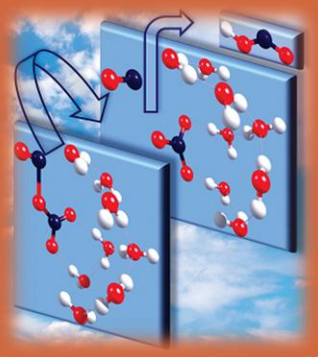
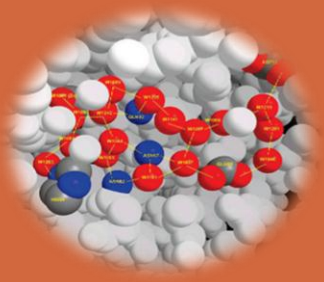
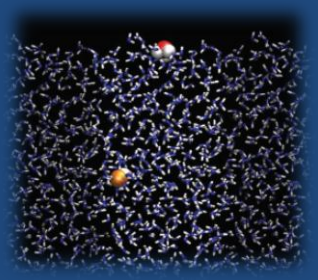
**The Hebrew University of Jerusalem**
Fritz Haber Research Center for
Molecular Dynamics


# Annual Report

2012

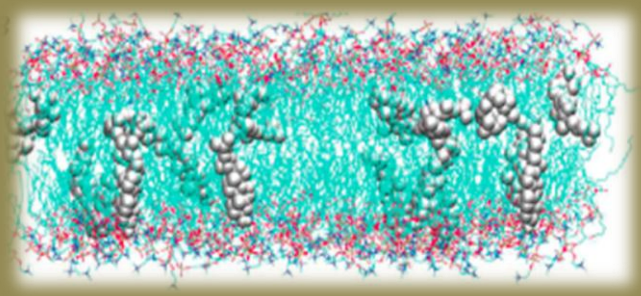






PRESENTED TO THE SCIENTIFIC ADVISORY COMMITTEE, THE BEIRAT

G. Meijer (Chair)
S. Arkin
M. Asscher
E. K. U. Gross
H. Grubmüller
N. Moiseyev
A. Nitzan



September 2012

# Table of Contents

# INTRODUCTION

The Fritz Haber Research Center for Molecular Dynamics was established in 1981 by the Minerva Foundation of the Max Planck Society and The Hebrew University. The purpose was to support and develop theoretical scientific research in the field of molecular reaction dynamics in Israel and to strengthen the scientific collaboration with German scientists in these fields. Since its inauguration, the center became a well-known establishment of molecular dynamics research in the scientific world with strong influence on the chemical and materials sciences. The scientific impact of the center can be estimated by statistical figures, discussed below, but this is not the only source of its success. At least of equal importance is that numerous graduate students completed their doctoral theses in the center, and a comparable number of post-graduate students from many countries began here their training as independent researchers. Indeed, about 4 dozens of our former students and post-docs now hold academic and research positions, and of these, a substantial number are professors at first rate academic institutions in various countries, including Germany (see Appendix 1 for details).

The original scientific focus of the center, molecular reaction dynamics, has changed in the course of time. Just as the term "molecular dynamics" evolved in science, so it developed in the center's activities. This issue as well as the goal of Israel-German collaboration is discussed in the section on the goals and activities below. As mentioned above, the mode of operation of the center and its "operational philosophy" is that the center is an umbrella for scientific research. We concentrate on offering the researchers important collective services and support for projects and collaboration with German scientists that are otherwise unachievable using regular funding venues. Details of these are described in the section below on "principles of operations".

The diversity of research topics, the scientific impact and level of collaboration with German groups are reflected in the "individual reports" and "recent publications" sections below. The individual reports include a report from each group leader of the center, as well as reports from 2 students of each group. Our collaboration with German scientists is also described in each of the reports, and we also include a special section on this topic below. This is followed by our research plan for the next 2 years. Finally, a financial report is included, followed by several appendices which give specific details concerning our activities.

## RESEARCH GOALS AND ACTIVITIES

The original focus of the research of the center emphasized molecular reaction dynamics, then at the forefront of chemical research. Over the years the field of Molecular Dynamics has evolved considerably and remains central to any fundamental physical/chemical process in matter. Thus the Molecular Dynamics field did not fade out in the course of time and, quiet contrarily, has bloomed and became even more relevant as the techniques and computer power evolved exponentially. Accordingly, the research done at the Fritz Haber Center has evolved, indeed, expanded and flourished throughout the years of its existence. Thus, the goal is still development of cutting edge molecular dynamics methods and applications but the fields of focus and scientific questions changed and with them the methods, approximations and general attitudes. As will become apparent in the individual research reports, the fields of activities by the different researchers form a significant sample of activities in the Molecular Dynamics world: quantum coherent control, charge transfer excitations, attosecond dynamics, coarse grained dynamics, quantum electronic dynamics in nanocrystals, dynamics in biophysical systems, pro-

ton-transfer dynamics in water environments and proton wires in proteins.

## PRINCIPLES OF OPERATIONS

Despite the great evolution in the fields of research over the years, described above, certain characteristics have not changed, coined by the founding director, Professor R. D. Levine, and strengthened by all subsequent directors, Professors R. Kosloff, R. B. Gerber, A. Ben-Shaul and R. Baer. These principles are the Fritz Haber operational philosophy:

1) Our scientific emphasis is on development of new theoretical and computational molecular dynamics methods for addressing the most challenging open problems in the respective fields of operations. This principle is reflected by our hiring policy, as we have in the past rejected excellent candidates because they did not focus on method development;
2) The center does not directly fund the research groups but instead offers centralized services and funds special events usually impossible to fund by "conventional sources". Thus the center forms an umbrella for a unified and high quality research environment for all students, postdocs and members, providing:
    a) The centralized computer center and communications services. The FH computing facility includes a large number of clusters composed of hundreds of computer nodes of varying strengths and capabilities. The smooth operation of these computers as well as the entire issue of computer and internet communications is overseen by a system manager, with a part time assistant which we "purchase" from the computing unit of the university. (One of our future plans is to strengthen this unit by hiring a staff PhD scientist to manage it, see below).
    b) Central common administrative and secretariat assistance, including managing salaries and tuition, travel reimbursements, guest services, help in seminar organization, as well as scientific editing, translating and typing.
    c) Academic activities organized by the center, such as the weekly Fritz-Haber seminar and the funding of many scientific meetings and workshops. A list of the recent seminars, conferences organized by members of the center and visitors is given in Appendix 2.
3) Cultivating vibrant collaboration with many science groups in Germany. Many of our visitors are from Germany; some were Minerva fellows who are now faculty members at various German academic institutes. The collaboration with German scientists is still very strong. For example, out of the ~145 papers published by scientists of the center in the past 3 years (2008-2010) 25 (more than 1/6) were in collaboration with scientists from Germany (see Figure 1).
4) The center helps its researchers draft gifted students by offering a prestigious prize (in effect - tuition stipend) for excellent 3$^{rd}$ year undergraduate students who are willing to participate in the research of a group of the center.

## INTERACTION WITH THE UNIVERSITY

Most of the principal investigators (members) of the center are faculty of the Chemistry Institute and the Faculty of Sciences of the Hebrew University of Jerusalem with the exceptions of Drs. Niv and Zemel who are faculty in the Agricultural and Medicinal Sciences respectively. The researchers of the center thus have teaching and other duties, for which they are paid by the university. The university pays part of the salary of the system administrator and is obliged by the contract with Minerva to share 50% of the funding expenses of the center. The center researchers interact strongly with some of the other researchers of the Chemistry Institute, whether directly or through joint courses, seminars etc. In addition, there is some direct scientific collaboration with other groups of the institute (examples: Kosloff-Ruhman, Harries-Friedler, Harries-Raviv, Levine – Willner, Levine – Porat, Baer – Ruhman). Non-members of the center often use its facilities, especially the computers. Until recently the system administrators of the center also supported a Chemistry Institute computer cluster which was used by many groups in the institute.

## THE BEIRAT

The Beirat oversees the operations of the Center and guides its operations. Annually, the center submits a report to the Beirat, detailing the scientific progress and activity, as well as a financial report and a budget proposal for the next year. The Beirat reports to Minerva on the program, and authorizes the budget and activities of the Center. The Beirat convenes every second year. The last meeting was held in Jerusalem in June 2009 and included an international symposium on Biophysical Dynamics (in 2011 there was a Minerva evaluation process instead of the meeting).

The members of the current Beirat are:

- Professor Dr. G. Meijer (Berlin, Germany), Chair
- Professor Dr. E. K. U. Gross (Halle, Germany)
- Professor Dr. H. Grubmüller (Göttingen, Germany)
- Professor S. Arkin, (Jerusalem, Israel, Vice President for R&D, Hebrew University).
- Professor M. Asscher (Jerusalem, Israel)
- Professor N. Moiseyev (Technion, Israel)
- Professor A. Nitzan (Tel-Aviv, Israel)

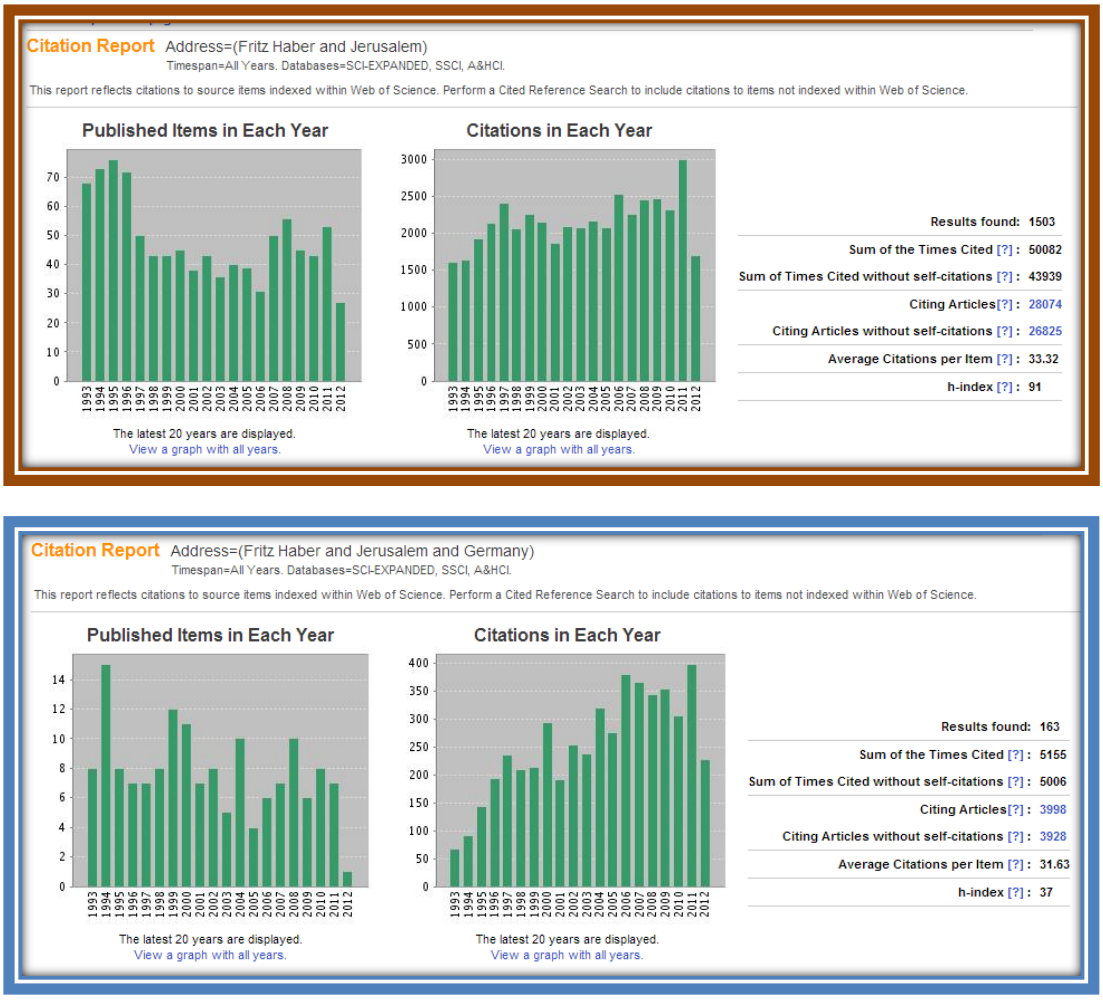



**Figure 1: Top: Citation report for the Fritz Haber Center (latest 20 years). Bottom: Citation report for joint Fritz Haber center and German publications.**

## STATISTICS OF SCIENTIFIC IMPACT

Since its inauguration the researchers of the center have published over 1500 scientific articles in refereed journals with direct affiliation to the Fritz Haber Minerva Research Center. These articles were cited in the scientific literature over 50,000 times with an average of 33 citations per paper and an "h-index" of 91 (see Figure 1). The citation rate is 3000 per year and about 50 papers are published yearly. The collaboration with

German scientist is intense, culminating in over 160 papers which were cited over 5100 times with an average of 32 citations per paper.

## PAST EVALUATION COMMITTEES

The scientific activities of the center have been extensively reviewed, 3 times, by international evaluation committees composed of world leading scientists. The first Minerva review was held in 1994 by a committee headed by Professor H. Schwarz and the second in 2002 headed by Professor Dr. H. –J. Werner. The members of the second evaluation committee were Professors E. J. Heller, W. H. Miller, M. Parrinello and K. Schulten. All reviews were based on an extensive 7 year report prepared especially for the evaluation. We also note that in 2009 an evaluation by the Beirat, chaired by Prof. Wolfgang Domcke was performed as well. In 2011 an evaluation, part of the cluster evaluation held by Minerva, was held in Jerusalem. The members of the third evaluation committee were Profs. Lorentz Cederbaum, Jürgen Gauss, Hermann Nicolai Erich Sackmann, Gerd Schön and Martin Wolf. All reports have been extremely enthusiastic, praising the achievements of the center. The reviews also provided useful advice about possible ways to improve the center's activities. The last committee recommended rejuvination of the center. In response to this recommendation, we have hired a new potential member, Assoc. Prof. Tsvi Tlusty, who will join our ranks on October 2013.

# PART I: ANNUAL SCIENCE REPORT, 2012

Originally, and in accordance with its name, research at the center has been mostly concerned with molecular reaction dynamics and closely related topics, such as laser-molecule and surface-molecule interactions. In the spirit of the period, the research has focused on processes involving small molecules and state-to-state processes, usually in the gas phase. Twenty five years later, a major part of the research carried out at the center is still concerned with molecular rate processes but emphasis has shifted towards larger and more complex systems than in the past.

Today, the characterizing theme of the center is its extremely diverse fields of operations, encompassing practically all aspects of molecular dynamics. Temperature-wise, our research starts from **$10^{-9}$ °K**, with chemical reactions of Bose-Einstein condensates; through the **1-100°K** regimes where noble-gas molecules are stable and molecular electronic devices operate; below the water freezing point **0 °C** regime for ice surfaces, and warming up to room temperature regimes where biological diversity rules and environemntal chemistry occurs; things then really start to cook up at around 1000°K which are characteristic of the diamond formation environment within Earth's Mantle; and finally intense heating up to **$10^5$ °K**, the effective temperatures achieved by powerful short pulse lasers which cause Coulomb explosion of molecules. Some of the research topics covered by the center are:

- Chemistry at water and ice surfaces
- Proton transfer processes
- Complex fluids
- Molecular dynamics with in the atmosphere
- Protein structure and dynamics
- The theory of bitter taste
- Assembly mechanism of viral particles
- Cell locomotion
- Molecular electronics
- Electronic structure
- Optical properties of nano-crystals
- Light-matter interactions and plasmonics
- Optimal Coherent Control
- Chemistry of Bose Einstein condensates
- Quantum thermodynamics
- Attosecond electron dynamics

This enlargement of scientific goals for the center has been approved, even encouraged, by past evaluation committees, in 1994, 2002 and

the extended 2002-2008 Beirat report. Indeed, we find that while strong expertise and the existence of a 'critical mass' of researchers in a specific field (molecular dynamics in our case) is imperative for success, the dialogue with researchers in neighboring fields of science is invaluable. Similarly, as attested by many joint publications, close collaboration with experimental groups is a characteristic of all research groups at the center.

The phenomena of interest, dealing mainly with dynamical, kinetic, and radiative processes, also involve a wide spectrum of inter-particle interactions and diverse molecular properties. A number of research projects are concerned with quantum effects such as chemical selectivity mediated by the coherent control of laser-matter interaction, ultra cold (nano K) chemistry, or novel architectures of quantum dots towards the development of chemically synthesized computers. At least four groups at the Center are engaged in the research of molecular or metallic clusters. These studies include the dynamics and thermodynamics of cluster-surface encounters and, on a more microscopic level, the internal dynamics, structure, spectroscopy and photochemistry of molecular clusters, especially water oligomers and ion-water complexes.

The theoretical understanding of the systems and phenomena mentioned above requires the development of new theoretical methods and sophisticated computational algorithms. Thus, all members of the Center are continuously involved in such developments and our recruitment efforts put strong emphasize on this aspect. Their record of theoretical contributions to molecular reaction dynamics, quantum nuclear dynamics, quantum electron dynamics, algebraic methods, coherent control, statistical and information theoretic approaches, diffusion kinetics, spectroscopy, quantum chemistry, protein structure and dynamics, as well as the statistical thermodynamics of complex fluids and biophysical systems are all well recognized internationally.

In the remainder of this chapter we provide a detailed scientific report concerning the research done in each of the groups of the center. The topics studied are also reflected in the lists of publications given in Part III.

# INDIVIDUAL RESEARCH PROGRESS REPORTS

## NOAM AGMON

Our main research theme in 2009 involved proton migration along hydrogen bonds (HBs) termed "proton wires", both in liquid water and in proteins.

## RESEARCH

### PROTONS ON MEMBRANES

Following a paper cited below, collaboration has been initiated with Prof. Peter Pohl, Univ. Linz, to analyze and interpret his experimental data pertaining to proton migration on membranes. The striking observation is that protons are attracted to membranes for a long time, and diffuse on the interface almost as fast as in bulk water. Diffusion theory models have been developed to fit the data and extract the physically relevant parameters.

- Noam Agmon and Menachem Gutman. Bioenergetics: Proton fronts on membranes (News & Views article). Nature Chemistry, 3, 840-842, 2011.

### INFRARED SPECTRA OF PROTONATED WATER

A post-doctoral fellow, Waldemar Kulig, is simulating the IR spectrum of a proton in both protonated water clusters and protonated liquid water. This research has concentrated on two bands that we believe were overlooked before, but are of significance for proton mobility in water:

a) **The proton transfer mode**: In liquid water the Zundel cation, $H_2O...H^+...OH_2$, transfers the excess proton between the two flanking water molecules. The proton transfer mode (PTM) is the asymmetric stretch of the central $O...H^+...O$ moiety. Yet, it has no accepted identification in the IR spectra of acidic aqueous solutions. In experiments of protonated gas phase water clusters it shifts with cluster size, making the connection with the solution spectra unclear. In paper [4] we have introduced a "clusters-in-liquid'' approach for calculating the IR spectrum from any set of charges, even single protons. We have applied this procedure to Multi-State Empirical Valence Bond trajectories of protonated liquid water, and to ab-initio molecular dynamics (AIMD) of the protonated water dimer and hexamer in the gas-phase. The calculated PTM is manifested in both systems as a peak near 1740 $cm^{-1}$, in quantitative agreement with a band of a similar frequency in the experimental IR spectrum of protonated water clusters.

b) **The "special-pair dance" mode**: In previous joint work with the Voth group, we have found that the distorted Eigen complex in protonated liquid water has interesting dynamics, where the nearest ligand changes identity on a timescale of about 50 fs. In this process, the center of excess charge (CEC) moves around the central oxygen atom of the Eigen complex, so it is expected to have a spectral signature in low frequency IR. Using classical nuclear dynamics with MS-EVB3, we have identified this band around 350 $cm^{-1}$. **A** student in the Voth group is currently running the nuclear dynamics quantum-mechanically using Centroid Molecular Dynamics (CMD). We plan to repeat the analysis on this quantum trajectory, to verify that quantum effects do not "wash-out" this spectral feature. Subsequently, we also hope to have it verified experimentally.

c) **Volume reactivity model for geminate recombination.** A post-doctoral fellow, Svetlana Khokhlova, has worked to obtain an alternative formulation for diffusion-influenced reversible geminate recombination. Instead of a pair reacting at contact, one particle can diffuse within the volume of the other. This is depicted by a generalization of the celebrated Feynman-Kac equation, extensively used in the theory of random walks. We have solved the ensuing equation in Laplace space for a reversible reaction, where a pair can both bind and unbind. In a first work [3], we obtained the solution for an initially bound pair. In a more recent work [5], we have obtained the Green func-

tion (in three dimensions) for any initial separation of the geminate pair.
Because an analytic solution can be obtained only in Laplace space, this solution is inverted numerically into the time domain and compared with a direct solution of the relevant PDE using our SSDP software.

**References:**


1) Noam Agmon and Menachem Gutman, Bioenergetics: Proton fronts on membranes (News & Views article). NATURE CHEMISTRY, 3 :840-842, 2011.
2) Noam Agmon, Liquid water: From symmetry distortions to diffusive motion. ACCOUNTS OF CHEMICAL RESEARCH, 45 :63-73, 2012.
3) Svetlana S. Khokhlova and Noam Agmon, Comparison of alternate approaches for reversible geminate recombination. BULLETIN OF THE KOREAN CHEMICAL SOCIETY, 33 :1020-1028, 2012.
4) Waldemar Kulig and Noam Agmon, Clusters-in-liquid IR identifies the proton transfer mode in acidic aqueous solution, submitted for publication.
5) Svetlana S. Khokhlova and Noam Agmon, Green function for volume reactivity of a diffusing particle: The reversible Feynman-Kac equation. To be submitted.


## PROTON WIRES IN CARBONIC ANHYDRASE AND GFP

A program for mapping proton wires in proteins has been developed by Mrs. Ai Shinobu during her M.Sc. work. Protons cannot migrate, like electrons, in vacuum or along the sigma bonds of a protein. Their motion requires a network of HBs, predominantly between (water or protein) oxygen atoms which are separated to 3 Å or less. Some proteins are flexible, and then HBs break and form continuously. But other proteins (such as the green fluorescent protein, GFP) are rigid and then a large fraction of the HB networks may be visible from its X-ray structure. Yet, to-date there has been no systematic effort in mapping proton wires in proteins. Mrs. Shinobu has done just this, through a computer program that uses X-ray structures from the Protein Data-Bank (PDB) to divide all HBed atoms in a protein into exclusive clusters, so that in each cluster there is a continuous pathway between any 2 atoms in the cluster, whereas there is no pathway connecting different clusters.

When applied to GFP, the program finds substantially larger clusters than those reported in the literature. Particularly notable is the discovery of a second large internal cluster on the other side of the chromophore than the "active-site cluster" reported before. This cluster is disconnected from the active site, so that the question is what may be its functional role? Our hypothesis is that it functions in executing PT reactions pivotal for the chromophore biosynthesis known to occur after protein folding takes place. There are 4 such PT steps, the last suggested to be extraction of a proton from a bridge carbon of the chromophore to create a carbanion intermediate. We suggest that Thr62, which is located on the new wire, may rotate to pick up this proton and deliver it to the new HB wire, as shown in Figure 2. The delocalization of the proton on this cluster then allows time for completion of the last dehydration step required to form the conjugated system.

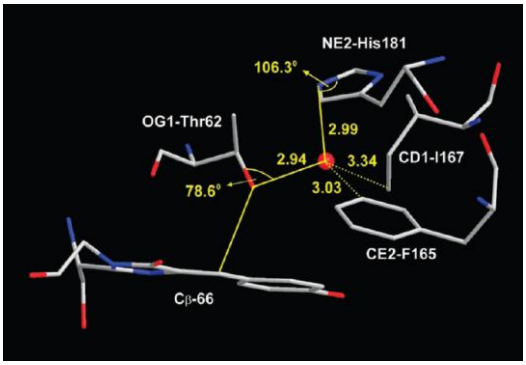



**Figure 2: Rotation of Thr62, perhaps together with a migration of a water molecule, are conjectured to play a role in the extraction of a proton from the C-beta carbon of Tyr66, which then becomes part of an extended pi-system of the GFP chromophore.**

In human carbonic anhydrase a proton exit pathway frequently discussed in via the rotation of His64. Other pathways are rarely ever discussed. We have found that there are pathways leading up from the "active site caldera", where the $Zn^{+2}$ center resides, to a bunch of carboxylates (Figure 3). These may act to trap a proton from solution and channel it along the surface

and into the active site whenever the enzyme operates in the reverse, dehydration direction.

References:


- A. Shinobu and N. Agmon, J. Phys. Chem. A 113, 7253–7266 (2009).

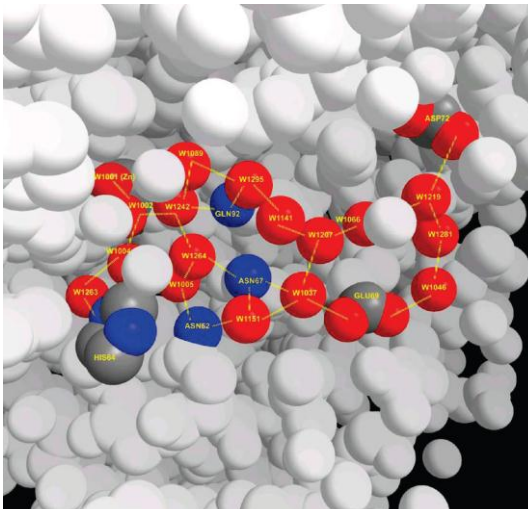




**Figure 3: A HB network extends from Tyr66 on the GFP chromophore, via the internalized Glu222 residue all the way to the surface of the barrel-structured GFP.**

## PROFESSOR AGMON'S GROUP 2008-2012

| Name | Status | Presently |
|---|---|---|
| **Hadas Lapid** | MSc | Ph.D. student at Weizmann Inst. |
| **Omer Markovitch** | MSc, 2008 | Ph.D. student at Weizmann Inst. |
| **Ai Shinobu** | PhD | Near graduation |
| **Dr. Soohyung Park** | Postdoc 2007-2008 | 2nd Postdoc Prof. Arun Yethiraj, Univ. Wisconsin |
| **Dr. Waldemar kulig** | Postdoc | Current |
| **Dr. Svetlana S. Khokhlova** | Postdoc | Current |

## SCIENTIFIC COLLABORATIONS

| Name | Institution |
|---|---|
| **Prof. Dr. Wolfgang Rettig** | Humbolt University, Berlin, Germany |
| **Prof. Dan Huppert** | Tel-Aviv University, Israel |
| **Prof. Attila Szabo** | NIDDK, NIH, Bethesda MD, USA |
| **Dr. Irina Gopich** | NIDDK, NIH, Bethesda MD, USA |
| **Prof. Kook-Joe Shin** | Seoul National Univ., Seoul, S. Korea |
| **Prof. Gregory A. Voth** | Univ. Utah, Salt Lake City UT, USA |
| **Prof. Joel M. Friedman** | Yeshiva Univ., Bronx NY, USA |
| **Prof. Huib J. Bakker** | FOM Institute for Atomic and Molecular Physics, Amsterdam, Nederland |
| **Dr. Gottfried J. Palm** | Univ. Greifswald, Germany |

## ACTIVE GRANTS

| Project | Period | Foundation | Total Grant |
|---|---|---|---|
| **Proton Mobility in Complex Environments** | 2011-2014 | US-Israel Binational Science Foundation | $84,000 |
| **Water Dynamics and Proton Mobility** | 2008-2012 | Israel Science Foundation | 600,000 ₪ |

| | | | |
|---|---|---|---|
| **Gentner Symposium 2010 (awarded 2008): "Proton Mobility in Chemical and Biological Systems"** | 2008 | Minerva Foundation | € 61,000 |
| **Protons in Water, Membranes and Proteins** | 2012-2015 | Israel Science Foundation | |

## CONFERENCE ORGANIZATION (PAST 5 YEARS)

| No. | Conference |
|---|---|
| **1** | Research Workshop of the Israel Science Foundation on "Diffusion, Solvation and Transport of Protons in Complex and Biological Systems" (Org. Ehud Pines). Hilton Queen of Sheba Hotel, Eilat, January, 13 - 17, 2008. Organizing Committee. |
| **2** | Organizer, 2010 Gentner Symposium on "Proton Mobility in Chemical and Biological Systems". To be held in Ma`agan, Lake of Galilee, Feb 7-12, 2010. Organizing committee: Shy Arkin, Klaus Gerwert and Helmut Grubmüller. |

## EDITORIAL BOARDS

1. The Israel Journal of Chemistry.
2. PMC Biophysics.

# ROI BAER

The 2007-2012 research in Roi Baer's group revolves mainly around developing new density functional and time-dependent density functional theories (DFT and TDDFT). Our methods allow applications of DFT to systems which were previously unattainable, such as charge transfer excitations, structure and properties of radical cations and band electronic structure of solids and large clusters. Some of these works are done in collaboration with Kronik's group in WIS, Daniel Neuhauser (UCLA) and Ulrike Salzner (Bilkent). Another venue is we have pursued is concerns fundamental concepts in the description of conical intersection in density functional theory, as described below. We have also studied electronic processes in nanocrystals and nanotubes, focusing on multiexciton generation (in collaboration with the Rabani group in TAU). Recently we developed new concepts in application of Monte Carlo methods to density functional theory.

## RESEARCH

### NEAR-FIELD MANIPULATION OF SPECTROSCOPIC SELECTION RULES ON THE NANOSCALE

(The theoretical part of this work is done in collaboration with Eran Rabani from TAU; the experimental work was primarily done by Prahsant Jain from the group of Paul Alivisatos in Berkeley).

In conventional spectroscopy, transitions between electronic levels are governed by the electric dipole selection rule, since electric-quadrupole, magnetic dipole, and coupled electric dipole-magnetic dipole transitions are forbidden in a far-field. We demonstrated that by using nanostructured electromagnetic fields, the selection rules of absorption spectroscopy can be fundamentally manipulated. We showed that forbidden transitions between discrete quantum levels in a semiconductor nanorod structure become allowed due to the near-field of a closeby noble metal nanoparticle. We used atomistic simulations analyzed by an effective mass model to show the breakdown of the dipolar selection rules finding that both "quadrupole" and "octupole" transitions become allowed. Our demonstration can be generalized to the use of nanostructured near-fields for enhancing light-

matter interactions that are typically weak or forbidden.

