking in chemistry.

The section "Gases - Quantities and Relationships" deals with the unique aspects of gases, accompanied by suitable and well-structured experiences, allowing students to develop a comprehensive and critical understanding of the relationship between physical and chemical properties of gases.

The aims include the development of practical skills, critical thinking, understanding chemical processes, and preparing students for advanced studies and future careers in science.

Chemical Education

S4b3
Principles, thinking skills, and implementation of the *Taste of chemistry* module

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The new chemistry curriculum in Israeli high schools calls for developing students' scientific understanding, higher order thinking skills, and problem solving abilities. Achieving this goal in the Taste of Chemistry module has been achieved through integration of learning scientific concepts and processes with real life examples while presenting societal and economical aspects. This study unit is part of a new set of learning materials for high school students, developed within the framework of reforming the Israeli advanced (three-unit) chemistry curriculum. The module concerns issues related to lipids, carbohydrates and proteins that are made concrete and relevant via nutritional, health and social aspects. Students' activities and questions involved five main thinking skills: (1) The ability to understand concepts and processes based on chemistry understanding levels, (2) transitions between multiple representations of molecular structures, (3) analyses of chemical and nutritional information presented in graphs and tables, (4) case studies, and (5) inquiry-based laboratory experiments.

We followed six chemistry teachers that implemented the unit in their classrooms using interviews and classroom observations. The teachers enjoyed teaching the unit since it made chemistry interesting for students and teachers alike. They indicated that students understood better nutritional issues, helping them make informed decisions regarding their eating habits. Teachers faced two challenges: they had to teach chemistry in context beyond the traditional subject matter and to integrate thinking skills beyond their pedagogical content knowledge. The teachers agreed on the importance of teaching these skills as they promote chemistry understanding and prepare students for their future professional life.
Chemistry in Context: A New Module

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Chemistry in Context: A New Module

The new module, "Chemistry in Context," aims to connect the students to their world and surroundings. It is designed to enhance the students' understanding of the role of chemistry in their daily lives and in the broader context of science and society. "Chemistry in Context" introduces students to various aspects of chemistry through practical experiments and discussions.

Building block: "Chemistry... In Us"

The module focuses on the practical and theoretical aspects of chemistry, aiming to make the subject more relevant and engaging for the students. It includes a series of experiments, discussions, and practical activities that help students understand the role of chemistry in their lives.

The module is based on the following topics:

1. "Breaking Cyst:" How to Balance Chemical Equations
2. "Antioxidants:" How to Protect Our Cells
3. "In Our Bodies:" Understanding the Chemical Equilibrium

The module also includes daily activities such as reading, discussion, and practical exercises. The module is designed to enhance the students' understanding of chemistry and its importance in their lives.

The module was successfully tested in 11 classrooms in the academic year 2011-2012.
Visualizations and real-life applications in teaching and learning the module: "From nanochemistry to microelectronics"

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Researchers emphasize the importance of integrating visualization tools and application aspects into science education in general and chemical abstract issues in particular. The new high school chemistry curriculum in Israel calls for shifting the focus of topics taught from traditional to modern, “high-tech” chemistry. In response, we developed a new module for honors students titled "From nanochemistry to microelectronics". This study unit concerns several abstract topics, including substances’ chemical properties derived from their electronic structure, atomic and molecular orbitals, electron excitation, and energy band in semiconductor solids.

Each chapter starts with a focus on a certain application that underlines the importance of understanding abstract concepts and processes in nanochemistry and microelectronics. The module integrates a variety of visual representation modes and learning activities that involve web-based simulations. Students are encouraged to develop higher order thinking skills. Most of the chemistry high school teachers had never taught these topics before.

We investigated the perceptions of six teachers who taught this module for the first time and ten pre service teachers. Initial findings indicate that pre and in service teachers perceive this module implementation as an opportunity to strengthen and renew their chemical education experience. Teachers recognized the importance of the visual representations for enhancing students' chemical understanding and indicated that the real-life applications motivate students' learning.
Entropy and the Second Law of Thermodynamics – Should we use the traditional terms "Order" and "Disorder" when we teach it?

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Teaching the concept of entropy and the second law of thermodynamics has never been an easy task for chemistry teachers and lecturers. Most of the difficulties have stemmed mostly from the abstract nature of entropy, which is difficult to visualize, and from the complex calculations that are needed to measure entropy changes quantitatively.