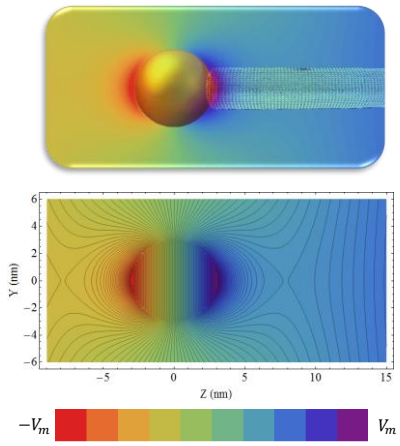



**Figure 4: Top: A schematic illustration of the geometry of a metal tipped nanorod used to model the effect of a near-field on the optical transitions of a nanoscale system. Bottom: isopotential contour lines of the near-field potential generated by a gold nanoparticle of 6nm diameter. $V_m$ is the maximal potential on the surface of the gold nanoparticle (see supporting information).**

The system studied is a semiconductor (CdSe) nanorod in close proximity to a gold nanosphere which acts as a near-field source schematically shown in Figure 4. The resonant near-field of the metal nanoparticle. produced under light excitation (polarized along the nanorod long-axis, assumed in the z direction), penetrates into the nanorod on one side, rapidly decaying away from the metal nanoparticle surface, providing a strong field gradient in the direction of the long-axis. When the system is exposed to a homogeneous external field $E(t) = E_0 e^{i\omega t} + cc$, oscillating at frequency $\omega$, the nanorod is subject to an electric potential $\phi(\boldsymbol{r}, \omega)$ and will undergo optical transitions, with a rate of absorption given by: $\Gamma(\omega) \propto \sum_{aj} \left|\langle \psi_a | \hat{\phi}(\omega) | \psi_j \rangle\right|^2 \delta(\varepsilon_a - \varepsilon_j - \hbar\omega)$ where $\varepsilon_a$ and $\varepsilon_j$ are, respectively the electron and hole eigenenergies, and $\psi_a(\boldsymbol{r}), \psi_j(\boldsymbol{r})$ are the corresponding orbitals. The above expression reduces to the well-known dipolar absorption spectrum when $\phi(\boldsymbol{r}, \omega) = -E_0 z$ for a uniform electric far-field. The conventional selection rules $\langle \psi_a | \hat{z} | \psi_j \rangle \neq 0$ are replaced by $\langle \psi_a | \hat{\phi}(\omega) | \psi_j \rangle \neq 0$.

The calculated absorption rate of CdSe and CdS nanorods (of length $L = 20\,nm$ and diameter $D \approx 2.8nm$ for CdSe and $D \approx 2.5nm$ for CdS) as a function of the size of the metal tip is shown in Figure 5. The spectra show two distinct peaks, which can be associated with transitions to different transverse bands composed of many longitudinal transitions. The spectra exhibit a small blue-shift as the metal tip diameter increases (see inset), and saturates above a metal tip diameter of ~6nm (see below for a detailed discussion of the blue shift). The saturation can be traced to two competing effects: The spatial extent by which the near-field decays into the rod (which would result in larger shifts as the diameter of the tip increases) versus the shortening of the electron/hole longitudinal wave length as the energy of the transition increases. A more dramatic effect observed in the near-field absorption spectrum is the enhancement of the absorption rate as the metal tip diameter increases, analogous to the surface enhanced Raman scattering phenomena.

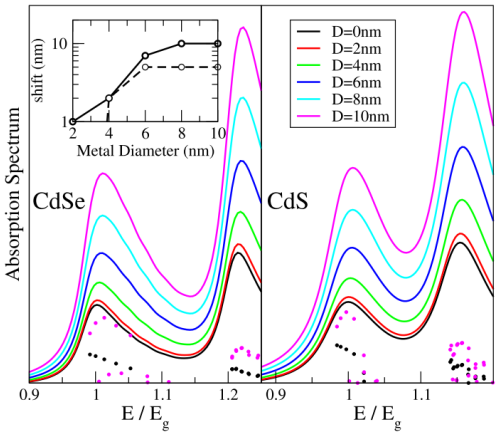



Figure 5: The absorption rates in CdSe (left) and CdS (right) 20 nm nanorods of aspect ratio 7½ (see SI for full details). The lines represent results for different metal tip diameters ranging from zero (black) to 10 nm (magenta) in steps of 2 nm. The relative oscillator strengths for the strongest transitions are also shown for individual transitions for the smallest and largest metal tip sizes. Inset: The absorption maximum (blue) shift as a function of metal tip diameter. Solid and dashed lines correspond to CdSe and CdS, respectively.

In Figure 5, we also show oscillator strengths of individual transitions calculated from the detailed atomistic model. The dipole allowed transitions, shown as black dots, can be associated with the electron-hole excitations of different longitudinal waves that follow the effective mass model selection rules $k_e = k_h$. Transitions that violate this selection rule while strictly forbidden in the effective mass model are weakly allowed in the atomistic calculation. But these transitions are not plotted in Figure 5 as their weak in intensity is below the threshold used to plot significant optical transitions. The lowest transition observed is $k_e = k_h = 1$, and higher transitions involve $k_e = k_h = 2$, and so on. In the effective mass model these transitions have identical oscillator strengths while in the atomistic calculation they decay with increasing $k_e = k_h$.

The transitions in the presence of the metallic tip are shown as magenta dots in Figure 5 for the largest tip studied. The near-field of the metal tip induces two novel phenomena:

- The strongest "dipole-allowed" transition is no longer at $k_e = k_h = 1$ but at a higher value depending on the size of the tip ($k_e = k_h = 3$ for the case shown) which contributes to the blue-shift observed in the absorption.
- More strikingly, we observe a large oscillator strength associated with transitions with selection rules $\mathrm{k_e} = \mathrm{k_h} \pm 1$ ("quadrupole allowed"), $\mathrm{k_e} = \mathrm{k_h} \pm 2$ ("octupole allowed"), etc. which are "dipole-forbidden" and therefore negligible in intensity in a far-field. In the effective mass approximation these transitions become allowed in the presence of a near-field, since $\langle \psi_a | \delta\hat{\Phi}(\omega) | \psi_j \rangle$ is non-zero even when $\mathrm{k_e} \neq \mathrm{k_h}$. These "dipole-forbidden" transitions appear at higher energies and also contribute to the blue-shift in the spectrum.

❖ P. K. Jain, D. Ghosh, R. Baer, E. Rabani, and A. P. Alivisatos, "Near-field manipulation of spectroscopic selection rules on the nanoscale", Proc. Natl. Acad. Sci. **109**, 8016-8019 (2012).

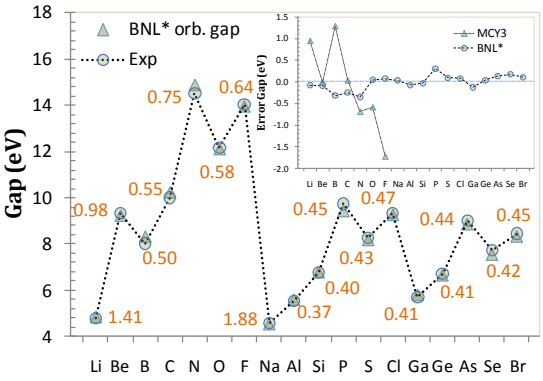



**Figure 6: GKS/BNL* HOMO-LUMO gaps (computed using the aug-cc-pVTZ basis set), compared with experimental fundamental gaps. The value of γ (in $a_0^{-1}$), determined by minimizing *J*, is indicated near each point. Inset: the deviation from experiment of GKS HOMO-LUMO gaps based on BNL* (this work) and MCY3.**

## FUNDAMENTAL GAPS OF FINITE SYSTEMS FROM THE EIGENVALUES OF A GENERALIZED KOHN-SHAM METHOD

We developed a broadly-applicable, physically-motivated first-principles approach to determining the fundamental gap of finite systems from single-electron orbital energies. The approach is based on using a range-separated hybrid functional within the generalized Kohn-Sham approach to density functional theory. Its key element is the choice of a range-separation parameter such that Koopmans' theorem for both neutral and anion is obeyed as closely as possible. We demonstrated the validity, accuracy, and advantages of this approach on first, second and third row atoms (Figure 6), the oligoacene family of molecules, and a set of hydrogen-passivated silicon nanocrystals (Figure 7). This extends the quantitative usage of density functional theory to an area long believed to be outside its reach.

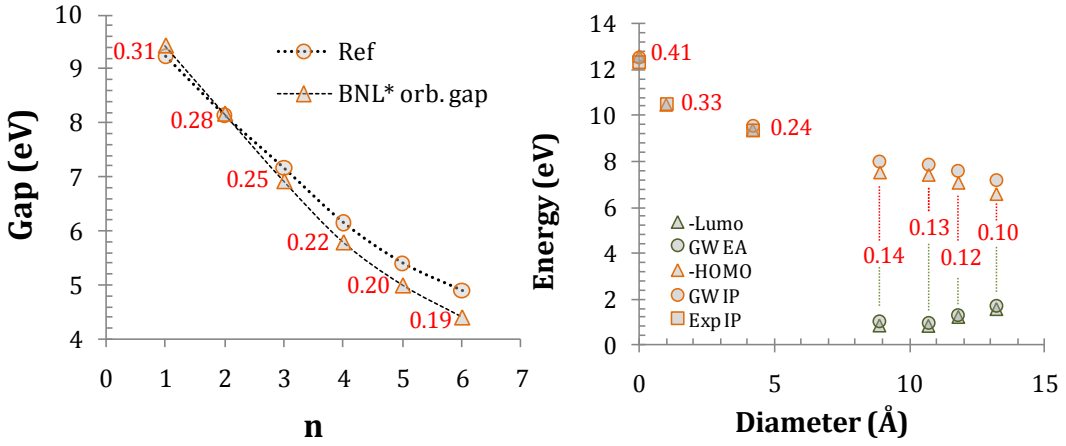



**Figure 7: Left: GKS/BNL* HOMO-LUMO gaps, compared with gaps computed from experimental (vertical) ionization potentials and best estimates of vertical electron affinities, for the polycyclic aromatic hydrocarbon linear oligomers , $C_{2+4n}H_{4+2n}$, with *n*=1 (benzene) to 6 (hexacene). The value of γ, determined by minimizing *J*, is indicated near each point. Right: GKS/BNL* HOMO and LUMO energies compared to GW and experimental ionization potentials (IP) and electron affinities (EA) of hydrogen terminated nano-crystalline spherical silicon fragments, as function of diameter. The values of the tuned range parameter are shown in red. In both systems the cc-pVTZ basis set was used. Geometries were obtained from a B3LYP calculation for the oligoacenes and from ref. for the Si nanocrystals.**

❖ T. Stein, H. Eisenberg, L. Kronik, and R. Baer, "Fundamental gaps of finite systems from the eigenvalues of a generalized Kohn-Sham method", Phys. Rev. Lett. 105, 266802 (2010).

## NON-MECHANICAL CONDUCTANCE SWITCHING IN A REALISTIC MOLECULAR TUNNEL JUNCTION

We proposed a molecular junction (Figure 8) with which it is possible to achieve excellent control of conductance. The junction has source-drain as well as gate electrodes, similar to a transistor, but the principle of operation is different. It is physically appealing since the gate strongly affects the HOMO-LUMO gap. We used our DFT method with which the orbital energies of the molecule have a physical meaning and therefore respond to the gate in a physical way (semilocal DFT orbital energies do not have this behavior).

To understand the operation, let us consider charge carriers in the molecule. The creation of a hole involves investment of energy $I$ (ionization energy), with $-I$, closely approximated by the highest occupied molecular orbital (HOMO) energy $\varepsilon_H$. In the quasiparticle picture, the hole has a single-particle wave function, described as a frontier DFT orbital on one of the donors (orbitals 1 or 3 of Figure 9). Similarly, addition of an electron to the molecule, releases energy equal to the electron affinity, $A$, which is closely approximated by the lowest unoccupied molecular orbital (LUMO) energy $\varepsilon_L$. The quasielectron wave function is orbital 2 in Figure 9, localized primarily on the MN acceptor.

We note that the donor orbitals 1 and 3 are spatially non-overlapping, with orbital 1 having slightly higher energy. This non-mixing of these left and right orbitals is due to an *interference effect* appearing when the PA segments are connected to the benzene ring in the *meta* positions where they become electronically decoupled.

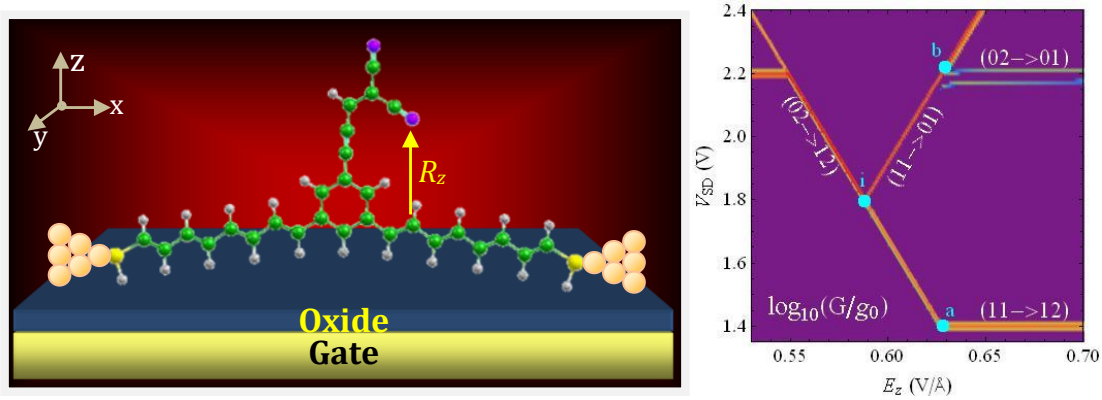



**Figure 8: Left: Schematic depiction of the molecular junction: two thiol-terminated short trans-polyacetylene (PA) segments $(SH-(HC=CH)_4-)$, acting as meta substituents on the aromatic ring of a 2-(3-phenylprop-2-ynylidene) malononitrile molecule. The thiol group facilitates bonding to gold metallic source drain electrodes. The PAs are electron donors determining the ionization potential ($I$~7 eV) of the molecule while the MN is an electron acceptor, endowing the electron affinity $A$~1 $eV$. The molecular plane is parallel to x-z plane and lies above a planar gate electrode which is parallel to the x-y plane. The latter creates an electric field $E_z$ in the vertical direction. The smallest vertical distance between MN and PA is large ($R_z \approx 5.9$Å), facilitating the high tunability of the fundamental gap $I-A$ by $E_z$. Due to interference effects, electric current cannot flow through the aromatic ring from left to right PAs but must go instead through the MN. Thus $E_z$ also controls the differential conductance channel of the junction. Beyond a critical gate field $E_z^* \approx 0.63V/$Å spontaneous intramolecular electron transfer occurs from PA to MN. Right: The conductance of the junction as a function of source drain voltage $V_{SD}$ and gate field $E_z$.**

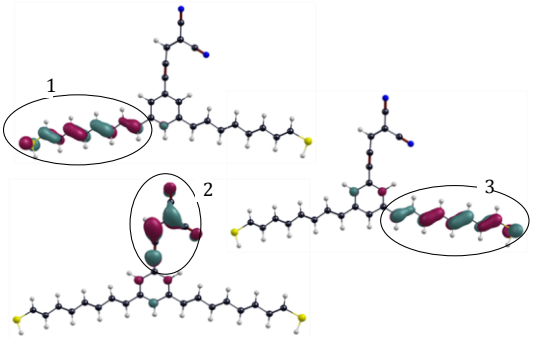



**Figure 9: Graphical depiction of three frontier orbitals dominating the electronic properties of the junction. The occupied orbitals 1 and 3 (localized on the left and right donors) and the unoccupied orbital 2 (localized on the acceptor). The energy of orbital 1 is slightly higher than that of 3.**

How does a negatively charged gate electrode in the x-y plane *below* the molecule affects its electronic structure? The electrode creates an electric field in the z direction $E_z$, or a potential difference $e\epsilon^{-1}\bar{z}E_z$ between the electron on MN and the hole on PA, displaced by a distance $\bar{z}$ and where $\epsilon$ is the molecular dielectric constant. Therefore, the gate-field affects the electron-hole energy gap as:

$$\varepsilon_g(E_z) = \varepsilon_g(0) - \frac{e}{\epsilon}\bar{z}E_z. \qquad (1)$$

In Figure 10 (left) we plot the DFT-calculated orbital gap $\varepsilon_g$ vs. the gate field $E_z$, showing linear dependence, from which:

$$-\frac{d\varepsilon_g}{dE_z} = 5.1e\text{Å} \equiv \frac{e}{\epsilon}\bar{z} \qquad (2)$$

An abrupt change in the gap occurs at a certain critical value of the field $E_z^* = 0.63$ V/Å. This critical behavior is due to a spontaneous charge transfer induced by the gate, clearly seen in Figure 10 (right), where the dipole moment and charge on the MN acceptor jump discontinuously at $E_z^*$. We have carefully checked, that if the sulfur atoms are held in place (as happens when the molecule is connected to the metallic leads), the geometry of the molecule is only slightly distorted by this internal electron transfer.

In Mulliken's theory, the energy of electron transfer from donor to acceptor is $E_{CT}(E_z) = I(E_z) - A(E_z) - E_{eh} \approx \varepsilon_g(E_z) - E_{eh}$ where $E_{eh} = \frac{e^2}{4\pi\epsilon_0\epsilon\bar{z}}$ is the energy of Coulomb attraction between the electron and hole. Charge spontaneously transfers from donor to acceptor once $E_{CT}(E_z) \le E_{CT}(E_z^*) = 0$ so from Figure 10 (left):

$$E_{eh} = \frac{e^2}{4\pi\epsilon_0 \epsilon \bar{z}} = \varepsilon_g(E_z^*) = 1.9eV. \qquad (3)$$

Using Eqs. (2)-(3) we can estimate the internal dielectric constant $\epsilon = 1.2$ and the electron-hole effective z-displacement $\bar{z} = 6.2\text{Å}$, the latter is in agreement with the minimal donor-acceptor z-displacement $R_z = 5.9\text{Å}$.

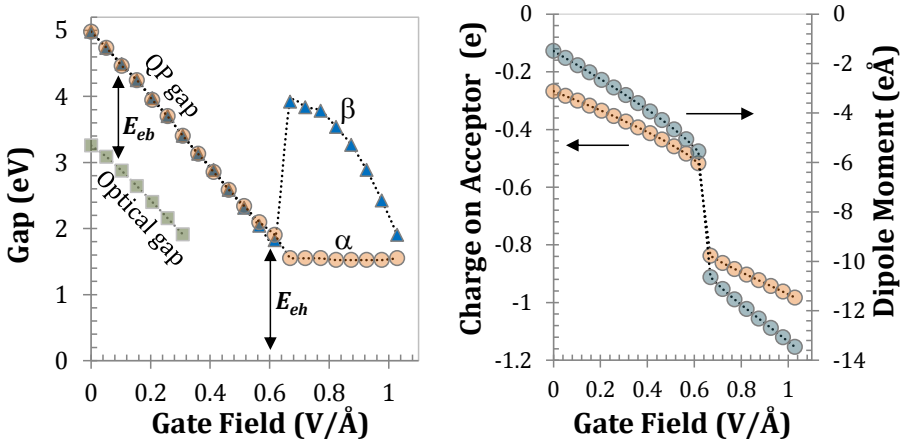



**Figure 10: BNL*-DFT spin-polarized LUMO-HOMO (quasi-particle) gap and TDDFT optical gap (left), z-component dipole moment and Mulliken charge on cyano groups (right) vs. gate field.**

In Figure 10 (left) we also plot the optical gap $\varepsilon_{opt}$, calculated from linear response TDDFT using the same functional. $\varepsilon_{opt}$ is the first excitation energy corresponding to a transition dipole moment pointing in the z direction. Note that $\varepsilon_{opt}$ depends linearly on $E_z$, predicting strong electro-absorption effects for z-polarized light in this junction. It is readily visible in Figure 10 (left) that the exciton binding energy, namely the difference $E_{eb} = \varepsilon_g - \varepsilon_{opt}$ ≈1.7 eV, is nearly constant. That the value of $E_{eb}$ is close to that of $E_{eh}$ of Eq. (3) is no coincidence as both describe electron-hole attraction energy.

Once $E_z > E_z^*$, i.e. the field is strong enough to induce charge transfer, a spin α (say) electron moves from one of the donors (orbitals 1 or 3) into the orbital localized on the acceptor (orbital 2). Orbital 2, the previous LUMO, now has its energy spin-dependent: the $\alpha$ orbital energy drops abruptly slightly *below* the HOMO level (due to the electron-hole binding energy $E_{eh}$ discussed above) and it get occupied by an electron while the $\beta$ orbital energy shoots up in energy above some of the other unoccupied levels of the PAs. This latter effect is due to Coulomb repulsion: the energy to add a *second* electron to the acceptor is much higher now, due to the presences of the first transferred electron. Thus, immediately after the charge transfer orbital 2 is no longer a frontier orbital: both the $\alpha$ and $\beta$ LUMOs are now donor orbitals and as a result the α and β gaps become independent of $E_z$. Further increase of the field lowers the energies of both spin components of orbital 2. The $\alpha$ component digs deeper into the occupied levels but the $\beta$ component energy reduces until it resumes its role as the LUMO at $E_z > 0.8\,V/\text{Å}$ making the $\beta$ gap once again field dependent.

Thus far, we discussed this donor-acceptor system as a molecule and not as part of a molecular junction. The junction we consider is formed by attaching the molecule to left and right metallic leads of chemical potential $\mu$. The thiol-terminated PA segments provide for very weak coupling and the molecule preserves much of its chemical and electronic properties: its orbitals and its orbital energies slightly shift to sharp differential conductance resonance channels. We imagine an experimental setup where the energy needed to transfer an electron from the molecule to the metal, i.e. $\mu - \varepsilon_H$ is controlled and kept fixed for all values of the gate field (in our

case, $\mu - \varepsilon_H = 1.1\ eV$). We assume a symmetric application of the bias potential $V_{SD}$ across the leads, where the chemical potential of the left (right) lead is $\mu + eV_{SD}/2$ ($\mu - eV_{SD}/2$). In this setup experimental realization of current through a resonance at energy $\varepsilon = E + \mu$ requires a bias of $V_{SD} > 2|E|$.

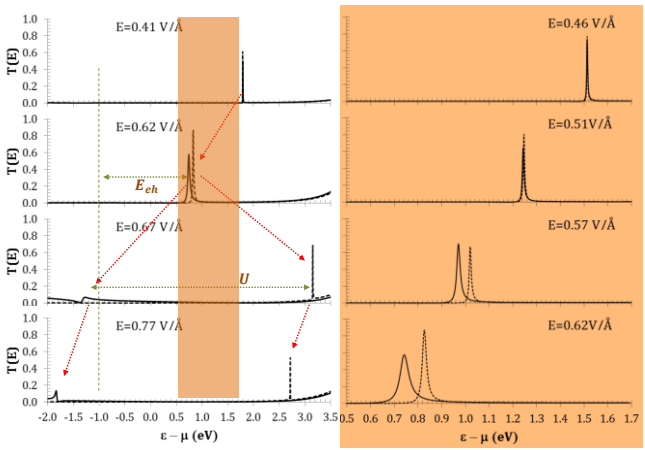



**Figure 11: The calculated transmittance function $T(E)$ through the junction, assuming clamped nuclei, from the zero bias BNL* Hamiltonians (Eq. (4)) at different gate fields. On the left, a broad energy view of the transmission channels, from $\epsilon - \mu = -4$ to $3\ eV$ at several gate fields and on the right a zoom into the energy range of 0.5 to 1.7 eV for gate fields, before the charge-transfer event. The full (dotted) line is the transmission of the α (β) spin states. The vertical line at -1.1eV is the position of the HOMO energy.**

We study the differential conductance of the junction using Landauer's theory, based on the ground-state DFT Hamiltonian where the peaks of the transmittance $T(E)$ (the probability for an electron of energy $\varepsilon = E + \mu$ to cross the junction from left to right) are directly associated with the differential conductance channels. In weakly bound junctions these position of these peaks are close to the quasiparticle energies which are close to the orbital energies of our DFT Hamiltonian. The transmittance $T(E)$ is calculated by:

$$T(E) = 4\ tr\{G^{\dagger}(\varepsilon)\Gamma_L G(\varepsilon)\Gamma_R\}, \qquad (4)$$

Where $\Gamma_i$ $(i = L, R)$ are absorbing potentials laid on the left and right PA segments and $G(\varepsilon)$ is the Green's function corresponding to the DFT Hamiltonian (see ref. for further details and explanations of this method).

The calculated $T(E)$, is plotted in Figure 11 for several values of the gate field $E_z$. Remarkably, at a very broad energy interval ($-4eV < E < 3eV$) the system displays only a *single* transmittance peak (which, under sufficiently large gate field, may split into two spin-polarized components, as discussed below). While there are many occupied and some unoccupied orbitals associated with the PA strands in this energy range (e.g. orbitals 1 and 3 in Figure 9), none of them seem to conduct current. This is due to the strong destructive interference effect associated with the connection of the PA strands in a meta-position on the benzene ring. The position of the conductance peak, with respect to the HOMO energy (the vertical line in Figure 11 (left)), is almost exactly equal to the gap $\varepsilon_g$ (Figure 10 (left)), indicating that transmission occurs through the LUMO orbital, i.e. orbital 2 of Figure 9, mainly localized on MN - the electron acceptor part of the molecule. Thus, the $T(E)$ peak at low fields corresponds to tunneling transmission of electrons through orbital 2. As a result, the source-drain voltage needed for reaching this conducting state is tunable by $E_z$. This can be seen in the right panel of Figure 11 zooming into the orange strip region of Figure 11 (left). As the gate field $E_z$ increases (by steps of $\approx 0.03 - 0.05V/\text{Å}$) the $V_{SD}$ position of the conductance peak drops by steps of $\approx 0.3eV$. This high tunability of differential conductance facilitates a

transistor-like operation mode for the junction, as current is reversibly switched on/off by the gate field.

As the gate field $E_z$ approaches the critical value $E_z^*$, the differential conductance resonance splits into two resonances of slightly different energies (Figure 11 (right)), each corresponding to a different value of the z-component of spin. At the critical gate field $E_z^*$ a catastrophic spin-split occurs: one spin resonance (say, spin α) shoots down in energy below the HOMO level (vertical line in Figure 11 (left)), gets occupied by an $\alpha$ electron and becomes a hole conducting channel, while the other resonance shoots up in energy and becomes an electron conducting channel. The energy splitting between these two spin resonances for gate fields slightly above $E_z^*$ is $U = 4.3eV$. As explained above, the drastic change of electronic structure happens because of the intramolecular charge transfer: a α electron transfers from one of the frontier orbitals (orbitals 1 or 3 of in Figure 9) of the donors to orbital 2 of the acceptor. Since the acceptor now populates an electron, conductance of $\beta$ electrons is blocked due to Coulomb repulsion (unless $V_{SD}$ is considerably increased). As the field $E_z$ is further increased beyond $E_z^*$, the hole differential conductance peak still responds to the field and can be further lowered, resulting in highly controllable spin-polarized differential conductance channel.

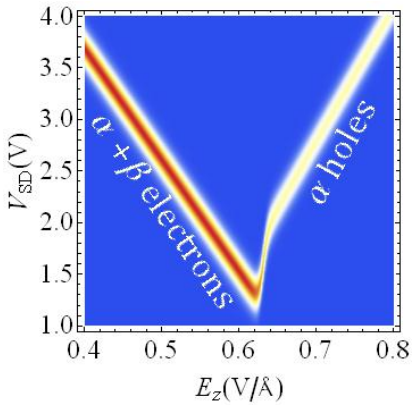



**Figure 12: Expected differential conductance of the molecular junction in Figure 8 as a function of gate field and source-drain voltage.**

We have also built a Hubbard model for this system which allows the study of non-equilibrium effects. The conductance patter is shown in Figure 8 (right). The non-equilibrium effects are the lines not seen in the equilibrium conductance of Figure 12.

❖ A. Baratz and R. Baer, "Nonmechanical Conductance Switching in a Molecular Tunnel Junction", J. Phys. Chem. Lett. **3**, 498-502 (2012).

## GROUND-STATE DEGENERACIES LEAVE RECOGNIZABLE TOPOLOGICAL SCARS IN THE ONE-PARTICLE DENSITY

In Kohn-Sham density functional theory (KS-DFT) a fictitious system of non-interacting particles is constructed having the same ground-state (GS) density as the physical system of interest. A fundamental open question in DFT concerns the ability of an exact KS calculation to spot and characterize the GS degeneracies in the physical system. In this work we provided theoretical evidence suggesting that the GS density, as a function of position on a 2D manifold of parameters affecting the external potential, is "topologically scarred" in a distinct way by degeneracies.

We consider 2-fold degeneracies and real Hamiltonians (no magnetic interactions). A basic notion is a 2D manifold of arbitrary parameters, $X$ and $Y$, that affect the external potential of a particle system (system I). The external potential is a function on the manifold $v\ \mathbf{r};X,Y$ and by solution of the Schrödinger equation, this potential produces a manifold of GS densities $n\ \mathbf{r};X,Y$. From the non-crossing rule it follows that in most 2D manifolds 2-fold degeneracies will appear as isolated points and higher degeneracies are practically never seen. A 2-fold degeneracy point can be assumed at the origin and polar coordinates used: $X = R\cos\phi$, $Y = R\sin\phi$. The density at the degeneracy is not well defined as there a continuous infinity of densities, corresponding to the infinite ways of combining the degenerate states. When the degeneracy is approached from a given direction $\phi$

on the manifold the density converges towards a limit function $n(\boldsymbol{r};\phi)$ (see Figure 13). This non-analytical behavior on the manifold is "the topological scar".

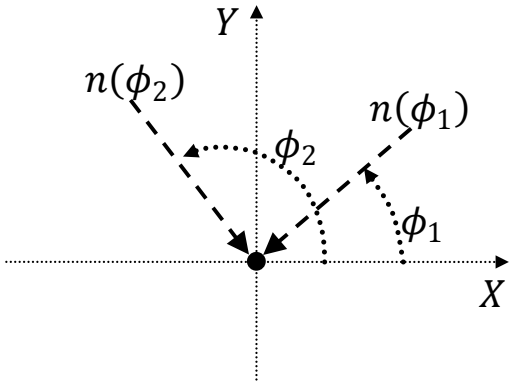



**Figure 13: The "topological scar": $n\ \phi_1$ and $n\ \phi_2$ are particle densities along two distinct paths converging into the same manifold point. If they are different a GS degeneracy exists in system I.**

Our paper gives several results concerning these scars. The main conclusion is that the scar will show up in the KS system (system II). We also show that the density itself contains information from which the Berry phase of the system I degeneracy can be reproduced. Furthermore, we argues that the KS Hamiltonian will either be degenerate in the origin or, more likely, will by undefined there (i.e. the KS Hamiltonian itself will have a scar). We also find that in points of non-degeneracy in system I the KS Hamiltonian will either be non-degenerate or will exhibit degeneracy with the density given as a *equal weight ensemble*.

❖ R. Baer, "Ground-State Degeneracies Leave Recognizable Topological Scars in the Electronic Density", Phys. Rev. Lett. 104, 073001 (2010).

## PROFESSOR BAER'S GROUP 2007-2012

| Name | Status | Presently |
|---|---|---|
| **Recca Granot** | Researcher | Dead Sea Works Inc. |
| **Dr. Ester Livhsits** | Research Assitant | Hebrew University |
| **Shlomit Yacobi** | Postdoc | TAU |
| **Dr. Yair Kurzweil** | Senior Researcher | Negev Research Center |
| **Dr. Helen Eisenberg** | Research Assistant | Current |
| **Omri Buchman** | PhD student | Current |
| **Adva Baratz** | PhD student | Current |
| **Tamar Stein** | PhD student | Current (leaves 9/12 for postdoc) |
| **Yael Cytter** | MSc student | Current |
| **Eitam Arnon** | BSc student | Current |
| **Efrat Hadded** | BSc student | Current |
| **Ben Shpiro** | BSc student | Current |

## PROFESSOR BAER'S SCIENTIFIC COLLABORATIONS 2008-2012

| Name | Institution |
|---|---|
| **Prof. Leeor Kronik** | Weizmann Institute |
| **Prof. Daniel Neuhauser** | UCLA |
| **Prof. Eran Rabani** | Tel Aviv University |
| **Prof. Stephan Kuemmel** | Bayreuth University |
| **Prof. Ulrike Salzner** | Bilkent University |

## ACTIVE GRANTS

| Project | Period | Foundation | Total Grant |
|---|---|---|---|
| **Developing a density functional theory studying molecular conical intersections and other electronic degeneracies** | 2010-2014 | Israel Science Foundation | $230,000 |
| **Novel time-dependent density functional methods for intermolecular charge-transfer excitations** | 2009-2013 | US-Israel Binational Science Foundation | $80,000 |
| **Catalytic partial oxidation of methane to methanol as an alternative fuel for transportation** | 2012-2016 | Israel Science Foundation | $160,000 |
| **Catalytic partial oxidation of methane to methanol as an alternative fuel for transportation** | 2012-2015 | ISAF | $120,000 |

## CONFERENCE ORGANIZATION (PAST 5 YEARS)

| No. | Conference |
|---|---|
| **1** | The Fritz Haber Symposium on Conductance Yad Hashmona, 2007. |
| **2** | Safed Summer school on density functiona theory (Chair: R. Baer, with: E. Rabani and L. Kronik), 2007. |
| **3** | 2007 Gentner Symposium on "Time dependent density functional theory". Hilton Queen of Sheba, Eilat, Dec. 2007. Chair: R. Baer, with: E. Rabani and L. Kronik. |
| **4** | The Fritz Haber Symposium Kibbutz Tsuba, 2009. |
| **5** | Victoria Buch Symposium 2010 |
| **6** | The Fritz Haber Symposium Givat Ram Campus, 2012 |

## EDITORIAL BOARDS

Physical Chemistry Chemical Physics (2006).
Annual Reviews of Physical Chemistry (2010-2014).
Theoretical Chemistry Accounts, Assoc. Editor (2011-2012).

# AVINOAM BEN-SHAUL

## RESEARCH

Our research in recent years has focused on two major topics: Cell adhesion and the properties of RNA. The progress achieved in these two fields is outlined in the two sections below.

### MOLECULAR AND THERMODYNAMIC ASPECTS OF CELL-CELL ADHESION

A major part of our research in the recent years has been focused on the molecular mechanisms and their statistical-thermodynamic reflection in the context of inter-cell adhesion and tissue segregation. This ongoing research has been carried out in close collaboration with the groups of Professors Barry Honig and Lawrence Shapiro from the department of Biochemistry and Molecular Biophysics of Columbia Medical School in New York. In Columbia university, various experiments are carried out, involving molecular cell biology and crystallographic studies; these are combined with a variety of theoretical and computational studies at different length and time scales. In Jerusalem, the work done is only theoretical, focusing mainly on the statistical thermodynamic aspects of the systems and phenomena involved. Below, after a brief general introduction, we describe the specific joint projects in recent years, focusing on the three major topics:

(i) Linking molecular affinity and cellular specificity in cadherin mediated adhesion. (ii) The mechanism underlying inter-cellular junction formation. (iii) Relating 3D measurements of receptor binding affinities with (quasi 2D) cell-cell adhesion mediated by membrane anchored receptors. The work described here has yielded several joint publications in leading international journals, and has been presented in numerous international forums by the PIs and some of the more junior researchers who took part in the research.

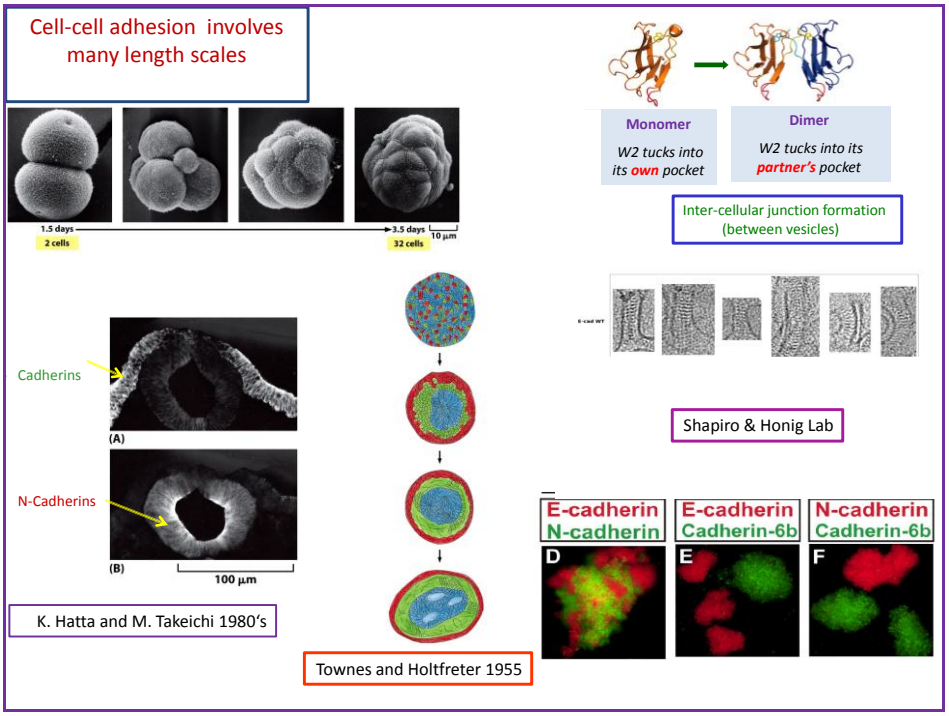



**Figure 14: Cell-cell adhesion involves many length scales. The left side of the figure shows the early stages of (mouse) embryo development. The cells are held together by cadherin dimers, (photo taken from Molecular Biology of the Cell). Below this figure is an electron micrograph describing the formation of the neural tube, with E-cadherins present in the epithelial tissue while N-cadherins are expressed by the cells constituting the neural tube. An older experiment (by Townes and Holtfreter) shows how a mixture of cells (derived from dissociated amphibian embryo) re-assemble into distinct, epithelial, mesodermal and neural tissues. The right side of the figure shows results obtained at Columbia University, which are directly relevant to the present research. The top figure illustrates the domain-swapping mechanism responsible for cadherin dimerization, as calculated and crystallographically determined by the Shapiro-Honig groups. Below this are shown segments of cadherin junctions between liposomes, as described in more detail in the second section. The bottom-right figure shows results of cell assays, revealing that cells expressing different cadherins segregate into distinct tissue.**

## INTRODUCTION

The research of cell adhesion involves many length and time scales, ranging from the atomic-scale resolution of the binding region between adhesion proteins, via the many-receptor-mediated adhesion between two cells, all the way to the macroscopic segregation of cell "mixtures" into well defined tissues. Some of these processes are illustrated in Figure 14.

Our research has been concerned with all the length scales phenomena depicted in Figure 14. The conclusions of this rtesearch are applicable to a wide range of cell-cell adhesion phenomena, yet all the specific calculations were carried out for cadherin receptors, which constitute an important and abundant family of adhesion proteins, that mediate cell-cell adhesion in epithelial, neural, heart and various other tissues. The ectoplasmic part of these proteins is composed generally of five nearly identical domains connected by relatively flexible linker regions. In the

presence of $Ca^{++}$ these molecules rigidify, in which conformation they can mediate cell-cell adhesion (hence their name "ca + adhesion = cadherin"). The cells adhere upon the formation of trans-dimers between cadherins that decorate the surfaces of apposed cell membranes. The dimerization is mediated by "domain swapping" between the apposed outermost (EC1) domains, as illustrated in Figure 15.

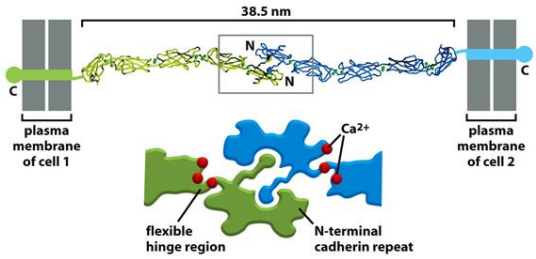



**Figure 15: Trans dimer formation is mediated by strand swapping, (see also the top-right corner of Figure 14). This figure is taken from Molecular Biology of the Cell, based on crystallographic structure determinations of cadherin dimers first done by Shapiro et al nnm at Columbia university, and continued in the Shapiro-Honig lab at Columbia.**

## LINKING MOLECULAR AFFINITY AND CELL ADHESION SPECIFICITY [1]

The differential expression of members of the cadherin family is known to play a central role in cell separation processes during morphogenesis, (see Figure 14). However, the molecular basis of cell sorting phenomena is poorly understood, in part because a relationship between cellular adhesive specificity and inter-molecular binding free energies of adhesion molecules has not been established. Our goal in this work was to provide a coherent relationship between the molecular and cellular aspects in inter-cell adhesion.

In the experimental part of this study, Analytic Ultra Centrifuge (AUC) and Surface Plasmon Resonance (SPR) measurements have yielded information on the homophilic and heterophilic binding energies of E-cadherins and N-Cadherins. It was found that Kd for N-cadherin dimerization is stronger than that for E-cadherin: the values measured at 37o were 25 µM for N-cadherin and 150 µM for E-cadherin; corresponding to -6.5 kcal/mole for N-cadherin and -5.3 kcal/mole for E-cadherin. It is difficult to derive absolute values of binding energy between N and E cadherins, yet SPR measurements have revealed the following order of binding strengths: N/N > N/E >~E/E. Cell assays of mixed cadherin population have shown that cells expressing N and E cadherins do not mix, yet the E-cadherin expressing cells "stick" to the more compact aggregate formed by the strongly adhering cells expressing N-cadherins. Cells expressing different classes of cadherins separate into distinct aggregates, as shown in Figure 16.

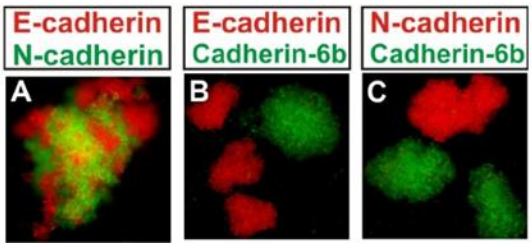



**Figure 16: *Cell aggregation assays* using (Chinese Hamster Ovary, CHO) cells transfected with N-cadherins and E-cadherins (A). E-cadherin and cadherin-6b (B), N-cadherin and cadherin 6b (C); see text for details.**

The theoretical analysis of this behavior was based on the notion that cell-cell adhesion is mediated by the interaction between many adhesion molecules, which thus amplify even small differences between the adhesion affinities of very similar cadherins. Explicitly, the number of trans dimers between two cells depends on both the surface density of cadherins and their binding affinities. Based on a rather straightforward theoretical analysis one can show that even though the N/E affinity is stronger than that of E/E – a cell mixture containing cells expressing E-cadherins and cells expressing N-cadherins will form separate cell aggregates if the inter-cell interactions energies satisfy the condition: $[W(N,N) + W(E,E)]/2 - W(N,E) > 0$, implying that the average homotypic affinity is strong than that of the heterotypic affinity. As shown in Figure 16, this is indeed the behavior observed in our cell assays. We note that aggregates of cells expressing N- and E-cadherins nevertheless touch each other, consistent with the fact that $W(N,E) < 0$. Also shown in the figure are popula-

tion assays involving Type-I and Type-II; these are known to not bind through their EC1 domains, and their aggregates are indeed well separated from each other. The experimental results and their theoretical analysis are detailed in [1].

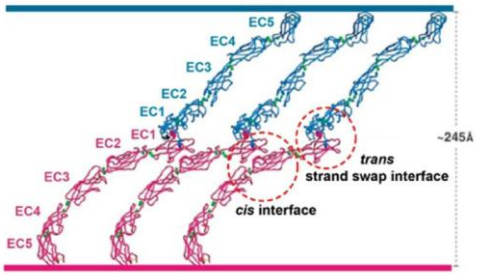



**Figure 17: Crystal structure of cadherin trans-dimers. Note that while cadherin monomers in the bottom layer are in contact via their cis interface, those in the upper layer are not – they are in contact with monomers along an off-plane direction, resulting in the formation of a 2D array.**

## THE FORMATION OF INTER-CELLULAR JUNCTIONS [2,3]

The adhesion between the cells comprising epithelial tissues (and most likely embryonic tissues too) is mediated by dense two-dimensional (2D) clusters of adhesive molecules – known as junctions. Two of the most important intercellular junctions, adherens junctions and desmosomes are made of cadherins. These are 2D arrays of trans dimers formed between monomers emanating from opposing cell surfaces. Lateral cis interfaces between cadherins from the same cell surface were proposed to play a role in cadherin clustering. In a joint publication [2] we presented a theoretical model for junction formation using vital structural information from the crystal structure of C and N cadherins, as determined in the Shapiro-Honig lab (Figure 17). This anisotropic lattice model accounts for the coupling between cis and trans interactions. Monte Carlo simulations were performed based on this model, revealing a "phase transition" between a dilute phase of freely diffusing cadherin monomers (and few dimers) and a condensed ordered 2D junction formed by dimers. Moreover, we showed that cis interactions, despite being too weak to be measured in solution, are critical to the formation of an ordered junction structure. The results were discussed in light of available experimental information on cadherin binding free energies, which are transformed from their bulk solution values to interaction energies on a 2D lattice.

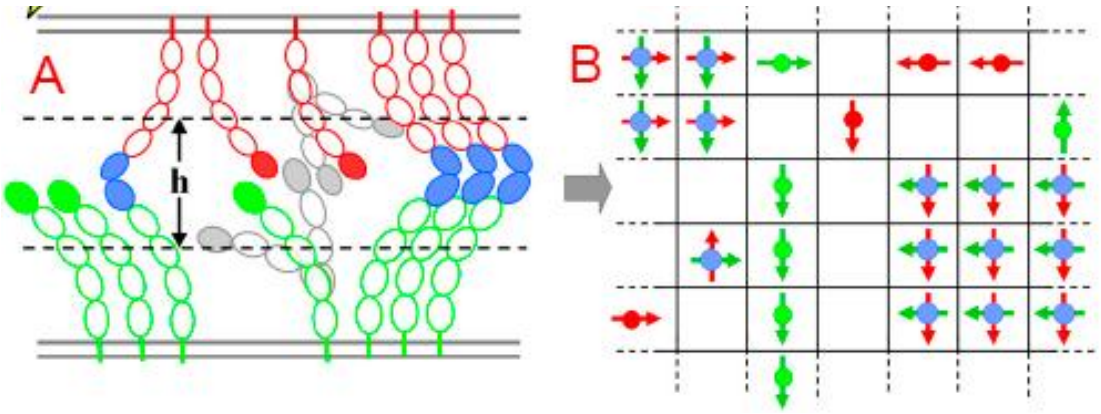



**Figure 18: The lattice model. A. Schematic illustration of two interacting cell surfaces. The "reactive" (EC1) domains are colored green and red as monomers, and blue as trans dimers. B. Mapping of the system on the left into an anisotropic 2D lattice models. Dimers aggregate into condensed regions whereas monomers can, at most, form linear aggregates.**

From the lattice model simulations phase diagrams were derived, delineating the range of cis and trans interactions necessary for the formation of inter-cell junctions, as a function of the overall surface density of receptors. In parallel to the theoretical model, the role of cis interactions has been studied experimentally (ref .[3]) using different types of measurements aiming, primarily, to elucidate the nature of adherens junctions. One class of experiments involved controlled measurements on liposomes rather than live cells. The liposomes were decorated

with cadherins and their aggregation behavior has been monitored by electron microscopy. The measurements clearly show the appearance of ordered 2D arrays of cadherins, exhibiting similar ordering to the kind observed in the crystal, and in accordance with our theoretical model. Upon mutation, which weakens the formation of the cis interface most of these structures have disappeared and liposome-liposome binding essentially eliminated. These experiments reveal the crucial importance of cis binding to intercellular junction formation. The results of the liposome experiments are summarized in Figure 19.

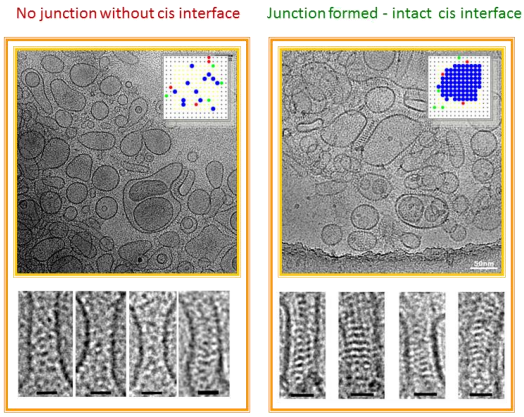



**Figure 19: Liposome experiments. Liposomes covered by wild-type E-cadherins form ordered adherens-like junctions, as shown on the right. Upon mutating the cis interface, no junctions are formed, as shown on the left. The insets show the corresponding lattice simulation - where an ordered, condensed, cluster of trans dimers (blue dots) represents an inter-cellular junction.**

## FROM 3D BINDING MEASUREMENTS TO 2D INTER-CELL ADHESION [4,5]

As discussed in the previous section, the association of plasma membrane proteins with molecules that are not part of the same cell (*trans* interactions) drive oligomerization processes between proteins on the same cell (*cis* interactions), which can activate downstream signaling events for cell surface receptors and/or the assembly of supramolecular structures such as adherens junctions. The structural and energetic bases of such phenomena are, in general, only poorly understood. A central problem is that equilibrium constants are generally measured in three-dimensional (3D) solution and are thus difficult to relate to the constrained two dimensional (2D) environment of a membrane surface. In a recent paper we presented a theoretical treatment relating the 3D affinities measured in solution to 2D affinities between membrane bound receptors, accounting directly for the structures of the membrane-bound molecules. Differences between the 3D and 2D environments were shown to result from constraints imposed by the membrane on bound proteins and also to depend on the structure and dynamical properties of the proteins involved. Using a computational algorithm combining Molecular Dynamics and Monte Carlo simulations we determined the ranges of spatial and angular ranges of motions of the membrane bound monomers and dimers which appear in the expression relating the 2D and 3D equilibrium constants of the dimerization reaction, (see below). This simulation procedure is described in detail in ref. [4], and is illustrated schematically in Figure 20 and Figure 21. A central finding of general relevance of our analysis is that changes in molecular flexibility upon *trans* binding appear to play a crucial role in driving the lateral, *cis,* clustering of adhesion receptors.

We are currently completing a comprehensive manuscript [5] in which we present a detailed statistical-thermodynamic derivation of an expression which is identical in form (but slightly different in interpretation) to the one used in Ref. [4] to calculate the ratio between the 2D and 3D equilibrium constants of trans and cis dimerization. In this derivation the focus is on factorizing the partition function of the interacting receptors to motions of the entire ectodomain (which determine the ranges of motion of monomers and dimers, $h_M$ and $h_T$ in Figure 20 and Figure 21, and $h_a$, $h_b$, and $h_{ab}$ in Figure 22 below).

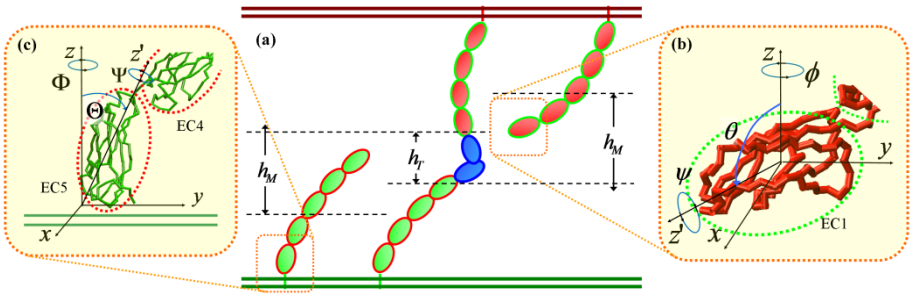



**Figure 20: Essential coordinates that characterize dimerization processes of classical cadherins in a 2D membrane environment. The five domains of cadherin's extracellular regions are represented by ellipsoids. Trans dimers (shown in blue) can be formed from two cadherin monomers from two apposing cell surfaces. The molecules are only free to diffuse in two dimensions and rotational motion is constrained. A third dimension is introduced through variations in the perpendicular displacement with respect to the membrane surface, defined by the variable h, which is different for the monomer (here denoted $h_M$ ) and trans dimer ($h_T$). In general, $h_M$ will be larger than $h_T$ since trans binding will limit molecular motion. The rotational degrees of freedom for EC1 domains are characterized by the three Euler angles, $\phi, \psi$ and $\theta$, as depicted in the right panel.**

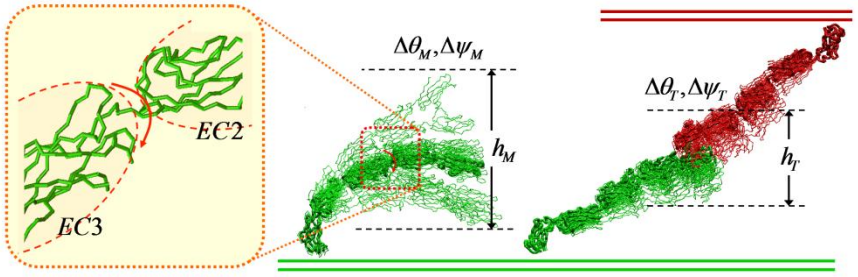



**Figure 21: Monte-Carlo simulations of the flexibility of the cadherin ectodomain. The rotations of the EC5 domain with respect to the membrane plane depend on the three Euler angles, $\Phi$, $\Psi$ and $\Theta$ of that domain, as shown in the upper left panel. The inter-domain hinge motion indicated by a red arrow is shown in the upper right panel. The lower part of the figure gives the superposition of different conformations in monomer and trans dimer generated by the simulations. The range of values for h, $\Delta\Psi$ and $\Delta\Theta$ can be obtained from the statistical distribution of simulation results. The decreased flexibility of the trans dimer with respect to the monomer is evident in the figure.**

Consequently the ratio between the 2D and 3D constants is given by the equation:

$$\Lambda = \frac{K_d^{(2D)}}{K_d^{(3D)}} = \frac{h_a h_b}{h_{ab}} \frac{\Delta\omega_a}{8\pi^2} \frac{\Delta\omega_b}{\Delta\omega_{ab}} \qquad (1)$$

with the first factor (involving the h's) represents the effects of the different spatial entropies of the membrane bound monomers and dimers, and the second factor is the ratio between the angular partition functions in 2D and 3D, accounting for the lower rotational entropy loss in 2D as compared to 3D.

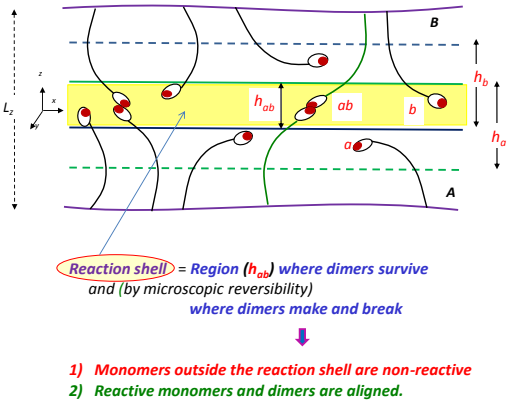



**Figure 22: The physical model underlying the derivation of Eq. (1). The Δω's in Eq. (1) correspond to the ranges of motion of the adhesive domains of monomers and dimers.**

The spatial and rotational factors act in different directions on the ratio between the two equilibrium constants; the spatial factor reduces dimerization affinity in 2D while the angular factor acts to increase this probability. Detailed MC simulations of interacting receptors (i.e., cadherins) provide numerical values of λ, which very well agree with the theoretical predictions of the equation above, supporting its physical interpretation.

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## RNA STRUCTURE AND FOLDING: VIRAL VS. RANDOM SEQUENCES

Our second major field of interest in the last decade has been the structure, energetics and thermodynamical-statistical properties long polynucleotide, primarily double stranded (ds) DNA and single stranded (ss) RNA. We were especially interested in distinguishing the properties of viral polynucleotide chains from other, biological non-viral sequences and, in the case of RNA, random sequences - for the sake of comparison. In the last years we have focused on ssRNA, and some of our findings are outlined below. It should be mentioned that this research is a part of an intensive ongoing collaborative research with the groups of professors William M. Gelbart and Charles Knobler from UCLA, who also run an active and exciting experimental lab. The work done in Jerusalem focuses on theory, and is largely assisted by collaboration with younger scientist (graduate students and postdocs) who spend rather long visit periods in the Frtiz Haber center.

### INTRODUCTION

As a result of partial complementarity (base pairing) between the nucleotides (nt) constituting single-stranded (ss) RNAs, these molecules develop secondary structures composed of double-stranded (ds) "duplexes" of contiguous base pairs (bp) connected by ss loops of unpaired nt. These components in turn determine the tertiary structure of RNA molecules and thereby their biological function. Accordingly, a great deal of theoretical and experimental work has been devoted to predicting and measuring the secondary structures of RNAs. Our interest in RNA structure and folding is a consequence of our previous work on the structure of viruses. Following several studies of bacterial viruses where the genomic material is double stranded DNA, we have focused attention on animal and plant viruses where the genomic material is generally single stranded RNA.

We have been mainly concerned with the geometrical and statistical characteristics of RNA, with particular emphasis on the difference between viral and non-viral RNAs. We have shown that viral RNAs are more compact than other RNA sequences, both biological and random sequences, and developed models for predicting their sizes and the scaling of their size (as measured the "maximum ladder distance" or the radius of gyration) with sequence length. Below we present a very brief outline of three recent papers that we have been published on this topic. In some of these analyses the first step was to map the complex secondary structure of the RNA molecule to a simpler, tree graph, composed of stems (double stranded duplexes) and vertices (the single stranded loops), Figure 23. More work is in progress and will be included in future reports.

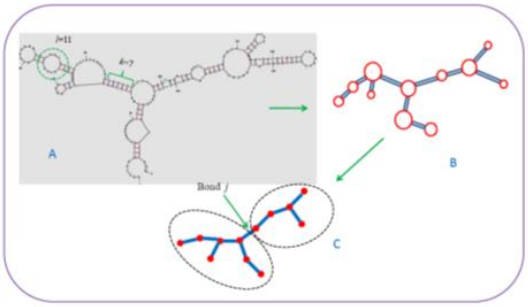

**Figure 23: Mapping an RNA secondary structure (A) onto a branched polymer (B) and to a tree graph (C).**

## THE ENDS OF A LARGE RNA MOLECULE ARE NECESSARILY CLOSE [1]

In this work we showed on general theoretical grounds that the two ends of single-stranded (ss) RNA molecules (consisting of roughly equal proportions of A, C, G and U) are necessarily close together, largely independent of their length and sequence. This is demonstrated to be a direct consequence of two generic properties of the equilibrium secondary structures, namely that the average proportion of bases in pairs is about 60% and that the average duplex length is about 4. Based on mfold and vienna computations on large numbers of ssRNAs of various lengths (1,000 to 10,000 nucleotides) and sequences (both random and biological), we find that the 5′–3′ distance—defined as the sum of H-bond and covalent (ss) links separating the ends of the RNA chain—is small: averaging 15–20 for each set of viral sequences tested. For random sequences this distance is about 12, consistent with the theory. We discuss the relevance of these results to evolved sequence complementarity and specific protein binding effects that are known to be important for keeping the two ends of viral and messenger RNAs in close proximity. Finally we speculate on how our conclusions imply indistinguishability in size and shape of equilibrated forms of linear and covalently circularized ssRNA molecules. A circle diagram, explaining why the ends of long RNA molecules are always close to each other is described in Figure 24.

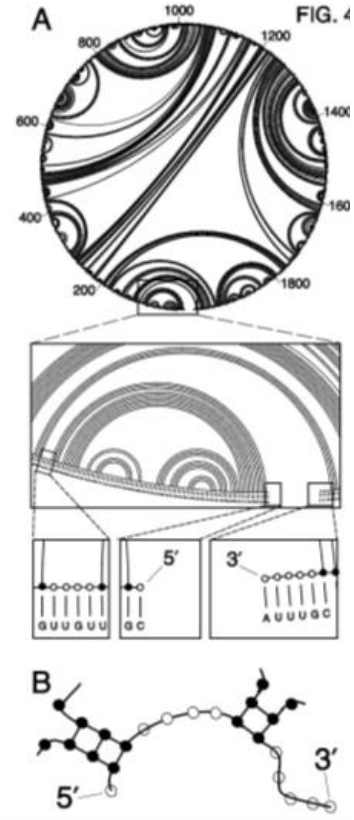


**Figure 24: Circle diagram depicting the vienna-predicted MFE secondary structure of a 2,117-nt viral ssRNA molecule, RNA3 of cowpea chlorotic mottle virus. The circle diagram was drawn with mfold. The external loop associated with the 5′ and 3′ ends is expanded in the lower panel of (A), and depicted schematically in (B); it consists of 2 duplex links and 11 ss links, and hence corresponds to an effective contour length, D, of 13.**

## A SEQUENTIAL FOLDING MODEL PREDICTS LENGTH-INDEPENDENT SECONDARY STRUCTURE PROPERTIES OF LONG SSRNA [2]

This study introduced a simple model (Figure 25) for folding random-sequence RNA molecules, arguing that it provides a direct route to predicting and rationalizing several average properties of RNA secondary structures. The first folding step involves identifying the longest possible duplex, thereby dividing the molecule into a pair of daughter loops. Successive steps involve identifying similarly the longest duplex in each new pair of daughter loops, with this process proceeding sequentially until the loops are too small for a viable duplex to form. Approximate analytical solutions are found for the average fraction of paired bases, the average duplex length, and the average loop size, all of which are shown to be independent of sequence length for long enough molecules. Numerical solutions to the model provide estimates for these average secondary structure properties that agree well with those obtained from more sophisticated folding algorithms. We also use the model to derive the asymptotic power law for the dependence of the maximum ladder distance on chain length.