Until recently, textbooks in physical and general chemistry have frequently and intensively used the terms order and disorder in relation to entropy changes. Thus, in order to help students visualize an increase in entropy, many texts use drawings that show the system before (ordered), or after the physical or chemical process (disordered or more ordered). The use of a pack of playing cards as an example is used many times as an analogue to model entropy changes. Lately, it has been claimed that the nature of entropy is better taught by describing its dependence on the dispersion of energy causing its distribution among a larger number of molecular motions (more microstates). This model can be also used to explain the dispersal of matter in adiabatic processes in which no energy exchange between the system and the surroundings occurs (i.e., when a gas fills a vacuum spontaneously or mixes spontaneously with another gas).

These modern explanations and views are already being considered and applied in the new textbook on "Thermodynamics and Kinetics" that we are presently writing now for high school students majoring in chemistry.

(Textbook presentation:) "Introduction to Quantum Mechanics: A Time-Dependent Perspective"

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Many students find time-dependent quantum mechanics the most interesting and understandable part of quantum mechanics. However, standard courses in quantum mechanics devote little attention to this perspective, and its relationship to the rest of the syllabus is disjointed. This book is an entirely original manifesto that develops quantum mechanics from beginning to end from the time-dependent viewpoint.

There are several compelling reasons to increase the fraction of time-dependent quantum mechanics in the standard curriculum. The time-dependent viewpoint is dynamic and very visual. It can be conveyed in an exciting and effective way to advanced undergraduates as well as graduate students. Many of the conceptual difficulties of beginning students of quantum mechanics disappear once they grasp the time dependent approach. To fully exploit the dynamic and visual character of this approach, a full library of computer animations has been designed to supplement the text of the book.

In addition to its pedagogical appeal, the time-dependent perspective provides the simplest and most natural interpretation of many of the frontier experiments in modern Chemical Physics -- from femtochemistry to transition state spectroscopy, from dynamic absorption to resonance Raman spectroscopy, from coherent control to photodissociation to reactive scattering. All these applications are treated in a unified way in this book, using a small set of conceptual building blocks.

The book is targeted at three audiences:
(1) Advanced undergraduates in Physics and Chemistry.
(2) Graduate students in Chemical Physics and Atomic, Molecular and Optical Physics.
(3) Researchers, both theoretical and experimental, in the above fields.

The book is divided into three parts, so that each of the above audiences can easily find the material appropriate for their level and their interest.
Keynote Lecture

**Synthesis of Symmetrical/Non-Symmetrical, Magnetic/Non-Magnetic Nano- and Micron-Scaled Particles of Narrow Size Distribution for Biomedical Applications: Medical Imaging, Drug Delivery, and Therapy**

Shlomo Margel¹, Tammy Tennenbaum¹, Sigalit Gura¹, Anna Galperin¹, Yonit Bogoslavsky¹, Benny Perlstein¹, Rina Ben-Shabat¹, Ofra Ziv¹, Eran Partouche¹, Udi Akiva¹, Sigal Baruch¹, Melany Omer-Mizrahi¹

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1. Maghemite nanoparticles of narrow size distribution were prepared by nucleation followed by growth of maghemite (γ-Fe₂O₃) thin films onto gelatin nuclei.

2. Nano and micron-scaled polystyrene particles of narrow size distribution were prepared by emulsion and dispersion polymerization processes, respectively. These particles have been used as template for preparation of new symmetrical and non-symmetrical particles of narrow size distribution, by swelling them with initiator and appropriate monomers, followed by polymerization at elevated temperature.

Functionalization of the particles described in (1) and (2) were performed by various surface modification methods, e.g. ozonolysis, graft polymerization, etc. The functional groups on the particles' surfaces have been used for binding of desired bioactive molecules, e.g. drugs. The naked and conjugated nano and micron-sized particles have then been used for different biomedical applications, particularly x-ray imaging, MRI imaging and drug delivery.
Chemical Challenges in Developing BL-1020 for the Treatment of Schizophrenia

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BioLineRx is developing the orally available antipsychotic compound BL-1020 for the treatment of schizophrenia. The compound is intended to retain the efficacy of currently available antipsychotic agents while exhibiting significantly reduced side effects associated with both typical (extra-pyramidal symptoms) and atypical (metabolic disturbances including weight gain, elevation of lipids, and glucose intolerance) antipsychotic drugs.

The active pharmaceutical ingredient of BL-1020 is an ester bond derivative of Perphenazine and γ-amino butyric acid (GABA) was obtained following a development program aimed at investigating the optimal route to obtain the BL-1020 API. Following an optimization of the coupling step, a wide salt screen was initiated, and the Tri-Maleate salt was selected due to its promising properties and lack of hygroscopicity. The Tri-Maleate salt is obtained using Trifluoroacetic acid deprotection of the Boc group (initially performed) followed by free base formation and in-situ precipitation of the salt from Maleic acid in Isopropanol.