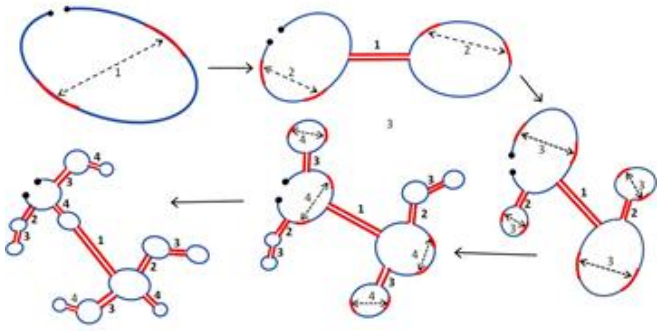

**Figure 25: Schematic illustration of the sequential folding model. First the longest duplex is formed (labeled "1"), resulting in the formation of two smaller daughter loops. These are then divided again by their respective longest duplexes (each labeled "2"), and so on. Only four "generations" are depicted here. The process ends when none of the loops can be divided by a viable duplex. As bases may be apportioned unevenly between daughter loops, some loops may reach the end of the process in fewer generations than others. The analytical solution described in Section 2 incorporates the simplifying assumption that all divisions are equal (hence all loops undergo the same number of divisions).**

## THE SIZE OF RNA AS AN IDEAL BRANCHED POLYMER [3]

Because of the branching arising from partial self-complementarity, long single-stranded (ss) RNA molecules are significantly more compact than linear arrangements (e.g., denatured states) of the same sequence of monomers. To elucidate the dependence of compactness on the nature and extent of branching, we represent ssRNA secondary structures as tree graphs which we treat as *ideal* branched polymers, and use a theorem of Kramers for evaluating their root-mean-square radius of gyration, $\hat{R}_g = \sqrt{\langle R_g^2 \rangle}$. We consider two sets of sequences – random and viral – with nucleotide sequence lengths ($N$) ranging from 100 to 10,000. The RNAs of icosahedral viruses are shown to be more compact (i.e., to have smaller $\hat{R}_g$) than the random RNAs. For the random sequences we find that $\hat{R}_g$ varies as $N^{1/3}$. These results are contrasted with the scaling of $\hat{R}_g$ for ideal *randomly*-branched polymers ($N^{1/4}$), and with that from recent modeling of (relatively short, $N \leq 161$) RNA tertiary structures ($N^{2/5}$).

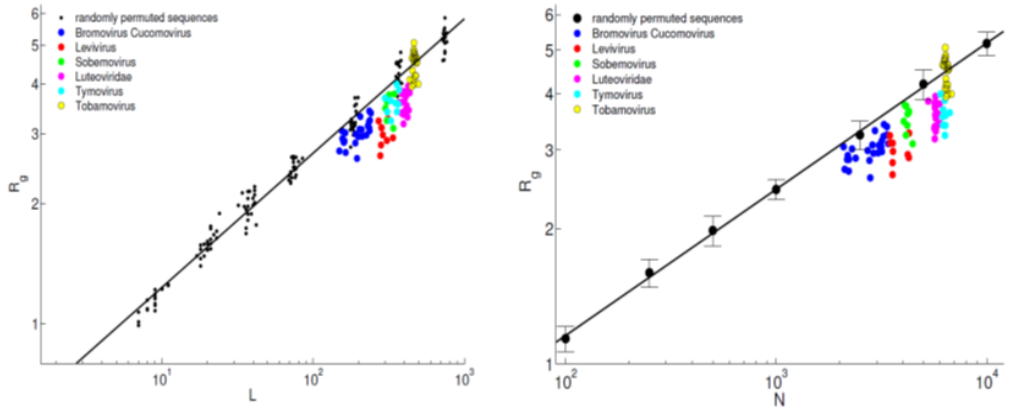


**Figure 26: A log-log plot of the radius of gyration of ssRNA vs. the number of loops (left), and vs the number of nucleotides (right). The balck symbols are for random sequences, the colored ones for viral sequences, as indicated. In both plots the slope is very nearly the same, 0.33. The same scaling is obtained whenfor the Maximul Ladder Distance, as defined and calculated in our previous work [4].**

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## PROFESSORS BEN-SHAUL'S GROUP (PAST 5 YEARS)

| Name | Status | Presently |
|---|---|---|
| **Dr. Shelly Tzlil** | PhD | Postdoc in the group of David Tirrell; Caltech |
| **Yifat Brill-Karnielly** | PhD | Near graduation; Will leave for postdoc in Cambridge UK |
| **Aron Yoffee** | Visiting student | PhD in UCLA |
| **Dr. Vladimir Teif** | Visitor from Belarus | Heidelberg |

## ACTIVE GRANTS

| Project | Period | Foundation | Total Grant |
|---|---|---|---|
| **Cadherin Mediated Cell-Cell Adhesion** | 2007-2011 | US-Israel Binational Science Foundation | $80,000 |
| **Coarse-grained Modeling of Long RNA Molecules: Viral vs, Non-Viral Sequences** | 2010-2013 | ISF | |

## EDITORIAL BOARDS, PRIZES

- Chemistry and Physics of Lipids
- PMC (PhyMathCentral) Biophysics
- Landau Prize for "Physics of Membranes, Polymers and Biomaterials".

## ROBERT B. GERBER

The main research activities of our group have been in the following topics: mechanisms and dynamics of atmospherically important reactions; vibrational spectroscopy of biological molecules; interactions of saccharides with water molecules and with ions; lifetimes, kinetic stability and other properties of new noble-gas molecules.

## RESEARCH

### NEW NOBLE GAS MOLECULES AND MATERIALS, AND THEIR PROPERTIES

We continue our efforts to discover new interesting molecules of the noble gases, materials made from these molecules, and properties that may open the way to applications. The work is carried out in close cooperation with the experiments of Professor Markku Räsänen of the University of Helsinki, a recognized world leader in the field. We highlight two results obtained in the period of the report:

d) "Di-Xenon Water": This molecule was discovered in a combined experimental-theoretic effort. Computationally, the existence of this species was predicted, its vibrational spectrum, that served as the tool of identification, was obtained, and later its intrinsic lifetime as a function of temperature was calculated. The results were reported in a JACS article (Khriachtchev et al, see below), that has already had a nice echo in the field. Most recently, the stability of this molecule in the presence of water molecules was computed, with the finding that $HXeOXeH(H_2O)_n$ exists for n=1,2,3, but not for n>3. This is due to hydrogen transfer that is enhanced as the network of hydrogen bonded waters at the molecule increases. The abundance of water in planetary systems is one reason for interest in the possible existence of this species in an astrochemical context.

e) Existence of HXeCCH in a liquid-like microdroplet of acetylene: This is a first prediction of the existence of a noble gas molecule in a hydrocarbon medium, in a liquid state. The prediction was made by Ab Initio Molecular Dynamics simulations, using the BLYP-D fumctopma; (Tsivion et al below), after verification of its validity for the system by tests against higher level methods. Figure 1 below shows snapshots from the simulation at 150K, from which the liquid-like nature of the solution is seen. Experimental efforts to check the prediction and prepare the system are being made in Helsinki. The importance of the result is that such solutions may be forms suitable for applications. In any case, the existence is predicted well above the cryogenic range.

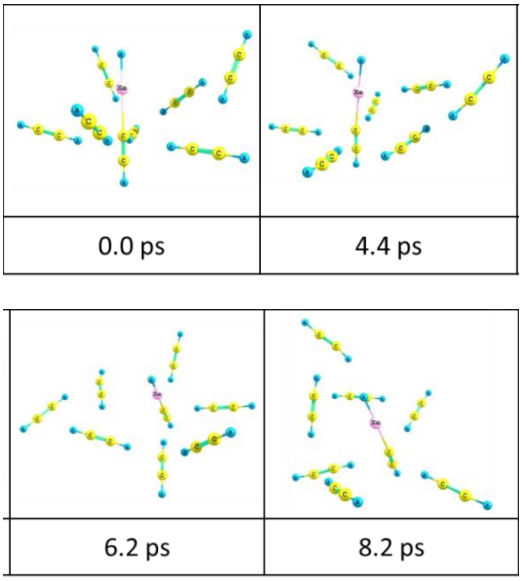


**Figure 27: Snapshots from AIMD simulations of HXeCCH in an acetylene cluster.**

❖ L. Khriachtchev, K. Isokaski, A. Cohen, M. Räsänen and R.B. Gerber, A Small Neutral Molecule with Two Noble Gas Atoms: HXeOXeOH,J. Am. Chem. Soc. 130, 6114-6118 (2008).

❖ E. Tsivion and R.B. Gerber, Stability of Noble Gas Hydrocarbons in Organic Liquid-Like Environment: HXeCCH Acetylene, Phys. Chem. Chem. Phys. 13, 19601-606 (2011).

## IONIZATION OF $N_2O_4$ IN CONTACT WITH WATER: MECHANISM, TIMESCALES AND ATMOSPHERIC SIGNIFICANCE

The hydrolysis of $NO_x$ species, in particular of $N_2O_4$, is a process of major atmospheric interest. A kinetic mechanism for the hydrolysis has been proposed by B.J. Finlayson-Pitts, and involves among other points the assumption that cleaves $N_2O_4$ into the ion pair $(NO^+)(NO_3^-)$, which are involved in subsequent reactions. However, no macroscopic evidence for this assumption is available. Simulations done by Yifat Miller, then a Ph.D. student in our group, in cooperation with Professor Finlayson-Pitts and her experimental group, give strong support for the assumed ionization, and provide quantitative data on the process and the microscopic mechanism involved.

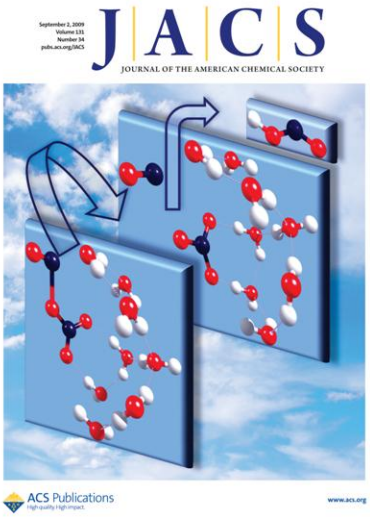


**Figure 28: Dynamics of ionization of (asymmetric) $N_2O_4$ in contact with water.**

The simulations used $N_2O_4$ on water clusters as a model system. Direct dynamics calculations were used, employing MP2 potentials "on the fly". The ab initio MP2 method has been demonstrated to be very reliable for water clusters, hence the importance of using it in the "on the fly" dynamics. The results show that a single water molecule suffices to induce ion pair formation at 300K, the process taking place on a picosecond timescale. The presence of several additional water molecules accelerates the process to a femtosecond timescale.

A referee report on the paper presenting this work hailed it as a very important result. This paper(Miller et al) was selected by the Editor as a Cover Article of the issue in JACS.

❖ Y. Miller, B.J. Finlayson-Pitts and R.B. Gerber, Ionization of $N_2O_4$ in Contact with Water: Mechanism, Timescales and Atmospheric Implications, J. Am. Chem. Soc. 131, 12180-85 (2009). (Cover Article)

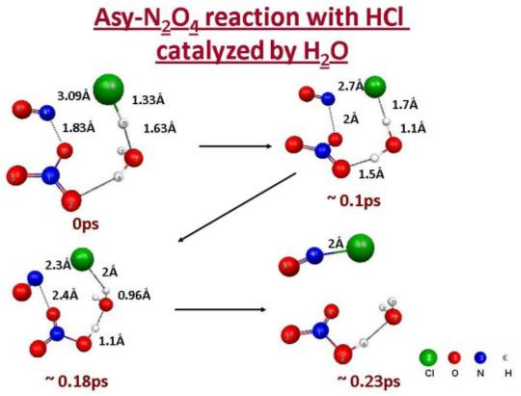


**Figure 29: Snapshots showing the formation of ClNO from ONONO2 in a cluster with a single water molecule.**

## CATALYTIC ROLE FOR WATER IN THE ATMOSPHERIC PRODUCTION OF ClNO

Computational studies by B. Njegic, a postdoc in our group, show that a single water molecule catalyzes the production of ClNO, a major source of atomic chlorine in the atmosphere, from $ONONO_2$ and HCl. These results provide a microscopic interpretation for experimental results by Finlayson-Pitts and coworkers, showing that production of ClNO from $N_2O_4$ and HCl is greatly accelerated at water films. The results point to a new key mechanism for the production of Cl in the atmosphere, and already had an impact in the atmospheric chemistry community. Snapshots from "on the fly" MP2 simulations of the process are shown in Figure 29.

A paper describing these results, published in PNAS, and selected as Cover Article for the issue.

- J.D. Raff, B. Njegic, W.L. Chang, M.S. Gordon, D. Dabdub, R.B. Gerber and B.J. Finlayson-Pitts, Surface-Mediated Reactions of Nitrogen Oxides with Hydrogen Chloride: Indoor and Outdoor Chlorine Activation Proc. Nat. Acad. Sci. 106, 13647-54 (2009). (Cover Article)

## EFFECT OF ICE ON PHOTOCHEMISTRY OF ADSORBED PEROXIDES

Excitation of light and the subsequent processes are tremendously important in the environment (e.g. absorbance of UV light by the ozone layer). However, light can also cause damage by invoking undesired reactions. It is crucial to know possible photochemical reactions and their products. Those reactions are then fitted to kinetic models which accounts for the concentration of all species in the atmosphere. This model is able to explain the depletion of the ozone layer. Here we model photochemical processes in atmospheric systems.

One very important system is peroxides in water droplets (e.g. methylhydroperoxide on a water cluster), which can be found in the atmosphere.

We modeled in a combined theoretical and experimental study the absorption spectra of this system.(1) We carried out molecular dynamics simulations on the ground state for three different temperatures, namely 50 K, 200 K and 220 K. Vertical excitation energy calculations on the structures from the ground state dynamics yields the absorption spectrum. For 200 K, the theoretical prediction of the lineshape fits qualitatively to the experimental lineshape.

In another study, we modeled the photoexcitation of peroxides on ice. Photoexcitation of peroxides on ice are tremendously reactive, as has been shown by a recent paper by Gerber et al. (2) and references therein. In this paper, the assumption was made, that the photoexcitation leads very fast to an internal conversion to the ground state along the O-O stretching coordinate. Therefore, only the dynamics on the ground state was studied in details assuming different O-O lengths and appropriate excess energies. An extension to the present study is the calculation of the excited-state dynamics immediately after the photoexcitation. We have performed non-adiabatic surface hopping dynamics with the OM2 hamiltonian implemented in the program package MNDO. We have compared the photodynamics of the bare peroxide to the peroxide absorbed on ice (3). Interestingly, there exist significant differences between both systems: The ice clearly accelerates the depopulation of the excited state to the ground state. The depopulation of the excited state in the solvated system happens in a timescale of about 150 femtosecond and fits to an exponential decay rate. In contrast, the populations of the excited states involved (S0, S1 and S2) of the bare peroxide oscillates much in this timescale and are about equally distributed at 150 fs. Both systems show unexpectedly an involvement of the second excited state in the photoexcitation dynamics. The early photochemical dynamics involves in almost all trajectories the rupture of the O-O bond. Surprisingly the cleavage of the O-O bond does not only happen in the ground state, it also occurs in the first and second excited states. The bare peroxide does not show any recombination of the fragments, whereas for the solvated peroxide in several cases the recombination of the fragments occurs. This can be explained by the considering the surrounding ice particles as a cage for the fragments and thereby prohibiting their prompt dissociation. For illustration, Figure 30 shows different states along one sample trajectory.

In summary, non-adiabatic surface hopping dynamics have been applied to understand the photochemistry of peroxide on ice. It has been shown, that ice has a catalytic effect on the depopulation of the excited state to the ground state.

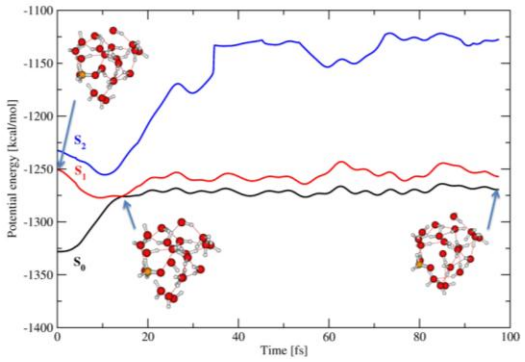


**Figure 30: Sample trajectory of the non-adiabatic surface hopping dynamics of adsorbed methyl hydroperoxide in water.**

(1) S.A. Epstein, D. Shemesh, V. Tran, S.A.Nizkorodov, R.B. Gerber, J.Phys. Chem.A. A.R.Ravishankara Festschrift, 116 (2012), 6068
(2) M.A. Kamboures, S.A. Nizkorodov, R.B. Gerber, P Natl Acad Sci USA, 107 (2010) 6600.
(3) D.Shemesh, R.B. Gerber, Molecular Physics, Bill Miller Festschrift, 110 (2012) 605

## ACTIVE GRANTS

## RECENT GROUP MEMBERS

| Name | Project(s) | Status | Presently at |
|---|---|---|---|
| Brauer, B. (current member) | Vibrational spectroscopy of large molecules | Postdoc | HU |
| Cohen, A. (current member) | New molecules of the noble gases | Postdoc | HU |
| Cwik, Y. | Structure of peptides | B.Sc. student | Ph.D. student at Maryland |
| Dvores, M. (current member) | Reactions of sugars | Ph.D. student | HU |
| Eshet, H. | | M.Sc. | ETH. Switzerland |
| Gantman, T. (current member) | Structures of protein ions in mass spectrometry | M.Sc. student | HU |
| Goldstein, M. (current member) | Algorithms for structure prediciton | Postdoc | Lecturer, J'lem College of Technology |
| Hirshberg, B. (current member) | Ab initio MD of chemical reactions | M.Sc. student | HU |
| Kerem, S. | Analysis of spectra | B.Sc. | HU |
| Kna'ani, R. (current member) | Vibrational spectroscopy of large mollecules | Ph.D. student | HU |
| Miller, Y. | Atmospheric chemistry | Postdoc | Senior Lectrer, BGU |
| Murdachaew, G. | Atmospheric reactions | Postdoc | University of Helsinki |
| Neuman, M. | Polynitrogen molecules (with Y. Haas) | M.Sc. | HU |
| Pele, L. (current member) | Algorithms for vibrational calculations | Ph.D. student | |
| Sagiv, L. (current member) | Semiclassical dynamics | Ph.D. student | HU |
| Sebek, J. (current member) | Raman and IR spectroscopies of hydrocarbons | Postdoc | HU |
| Segev, E. | Dynamics of structural changes in peptides and proteins | Ph.D. student | Lecturer, Holon College of Technology |
| Shahar, A. (current member) | Protein structural changes in mass spectrometry | M.Sc. | HU |
| Shemesh, D. (current member) | Photochemical dynamics | Postdoc | HU |
| Smilovitz-Ofir, M. (current member) | Vibrationally-induced processes in small biomolecules | Ph.D. student | HU |
| Suwan, I. | Vibrational states of polyatomics | Postdoc | Lecturer, Palestinian College |
| Tsivion, E. (current member) | New molecules of the nobel gases | Ph.D. student | HU |
| Zmiri, L. | Structure of protein ions | M.Sc. student | High school teacher |

## SCIENTIFIC COLLABORATIONS

| Name | Project(s) | Institution |
|---|---|---|
| Profs. J. Manz & N. Schwentner | Analysis and control of ultrafast reactions | Freie Universität Berlin |
| Prof. B. Abel | Dynamics of atmospherically-relevant reactions | Göttingen University |
| Prof. M.S. Gordon | Vibrational reactions of biological molecules | Iowa State University |
| Profs. V.I. Feldman; M. Räsänen | Complexes of noble-gas compounds | Moscow State University; University of Helsinki |

## ACTIVE GRANTS

| Project | Period | Foundation | Total Grant |
|---|---|---|---|
| Mechanisms of atmospheric reactions | 4 yrs + renewal 4 yrs (below) | ISF | NIS 688,000.- |
| Atmospheric reactions of molecules on ice, water, and silica surfaces | 4 years | ISF | Granted – inception oct. 12 |
| "Prediction" – Identification of hazardous materials using algorithms of computational vibrational spectroscopy | 2 yrs + 1 yr extension | Ministry of Defence – DARPA (USA) | NIS 1,100,000.- |
| Polynitrogens | 3 yrs | Ministry of Defence | NIS 165,500.- |
| Acetylenic compounds of noble gases | | Ministry of Defence | USD 118,000.- |

## PRIZES, HONORS, EDITORIAL AND REVIEW BOARDS ETC.

Honors:

- Foreign Member, Finnish Academy of Science & Letters – elected 2007;
- *Festschrift for R.B. Gerber* – Special Issue of *The Journal of Physical Chemistry, J. Phys. Chem.* A, Vol. 113, Issue 26 (2009). Guest Editors: A. B. McCoy, A.I. Krylov and V. Buch.
- *Appointed Finland Distinguished Professor (FiDiPro) for 2011*-2015.

*Editorial Boards*:

- Member, Editorial Board – *Computational Materials Science* – 1992-2007;
- Advisory Editorial Board Member – *Chemical Physics Letters* – 2010 – 2012;
- Editorial Board – *Journal of Modern Physics* -2012 –
- Member of the Editorial Advisory Board Chemical Physics
- Member of the Editorial Board of Physical Chemistry – Chemical Physics (PCCP) – 2012-2015

# DANIEL HARRIES

The group's research focuses on how biologically complex solvation environments direct macromolecular association and lead to formation of complexes that can carry specific functions in cells. We have been following the effects of crowded and stressed environments on the folding and self assembly of peptides, assembly of viral chromatin, and even the organization of proteins in membranes under the stress of cholesterol. Our aim is to formulate a unified molecular mechanism of these stressed environments. In the following we describe highlights from our endeavors.

## RESEARCH

### PEPTIDE AND PROTEIN FOLDING AND AGGREGATION IN STRESSED AND CROWDED SOLUTIONS

#### COSOLUTE EFFECT ON PROTEIN FOLDING

Many cosolutes markedly effect the properties of biomacromolecules in aqueous solutions. Notably, various cosolutes modulate protein folding equilibrium. Protective osmolytes, for example, are naturally occurring, molecularly small cosolutes widely found in many biological systems. These osmolytes are known to stabilize proteins and peptides in their native folded conformation, and therefore garner considerable interest for technological applications. Molecularly larger cosolutes, such as the polymers PEG and dextran, also stabilize proteins in their folded state. On the other hand, denaturants, such as urea and salts, guandinium chloride for example, are known to destabilize proteins. The thermodynamic basis for cosolute action is well described in terms of their preferential interactions, whereby stabilizing cosolutes are preferentially excluded from the protein solvent accessible surface area. However, the molecular mechanism for their action has not yet been resolved.

We have been following the mechanism responsible for cosolute action by using Circular Dichroism (CD) and computer simulations to explore the folding process of a 16 amino acids peptide. In this effort, an important goal is to dissect the change in free energy upon cosolute addition into the associated contributions of enthalpy and entropy, forming a "thermodynamic fingerprint" for biomolecular processes in the presence of cosolutes. As stabilizing cosolutes are excluded from protein surfaces, they were commonly thought to be "crowders" that act through an entropic-driven process. Our experiments show that the polymers PEG and dextran indeed tend to stabilize proteins through an entropic mechanism. Surprisingly however, compatible osmolytes, such as sorbitol and trehalose, act through an enthalpic-driven process. This difference may indicate these cosolutes act through different molecular mechanisms, giving rise to a similar stabilizing effect. Our molecular dynamics simulation of the model peptide in water and sorbitol solutions has traced the enthalpic contributions to changes in hydrogen bonding within the solution.

Using computer simulations, we aim to further elucidate the molecular origin of osmolyte-induced effects on protein folding. Through Monte-Carlo simulation of simple ternary mixtures, we wish to clarify how different cosolutes can exhibit different "thermodynamic fingerprints" in their seemingly similar stabilization of protein folding. Using all-atom simulations of our model peptide we will be able to follow specific molecular changes induced by osmolyte addition (Figure 31).

The study was led by Regina Politi and Liel Sapir.

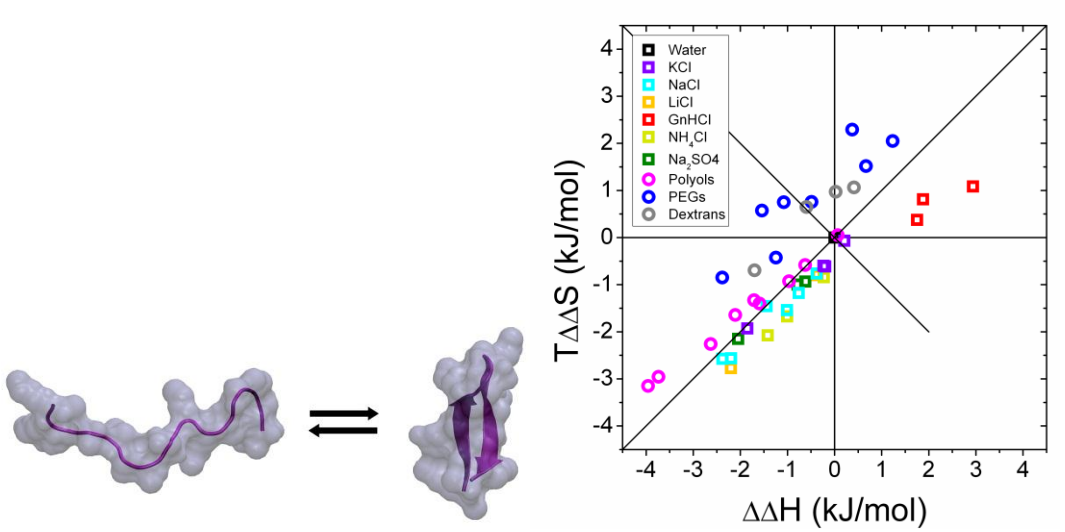


**Figure 31: Left: Schematic of the folding of a 16-amino acid long peptide. Representations demonstrate the decrease in solvent accessible surface area (SASA) in the folding process. Right: Entropy versus enthalpy plots for changes in peptide folding upon cosolute addition. Different cosolutes accommodate different regions of the plot, depending whether they are stabilizing/destabilizing and whether their effect is dominated by entropy or enthalpy.**

## COSOLUTE EFFECTS ON AMYLOID AGGREGATION

Beyond their effect on peptide stability, cosolutes also strongly affect the process of protein self-assembly termed amyloid aggregation. This condition often stems from misfolded proteins or peptides, and is thought to be the underlying cause of pathologies such as Alzheimer's disease and type II diabetes. In the last two decades, much experimental data has been gathered on the way cosolutes affect amyloid formation. It was found that while some chemicals tended to promote the kinetics of aggregation, others inhibited it. There is no currently accepted molecular level theory to predict the inhibition of this process. Using CD and fluorescence spectroscopy, we have tested the effect of different cosolute families of chemicals on the amyloid aggregation of a model peptide. The experiments show that different families, despite lacking specific binding, will produce dramatically different aggregation kinetics. We found that while small molecules such as the osmolytes sorbitol and glycerol inhibited the onset of aggregation, longer PEG polymers did little to affect the kinetics. In addition, the osmolytes caused a larger mass of monomers to undergo fibrillation. A novel kinetic model showed that this difference may be the results of a lower rate of fibril breakage and monomer dissociation in the presence of polyols versus polymers.

In order to probe the underlying mechanism governing these effects, we are currently conducting coarse grained molecular dynamic simulations of the model peptide system with two cosolutes – sorbitol and triethylene glycol – that experimentally exhibited disparate behaviors. Using coarse grained simulations allows us to probe longer time scales on larger systems, and obtain better sampling from our simulations. We calibrate the simulation box according to rigorous thermodynamic parameters, maintaining close relations with both experiments and all-atom simulations. We hope that these simulations will result in a detailed picture that can link the observed kinetics to the molecular level and the thermodynamics of this complex system.

The study is carried out by Shahar Sukenik. The simulations are conducted on the JUROPA cluster of the Jülich Supercomputing Centre, as part of the European Soft Matter Initiative.

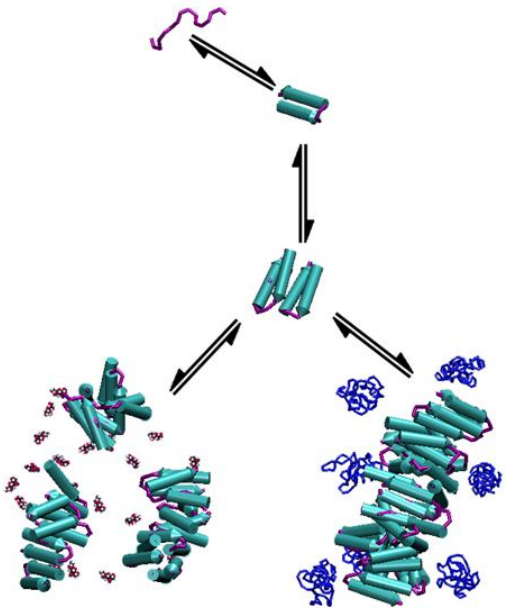

**Figure 32: Schematic of some of the ways in which cosolutes may modulate the stability of peptide aggregation. Peptides exist in solution in a large number of accessible conformations or intermediates (top). The probability of a certain subset of peptide conformations can become dominant in the presence of cosolutes. It was shown that, at least in some cases, large polymers (bottom right) can allow aggregation while smaller protecting osmolytes (bottom left) may help stabilize smaller clusters that mature only at longer times. The schematic is based on our preliminary coarse grained simulations that result in peptide self-assembly into linear aggregates on attainable simulation time scales of several microseconds.**

## CHOLESTEROL AND ITS METABOLIC PRECURSOR AND THEIR ORDERING IN LIPID MEMBRANES: IMPLICATIONS TO HEALTH AND DISEASE

Cholesterol is so essential to the proper function of mammalian cell membranes that even strikingly small inborn errors in cholesterol synthesis can be devastating. Changes in the physiological balance of cholesterol have been linked to various pathologies ranging from coronary heart disease to genetic metabolic disorders that involve the biochemical pathways of cholesterol synthesis. But while it has long been recognized as vital to proper cellular membrane function, cholesterol is unjustly vilified. A striking example is the Smith–Lemli–Opitz syndrome (SLOS) caused by an inborn deficient activity of 3b-hydroxysterol D7-reductase (DHCR7), the enzyme responsible for the final step in cholesterol synthesis from 7-dehydrocholesterol (7DHC) to cholesterol. This DHCR7 deficiency is responsible for the accumulation of 7DHC and reduced levels of cholesterol in patients with SLOS, leading to multiple congenital malformations.

Puzzlingly, these dire consequences are due to just one double bond present in 7DHC but not in cholesterol. To try and resolve this puzzle, we have been combining molecular dynamics simulations with small angle X-ray diffraction experiments to compare mixed sterol/DMPC membranes over a wide range of sterol compositions for the two types of sterols: cholesterol and its immediate metabolic precursor 7DHC. We find that while most membrane properties are only slightly affected by the replacement of one sterol by the other, the rigidity of membranes containing cholesterol is significantly larger than that of membranes that contain 7DHC over a large range of sterol concentrations.

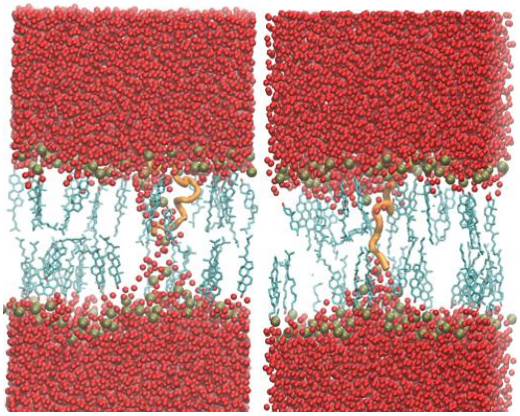

**Figure 33: Peptides fold in membranes that contain cholesterol, but fail to do so in membranes containing 7DHC. Left panel shows molecular dynamics simulations that show cholesterol (in blue) containing membranes with folded dynorphin peptide (in gold) inserted, while the right panel shows a peptide that fails to fold when 7DHC replaces cholesterol. For clarity, lipid molecules are omitted in images.**

These findings have led us to hypothesize that membranes that contain 7DHC affect proteins that reside in membranes differently from cholesterol containing membranes. This could lead to structural (conformational) differences in membrane proteins that can alter their biological

function. We have found first evidences for these effects in the membrane peptide dynorphin that is involved in neuronal activity. We find that while dynorphin folds into its functional form in lipid membranes containing cholesterol, it fails to do so in membranes with 7DHC, see Figure 33. This is a direct indication that cholesterol in membranes can affect biological function through changes in membrane material properties, possibly explaining at least some of the phenotypes of cholesterol related metabolic diseases. Our conclusions from this joint project between our lab and the lab of Harel Weisntein (Cornell Medical School, NYC) have been reported in three publications in the scientific literature.

## PACKAGING AND STRUCTURE OF THE SV40 VIRUS

The formation of viruses from proteins and nucleic acids is a striking example of complex self assembly. Many viruses form icosahedral, almost spherical capsids, inside which nucleic acid is packaged. Bacteriophages, for example, package linear dsDNA using motor proteins, thereby achieving dense, highly ordered and pressurized DNA organization. Other viruses package linear ssRNA through direct electrostatic interactions between RNA and capsid protein that nucleate capsid assembly. These viruses typically show high density of RNA lining the interior of the viral capsid.

The genome of simian virus 40 (SV40), a non-enveloped icosahedral virus and member of the polyomaviridae, poses additional constraints to packaging. The viral genome is a 5.2kb circular dsDNA, wrapped around histone octamers, forming a chromatin-like structure with ~20 nucleosomes, termed the 'minichromosome' [1-3]. During assembly, capsomers are added around the minichromosome leading to its compaction. In this process, the minichromosome must overcome the frustration arising from internucleosomal (predominantly steric) interactions, as well as confinement by the capsid walls. The 3-dimentional, higher order structure of the closed circular minichromosme within the capsid of polyomaviruses (as well as papillomaviruses) confined inside this nanometric-sized cavity remains unknown.

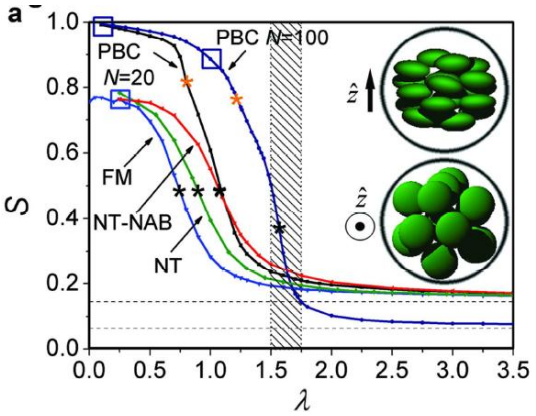


**Figure 34: Order and disorder transitions in nucleosoms of the SV40 virus. The order parameter within simulated capsids of SV40 show a pseudo-critical point for ordering within the virus (marked as FM). At higher values of the parameter $\lambda$, corresponding to low salt concentrations, the nucleosomes are disordered, while at low enough values they are predicted to order (high S value). These results indicate that the SV40 under physiological conditions is expected to be in a "molten droplet" state, in contrast to the more ordered state expected in the bulk (navy blue line).**

Using small-angle X-ray scattering we determined the three-dimensional packing architecture of the minichromosome confined within the SV40 virus. In solution, the minichromosome, composed of closed circular dsDNA complexed in nucleosomes, was shown to be structurally similar to cellular chromatin. In contrast, we find a unique organization of the nanometrically encapsidated chromatin, whereby minichromosomal density is somewhat higher at the center of the capsid and decreases towards the walls. This organization is in excellent agreement with a coarse-grained computer model, accounting for tethered nucleosomal interactions under viral capsid confinement. With analogy to confined liquid crystals but contrary to the solenoid structure of cellular chromatin, our simulations indicate that the nucleosomes within the capsid lack orientational order. Nucleosomes in the layer adjacent to the capsid wall, however, align with the boundary, thereby inducing a 'molten droplet' state of the chromatin. These findings indicate that nucleosomal interactions suffice to

predict the genome organization in polyomavirus capsids and underscore the adaptable nature of the eukaryotic chromatin architecture to nanoscale confinement. This study was performed by Gadiel Saper, in collaboration with the groups of Uri Raviv and Ariella Oppenheim (HUJ).

## FUTURE PROJECTS

A major focus in coming years will be the study of macromolecular assembly in ever more complex solutions. Specifically, we are interested in how such molecules arrange in ionic liquids and deep eutectic solvents. Ionic liquids are salts that are found in the liquid state around room temperature. The low melting point in due to frustrations in the arrangement of ions that is enhanced by non-Coulombic interactions (such as large nonpolar groups present on the ions). Deep eutectic solvents are mixtures (for example choline salts and urea) with very low melting points compared with their unmixed constituents. These solvents form a new family of compounds that are completely different to aqueous solutions, and pose multiple opportunities as well as challenges to understand their salvation behaviors. We are collaborating with the group of Dominik Horinek (Regensburg) on modeling these special solvents and their interactions with macromolecules such as polycarbohydrates, and complimenting neutron diffraction experiments are planned in collaboration with the Oak Ridge National Lab (through a travel grant awarded to Liel Sapir).

## COLLABORATIONS

- George Khelashvili, Harel Wienstein (Cornell medical school, NY, NY),
- Georg Pabst (Austrian Academy of Sciences, Austria), Rachel Yerushalmi-Rozen (BGU)
- Rudi Podgornik (Slovenia), David Andelman (Tel Aviv U), Dganit Danino (Technion)

## CONFERENCE ORGANIZATION SINCE 2006

- Biophysics mini-symposium (14 Feb 2007, Hebrew University, with Drs. U. Raviv and A. Friedler).
- From Macromolecular to Cell Biophysics (June 3-4, 2008, Mishkenot, Jerusalem with D. Andelman and W. M Gelbart).
- Biomolecular simulations (2009, Safed, with M. Niv, D.T. Major, and K. Levy).

## HARRIES GROUP

- Dr. Jennifer Galanis, Postdoctoral fellow
- Regina Politi, PhD student
- Gadiel Saper, Msc Student, 2007-2008: faculty prize for academic achievements
- Shahar Sukenik, Msc Student (joint with Assaf Friedler)
- Liel Sapir, BSc student, Dean's prize 2007, 2008

## GRANTS FOR PROFESSOR HARRIES'S GROUP, 2002-2008

| Granting Agency | Period | Amount |
|---|---|---|
| **Israel-Slovenia collaboration, Ministry of Science** | 2007–2009 | $80,000 |
| **Alon Fellowship** | 2006–2009 | $100,000 |
| **Israel Science Foundation (ISF)** | 2007–2011 | $160,000 |
| **Israel Science Foundation (ISF), equipment** | 2007 | $50,000 |
| **Israel Science Foundation (ISF), Workshop** | 2009 | $17,000 |
| **James-Franck Foundation (with Dr. Uri Raviv)** | 2009 | $100,000 |

## PRIZES, MEMBERSHIPS SINCE 2006

- Alon Fellowship, 2006
- Biophysical Society member
- American Chemical Society member
- Best teacher award in Faculty of sciences, 2009

## RONNIE KOSLOFF

Our research efforts foucused on quantum phenomena: *Quantum Thermodynamics, Quantum Optimal Control and Photoassociation.* In addition we have an applied research effort devoted to public safety: defense against improvised explosives where we found a new phenomena of weak detonation.

## RESEARCH

### QUANTUM THERMODYNAMICS

The highlight of our research was to decipher the third law of thermodynamics. Thermodynamics was initially formed as a phenomenological theory, with the fundamental rules assumed as postulates based on experimental evidence. The well-established part of the theory concerns quasistatic macroscopic processes near thermal equilibrium. Quantum theory, on the other hand, treats the dynamical perspective of systems at atomic and smaller length scales. The two disciplines rely upon different sets of axioms. However, one of the first developments, namely Planck's law, which led to the basics of quantum theory, was achieved thanks to consistency with thermodynamics. Einstein, following the ideas of Planck on blackbody radiation, quantized the electromagnetic field.

With the establishment of quantum theory, quantum thermodynamics emerged in the quest to reveal the intimate connection between the laws of thermodynamics and their quantum origin. Following this tradition, we set out to study the quantum version of the third law of thermodynamics, in particular quantifying the unattainability principle. Apart from the fundamental interest in the emergence of the third law of thermodynamics from a quantum dynamical system, cooling mechanical systems reveal their quantum character. As the temperature decreases, degrees of freedom freeze out, leaving a simplified dilute effective Hilbert space. Ultracold quantum systems contributed significantly to our understanding of basic quantum concepts. In addition, such systems form the basis for emerging quantum technologies. The necessity to reach ultralow temperatures requires a change of focus to the cooling process itself, namely quantum refrigeration.

There are seemingly two independent formulations of the third law. The first, known as the Nernst heat theorem, implies that the entropy flow from any substance at absolute zero temperature is zero. At steady state the second law implies that the total entropy production is non-negative, $\sum_i -\frac{\dot{Q}_i}{T_i}$ where $\dot{Q}_i$ is positive for heat flowing into the system from the $i$-th bath. In order to insure the requirement of the second law when one of the heat baths (labeled $k$) approaches the absolute zero temperature. It is necessary that the entropy production from this bath scales as $\dot{S}_k \approx T_k^{\alpha}$ with $\alpha \geq 0$. For the case where $\alpha = 0$ the fulfillment of the second law depends on the entropy production of the other baths, which should compensate on the negative entropy production of the $k$-th bath. The first formulation of the third law slightly modifies this restriction. Instead of $\alpha \geq 0$ the third law imposes $\alpha > 0$ guaranteeing that at the absolute zero $\dot{S}_k = 0$.

The second formulation of the III-law is a dynamical one, known as the unattainability principle: *No refrigerator can cool a system to absolute zero temperature at finite time*. This formulation is more restrictive, imposing limitations on the spectral density and the dispersion dynamics of the heat bath (Levy and Kosloff, PRL 108, 07604 (2012) and ibid PRE 85, 061126 (2012)).

We quantify this formulation by evaluating the characteristic exponent $\zeta$ of the cooling process:

$$\dot{T}(t) \approx -T^{\zeta}, T \to 0,$$

namely, for $\zeta < 1$ the system cools to zero temperature at finite time. This equation can be related to the heat flow:

$$\dot{Q}_k\big(T_k(t)\big) = -c_V\big(T_k(t)\big)\dot{T}_k(t)$$

where $c_V$ is the heat capacity of the bath.

The minimum requirement fora quantum thermodynamical device is a system connected simultaneously to three reservoirs. These baths are termed hot, cold, and work reservoir as described in Fig. 1. A quantum description requires a representation of the dynamics working medium and the three heat reservoirs. There are two major types of quantum heat engines continuous like turbines and discrete such as Otto cycles. After ten years of concentrating on reciprocating engines we returned to study continuously operating refrigerators. Explicitly we analyzed quantum absorption refrigerators and compared them to power driven refrigerators (Levy and Kosloff, PRL 108, 07604 (2012) and ibid PRE 85, 061126 (2012)). We found that the essence of a quantum device is its non linear character. At low temperature all refrigerators show similar scaling where upon optimizing, $\omega_c \propto T_c$ .

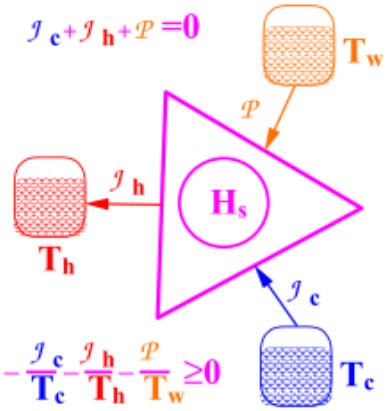


**Figure 35: The quantum trickle: A quantum refrigerator designated by the Hamiltonian $\hat{H}_s$ coupled to a work reservoir with temperature $T_w$, a hot reservoir with temperature $T_h$ and a cold reservoir with temperature $T_c$. The heat and work currents are indicated top: I-law, bottom II-law. In steady state $\mathcal{J}_h+\mathcal{J}_c+\mathcal{P}=0$. When heat is used to drive the refrigerator it is called an absorption refrigerator**

We also continued our studies on quantum reciprocating refrigerators operating on an Otto cycle (Feldmann & Kosloff, PRE 85, 051114 (2012) and PRE 82, 011134 (2010); Hoffmann, Salamon, Rezek, and Kosloff, Epl 96, 60015 (2011)). Four stroke Otto refrigerator cycles with no classical analogues were studied. Extremely short cycle times with respect to the internal timescale of the working medium characterize these refrigerators. Therefore, these cycles are termed *sudden*. The sudden cycles are characterized by the stable limit cycle, which is the invariant of the global cycle propagator. During their operation the states of the working medium possess significant coherence which is not erased in the equilibration segments due to the very short time allocated. This characteristic is reflected in a difference between the energy entropy and the Von Neumann entropy of the working medium.

Another effort was to find the fastest frictionless adiabatic move. In this context we have $\hat{H}_0$ a reference Hamiltonian and a control part $\omega(t)\hat{H}_1$ where $\left[\hat{H}_0,\hat{H}_1\right]\neq 0$ How should we change $\omega(t)$ from an initial to a final value such that the system at the beginning and the end will remain in a thermal state? Such motion is required in magnetic cooling or in expanding a BEC. We term such transformations as being frictionless. We have studied this problem using optimal control theory and found solutions that have a superior scaling to the adiabatic control (Salamon, Hoffmann, Rezek, and Kosloff, PCCP 11, 1027 (2009), Rezek, Salamon, Hoffmann, and Kosloff, Epl 85, 30008 (2009), Hoffmann, Salamon, Rezek, and Kosloff, Epl 96, 60015 (2011)). We found the scaling of the minimum time of the transformation with the frequency $\omega_c$.

These studies were performed by Tova Feldmann, Yair Rezek and Amikam Levi in collaboration with Peter Salamon, Karl Heintz Hoffmann and Robert Alicki.

## QUANTUM OPTIMAL CONTROL THEORY

Quantum optimal control is devoted to finding control paths that lead a system from an initial state to a final objective. In recent years a connection has been found to the field of quantum

computing where the objective is a unitary transformation.

## NOISE AND CONTROLLABILITY: SUPPRESSION OF CONTROLLABILITY IN LARGE QUANTUM SYSTEMS

A closed quantum system is defined as completely controllable if an arbitrary unitary transformation can be generated using the available controls. In practice, control fields are a source of unavoidable noise. Can one design control fields such that the effect of noise is negligible on the timescale of the transformation? Complete controllability in practice requires that the effect of noise can be suppressed for an arbitrary transformation. The present study considers a paradigm of control, where the Lie-algebraic structure of the control Hamiltonian is fixed, while the size of the system increases, determined by the dimension of the Hilbert space representation of the algebra. We show that for large quantum systems, generic noise in the controls dominates for a typical class of target transformation; i.e., complete controllability is destroyed by the noise (Khasin and Kosloff, PRL 106, 123002, 2011.). (Work of Michael Khasin).

The major task in quantum control theory is to find an external field that transforms the system from one state to another or executes a predetermined unitary transformation. We investigated the difficulty of computing the control field as the size of the Hilbert space is increased. In the models studied the controls form a small closed subalgebra of operators. Complete controllability is obtained by the commutators of the controls with the stationary Hamiltonian. We investigate the scaling of the computation effort required to converge a solution for the quantum control task with respect to the size of the Hilbert space. The models studied include the double-well Bose Hubbard model with the SU(2) control subalgebra and the Morse oscillator with the Heisenberg-Weil algebra. We find that for initial and target states that are classiï¬ed as generalized coherent states (GCSs) of the control subalgebra the control field is easily found independent of the size of the Hilbert space. For such problems, a control field generated for a small system can serve as a pilot for finding the field for larger systems. Attempting to employ pilot fields that generate superpositions of GCSs or cat states failed. No relation was found between control solutions of different Hilbert space sizes. In addition the task of finding such a field scales unfavorably with Hilbert space sizes (Kallush and Kosloff. PRA, 83, 063412, (2011), ibid 85, 013420, (2012)).

Work of Shimshon Kallush.

## STUDY OF PHOTOASSOCIATION

Molecules can be assembled from atoms using laser light. This process is termed photoassociation. With the advent of femtosecond lasers and pulse shaping techniques, photoassociation became a natural candidate for coherent control of a binary reaction. Coherent control has been conceived as a method to determine the fate of chemical reactions using laser fields. The basic idea is to employ interference of matter waves to constructively enhance a desired outcome while destructively suppressing all undesired alternatives. Control is exerted by shaping the laser pulses, the simplest control knobs being time delays and phase differences. Over the last two decades, the field of coherent control has developed significantly both theoretically and experimentally. However, a critical examination of the achievements reveals that successful control has been demonstrated almost exclusively for unimolecular processes such as ionization, dissociation and fragmentation. It is natural to ask why the reverse process of controlling binary reactions is so much more difficult.

The main difference between unimolecular processes and a binary reaction lies in the initial state a single or few well-defined bound quantum states vs an incoherent continuum of scattering states. For a binary reaction, the nature of the scattering continuum is mainly deter-

mined by the temperature of the reactants. As temperature decreases, higher partial waves are frozen out. At the very low temperatures of ultracold gases, the scattering energy of atom pairs is so low that the rotational barrier cannot be passed, and the scattering becomes purely $s$-wave. In this regime, the reactants are pre-correlated due to quantum threshold effects (Koch and Kosloff, PRL 103, 260401 (2009)) and the effect of scattering resonances is particularly pronounced. At a temperature of about $100\mu K$, photoassociation with femtosecond laser pulses has been demonstrated. Coherent transient Rabi oscillations are observed as the prominent feature in the pump-probe spectra. The transients are due to long tails of the pulses caused by a sharp spectral cut necessary to avoid excitation into unbound states.

The situation changes completely for high temperatures where the scattering states can penetrate rotational barriers due to the large translational kinetic energy. The association process is then likely to happen at short internuclear distance close to the inner turning point and for highly excited rotational states. In this case, the large spectral bandwidth of femtosecond laser pulses is ideally adapted to both the broad thermal width of the ensemble of scattering states and the depth of the electronically excited state potential in which molecules are formed. The disadvantage of this setting is that the initial state is completely incoherent, impeding control of the photoreaction.

We have recently demonstrated generation of both rotational and vibrational coherences by two-photon femtosecond photoassociation of hot atoms. (Rybak, Amitay, Amaran, Kosloff, Tomza, Moszynski and Koch, Faraday Discuss 153, 383 (2011); Rybak, Amaran, Levin, Tomza, Moszynski, Kosloff, Koch and Amitay, PRL 107, 273001, (2011)). This is a crucial step toward the coherent control of photoinduced binary reactions since the fate of bond making and breaking is determined by vibrational motion.

Employing multi-photon transitions comes with several advantages: The class of molecules that can be photoassociated by near-IR/visible femtosecond laser pulses is significantly larger for multi-photon transitions compared to one-photon excitation. Femtosecond laser technology is most advanced in the near-IR spectral region. Due to different selection rules, different electronic states become accessible for multi-photon transitions compared to one-photon excitation. Control strategies differ for multi-photon and one-photon excitation. In particular, large dynamic Stark shifts and an extended manifold of quantum pathways that can be interfered come into play for multi-photon excitation. The theoretical description needs to account for these strong-field effects.

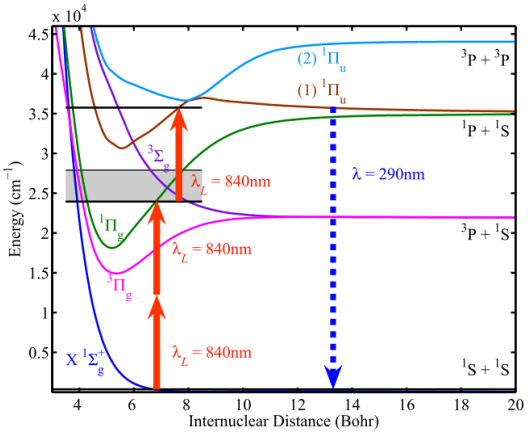


**Figure 36: Potential energy curves of the electronic states of $Mg_2$ involved in the two-photon photoassociation probed by a time-delayed pulse. The shaded region indicates the vibrational band populated after photoassociation.**

This study is an experimenal-theoretical collaborative effort with the groups of Zohar Amitay at the Technion, Christian Koch at Kassel and Robert Moszynski at Warsaw.

## WEAK DETONATION

We are participating in a collaborative effort to study improvised explosives. To tackle the potential danger we are setting up simulation methods. We studied for example methods to diffuse safely TATP (Dubnikova, Kosloff, Oxley, Smith, Zeiri, JPC, 115, 10565 (2011)). To put these efforts on a sound scientific basis we

studied the development of a detonation wave in a model system.

Explosives are characterized by a detonation wave propagating through the material. After initiation, the velocity of the detonation front reaches a steady state that exceeds the speed of sound in the material. We performed an analysis of a model solid explosive with the purpose of correlating the microscopic structure and interatomic forces to the bulk detonation properties. The investigation was based on a classical molecular dynamics simulation with a simple force field. The initial goal was to construct a first principle model which is able to qualitatively reproduce a stable detonation wave. The microscopic parameters considered are the crystal structure, the intermolecular forces that stabilize this structure, and the intramolecular potentials which yield the driving chemical reaction. The investigation unraveled a new type of a solitary-like detonation wave which is directly driven by the one-step exothermic chemical decomposition. From a hydrodynamical perspective it can be classified as a weak detonation (Am-Shallem, Zeiri, Zybin, and Kosloff, PRE 84, 061122 (2011)). This is a novel observation a detonation wave that is both supersonic with respect to the burnt and unburnt explosive material.

Work of Morag Am Shalem, Yehuda Zeiri and Sergey Zabinn.

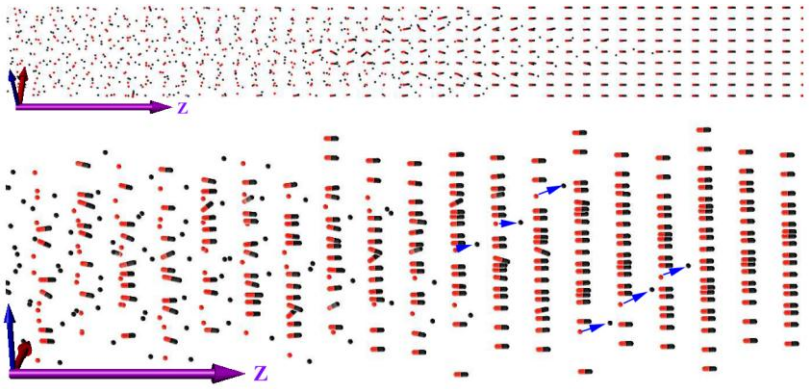


**Figure 37: A snapshot of the detonation wave. The propagation axis is the $Z$ direction. Periodic boundary conditions are used in the $X, Y$ directions. The right hand side shows the unperturbed crystal structure. The red objects represent the heavy particles (N). The black objects represent the light particles (C). On the left side of the image one can observe the burnt material after the passage of the shock wave. The shock-front is characterized by pilot-cascades of light particles emitted by the decomposing molecules. These initiate the next layer in a domino-like effect. The lower panel is an enlarged viewpoint of the detonation front. The arrows indicate decomposed N-C pairs, corresponding to the pilot cascade. This simulation was carried out with exothermicity of 6 eV and a barrier of 0.25 eV. Eventually, in this simulation, in approximately 20 layers, most of the material is decomposed.**

## COLLABORATIONS

We have developed very close collaborations with the Group of Dr. Christiane Koch now in Kassel on the theme of ultracold molecules and coherent control. We developed an experimental-theoretical collaboration on two-photon photo-association of Mg atoms with the group of Zohar Amitay at the Technion, Christiane Koch at Kassel and Robert Moszynski at Warsaw. This is a first step toward a general scheme to control binary reactions. We have an international collaboration on optimal control with Peter Salamon from San Diago and Karl Heinz Hoffmann from Chemnitz. We are also collaborating with the group of Phill Gould in the University of Connecticut on control experiments on photo-association of Rb atoms. Collaboration with Mark Ratner from Northwestern University on solar energy and the surrogate Hamiltonian. In addition we have been working with the experimental groups of Professor A. G. Wöste in Berlin and Matthias Wei-

demüller at Heidelberg. We are currently collaborating with Professor Robert Alicki from Gdansk.

## FUTURE PLANS

The field of quantum thermodynamics has emerged into the limelight. The activity in this subject has intensified.

We will therefore increase our efforts in studying quantum refrigerators and decipher the third law of thermodynamics.

Using our new insight on quantum absorption refrigerators (Levy and Kosloff, PRL 108, 070604 (2012)) we intend to study related devices. In addition we will try to connect our insights to other quantum devices and find connections to quantum information processing.

We intend to further study photoassociation of both hot and cold molecules with the purpose of controlling binary reactions. This will continue to be our major international collaboration with the group of Christiane Koch from Kassel, Matthias Weidemüller in Heidelberg, Robert Moszynski in Warsaw and Zohar Amitay in Israel.

We intend to study molecular ultrafast spectroscopy under dissipative conditions. We will collaborate with Professor D. Miller in Hamburg on weak field coherent control.

We will return to the issue of developing algorithms for simulating quantum dynamics from first principles. We found a new direction applicable for solving the time dependent Schrödinger equation with an explicitly time dependent Hamiltonian and nonlinearities (Ndong, Tal-Ezer, Kosloff and Koch. JPC 132, 064105 (2010); Tal-Ezer, Kosloff, Schaefer, J. Sci. Comput., 52 (2012)).

## RECENT GROUP MEMBERS

| Name | Project(s) | Status | Presently at |
|---|---|---|---|
| Michael Khasin | Quantum simulations | PhD 2008 | NASA |
| Yair Rezek | Quanum Thermodynamics | PhD 2012 | McGil |
| Morag Am Shalem | Weak field Cohernt Control | Graduate | Jerusalem |
| Ido Shefer | Harmonic Generation | MsC 2012 | Graduate Jerusalem |
| Amikam Levi | Quantum Refrigerators | Graduate | Jerusalem |
| Saieswari Amaran | Quantum Dynamics | Postdoc 2008-11 | India |
| Chen Levi | Quanum Dynamics | PhD 2010 | Israel |
| David Furman | Energetic Materials | Graduate | Israel |

## ACTIVE GRANTS FOR PROFESSOR KOSLOFF

| Granting Agency | Period | Amount |
|---|---|---|
| **Niedersachsen** | 07.2010 – 08.2007 | € 112,500 |
| **D.F.G** | 12.2009 – 07.2007 | € 116,900 |
| **Homeland security** | 06.2009 – 07.2008 | $ 31,000 |
| **Quantum Computing** | 11.2009 – 11.2008 | $ 25,500 |
| **Government Grant** | 12.2009 – 11.2005 | ₪ 115,000 |
| **ISF** | 09.2009 – 10.2007 | ₪ 334,000 |
| **Government Grant** | 10.2009 – 08.2007 | ₪ 400,000 |

## SCIENTIFIC COLLABORATIONS

| Name | Project(s) | Institution |
|---|---|---|
| Christian Koch | Quantum Control | University of Kassel |
| Robert Moyszinski | Electronic structure | University of Warsaw |
| Zohar Amitay | Photoassociation | Technion IIT |
| Phill Gould | Cold Photoassociation | UCon |
| Mark Ratner | Surrogate Hamiltonian | Northwestern |
| Peter Salamon | Optimal Control | San Diego State |
| Karl Heintz Hoffman | Optimal Control | Chemnitz |
| Dewian Miller | Coheret Control | Hamburg |

## ACTIVE GRANTS

| Project | Period | Foundation | Total Grant |
|---|---|---|---|
| Quantum Thermodynamics | 2009-2013 | ISF | 400000 Shekel |
| Homland Security Center of Excelenace | 2007-2013 | USA Gov | 120000 $ |
| Energetic Materials | 2008-2012 | Israel Gov. | 400000 Shekel |
| QUAINT | 2012-2017 | FP7 EU | 30000 Eur |

## CONFERENCE ORGANIZATION (PAST 5 YEARS)

| No. | Conference | Organizers |
|---|---|---|
| 1 | Safed Workshop on Cooling and Thermodynamics of Systems, 26 - August 31, 2007 | David Tannor, Ronnie Kosloff and Tal Mor |
| 2 | Batsheva de Rothschild Seminar on Ultrafast-Ultracold Processes, February 24 - February 29, 2008 | Ronnie Kosloff, David Tannor, Zohar Amitay and Christiane Koch |
| 3 | GRC Quantum Control of Light & Matter, July 31 August 5 2011 | Ronnnie Kosloff and Gustav G. Gerber. |
| 4 | Batsheva de Rothschild Workshop on Quantum Control, September 2-7, 2012 | Ronnie Kosloff, David Tannor, Zohar Amitay and Yaron Zilberberg |

## PRIZES, HONORS, EDITORIAL AND REVIEW BOARDS ETC.

- ICS Prize
- Member of the International Academy of Quantum Molecular Science

## ADVISORY EDITORIAL BOARD

- Israel Journal of Chemistry
- Advisory Editorial Board Journal of Computational Chemistry
- Advisory Editorial Board of Computer Physics Communication.
- Editorial board: Advances in Chemical Physics

## RAPHAEL D. LEVINE

The work is with the cooperating German investigators Rainer Weinkauf of the Heinrich-Heine-Universität Düsseldorf; Silvia Karthaeuser, Rainer Waser of the Forschungszentrum Jülich; Thomas Halfmann of the Technische Universität Darmstadt; Eleftherios Goulielmakis, Reinhard Kienberger, Ferenc Krausz, of the MPI für Quantenoptik, Garching; and, most recently, Marc Vrakking of the MBI, Berlin.

Seven graduate students have been actively involved. Three from HUJI, one from Berlin, one from Darmstadt and two from Liege. There was an active exchange of students between the different groups.

In 2011 there were three noteworthy events for our work on electron dynamics. The most recent is an outgrowth of discussions with Ferenc Krausz and Eleftherios Goulielmakis of the MPI in Garching that we examine the electron dynamics in the first optically allowed excited states of $N_2$ and CO. This study has been in progress when we recognized that there will be a very significant mass effect. Consultations and extensive discussions with Prof. Mark Thiemens has finally led to a just completed first experiment at the Advanced Light Source. ALS, in Lawrence Livermore Laboratory at Berkeley. This work is described in an annex to this report and will also be the subject of the oral presentation to the Beirat.

A second major development has been the preparation and subsequent approval of a joint research proposal on ultrafast electron dynamics and reactivity with Prof. Marc Vrakking of the MBI in Berlin. This has been funded to the Einstein Stiftung. We already have a first paper published with the Berlin group in anticipation of their experiment on ABCU [2]. This choice is motivated in part by the very rigid nuclear frame in ABCU which means that there is an usually long time interval for exploring pure electron dynamics unaccompanied by nuclear motion. Jointly with Prof. R N Zare I was awarded the Bernstein medal in Stereodynamics and on that occasion I spoke on ABCU.