This BL-1020 TriMaleate salt was used in BiolineRx’s phase I clinical trials human exposure of BL-1020 at the maximal single administration dose of 40 mg per adult and contained up to 2.0% w/w TFA counter-ion which was not totally removed during the free-base transformation.

Due to regulatory reservations regarding the presence of TFA counter-ion in repeated dose clinical trials and the endeavour to generate a more stable formulation and up-scalable synthesis process, a second phase of salt screen and development program was undertaken to further optimize the synthetic route, circumventing altogether the use of TFA. The Tri-Mesylate salt was found to be the most stable, pure and non-hygroscopic salt and was obtained in a one step synthesis. The production of BL-1020 Tri-Mesylate was scaled-up to kilogram lots, and said compound is the salt form of choice for future clinical trails.
The Use of Silica Encapsulation in Upgrading Active Ingredients

Ofer Toledano

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Sol-Gel Technologies is a groundbreaking nano-engineering company that aims to optimize the efficacy and increase the safety of drugs and active ingredients by entrapping them in silica spheres.

Sol-Gel's technology is based on the sol-gel chemical process in which amorphous silica is made by forming interconnections among colloidal nano-sized particles (the “sol”) under increasing viscosity until a rigid mass is formed with about half the density of glass (the “gel”).

In a “room temperature” process, active ingredients are entrapped and isolated in the silica shell of innovative sol-gel microspheres and their delivery is controlled. The texture and size of the shell can be monitored and optimized by altering parameters (such as temperature, type and concentration of reagents, nature and concentration of catalyst, solvent, drying methodologies, etc.) involved in the sol-gel reaction.

Recognized as a &AS;ingredient by the FDA, amorphous silica is making the Sol-Gel technology a potentially valuable innovation for the pharmaceutical and cosmetic markets.
Materials Degradation under Low Earth Orbit Space Conditions

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The long-term durability of materials operating in the space environment remains a principal issue in their development and application, since the space environment contains a variety of elements that are potentially hazardous for spacecraft hardware. The main hazards include atomic oxygen, UV radiation, ionizing radiation (electrons, protons), high vacuum, thermal cycles, plasma, micrometeoroids and man-made debris. Due to separate, combined or synergistic interactions with these space hazards, polymers in particular suffer a relatively rapid erosion, structure modification and surface roughening. This may lead to irreversible degradation of optical, thermal, electrical and mechanical properties.

The high cost and the limited availability of in-flight experiments, and the demands for accelerated tests simulating long duration missions, result in a need for ground simulation systems to study the space environmental effects on materials. A variety of ground simulation systems were used in the lab for this purpose. They include: i) an advanced system that combines simulation of various elements of the space environment (vacuum, temperature, UV radiation and contamination) together with in-situ surface analysis techniques (XPS and Auger), ii) an RF plasma source used for atomic oxygen simulation, iii) an outgassing system used to study contamination phenomena and mechanisms, iv) cobalt-60 gamma sources used for simulation of ionizing radiation, and v) a laser driven flyer system that simulates artificial debris effects.

The present talk will review the space environment constituents and their interaction with polymers. Examples of degradation of materials exposed to the space environment and to ground simulation facilities will be shown. A special emphasis will be given to space hypervelocity debris impact on polymers and the associated fracture mechanism. Other issues discussed will include the erosion mechanisms under atomic oxygen attack, synergistic effects, and introduction of new materials that will endure the harsh space environment.

Tamar Van der Boom\textsuperscript{1}, Rachel Teitelbaum\textsuperscript{1}, Mark Cohen\textsuperscript{1}
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In January 2006, the United States Patent and Trademark Office set forth a series of proposed rule changes, which will significantly change current patent practice, in particular in the Chemical Arts. These changes in practice, if accepted, will introduce much uncertainty in terms of the scope of protection afforded, and will result in a considerable increase in the expense at which such protection is obtained.

Some of the proposed changes include, for example:

(a) limitation of the number of claims examined in a single Patent Application
(b) limitation of the number of Continuation or Continuation-In-Part Applications, or Request for Continued Examinations permitted to only one per Parent Application.

Such limitations, if enacted, will necessarily result in an increase in the number of applications filed for a given series of compounds.