For some time the work on the Stereodynamics of Ultrafast Electronic Motion, as in ABCU, has been gaining attention. I am therefore very pleased to report that the 2012 International Conference on Dynamical Stereochemistry has chosen this as it key theme and has invited me to talk. This is planned for November 2012 in Orsay.

The third development of 2010 is the publication of a joint communication with the group of Thomas Halfmann of Darmstadt on STIRAP implemented logic [3]. My student Dawit Hiluf was hosted by the Darmstadt group and Fabian Bail of Darmstadt visited Jerusalem.

In 2011 we also continued our work on our favorite example of LiH where we started the project with the MPQ. We studied an example where the laser field is of non negligible intensity and therefore distorts the electronic distribution while the laser is on[4].

Last but not least I am pleased to report on cooperation within Israel where our joint experimental/theoretical work with Prof. Uzi Even of TAU has been sent for publication.

(1) Muskatel, B. H.; Remacle, F.; Thiemens, M. H.; Levine, R. D. On the strong and selective isotope effect in the UV excitation of N(2) with implications toward the nebula and Martian atmosphere, PNAS 108, 6020, (2011). (2) Mignolet, B.; Gijsbertsen, A.; Vrakking, M. J. J.; Levine, R. D.; Remacle, F. Stereocontrol of attosecond timescale electron dynamics in ABCU using ultrafast laser pulses: a computational study, PCCP, 13, 8331,(2011). (3) Beil, F.; Halfmann, T.; Remacle, F.; Levine, R. D. Logic operations in a doped solid driven by stimulated Raman adiabatic passage, PhysRevA, 83,(2011). (4) Remacle, F., Levine, R. D. Attosecond pumping of nonstationary electronic states of LiH: Charge shake-up and electron density distortion, PhysRev A, 83,(2011).

## OBSERVATION OF SELECTIVE ISOTOPE EFFECT IN THE ULTRAVIOLET EXCITATION OF $N_2$: A COMPUTATIONAL STUDY

Isotope effects associated with gas phase N2 photolysis are used to interpret Martian atmospheric evolution, icy satellite atmospheric chemistry and meteorite isotopic anomalies from nebular N2 photochemistry. To interpret observations at the highest level, fundamental understanding of the precise wavelength dependency of the process must be known. In this paper VUV isotopic photodissociation effects are calculated as a function of wavelength at different wavelength slices in the 12.5-15 eV range. A very strong wavelength dependence is observed, which is significant for experiments. An observable effect is possible for the width of the beam profile at the advanced light source, ALS that may produce sufficient photolysis product for high precision isotopic analysis. A significantly more pronounced effect is predicted for a beam narrower by a factor of four providing a potential experimental test of the model. The spectrum is computed ab initio. It manifests two physical mechanisms for the isotope effect and they can be discriminated using a narrow beam. The fractionation is larger for the rarer heaviest isotopomer 15N15N and half as large for 15N14N.

In applications in the atmosphere and especially early solar system photochemistry, the high resolution energy dependency may become amplified. When solar light propagates through a medium, those solar peaks that are resonant with absorbing transitions will be preferentially depleted. The composition of the solar light will therefore vary along the propagation axis. This is the well known isotopic shielding effect. The role of this effect in preferential absorption of solar radiation by molecules of different isotopic composition, continues to be a subject of active research and debate, particularly for CO (5-12). An important step in enhancing understanding of the role of this process in astronomical situations is providing quantitative details of the preferential absorption of different isotopomers in an optically thin layer where all molecules experience the same light spectrum. This is attainable by reducing the path length such that opacity effects are negligible. As a contribution to understanding isotope effects associated with dissociation we report the computed frequency dependent isotopic fractionation. This high resolution wavelength examination is significant to explore giving the high degree of light structuring in natural systems. Furthermore, the calculations are carried out for conditions that allow an experimental checking. In much of the relevant UV spectral region, it is difficult to test the wave length dependence of the isotopic effect under laboratory conditions .The issue is not in the tenability of the light source, of which there are many, the limit is that one must produce sufficient high precision isotopic to test the observed model. At present, at the part per thousand sensitivity measurement ability of 15N/14N this is achievable through off line isotope ratio measurements. This protocol for example has been achieved by (10) for CO at the Advanced Light Source facility at Berkeley. As such, synchrotron radiation is an excellent option for model testing, though future laboratory based analysis may be used and the present calculations will be important for development of such techniques. In this paper, the calculations of wavelength dependent photolysis are performed using as a VUV light source comparable to the beam energies and widths available from the advanced light source, ALS, at the Lawrence Berkeley Laboratory. This beam has a width of ~0.5 eV at FWHM (see Figure 38) (12) and we here use the same beam profile, and one with a smaller width at all the frequencies in the energy range of 12.5 to 15 eV. The beam width at the ALS is controlled by an undulator and may in fact be tightened to 50-100 mev (13) but with a restriction in photon fluence by a factor of ~1000. The FWHM chosen is limited by the number of photons required to produce sufficient product to collect and isotopically analyze off-line by state of the art isotope ratio mass spectrometry at the isotopic precision required to test the model (10). The present results are of significance because they not only provide further details on the high energy sensi-

tivity of isotopic photodissociation, they also provide guidance for future synchrotron and laboratory based experiments. To test the existing model (14) several wavelengths for experimental observation must be selected and are critical for the design of the experiment.

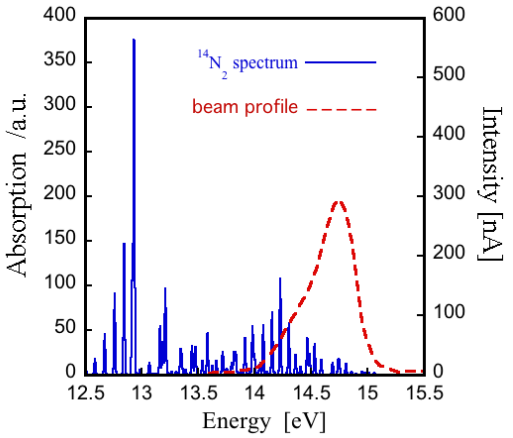


**Figure 38: The ab initio computed spectrum of 14N14N vs. the frequency in the energy range 12.5-15.5 eV and the beam profile, dashed line, available from the ALS, (12) at an energy of 14.75 eV. The computed rate of absorption is proportional to the area under the product of both. We generate the rate of absorption J vs. energy by varying the central frequency of the beam while maintaining its shape constant.**

When there is an almost negligible reduction in the intensity of the incident light the absorption rate for the molecules that absorb light is the product of the molecular absorption cross section and the incident light intensity. Both depend on the frequency and for an incoherent source integration over the relevant range in frequency is required. Unlike the solar spectrum, in the lower part of the energy range of interest the beam profile of the ALS that is planned to be used in the experiment (12) is relatively broad, as shown in figure 1. The width is set by the need for providing a sufficient number of photons to produce ample product for a off line high precision isotope ratio analysis It is roughly 0.5 eV FWHM (10), so that for a molecule such as N2, typically more than one vibrational state is within the range in frequency where the beam intensity is high as can be seen in Figure 38. In our calculations, the effect of energy and beam width are quantitatively assessed and reported. The short summary is that reducing the beam width significantly enhances the magnitude of the observable effect.

We have recently analyzed the absorption spectrum of different isotopomers of diNitrogen (14). Another very recent study is (15). Other recent high-level studies include works include (16,17).

It is qualitatively and even semi quantitatively reasonable to distinguish between two sources of an isotope effect that can lead to isotopic selectivity in light absorption. One specific effect is the very long recognized mass-dependent shift of vibrational spectral lines. This small but finite shift is amply sufficient to allow for an almost complete spectral separation whereby one isotopomer absorbs and the other not. There are different options for scavenging those molecules that absorbed and in practice this matters in terms of the efficiency of isotope separation. In principle with a frequency stabilized light source one can use this isotope effect to achieve an almost complete isotope separation. The mass-dependent isotope energy shift is inherently included in our computation but it cannot be the entire origin of the experimental effect that we look for because the shift is far smaller than the width of the light beam from the ALS. There are even smaller shifts of the vibrational energy states such as due to coupling to the triplet states, see e.g., (17). These couplings are however weak and the resulting shifts are insignificant compared to the energy resolution that is discussed here.

There exists however a second isotope effect that affects the relevant absorption spectrum. Simplistically the effect modifies the spectral intensities (14) and is complementary to the familiar effect of a shift in the spectral position resulting from isotopic substitution. Even in the most elementary description of a diatomic molecule there is an isotopic shift of the intensity due to a change in the Franck Condon factors. The effect is larger in diHydrogen and smaller in heavier diatomics due to the far smaller fractional change in the mass. This effect on spectral intensities is systematic and goes together with

the shift in frequency. It is not this effect that we highlight. Rather, we discuss an accidental effect due to the coupling of different excited electronic diabatic states. In the VUV range these are the excited valence and Rydberg states (18,19). Valence excitation is accompanied by a significant weakening of the N-N bond. The potential energy curve, (see (20) for accurate computations) is then likely to cross the potential of the more strongly bound Rydberg states. This crossing gives rise to localized perturbations in the spectrum and it is in the region of these perturbations that we expect the second concurrent isotope effect. Its origin is the accidental mixing of the valence excited states that carry a high oscillator strength, and the Rydberg states. It is localized in energy and occurs when a vibrational level is perturbed while the levels above and below it in the ladder remain largely unmixed (21,22). The energy region of intensity scrambling is therefore of the order of a vibrational spacing or more. This second effect can thus be experimentally significant even for a relatively broad in frequency light beam.

We compute the spectrum as follows. We first generate a basis of 250 excited vibronic states. In the energy range, 12.5-15 eV, of interest, it is a practically numerically complete basis for states that are one photon accessible from the ground state. Basis states carry a label of □ or □ electronic symmetry that is an exact symmetry at our level of approximation. One valence excited and two Rydberg diabatic states are identified for each symmetry (18). The potential energy curves for each diabatic state are those computed by Spelsberg and Meyer in ref (20). These are smoothly varying potentials and we compute 45 vibrational eigenstates for each curve except the lowest lying and shallow b valence excited state for which 25 states are computed below the continuum. The label of which isotopomer enters at this stage because it is needed to specify the kinetic energy operator. A Hamiltonian matrix in the vibronic basis is diagonalized. The Hamiltonian matrix has a block form. Along the diagonal are block diagonal matrices that are the vibrational spectrum of a given diabatic electronic state. These matrices are diagonal because the different vibrational states of the same electronic state are orthogonal. The diagonal matrices are coupled by off diagonal matrices that are the vibronic couplings. These are computed as vibrational matrix elements of the electronic coupling of different diabatic states. The Hamiltonian matrix has two large and uncoupled blocks corresponding to the two electronic symmetries that can couple to the ground state by one photon excitation. The oscillator strength, □, to the resulting eigenstates is computed from the matrix representation of the transition dipole operator from the vibrations of the ground electronic state, where 45 states are included. The spectrum as a function of frequency is given by these oscillator strengths, each with a room temperature rotational envelope. This more traditional method of computing the spectrum has been verified against the time dependent approach described in (14).

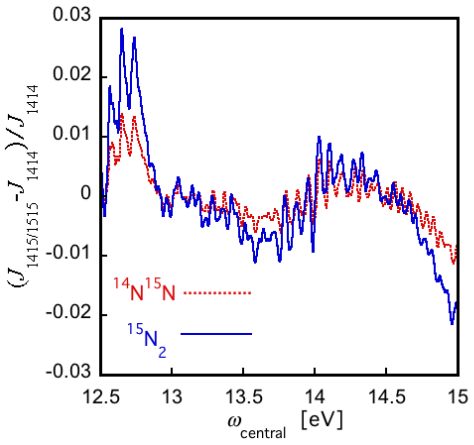


**Figure 39: Predicted excess isotopic fractionation for the two rarer isotopomers of N2 vs. the central beam frequency $\omega$ for a beam with a profile expected from the advanced light source, as reported in (12). $J_\omega = \int I_\omega(\nu)\sigma(\nu)d\nu$ where $I$ is the beam flux and $\sigma$ is the oscillator strength for the particular isotopomer.**

Figure 39 shows the results when integrating over the computed spectrum multiplied by the expected beam profile. Shown is the rate of absorption J of the two rarer isotopomers relative to that of the abundant, 14N14N, isotopomer vs. the central frequency □ of the beam. The fractionation rises above 10 ‰. Despite the (0.5eV)

width of the ALS beam, cf. figure 1, it is seen that the effect does vary with the central frequency of the beam, reflecting different states residing within and out of the beam center. The fractionation is not large, about 10 per mil at selected wavelengths for 14N15N, but it is within experimental feasibility. (For nitrogen typical errors associated with measurement are of the order of 0.03 per mil).

A two orders of magnitude larger effect is reported in figure 3 where the beam width is reduced by a factor of ten. Reducing the width by a factor of four suffices for an order of magnitude larger isotope effect. Larger isotopic enhancements at higher wavelength resolution will occur. But testing is limited by the amount of product that is produced by photolysis and separated for off-line isotope ratio analysis. Advances in this capability (13) will provide a tighter examination of the model.

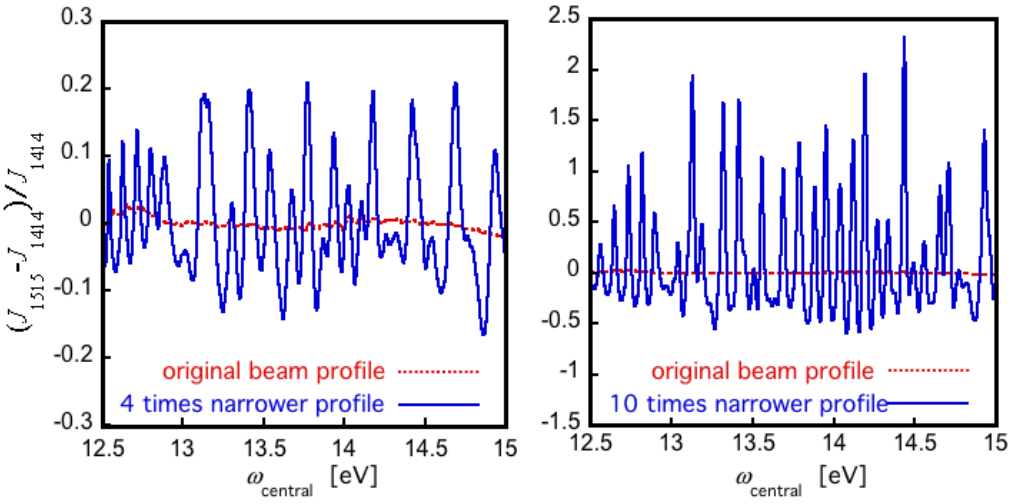


**Figure 40: The very significant enhancement of the isotopic fractionation predicted for narrower beams, left panel: width of 0.13eV FWHM, right panel; width of 0.05eV FWHM. Note the change in the scale of the ordinate between the left and right panels and that the scale in figure 2 is one order of magnitude smaller. The isotope effect is shown only for the rarest isotopomer $^{15}N^{15}N$ (blue online). The predicted effect for the more common, $^{14}N^{15}N$ isotopomer, is about half as large. The effect computed for the original beam profile shown in Figure 39 is here plotted as a dotted line.**

Figure 40 shows the results predicted for isotopic fractionation when the beam width is ¼ as large, left panel and 1/10 as large, right panel, as for figure 1. There is a dramatic enhancement in selectivity suggesting that experiments with a narrower slit will be the most sensitive for testing the model of (14). Experimental choice of wavelengths associated with the peaks and valleys in the rate will afford the largest range. When the beam profile is reduced by a factor of 10, the isotopic structure is even more observable at a wavelength of approximately 14.4 eV there is a near full factor of two enrichment in the heavy isotopes of nitrogen compared to nearby surrounding wavelengths. This dramatically shows the tight structuring of the isotopic dependency. In applications in natural environments where there are strong source wavelength variations, optical shielding (both self and non self), and dust effects, this information is critical in interpretation of the observational data. Furthermore, the structure in figure 3 suggests that photochemical experiments at higher energy resolution will be an excellent test of the present calculations.

In conclusion, using an ab initio computed spectrum of N2 in the far UV we show that it is possible to use the ALS or a similar tunable light source (of suitable photon flux for isotopic measurement) to demonstrate isotopic fraction-

ation in the absorption and to test photochemical isotope effect models. The origin of the effect is due to both isotopic shift of position and of intensity of the absorption lines. The latter is due primarily to the localized and accidental mixing of valence excited and Rydberg states.

Acknowledgments: We thank T.J. Martinez, J. Troe and G. J. Wasserburg for their comments on our work. MHT acknowledges numerous helpful discussions with S. Chakraborty, G. Dominguez and R. Shaheen and Antra. Details of the ALS operation by S. Chakraborty were most helpful. The work of BHM, FR and RDL is supported by the James Franck Program for Laser-Matter Interaction. The work of RDL and FR and the computational facilities for this project is also supported by the EC FET Nano-ICT project MOLOC. Support for MHT was provided by NASA Origins of Solar Systems and Cosmochemistry programs.

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## FUTURE RESEARCH

Our plans for research are to continue the work on mass effects in electronic reorganization with special relevance to isotopic fractionation in CO. We will also continue with our studies of ultrafast electron dynamics in N2 with special reference to the role of the vibrational motion. We propose to continue and expand on the collaboration with Prof. Marc Vrakking and the MBI. My graduate student Dawit Hiluf is a lecturer at Mekelle University in Ethiopia on official leave here to get his PhD. I am pleased to report that we just secured funding from the EU to continue his work on optically addressed parallel logic.

## PROFESSOR LEVINE'S GROUP 2008-2012

| Name | Status | Presently |
|---|---|---|
| **Dr. Haya Kornweitz** | Postdoc | Ariel University Center |
| **Dr. Tamar Raz** | Postdoc | Jerusalem College of Technology |
| **Dr. Menashe Rajuan,** | PhD | Hi-Tech company |
| **Dr. Dan Steintiz** | PhD | Jerusalem College of Technology |
| **Dr Nataly Kravchenko-Balasha** | Postdoc | Current |
| **Dr. Ayelet Gross** | PhD | Hi-Tech company |
| **Michael Klein** | PhD | Current |
| **BenZion Harel Muskatel** | PhD | Current |
| **Sawsan Salameh** | PhD | Current |
| **Noa Richke** | MSc | Politics |
| **Laurent Jutier** | Postdoc | Current |
| **Jayanth Ajai** | PhD | Current |
| **Rameshkumar Arumugam** | PhD | Current |
| **Dawit Hiluf** | PhD | Current |

## MASHA Y. NIV

My overall scientific goal is to deepen our understanding of molecular recognition in signaling processes in taste recognition and metabolism, and to enable rational design of signal-modulating agents. Protein kinases

My lab is focused on I) PKs involved in metabolism and diabetes - great challenges in human health research - and on II) taste recognition, mainly the bitter-taste receptor subfamily of GPCRs, studying both the basic principles of molecular recognition of taste and working towards applications in food science and health and disease.

**I)** Inhibiting protein-protein interactions by peptides and peptidomimetics is a novel approach to selective modulation of protein kinase activity (publications 19, 22, 23 and review 1). Due to high flexibility of peptides and the large and flat protein surfaces to which they bind, appropriate computational tools for designing and optimizing peptidic and peptidomimetic modulators are needed (publication 28, 29 and review 4). We analyzed the protein surface of representative

protein kinases, and identified novel, previously unknown specificity determinants responsible for substrate recognition (publication 29). This analysis enabled rationalization of the structural-activity relations of series peptidomimetic compounds (publication 28) for the Akt/PKB kinase. Our recent study of the events involved in inactivation of this kinase (publication 26) showed that detachment of the ligands and A-loop dephosphorylation lead to stronger correlation and anticorrelation of motions and to increased mobility in the N-lobe and in the HJ-αG region of the C-lobe. Publication 26 highlighted the importance of protonation in the protein-peptide interactions. This work lead to our recent survey of the current state of modeling of protonation states in peptides (invited review 4).

**II)** The taste of food is a key aspect to food consumption and it becomes clear that tastants play important roles also in metabolism. Many processes in odor and taste perception are governed by G-protein coupled receptors (GPCRs). Recent advances in GPCR crystallography provide excellent opportunities for structure-based computational research (invited reviews 2 and 3 and book chapter 1 (submitted). Bitterness of food, recognized by a family of 25 bitter-taste receptors, plays a key role in food palatability. *But how can a few bitter taste receptors recognize hundreds of dissimilar bitter molecules?* To begin answering this question, one must first compile information on the identity and chemical structures of the bitter molecules. Ayana Wiener, during her MSc in my lab, used text- and data-mining techniques to rectify this situation by compiling a database of chemical structures of all compounds known to be bitter. The database, BitterDB (publication 27) became publicly available in August 2011 and is searchable by fields such as molecular weight, solubility, association with a particular receptor, etc. We have tens of users that have joined the BitterDB mailing list, and over 4000 of users worldwide.

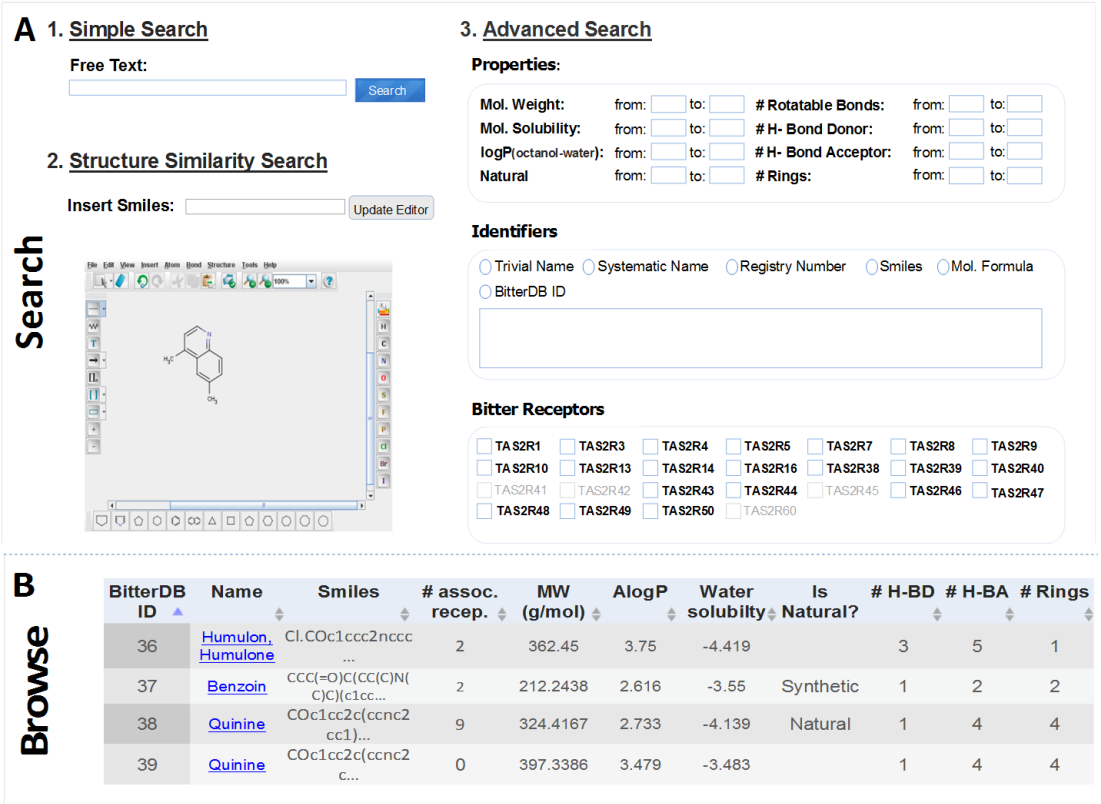


**Figure 41: Examples of user interfaces in BitterDB.**

To study the molecular determinants of bitter molecules recognition by their receptors, we established a collaboration with Prof. Meyerhof's group at the German Institute of Nutrition

(DIFE), one of the leading experimental labs in the field. We used molecular modeling and ligand-docking techniques to predict and compare the binding pockets in several bitter taste receptors. We found that the binding mode of the same tastant may vary between two bitter taste receptors, and the same bitter taste receptor may bind ligands in different sub-sites within the binding pocket (publication 25 and submitted publication 34).

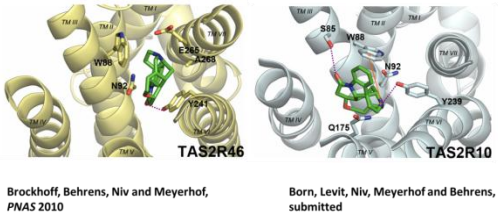


**Figure 42: Different binding modes of strychnine in the binding sites of two bitter taste receptors.**

Analysis of the chemical and structural features of the known ligands of bitter taste receptor hTAS2R14 was combined with the iterative computational-experimental elucidation of the binding site residues in this receptor. These ligand-based and structure-based features were used to screen the BitterDB compounds which were not yet assigned to particular receptors (but are known to taste bitter to human). Several predicted compounds were tested in functional assays in the Meyerhof lab, and were indeed found to activate hTAS2R14 (work in progress). In addition, we are analyzing the BitterDB compounds in order to identify additional bitter compounds (work in progress). Similarly, in a recent work on another subfamily of GPCRs, virtual screening identified potential novel human PKR (hPKR) ligands within the dataset of approved and investigational drugs (publication 30).

Taste receptors, and many other GPCRs (such as serotonin), have been recently shown to homo- and heterodimerize. The physiological role of the dimerization has been established in some cases, but is still unknown in many others. To elucidate the role of dimerization signaling, dimerization-deficient, but otherwise intact receptors are needed. We established a collaboration with Prof. Ponimaskin's lab in Germany, in which we were able to obtain GPCRs with reduced dimerization ability by re-engineering the predicted interface residues (publication 32).

A list of publications from the past 3 years (2009-2012)

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34) Born S, Levit A, Niv, MY, Meyerhof W and Behrens, M "The human bitter taste receptor TAS2R10 is optimized for diverse ligands" (in revisions). (Collaboration with Professor Meyerhof, Germany).

Review articles

1. Rubinstein M and Niv M.Y. (2009) Peptidic modulators of protein-protein interactions: progress and challenges in computational design, Biopolymers 91(7):505-13.
2. Yarnitzky, T., Levit, A. and Niv M.Y., (2010) Recent advances in modeling G-protein-coupled receptors, Curr Opin Drug Disc Dev, 13:317-325;
3. Levit. A., Barak D., Behrens, M., Meyerhof W. and Niv, M.Y. (2012) Homology model-assisted elucidation of binding sites in GPCRs, Methods in Mol. Biol. Series, Invited review – in press. (Collaboration with Professor Meyerhof, Germany)
4. Ben-Shimon, Shalev and Niv MY, Computational treatment of protonation states in peptide folding and binding (in Current Pharmaceutical Design Hot Topic issue), invited review, accepted;
5. Kowalsman N and Niv MY, "GPCRs & company: databases and servers for GPCRs and interacting partners" in: Computational Approaches to G Protein-Coupled Receptor Modeling and Simulation in Support of Rational Drug Discovery Editor: Marta Filizola Publisher: Springer, invited review, submitted.

## CONTRIBUTION OF FRITZ HABER CENTER TO OUR RESEARCH

The Fritz Haber Center is instrumental to our ability to carry out simulations, because it provides the physical space and the system administration to our high performance computing cluster. The system administration support provided to my lab via the Fritz Haber Center is excellent, and is essential for our productivity. Our recent and ongoing work (e.g. publications 26,29,30, submitted publication 34) relies on the excellent technical support at Fritz Haber Center for carrying out MD simulations, docking, virtual screening and other computationally-heavy tasks.

## STUDENT REPORTS

### TALI YARNITZKY, PHD

I am an investigator at the lab of Dr. Masha Niv since January 2010. I joined the lab after an extensive experience at the industry (~10 years) in the field of drug discovery. My PhD work was done at the Weizmann Institute of Science under the supervision of Prof. Talila Volk. In Masha Niv lab I am working on several major projects involving protein-ligand interactions of two key protein families, protein kinases (PKs) and G-protein-coupled receptors (GPCRs).

My projects include:

1. Structure-function relationship of odorant receptors and identification of their natural ligands.

2. Discovery of kinase inhibitors:

*Memory enhancing drugs and their use in Alzheimer disease prevention.

*Developing an anchor-driven flexible peptide docking method.

Structure-function relationship of odorant receptors and identifying their natural ligands.

This work is done in collaboration with Prof. Dr. Jörg Strotmann, Hohenheim University, Germany.

The ability of the mammalian olfactory system to detect a vast repertoire of different odorants is based on the large number of diverse odorant receptors (ORs), which are members of the GPCR family. A small group of these ORs, the OR37 family, is unique because its members share a high degree of sequence homology and are high-

ly conserved during evolution. In addition, they are found exclusively in mammals. It was suggested by Prof. Strotmann that these receptors may respond to compounds from tissues and organs that exist uniquely in mammals (e.g. skin or hair). Mice were exposed to such compounds and activation of OR37 glomeruli was monitored. Stimulation with long chain hydrocarbon compounds with different functional groups revealed that they elicited an activation of defined OR37 glomeruli, each of them responding preferentially to an aldehyde with different chain length. These results indicate that OR37 receptors may be tuned to distinct fatty aldehydes with a significant degree of ligand specificity. We want to explore the structural reason for this specificity, and to identify additional ligands of the OR37 receptors using an iterative combination of experimental and computational tools. Toward these goals, we have used a combination of various computational tools.

Extensive sequence analysis was done of OR37 receptors (subfamily members and across species) and then molecular modeling of the 3D structure of these receptors was performed using I-Tasser Server (Figure 43). To explore the conformational space of the known active aldehyde ligands, preliminary short molecular dynamics simulations of these ligands were carried out using CHARMM and Discovery Studio v3.1, Accelrys (Figure 44). In addition, we carried out fragment-based search for identifying binding spots for aldehydes in order to predict a putative binding site for these ligands. Based on these results, additional ligands were predicted to bind the receptors and will be analyzed experimentally in order to check their activity towards OR37 receptors.

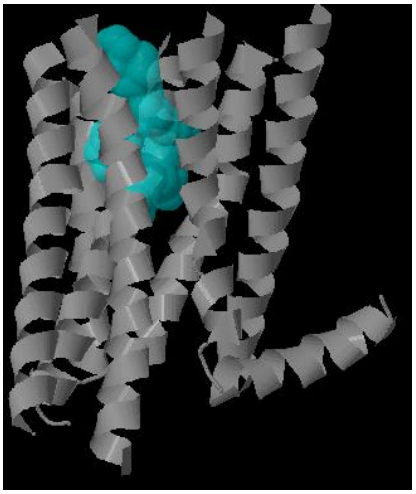

**Figure 43: A structural model of OR37 subtype B. The receptor is shown in grey ribbon, and the putative binding site in cyan. The model was created by I-Tasser server and analyzed by Discovery Studio, Accelrys.**

Our future plans include docking of active ligands into the receptor binding site and based on these results, identification of additional potential binders for the receptors.

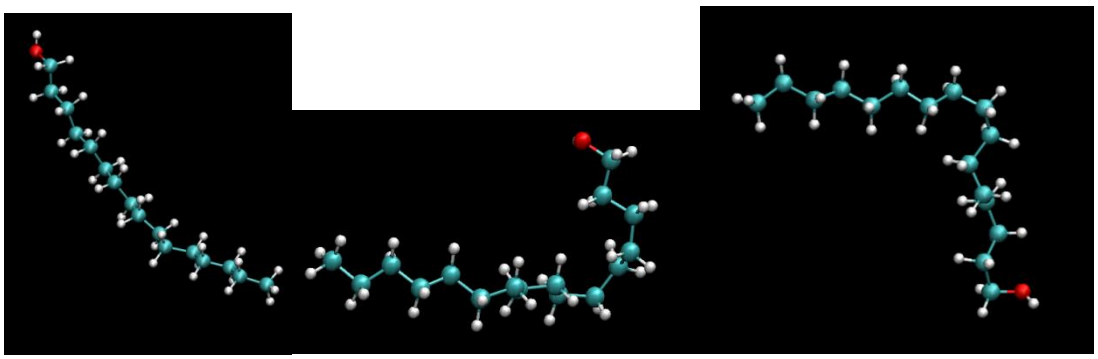

**Figure 44: Representative conformationas of a known active aldehyde ligand. Molecular dynamics simulation of the ligand was carried out using CHARMM and Discovery Studio v3.1, Accelrys.**

## DISCOVERY OF PROTEIN KINASE INHIBITORS: MEMORY ENHANCING DRUGS AND THEIR USE IN ALZHEIMER DISEASE PREVENTION

This work is carried out in collaboration with Prof. Kobi Rosenblum from Haifa University, Israel. Eukaryotic Initiation Factor 2 (eIF2) is one of the best-characterized mechanisms for down-regulating protein synthesis in eukaryotes in response to various cellular stress responses. It has been shown that following activation, PKR phosphorylates eIF2alpha and causes a decrease in protein synthesis. Therefore, inhibition of PKR causes elevation in protein synthesis. The Rosenblum group has identified a PKR inhibitor termed C-16 as a small molecule which is capable of crossing the BBB, reducing eIF2α phosphorylation and triggering cognition enhancement in a rodent model.

Using computer-aided drug design tools, we predicted additional small-molecule compounds that may lower eIF2alpha phosphorylation, via binding to the ATP-binding site of PKR. These methodologies include both structure-based and ligand-based techniques and their combined approaches. In the structure based approach, we utilized the known crystal structure of PKR, the structure of the small-molecule compound C-16 and other structurally similar kinases complexes (such as CDK2-inhibitor complex), to predict the ligand binding site within PKR, important residues within this binding site, and possible interactions between these residues and the C-16 ligand. This data was used to predict whether additional small molecule ligands from several compound libraries will bind to the target's binding site. In the ligand-based approach, we used the compound C-16 and additional known inhibitors of PKR to produce several screening models. A 2D model based on chemical characteristics of these compounds and a 3D pharmacophore model, based on the steric and electrostatic features of the compounds were generated, and the resulted models were used to perform additional screening of various compound libraries. All the work was done using protocols from Discovery Studio v3.1 (Accelrys, Inc.), and Maestro and Canvas software (Shrodinger). Combining the results from both screening methods on these libraries, we chose, purchased and analyzed several compounds for their activity towards PKR. Three of these compounds were already tested: 2 of these were potent inhibitors of PKR (IC50 <10uM).

Future plans include additional computational screening based on the chemical information of the newly identified inhibitors, in order to design de novo novel inhibitors of PKR.

## DISCOVERY OF PROTEIN KINASE INHIBITORS: DEVELOPING AN ANCHOR-DRIVEN FLEXIBLE PEPTIDE DOCKING METHOD*

Protein kinases play a key role in various cellular functions and have become targets for the treatment of including cancer, diabetes and autoimmune disorders. Inter- and intra-molecular peptide-mediated interactions of kinases act as specific regulators of activity. Novel kinase-targeting peptides are now being developed alongside the conventional ATP-binding site small molecule compounds. Structural information is necessary for optimizing these peptides and developing peptidomimetics. Obtaining experimental structures of protein/peptide complexes is not trivial, and computational tools are therefore instrumental in elucidating these structures. The key computational challenge is the flexibility of peptides that have many more degrees of freedom than classical drug-like small molecules. Very few computational docking procedures have been developed specifically for predicting the position and conformation of a peptide in a complex with a protein. One such approach has been developed by Dr. Niv. This protocol is based on anchor-driven simulated annealing molecular dynamics (SAMD) in which a known interaction (an anchor) is introduced via a constraint. This protocol has been validated in other protein groups and now we are adapting it for use in kinase-peptide complexes.

## AVI BEN-SHIMON, PHD (NIV LAB)

I joined the lab of Dr. Masha Niv as a post-doctoral fellow in May 2010, after accomplishing a PHD degree in computational biology at the Weizmann Institute of Science under the supervision of Prof. Zippora Shakked and Dr. Miriam Eisenstein. During my PHD, I developed ANCHORSmap, a novel computational mapping algorithm that is capable of identifying amino acids anchoring spots on protein surfaces [5]. At present, ANCHORSMAP is the only computational method that was specifically designed, calibrated and tested for the ability to detect anchoring spots that stabilize protein-protein or protein/peptide interactions. During my PHD, the method was used in several studies and successfully explained the selective translocation of the nuclear transport proteins through the pore [4] and the different peptide inhibition results obtained for two metalloproteases (collaboration with the group of Prof. Irit Sagi at the Weizmann Institute).

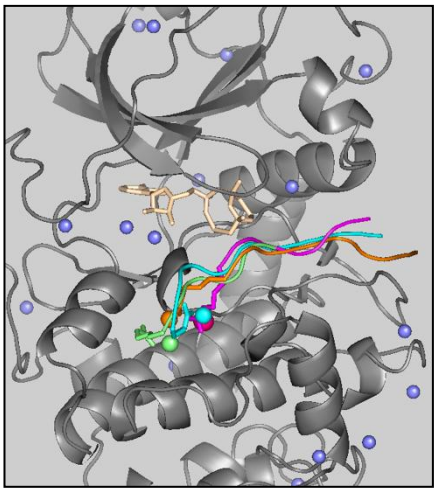

**Figure 45: The detection of Arginine anchoring spots on the surfaces of four different kinases. In gray, an overview of the PKB kinase structure with the top 20 Arginine anchoring spots detected for it (blue spheres). ATP is shown in light-brown. Arginine containing peptides, from four different experimentally determined kinase-peptide complexes and their corresponding top ranking anchoring spots are colored in cyan, magenta, orange and green, for the PKB, PKA , PAK4 and the PIM1 kinases respectively.**

Scientific background for my work in Dr. Niv's lab: The regulation of almost every process in the cell is governed by protein-protein interactions. Therefore, the ability to design new modulators of protein-protein interaction is of high importance for the study of cell signaling mechanisms, for enhanced understanding of the molecular recognition process and for paving the way for the discovery of new therapeutic agents. Targeting protein-protein interactions using small molecules is an enormously challenging task, because of the characteristically flat surface associated with protein interfaces [1]. Peptides are particularly suitable for this task, as their chemistry and structures are compatible with those of the target proteins. Importantly, peptides and peptidomimetics offer a huge chemical space that is reachable by simple synthesis, enabling the desired specificity and affinity required for efficient binding at the distinctive protein-protein interface environment. Thus my main research goal at Niv's lab is to develop and apply computational tools which will facilitate rational modification of natural peptides and de-novo design of peptidic modulators.

Results: After joining Dr. Niv's lab, I applied ANCHORSmap to study the surfaces of protein kinases in order to identify anchoring spots and to decipher kinase specificities towards their peptidic substrates. This work was published [2] and presented at the PDB40 Symposium (CSHL, 2011), which I attended with NSF early scientist travel award funding. For an example of anchoring spot detection on kinases surfaces, see Figure 45.

In collaboration with the groups of Prof. Chaim Gilon and Prof. Alex Levitzki at the Hebrew University we were able to rationalize the structure-activity relations of peptidomimetic inhibitors designed for protein kinase B (PKB) [3]. For example, in figure 2 it can be seen that the 3rd top ranking Arg binding position and the 2nd top ranking Lys binding position detected by ANCHORSmap on the entire surface of the PKB kinases, could potentially accommodate a residue from position P+2 of a putative substrate/inhibitor peptide. 7Å separate the $C\beta$ atom at the P+2 peptide position and the detected

anchoring spot for a positive moiety. This explains why the most potent peptide inhibitors in the investigated library were characterized by 3 or 4 carbons that separate between the inhibitor backbone at the P+2 position and a positive moiety; shorter or longer carbon linkers would fail to optimally fit the positively charged moiety into the anchoring spot.

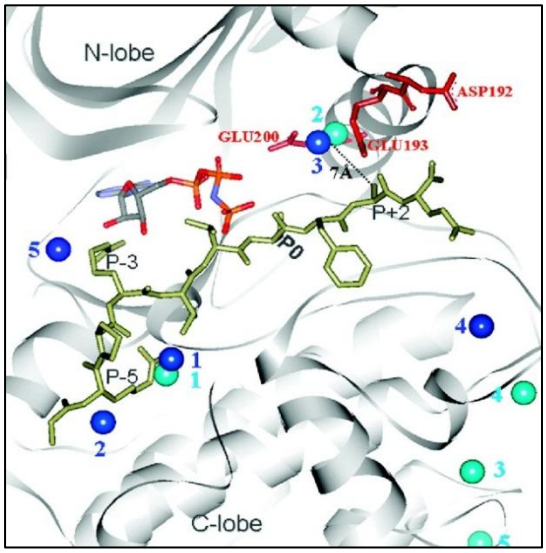


**Figure 46: Arg and Lys anchoring spots detected on the surface of PKB/Akt. The unbound structure of PKB/Akt (3D0E) and the superimposed GSK3β-peptide (1O6K) are shown in gray and olive green, respectively. ANP is shown in ball and stick representation. Acidic residues on helix αC are shown as red sticks. The top five predicted Arg and Lys anchoring spots are shown as blue and cyan spheres according to the positions of the Arg Cζ and Lys Nζ atoms, respectively. Blue and cyan numbers stand for ranking order.**

Future work: The large number of degrees of freedom in peptidic modulators prevents the use of standard computational docking tools usually applied in the field of small molecules. The large computational load derived from this obstacle requires many compromises. For example, currently available peptide docking methods almost exclusively keep the protein backbone fixed during the docking procedure in order to reduce the complexity of the problem. In fact the number of degrees of freedom is actually even higher if all the possible protonation states of titratable residues are considered [1].

In theory, molecular dynamics (MD) in explicit conditions could be used as a reasonably and accurate way for fully flexible approach to dock a peptide to its protein receptor. In practice however, such approach is prone to sampling and convergence problems which make it extremely computational intensive, and thus infeasible. Fortunately, the sampling and convergence problems inherent in regular explicit MD simulation can be partly overcome by considering one or more of the ideas presented below:

a. Using implicit solvent - implicit solvent representation dramatically accelerates the simulation by reducing the computational load and enhancing sampling.
b. Applying a simulated annealing (SA) scheme - an appropriate SA protocol could dramatically reduce the convergence problem, overcoming energetic barriers which are difficult to cross by normal simulation at ~300K.
c. Large integration time step (LITS) – normally, MD simulations are preformed with integration time step of 1-2 fs. Representing the hydrogen atoms as virtual sites can potentially increase the integration time step to 5-6 fs. This could accelerate the simulation by as much as ~3 fold.
d. Anchor-driven docking - Restricting even a single anchoring residue of the peptide to its binding location on the protein surface (anchoring-spot) during the simulation reduces dramatically the conformational space search needed. This approach was already shown to be highly efficient in previous studies preformed by Dr. Masha Niv (Niv and Weinstein JACS 2005). The unique and well-validated anchoring-spots information supplied by ANCHORSmap will be used to guide the docking simulation.

My future main goal is to develop a fully flexible protein-peptide docking protocol that considers all the four ideas above. This accelerated LITS anchor-driven SA MD simulation in implicit conditions is expected to supply a reasonable balance between flexibility, accuracy and computational load. In order to examine the physical feasibility of the suggested protocol, it will be tested and calibrated first on the ability to correctly fold known peptide and mini-protein structures. If successful, it will be combined with the anchoring-spot information to form a complete protocol for peptide docking. By working first on the folding problem it is possible to examine the

appropriate force filed, type of implicit solvent etc. on isolated and relatively small systems. Additionally, the folding protocol will provide a set of conformations of the free peptide, which will be used as input for peptide docking, further accelerating the conformational search during the docking simulation.

The preliminary folding results on a limited set of peptides and mini-proteins (7-28 AA long), are promising. An example of a structure predicted for the 10 amino acid Chignolin peptide using the protocol we developed, is presented in figure 3. Many folding and unfolding events are obtained during the 120 ns of the simulation (Figure 47A) and the sampled potential energy represents an energetic funnel, as low RMSD toward the experimental structure is reached (Figure 47B). The lowest energy structure with respect to the experimental NMR structure is shown in Figure 47C.

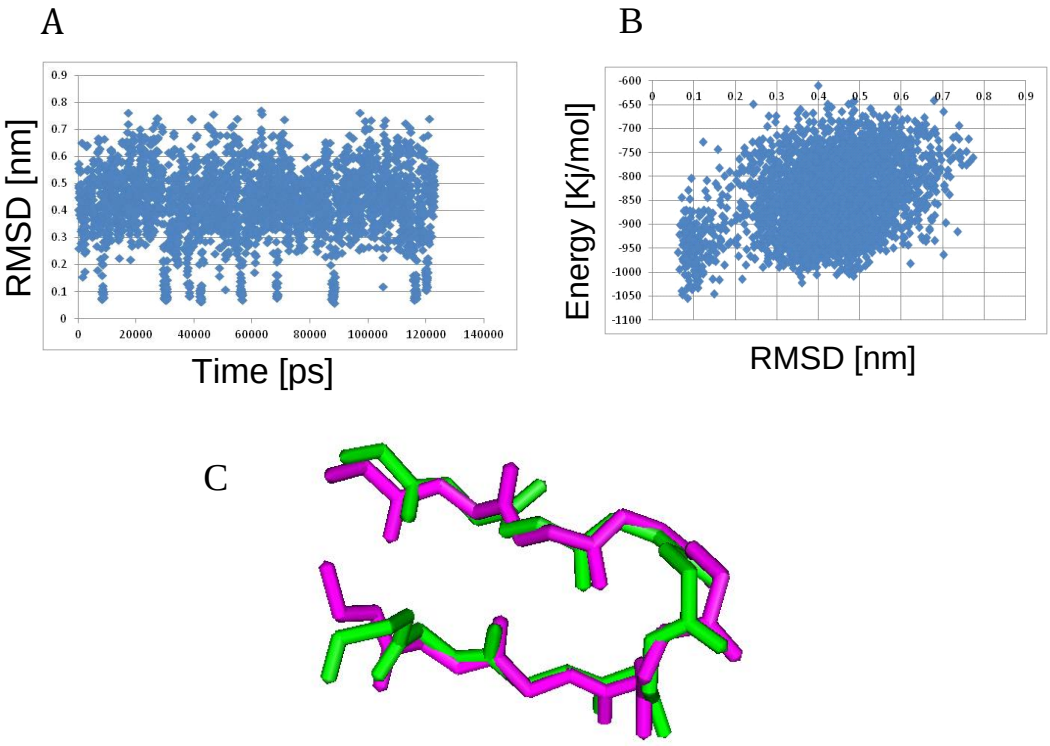


**Figure 47: predicting the structure of the 10 amino acid Chignolin peptide. A. The simulation progress as function of RMSD. B. RMSD as function of the potential energy. C. The lowest energy structure (magenta) in compression to the NMR structure, pdb code 1UAO (green).**

## DR. NIV'S FUTURE RESEARCH PLANS (2 YEARS)

We are exploring the structural and chemical aspects that enable "broad tuning" or "multi-specificity" of GPCR receptors towards diverse ligands by analyzing the chemical space of the known ligands, and comparing it with the structural, energetic, and dynamic features of the receptors (Anat Levit and Ayana Wiener).

To predict cross-reactivity patterns of bitter taste and of various odorant receptors, we are adapting innovative algorithms from the field of web-based retail, in collaboration with Prof. Lior Wolf from Tel Aviv University (Ayana Wiener).

We are continuing our fruitful collaboration with the Meyerhof lab in Germany (currently funded by DFG), to explore the evolution of molecular determinants for bitter taste perception, and to identify and design selective novel bitter agonists

and antagonists. Anat Levit and Maria Verbov are involved in these projects.

We will use state-of-the-art methods, including our in-house tools for peptides docking and dynamics, to study the interactions between bitter-tasting peptides and their cognate receptors (Lizi Hazan, Amirim student), and of aliphatic flexible odorants with their receptors (Dr. Tali Yarnitzky, in collaboration with Strotmann's lab in Germany, funded research).

Not only will these research directions provide insights into the evolution and molecular details of bitterness perception, but they will also contribute to our understanding of fundamental aspects of GPCR tuning and selectivity.

## COLLABORATIONS WITH GERMAN SCIENTISTS

We have a collaboration with Prof. Dr. Ponimaskin (Hannover school of medicine), which lead to a recent publication that elucidated the dimeric interface in serotonin receptor homodimer (32). Most recently, we have submitted a joint full proposal via the European network for funding, ERA-NET NEURON with Professor Ponimaskin and Professor Alexander Dityatev (DZNE, Magdeburg, Germany). The full proposal was submitted after pre-proposal screening, in which 33 out of 198 pre-proposals were chosen for full submission.

We work towards establishing a European network focused on GPCR research, via COST mechanism, "GLISTEN, GPCR-Ligand Interactions, Structures, and Transmembrane Signaling Research Network". I am the chairman of 1 out of 4 Workgroups. Full proposal submitted after approval of the pre-proposal and a meeting in Amsterdam in 2012, and is organized and lead by Dr. Peter Kolb, Philipps-University Marburg, Germany.

We have recently began a collaboration with Dr. Joerg Strotmann from the University of Hohenheim (funded), to elucidate the ligands of the unique odorant receptors subfamilies.

A major topic in the lab, and an ongoing collaborative research (funded by the DFG) is the study of bitter taste receptors and their interactions with ligands. We are actively collaborating with Professor Wolfgang Meyerhof and Dr. Maik Behrens at DIFE, Germany. Join publication 25 and joint review 3 have been published. Publication 32 is in revision, and and the ongoing research is expected to culminate in several additional publications. We typically meet once a year. This summer the meeting took place during a conference in Sweden in June 2012, and Anat Levit, a PHD student in the lab who works on bitter taste receptors, is visiting Meyerhof's lab in September 2012.

## VISITORS FROM GERMANY

- Professor Evgeni Ponimaskin (Hannover Medical School).
- Professor Heinz Breer (University of Hohenheim)

## SCIENTIFIC COLLABORATIONS

| Name | Project(s) | Institution |
|---|---|---|
| Professor Wolfgang Meyerhof* | Bitter taste | German Inst. of Nutrition (DIFE) |
| Professor Jorg Strotmann* | Odorant receptor ligands | University of Hohenheim |
| Professor Zehava Uni | Chicken bitter receptors | The Hebrew University |
| Professor Oren Froy | AMPK kinase modulation | The Hebrew University |
| Professor Kobi Rosenblum | Kinase inhibition for memory enhancement | Haifa University |
| Professor Evgeni Ponimaskin | GPCRs dimerization | Hannover School of Medicine |

*these collaborations are funded by German resources (trilateral Germany-Israel-Palestine DFG and Hohenheim-HUJI funding)

## RECENT GROUP MEMBERS

| Name | Project(s) | Status | Presently at |
|---|---|---|---|
| Marina Shudler | Kinase dynamics | MSc | Start-up in UK |
| Dr. Shu Cheng | Kinase dynamics | postdtoctoral | Postdoc in US |
| Dr. Noga Kowalsman | Molecular recognition in GPCRs | postdoctoral | Just finished project |
| Anat Levit | Molecular recognition in GPCRs, bitter taste | PhD | Graduating in 2013 |
| Morin Shavro | Kinase dynamics | MSc | Graduating in 2012 |
| Ayana Wiener | Molecular recognition in GPCRs, bitter taste | MSc, now PhD | Graduating in 2016 |
| Dr. Avi Ben-Shimon | Peptides dynamics and design | postdoctoral | in the lab till 2013 or 2014 |
| Dr. Tali Yarnitzky | Kinase drug design, odorant receptor ligands | Research assoc. | In the lab |
| Maria Verbov | Bitter taste recognition | MSc | Graduating in 2013 |
| Lizi Hazan | Bitter taste of peptides | Special honors (amirim) student | Project finishes in 2013 |
| Shira Cheled | Bitter recognition by chicken receptors | PhD (joint with Prof. Uni) | Graduating in 2016 |

| **Dr. Masha Niv's grants since 2007** | | | |
|---|---|---|---|
| Project | Period | Foundation | Total |
| Block Dynamics of Protein Kinases | 2008-2010 | BSF | 40,000$ |
| Computational studies of AMPK | 2007-2010 | intramural | 24,000$ |
| Computational and experimental analysis of oligomerization | 2009-2012 | Niedersachsen | 109,000 euro |
| Bitter taste receptors | 2008- | intramural | 60,000 shekel |
| Biomolecular Simulations and Modeling - conference organization | 2009 | intramural | 1000 $ |

## CONFERENCE ORGANIZATION

2009 Chair of "Conformational Changes" session, initiator and co-organizer of "Biomolecular Modeling and Simulations" conference, Safed, Israel, partially funded by the Fritz Haber Center.

2011 Organizer and chair of Structural Studies of Receptors Symposium in European Chemoreception Research Organization (ECRO), Manchester England

2012, Chair in the A research workshop of the Israel Science, joint with European Molecular and Cellular Cognition Society (EMCCS), Haifa, Israel

2013 Track chair for "In silico Drug Design and in silico Screening" in Drug Discovery and Therapy World Congress, Boston, US (Responsible for inviting 15 international speakers)

## EDITORIAL BOARDS

Advances in Bioinformatics

## ASSAF ZEMEL

## RESEARCH ACTIVITY

Cell shape and the rigidity of the surroundings were shown to play an important role in the regulation of central cellular processes such as cell proliferation and differentiation. An understanding of cellular mechano-sensitivity and the molecular mechanisms involved in mechanical processes such as cell motility and division have been the subject of intense study in recent years. Our research focuses on several issues related to the mechanical activity and sensitivity of cells. We study the early stages of cell adhesion in which the cell shape and cytoskeleton structure establish. The consequences of these processes are believed to influence long term processes in the cell and to dictate the cell fate. On the molecular level, we study how ensemble of motor proteins and cytoskeletal filaments produce self-organization, movements and forces in the cell. Our initial work in this field concerned the sliding dynamics of microtubule and actin bundles that are cross-linked and powered by molecular motors; these bundles are common structures in many cellular processes including cell division, muscle contraction and nueronal growth. Finally, we are also interested in understanding the collective response of ensemble of cells to elastic stresses produced either internally, by the contractile activity of the cells, or applied externally by forces such as blood pressure, muscle tension and gravity.

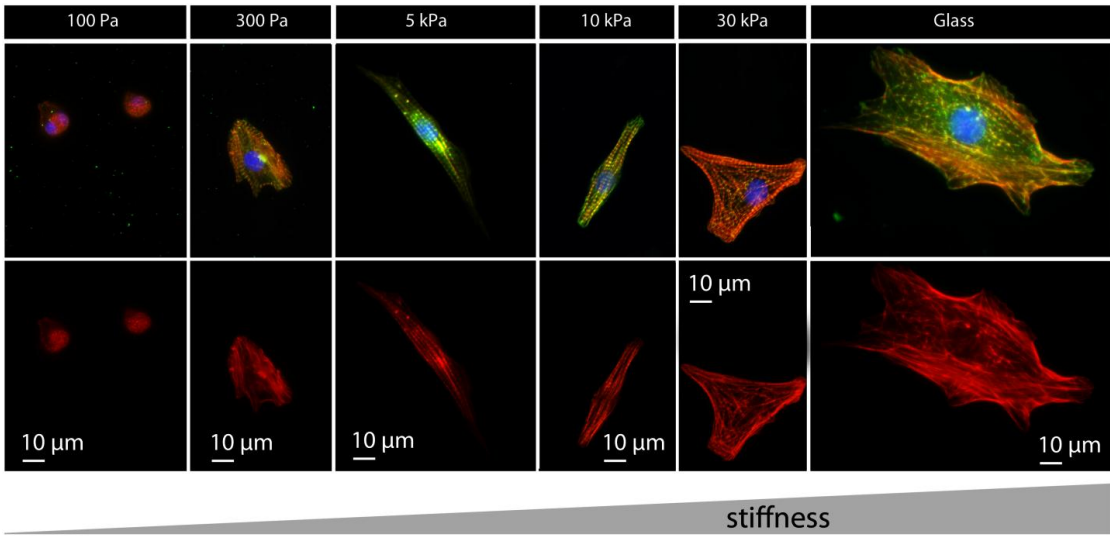


**Figure 48: Neonatal rat, ventricular myocytes (heart cells), grown on substrates of varying rigidities. F-actin stained in Red, α-actinin stained in Green, nucleus stained in Blue. Adapted from Ref [3].**

### IMPLICATIONS OF FORCE BALANCE IN THE DETERMINATION OF CELL SIZE, SHAPE AND INTERNAL STRUCTURE

The elastic rigidity of the cellular surroundings has been shown to play a central role in the determination of cell function and fate. In addition, numerous studies in recent years have shown that the rigidity of the extracellular environment governs many morphological characteristics of cells, including the size (or spreading area on a surface), the shape - or aspect ratio – of cells, as well as the internal organization of the cytoskeleton [1,2]. Figure 48, reproduced from Ref. [3], summarizes many structural features that are

governed by the rigidity of the cellular surroundings. Here, neonatal rat heart cells were placed on substrates of varying rigidity. As also common to other cell types, the cells appear to form round and small morphologies on soft substrates and their area increases monotonically with the matrix rigidity. Most prominent in Figure 48, however, is the optimal elongation of the cells and the alignment of F-actin bundles parallel to the long axis of the cell when plated on the substrates of intermediate rigidity; this rigidity regime happens to be similar to that of heart muscle. Thus even when grown on flat, homogeneous and isotropic substrates the cells seem to adopt the proper structure of muscle cells given the right rigidity.

Another striking demonstration of such behavior (Figure 49) has recently been reported with human mesenchymal stem cells [4,5]. Cells plated on substrates with the rigidity of muscle tissue not only adopted the elongated morphology of muscle cells, but after a week of culture showed optimal expression of differentiation markers that indicate their specification to muscle cells.

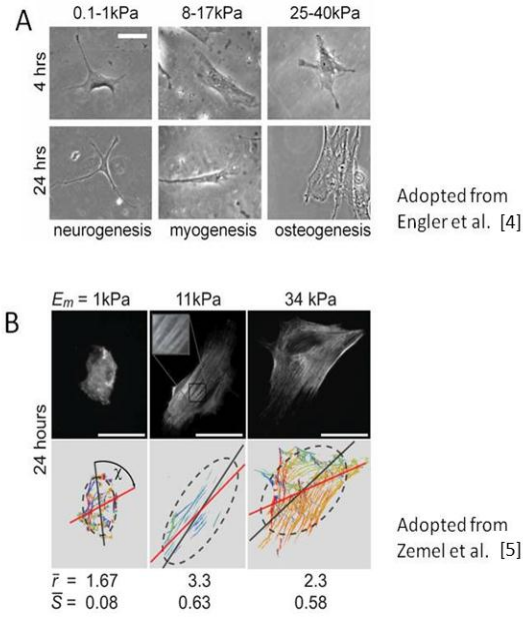


**Figure 49: Human mesenchymal stem cells grown on substrates of varying rigidities. Panel A, shows the distinct cell morphologies that were obtained on the respective substartes, and Panel B, shows our analysis of the orientational distribution of the acto-myosin stress-fibers in the cytoskeleton; see text and Refs. [4] and [5] for details.**

To gain insight into the physical mechanisms These observations evidently raise an important question about the mechanical interplay between the cells and their environment, namely, what is special about the moderate rigidity regime that optimally induces cell elongation and maximal alignment of the cytoskeleton.

involved in this important phenomenon, we first focused on the alignment of the contractile, acto-myosin stress-fibers in the cytoskeleton of adhering cells that are thought to play an essential role in the active, mechano-sensitivity of the cell [1,2]. We demonstrated, both theoretically and experimentally, that the matrix rigidity regulates the polarization of stress-fibers in cells and dictates the preferential alignment of the stress-fibers along the long axis of the cell. In addition, we showed that the alignment of stress-fibers in stem cells depends non-monotonically on the matrix rigidity, attaining a maximum value for an optimal value of the matrix rigidity [5,6].

The cell was modeled as an active, elastic inclusion in an infinite, homogeneous and isotropic medium; we considered both two and three dimensional geometries. For simplicity the cell was assumed to have a spheroidal shape (ellipse in 2D) oriented with its long/short axis parallel to the z/x axis of a Cartesian coordinate system. The theory included both the passive forces arising from the elasticity of the cell and the surrounding medium, as well as the active forces exerted and regulated by the cells; this extends the treatment of passive inclusions in solids [7, 8] to living matter. The active acto-myosin forces in the cytoskeleton were modeled by a local distribution of “force dipoles” [9–10] that arise from the equal and opposite forces exerted by myosin motors at two nearby points on actin filaments. These are represented by a tensor quantity $\langle p_{ij} \rangle$ which is the average (active) dipole density per unit volume. To relate the local polarization of the active forces in the cell to the local averaged stress, we invoked the use of an active cell polarizability as follows:

$$\langle p_{ij}^{a} \rangle = \langle p_{ij} \rangle - \langle p_{ij}^{0} \rangle = -\alpha_{ijkl}\sigma_{kl}$$

where summation over repeated indices is implied. Here, $\langle p_{ij}^0 \rangle$ , is the early time value of the average cellular dipole, $\langle p_{ij} \rangle$ is its actual value after the cell has polarized, and $\langle p_{ij}^a \rangle$ is the active polarization tensor. The (fourth rank) tensor $\alpha_{ijkl}$ is the cell polarizability tensor. This tensor couples (in an averaged and phenomenological manner) the active variations of the mean cellular dipole to the elastic stresses developed in the cytoskeleton. Refs. [4,5] discuss two forms of the polarizability tensor. One can show that for a particularly simple polarization mechanism, in which the forces polarize only parallel to the stress direction it is given by a simple scalar quantity, $\alpha$.

The anchoring of a cell to the extracellular matrix as well as the active spreading on a surface, involve a global shape or volume deformation that produce elastic stresses in the cell and the matrix [1,2]. Our theory shows that for a cell that possesses some shape anisotropy, an isotropic adhesion-induced prestress in the cytoskeleton may initiate a spontaneous polarization of the stress-fibers. In addition, we find that the polarization anisotropy (difference between stress-fibers aligned along the long axis and those oriented along the short axis of the cell) of the stress-fibers is maximal when the rigidity of the cell and the matrix are similar. In this range, the stress anisotropy resulting in the cell is most sensitive to the cell shape. Experiments were carried out to demonstrate this optimization using human mesenchymal stem cells plated on substrates of varying stiffness. The overall cell morphology was quantified in terms of the aspect ratio, $r$, and an analysis of stress-fiber formation and polarization was demonstrated for the first time by staining for actin and non-muscle myosin IIa.