Recent case law regarding Patent Applications in the Chemical Arts will be discussed, as well as any anticipated effects the proposed changes may have on some of these decisions.
Keynote Lecture

Evolution of New Enzymes: One Chemistry, Many Reactions

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In spite the robustness and perfection of their action, enzymes posses a remarkable ability to rapidly change and adopt new functions (evolvability). Yet how enzymes with new functions and structures evolve (and sometimes, in a matter of months or years, as with enzymes that degrade man-made chemicals) is still a puzzle.

I will describe our research regarding promiscuous enzyme functions, and how they provide evolutionary starting points. I will show how, starting from a promiscuous starting point, we can reproduce the divergence on new enzyme functions. Many of our laboratory evolution experiments involve selection in artificial cell-like compartments. In each compartment, a single gene can be transcribed and translated to give many copies of the protein it encodes. I will show how gene-libraries of billions of enzyme variants are selected in these compartments by virtue of the linkage between the gene and the activity of the proteins it encodes.

Finally, I will address some general lessons derived from these experiments. It appears that functional promiscuity, conformational diversity, and protein modularity, are the major facilitators of enzyme evolution, thus enabling a single ‘core’ active-site chemistry to diverge into many different substrate, reaction, and product specificities.
Title to be announced

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No abstract available at printing time.
In the last several years, we have conducted structure-function studies of two different types of voltage-dependent ion channels, specifically, voltage-dependent calcium channels and voltage-dependent potassium channels. The calcium channel complexes enable the passage of Ca$^{2+}$ from the extracellular milieu into the cell while in contrast, the potassium channel complexes enable K$^+$ flow in the opposite direction. Intracellularly, Ca$^{2+}$ plays a central role in signaling and regulates processes ranging from contraction to secretion to gene transcription, while K$^+$ plays the key role in the action potential of excitable cells. Both channel complexes are important cellular signal transduction centers and therefore highly regulated by auxiliary subunits and other proteins. I will describe our recent structural and functional findings using biochemical, biophysical and crystallographic methods and ongoing experimentation that focuses on this regulation.
In Vivo Incorporation of Unnatural Amino Acids into Proteins: from Archaea to Mammals

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Recently, we have described how E. coli and S. cerevisiae translational machinery and genetic code can be manipulated in order to introduce unnatural amino acids site specifically into proteins in vivo. Since then numerous unnatural amino acids were incorporated successfully into proteins in both organisms. In both cases an efficient selection scheme was developed in order to evolve a synthetase that will charge the corresponding tRNA only with an unnatural amino acid and not with any of the other 20 natural occurring amino acids.

Particularly robust is the system that was developed for the evolution of tyrosyl synthtases in E. coli. where protein expression levels are as high as wild type protein.

Here we would like to describe how we have taken advantage of the efficient selection system for the evolution of Methanococcus jannaschii (Mj) TyrRS in E. coli and adapted it for the site specific incorporation of unnatural amino acids into proteins expressed in mammalian cells.

The suggested hypotheses for the switch between bacteria to mammalian cells and the approach that was taken to test it will be described in details, by the design of a new hybrid tRNA synthetase and the subsequent incorporation of unnatural amino acids for which tRNA synthetase was evolved in E. coli and then were incorporated into proteins in mammalian cells.
Selenoenzymes have a central role in maintaining cellular redox potential. These enzymes have selenenylsulfide bonds in their active sites that catalyze the reduction of peroxides, sulfoxides and disulfides. The selenol/disulfide exchange reaction is common to all of these enzymes and the active site redox potential reflects the ratio between the forward and reverse rates of this reaction. The preparation of enzymes containing selenocysteine (Sec) is experimentally challenging. As a result, little is known about the kinetic role of selenols in enzyme active sites, and the redox potential of a selenenylsulfide or diselenide bond in a protein has not been experimentally determined. In order to fully evaluate the effects of Sec on oxidoreductase redox potential and kinetics, glutaredoxin 3 (Grx3) and all three Sec variants of its conserved 11CXX14C active site were chemically synthesized. Grx3, Grx3(C11U) and Grx3(C14U) exhibited redox potentials of -194, -260 and -275 mV, respectively. The position of redox equilibrium between Grx3(C11U-C14U) (-309 mV) and thioredoxin (Trx) (-270 mV) suggests a possible role for diselenide bonds in biological systems. Kinetic analysis is consistent with the hypothesis that the lower redox potentials of the Sec variants result primarily from the greater nucleophilicity of the active site selenium rather than its role as either a leaving group or a ‘central atom’ in the exchange reaction. The 102 to 104-fold increase in the rate of Trx reduction by the seleno-Grx3 analogs demonstrates that oxidoreductases containing either selenenylsulfide or diselenide bonds can have physiologically compatible redox potentials and enhanced reduction kinetics in comparison with their sulfide counterparts.