The bottom panel of Figure 50 shows several representative images of cells, 24 hours after they were plated on substrates of Young's modulus, $E_m = 1, 11$ and $34$ kPa. For comparison, the mean Young's modulus of the cell, $E_c$, was estimated by atomic force microscopy to be $\approx 10$ kPa. The bottom row in that panel is the corresponding image analysis results, showing color-coded orientations of stress-fibers in the cell.

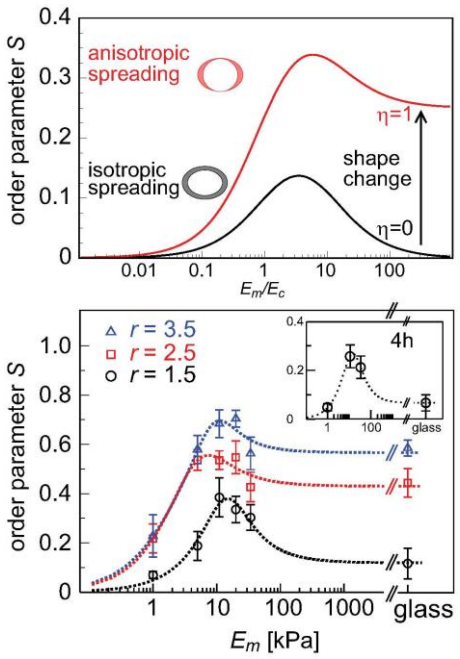


**Figure 50: The effect of axial cell elongation on stress-fiber polarization and experimental values of the order parameter S for different elastic substrates; upper panel shows a calculation of the 2D order parameter as a function of thematrix rigidity, for two cases: the cell spreads isotropically on the substrate (black curve); the cell spreads anisotropically on the substrate (red curve). The two illustrations left of the curves show top views over the cell, before (shown as blank) and after (shown as shaded) cell spreading. In the asymmetric spreading case, r corresponds to the cell shape in an infinitely rigid matrix. For both curves we used $r = 2$ and $\alpha = 0$. Lower panel shows the experimental values of the stress-fiber order parameter, 24 h after plating the cells, for the three groups of cells (of aspect ratios $r = 1.5, 2.5$ and $3.5$) as a function of Young's modulus of the matrix, $E_m$. Within each of the different groups, $S$ is maximal for the $11$ kPa matrix and generally increases with aspect ratio $r$, in agreement with our theoretical predictions. The error bars denote the standard error of the mean and theory curves (dotted lines) are shown to guide the eye.**

The figure also shows that stress-fibers optimally polarize on the matrix with intermediate rigidity, $11$ kPa, as seen by the value of the orientational order parameter of the stress-fibers, $S = \langle \cos(2\theta) \rangle$; where $\theta$is the angle of each stress-fiber from the long axis of a fitted ellipse. This parameter can be shown to be equal to $(\langle p_{zz} \rangle - \langle p_{xx} \rangle)/p$, where $\langle p_{zz} \rangle$and $\langle p_{xx} \rangle$ are the

diagonal elements of the polarization tensor and $p$ is the trace.

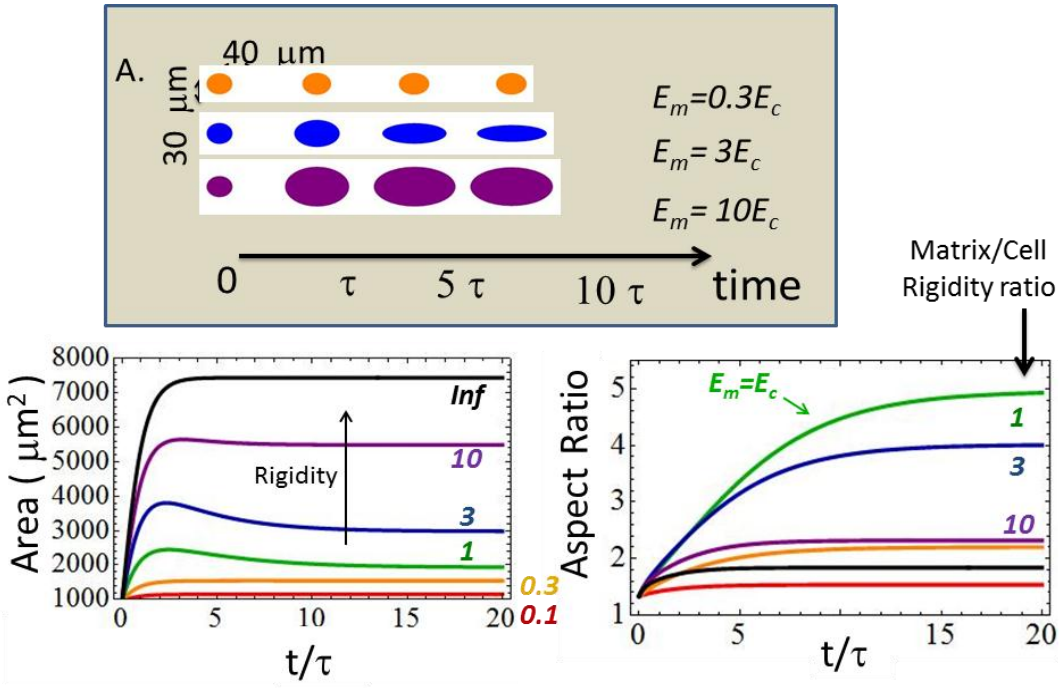


**Figure 51:** ***Calculation of spreading dynamics and shape acquisition of biological cells on elastic substrates.*** **Top panel shows snapshots of cell spreading dynamics on substrates of varying ratios of the matrix- to- cell Youngs' moduli, $E_m/E_c = 0.3, 3, 10$; $\tau$ is the dynamics relaxation time – estimated to be on the order of 0.5-1 hours. Bottom panels show the evolution of cell spreading area and aspect ratio. Consistent with the findings shown in Figure 47 and Figure 48 and the recently published data in [3,5,6,12], we find that cells optimally elongate for moderate rigidity of the substrate namely when $E_m = E_c$. The non-monotonic behavior of the area curve is found to result from an elastic Poisson effect (not shown).**

Since our model treats the cell as an ellipsoid with given (and fixed) aspect ratio, $r$, the cells were sorted by their aspect ratio and the order parameter was evaluated for each group of cells separately. The bottom panel of Figure 50 shows the experimentally measured order parameter, $S$, as a function of the Young's moduli of the substrate $E_m$, for three groups of cells of $r = 1.5, 2.5, 3.5$. Theoretical curves (dashed lines) are shown to guide the eye. We find that for all cell shapes the orientational order parameter depends non-monotonically on the matrix rigidity showing a maximum for an intermediate value of the matrix rigidity. This non-monotonic dependence is more pronounced for the more rounded cells in the ensemble. For the more elongated cells (of aspect ratios 2.5 and 3.5), we find a shallower maximum and relatively high values of the stress-fiber polarization even at high values of the matrix rigidity. These observations can be explained as follows. Since in the early state of cell adhesion the cytoskeleton is still in an isotropic gel state, the elastic forces the cell exerts are likely to be isotropic. However, even in this case our theory shows that for an intermediate value of the matrix rigidity, a small anisotropy of the cell shape may result in a breaking of symmetry of the elastic stress in the cell. This shape-induced stress anisotropy may feedback on the early-time force dipoles in the cytoskeleton, and cause a spontaneous orientation of the stress-fibers along the long axis of the cell. For either very high or very low matrix rigidity no stress propagates out of the cell (because in the former case the matrix is too soft to maintain a stress in the cell, and in the latter case the cell cannot deform the matrix) and hence the isotropic pulling forces of the cell result in an isotropic stress in the cell. We thus find a maximum of cell polarization on the matrix with moderate rigidity. Our experiments show that the more elongated cells polarize even when plated on very hard sub-

strates. The upper panel of spreads anisotropically and exerts anisotropic forces on the substrate (red curve). We find that in the latter case the orientational order parameter shows a shallower maximum. We thus hypothesize that the concurrent elongation of the cells on the surface results in an axial contribution to the elastic stress in the cytoskeleton that in turn, is responsible for the polarization of the stress-fibers along the long axis of the cell. Our theory shows that this contribution increases monotonically with the matrix rigidity [5,6]. These findings unravel a fundamental and general relation between the cell shape, matrix rigidity and the polarization of stress-fibers in the cytoskeleton. The remodeling of the cytoskeleton architecture is an important consequence of cell adhesion.

The insight gained in this study has recently been used to develop a model for the ***dynamics of cell spreading on elastic substrates*** (Figure 51). The model captures correctly the striking phenomenon that *cell spreading anisotropy* optimizes when the cell and substrate have comparable rigidities. The details of this model and comparison with experimental results will be published in a forthcoming paper.

In summary, the interplay of cell-matrix mechanical interactions has been studied using a simple elastic model of the cell and the substrate. We found that both the cytoskeleton and cell shape anisotropy optimize when the cell and matrix have comparable rigidities. In this special regime of rigidities the breaking of symmetry of the elastic stresses that develop during spreading is most pronounced. On very soft substrates no stresses can develop and the cells remain round and small. On very hard substrates, no deformation of the substrate is possible. Consequently, the resulting stresses in the cell have the same symmetry as the traction forces exerted by the cell. Thus, a cell that spreads isotropically on the surface, and whose acto-myosin distribution is isotropic to begin with, would develop isotropic stresses – and no polarization will occur. For substrates of intermediate rigidity higher stresses typically develop along the long axis of the cell simply because more numerous adhesion contacts can be formed along that direction. Consequently, the breaking of symmetry of the elastic stresses is highest in this case, causing optimal elongation of the cell and maximal polarization of the cytoskeleton.

## SLIDING DYNAMICS AND FORCE GENERATION BY ACTIVE BUNDLES OF CYTOSKELETAL FILAMENTS, CROSS-LINKED BY MOLECULAR MOTORS

Interactions of multiple molecular motors with bundles of actin and microtubule filaments form the basis for many cytoskeletal processes including axonal growth, muscle contraction, and cell division. Continuum models based on generalized diffusion equations have been suggested to quantify the dynamics of such active bundles [13,14]. In highly cross-linked and densely packed filament bundles, however, a major complication arises due to the multiple interactions that each filament forms with its neighbors, see Fig. 5. To theoretically explore the effects of these interactions on the self-organization, dynamics and forces generated in such bundles we developed a computer simulation algorithm that allows us to calculate the velocities and the forces acting on the filaments in a self-consistent manner [15,16]. We used our simulations to predict the dynamics and self-organization of filaments in 1D bundles of filaments; this has been done for different motor types, at different densities and subject to different boundary conditions. We found that highly cross-linked bundles exhibit a percolation threshold beyond which the dynamics become strongly sensitive to the boundary conditions. In finite sized bundles with absorbing boundary conditions, interactions between multiple filaments result in significant acceleration of the filaments. In contrast, in ringed bundles, the long-ranged interactions between the filaments result in substantial slowing down of the filaments; in this case the motors behave as 'brakes' to the motion. The filaments in loosely connected bundles, on the other hand, undergo local diffusion-drift dynamics consistent with previous continuum models. Our

simulations also demonstrate the sorting phenomena of filaments of opposite polarity in mixed bundles and reveal characteristic scales and conditions for spontaneous pattern formation in the bundle.

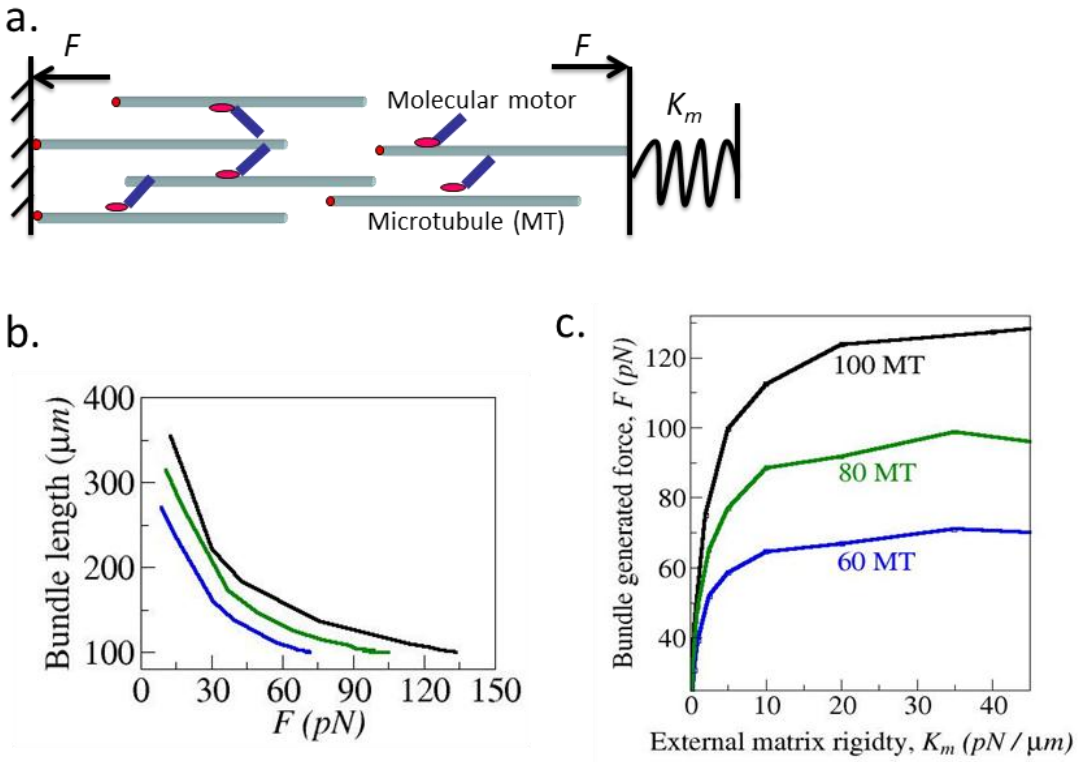


**Figure 52: Force generation by 1D bundles of cytoskeletal filaments cross-linked by ensembles of molecular motors. Panel a. illustrates the simulation setup – a bundle of filaments expands against a linear spring with constant km. Panel b. shows the steady-state length of the bundle as a function of the steady-state force developed in the bundle, plotted for bundles consisting 60, 80, 100 filaments (e.g., microtubules). The bundle is seen to rigidify under compression. I.e., the slope, dF/dL, increases as the bundle becomes smaller in length. Finally, panel c. shows the dependence of the steady-state force on the elastic rigidity of the external spring, km, plotted for different numbers of filaments in the bundle.**

Most recently, Avinoam Bronshtein, a MSc student in our group, studied the dynamics and statics of force generation in such bundles. We find that the steady-state length of the bundles scales inversely with the steady-state force generated in the bundle. This is due to the continuous tapering of the bundle during spontaneous expansion; generally, the thicker the bundle, the stronger the force it exerts. Consistently, as the number of filaments in the bundle increases, more force can be generated per given length of the bundle (panel b). For the same reason, the apparent bundle rigidity increases under compression; this can be seen from the slope of the curves drawn in panel b. Interestingly, we find that the steady-state force increases with the rigidity of surroundings (a spring in our case). This property will be used in our development of a model for neuron growth in forthcoming research.

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## GROUP MEMBERS

- Avinoam Bronshtein - M. Sc student.
- Noam Nisanholtz - M.Sc student.
- Dr. Doron Kabaso - Postdoctoral Scholar.

## COLLABORATORS IN GERMANY

- Dr. Florian Rehfeldt, III. Physics institute, Georg-August-University, Göttingen, Germany.
- Dr. Ralf Kemkemer, Max-Planck-Institute for Metals Research, Dept. New Materials and Biosystems, Stuttgart, Germany

## GRANTS

| Year | Foundation and topic |
|---|---|
| 2009—2013 | Israel Science Foundation. A. Zemel<br>"Active responses of cells to the mechanical properties of their environment". $210,000. |
| 2010—ongoing | Eliyahu and Tatiana Leszczynski fund. A. Zemel<br>"Mechanically-induced self organization and patterning of cells". $15,000. |
| 2011—2014 | Niedersachsen-Israeli Research Cooperation Program,<br>A. Zemel and F. Rehfeldt,<br>"Experimental and theoretical study of cellular *mechano*-sensitivity". € 105,000 (each) |

# PART II: CENTER ACTIVITIES

## INTRODUCTION

The scientific acitivities of the center are primarilly performed by about 80 active researchers throughout the year. This number includes research students, post-doctoral fellows, long term visitors and sabbaticallists and faculty. We refer the reader to the research report given in part I of this report and to the list of personell in part III.

Listed among our major activities is the Fritz Haber seminar, running continuously for 30 years now and has hosted a large variety of scientists in the molecular dynamics and related fields. The list of our speakers is both long and broad. Long, because we have 2-3 dozens of speakers per year. And broad, in two ways. First, in the persona: our speakers are at times the leading scientists in their respective fields and at times graduate students delivering their first public talk. Also, broad in the range of topics: from quantum mechanics of cold atoms through chemical dynamics and biophysics up to intense laser-molecule interactions. Please find in an appendix, Part IV a lisiting of the guests and seminars in recent years.

The Fritz Haber center is also continually supports conferences, meetings and workshops. Below, please find a subsection listing these in recent years.

The center also supports development of teaching materials mainly in quantum molecular dynamics, through JAVA simulations and JAVA 3D graphics. Please see below description of this endeavor.

This year, under intiative of Prof. Agmon and his Student Ai Shinobu, the center organized a special series of tutorials on quantum chemical packages where students learned the principles and hands on information for using these tools.

## CONFERENCES AND WORKSHOPS BY THE CENTER (2007-2012)

The Center and Members have organized numerous international meetings and symposia since its foundation. The Center also supports, generally modestly, symposia in research fields related to its scientific activities; especially symposia involving the Center's members in the organizing committees, or as invited speakers. Below, is the list of meetings supported since 2007.

### TAIWAN-ISRAEL BINATIONAL MEETING: DYNAMICS ON MANY LENGTH (AND TIME) SCALES

Professor Levine was on the organizing committee of this bi-national meeting held at the Israel Academy of Sciences and Humanities in Jerusalem March 13-14, 2007.

### FRITZ HABER DOUBLE-DAY SYMPOSIUM ON CONDUCTION IN MOLECULAR SYSTEM

Professors Baer and Kosloff organized this double-day symposium on conduction at Yad Hashmona, June 10-11, 2007.

### SAFED WORKSHOP ON COOLING AND THERMODYNAMICS OF SYSTEMS

Professor Kosloff was on the organizing committee of this workshop which was held at the Hotel Merkazi in Safed, August 26-31, 2007.

## SAFED SUMMER SCHOOL ON DENSITY FUNCTIONAL THEORY

Professor Baer was on the organizing committee of this workshop which was held at the Hotel Rimonim in Safed, September 1-6, 2007.

## GENTNER SYMPOSIUM 2007 ON TIME DEPENDENT DENSITY FUNCTIONAL THEORY

Professor Baer was the chairman of the organizing committee of this MINERVA-Gentner Symposium. Hilton Queen of Sheba, Eilat 16-21 2007.

## DIFFUSION, SOLVATION AND TRANSPORT OF PROTONS IN COMPLEX AND BIOLOGICALS SYSTEMS

Professor Agmon was a member of the organizing committee of this ISF workshop. Hilton Queen of Sheba, Eilat, January 13-17 2008.

## BAT-SHEVA DE ROTHSCHILD SEMINAR ON ULTRAFAST-ULTRACOLD PROCESSES

Professor Ronnie Kosloff was a member of the organizing. February 24 - February 29, 2008.

## 1ST INTERNATIONAL SYMPOSIUM ON IMPROVISED EXPLOSIVES

Organizer: Professor Kosloff, May 18 – 22, 2008. Venue: Rosh Hanikra Holiday Village.

## FROM MACROMOLECULAR TO CELL BIOPHYSICS

Dr. Daniel Harries was a member of the organizing committee. June 3 - June 4, 2008.

## SYMPOSIUM ON INTERFACES

Professor Roi Baer was the organizer May 25-26, 2009.

## BIOMOLECULAR MODELING AND SIMULATION WORKSHOP

Organizers: Dr. Daniel Harries and Dr. Masha Niv. Safed, September 13 - 16, 2009

## COMPUTATIONAL CHEMISTRY SYMPOSIUM

Organizers: Dr. Avital Shurki and Professor Roi Baer. Jerusalem, December 10, 2009.

## GENTNER SYMPOSIUM ON PROTON MOBILITY IN CHEMICAL AND BIOLOGICAL SYSTEMS

Professor Noam Agmon is chair of the organizing committee. February 7 - 12, 2010 in Maagan Village.

## A SYMPOSIUM IN MEMORY OF PROFESSOR VICTORIA BUCH

Organizer: Professor Roi Baer. May 10, 2010.

## STRUCTURAL STUDIES OF RECEPTORS SYMPOSIUM IN 22ND EUROPEAN CHEMORECEPTION RESEARCH ORGANIZATION (ECRO)

Chair: Masha Y. Niv. Sept 7 - 10, 2011, Machester UK.

## GRC QUANTUM CONTROL OF LIGHT & MATTER

Chairs: Ronnie Kosloff and Gustav G. Gerber. July 31 - August 5, 2011.

## BATSHEVA DE ROTHSCHILD SEMINAR ON LASER CONTROL OF CHEMICAL REACTIONS: TOWARD DECIPHERING MECHANISMS AND UNDERSTANDING THE THEORETICAL AND EXPERIMENTAL LIMITS

Organizers: Professors Ronnie Kosloff and David Tannor, Safed, Sept 2-7, 2012.

## DEVELOPING TEACHING MATERIAL

For several years now, groups in the center have been developing unique teaching aids for quantum mechanics. The tools can be seen in the center website under the "Science Education" tab. The tools are Java 3D applets which describe many aspects of quantum mechanics in a way that is easily grasped by students and scientists. Here you will find applets that allow the manipulation of wave functions, their time evolution, calculation of correlation functions s and even the Wigner distribution point of view.

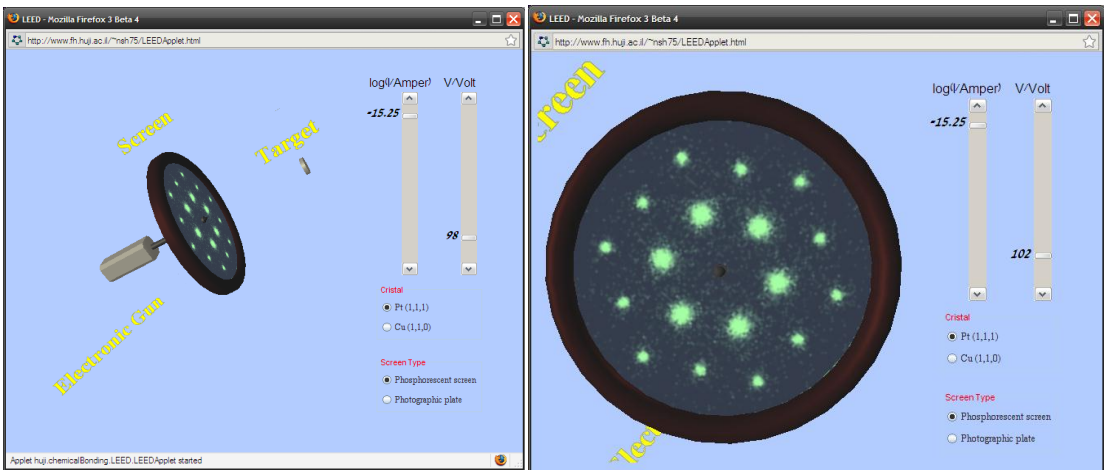


**Figure 53: In this applet the simulation of a well known experiment, in which electrons accelerated by an electron gun, shot at a metal surface on which they impinge and scatter towards a fluorescent screen. A bright dot appears on the screen where an electron collided with it. The electron impingement continues at a rate determined by the student (the current/Amperes). The student can also control the velocity (Voltage/Volt) of the electrons. The applet is 3 dimensional so the students can rotate it and see the electron gun and the positions of the metal surface (right panel).**

An example of an applet is described graphically in Figure 53. It simulates graphically a well-known experiment where electrons shot from an electron gun hit a metal surface and scatter onto a fluorescent screen. This applet teaches the students several basic concepts in quantum mechanics. First, particles such as electrons have a wavy aspect since they exhibit interference pattern onto the screen. Second, the quantum mechanical wave function is a *probability amplitude* wave: the student can lower the rate electrons are shot at the screen and thus observe each electron separately as it impinges on the screen in a random location, uncorrelated with the other electrons. The student will see that some points on the screen are brighter than others. These brighter spots are formed when many electrons tend to impinge at the locations where the wavefunction has maxima. Third, the interference pattern of bright spots toggles between hexagonal to square when the student switches the metal surface serving as a grating from Platinum to Copper. Fourth, the student can study the de-Broglie relation $p = h/\lambda$ between the particle aspect, namely the "momentum" $p$, and the wavy aspect, namely the "wave length" $\lambda$ (the constant $h$ is "Planck's constant"). By changing the velocity of the electrons shot at the screen, the student can explore the relation between velocity and the distance between bright spots which reflects the wave length.

# PART III: STATUS REPORT SEPTEMBER 2012

## PERSONNEL

### MEMBERS OF THE CENTER AND THEIR MAIN RESEARCH TOPICS

There are currently 9 groups in the center, headed by faculty members. The selection of new members is done by considering the goals and character of the center. Usually the director initiates such a procedure. The members are assembled to discuss the candidate and if agreed, the Beirat is requested to authorize such an addition. Candidates are required to be excellent scientists and emphasis is put on candidates that are interested in developing new theories and new computational techniques in the various domains of molecular dynamics, as opposed, for example, to emphasis on new applications of known techniques. New members are usually young scientists with activities that significantly broaden the domain of operations of the center. In 2009 two such new members were selected namely, Drs. Masha Niv and Assaf Zemel. Both of these young researchers were students in the center and their postdoc studies have exposed them to new emerging scientific fields.

The current members of the center are:

1) Noam Agmon, Full Professor: Proton dynamics in excited state green fluorescent protein; Proton solvation and mobility; ligand binding to hemes; kinetics of bimolecular interactions.
2) Roi Baer, Full Professor: Electronic structure and dynamics with applications to strong laser molecule interaction, ionization dynamics and molecular electronics; density functional theory (DFT) and time-dependent DFT; spectroscopy and photovoltaics of nanocrystals, metal nanoparticles and nanotubes.
3) Avinoam Ben Shaul, Full Professor: Membranes, macromolecules and their Interactions; Viruses - assembly, structure and energetics; Self-assembling complex fluids.
4) R. Benny Gerber, Full Professor: Chemistry and chemical dynamics of noble gas atoms; Vibrational spectroscopy of large molecules; Mechanisms and dynamics of processes in atmospheric chemistry; Chemical reactions at aerosol surfaces; Dynamics at low temperatures, photochemical reactions in low-temperature solids and clusters and matrices.
5) Daniel Harries, Senior Lecturer: Electrostatic interactions between macromolecules in solution; Micro-molecular crowding and osmotic Effect on peptide folding and aggregation; Patterning in granular systems governed by crowded environments.
6) Ronnie Kosloff, Full Professor: Coherent chemistry: light induced processes; Coherent control and laser cooling; Dynamical processes on surfaces; Quantum thermodynamics; Computational and teaching methods.
7) Raphael D. Levine, Full Professor Emeritus: Chemistry under extreme conditions; Chemistry on multi electronic states; Ab initio reaction dynamics; Dynamics of high Rydberg states; Dynamics and spectroscopy in congested level systems; Reaction dynamics and mechanism in large systems including clusters and in solution; Algebraic techniques for structure and dynamics in anharmonic systems; Dynamics in phase space, including the application of information theory
8) Masha Y. Niv, Senior Lecturer: Bitter taste - molecules, receptors and recognition. Activation, specificity and dynamics of GPCRs. Protein kinases: conformational dynamics, molecular recognition, inhibitors design. Structure, function and flexible docking of peptides and peptidomimetics.
9) Assaf Zemel, Senior Lecturer: Response of cells to mechanical cues in their surroundings; cell adhesion, cell shape and cytoskeleton structure; elastic interactions of cells; patterning, aggregation and alignment of cells; interaction of motor proteins and cytoskeleton filaments producing forces and movements of cells including, stress-fiber assembly, axonal growth and blood platelet formation.

The Chemistry Institute at the Hebrew University has decided to offer a faculty position to an excellent new recruit in theoretical chemistry (many body quantum electronic dynamics), an Israeli citizen who is an assistant professor in an

excellent university in the USA. This nomination still has to be approved by the higher committees of the university.

## RESEARCH STAFF

During the past year 85 scientists have been active at the Center, including faculty members (9), non-faculty staff (4) long-term visitors (10), postdoctoral fellows (16) and research students (BSc (5), MSc (12) and PhD (25)). Two system managers are responsible for the maintenance and frequent upgrading of the diverse computing facilities of the Center and those of its members.

## SCIENTIFIC (NON-FACULTY) STAFF

- Dr. Brina Brauer
- Dr. Faina Dubnikov
- Dr. Helen Eisenberg
- Dr. Tova Feldman

## LONG TERM VISITING SCIENTISTS 2011/2012

- Dr. G. Ajaykumar, UCLA
- Dr. Y. Bohbot, Biological Institute
- Prof. A. Dell-Hammerich, University of Illinois
- Dr. Garold Murdachaew, PNNL
- Dr. S. Kallush, ORT Braude
- Dr. G. Katz, Kibbutz Afikim
- Prof. D. Neuhauser, UCLA
- Prof. F. Remacle, University of Liege
- Dr. N. Rom, Rafael Technologies
- Prof. H. Tal-Ezer, Tel-Aviv Yaffo College

## POSTDOCTORAL FELLOWS AND RESEARCH ASSOCIATES (2011/2012)

- Dr. Saieswari Amaran
- Dr. Arik Cohen
- Dr. Moshe Goldstein
- Dr. Ayelet Gross
- Dr. Laurent Jutier
- Dr. Doron Kabaso
- Dr. Svetlana S. Khokhlova
- Dr. Waldemar Kulig
- Dr. Regina Politi
- Dr. Jiri Sebek
- Dr. Dorit Shemesh
- Dr. Ehud Tzivion
- Dr. Shu Cheng
- Dr. Noga Kowalsman
- Dr. Avi Ben-Shimon
- Dr. Tali Yarnitzky

## RESEARCH STUDENTS 2011/2012

PhD: Ajay J; Amshallem M; Bar L; Baratz A; Buchman, O; Cnaani R; Dvoris, M; Hiluf D; Jacoby S; Klein M; Levy A; Muscatal H; Arumugam R; Rezek Y; Sagiv L; Shinobo Ai; Shmiloviz-Ofir M.; Sapir L; Schafer I; Stein T; Sukenik, S;Levit A; Wiener A; Hazan L; Cheled S.

MSc: Cytter Y; Hirshberg B; Saper G; Shachar A; Zmiri, L; Gentman T; Furman D; Shudler M; Shavro M; Verbov M; Bronshtein A; Nisanholtz N.

BSc: Arnon E; Haddad E; Shpiro B; Ristov S; Rosman A;

# ADMINISTRATIVE-TECHNICAL STAFF

## ADMINISTRATIVE-TECHNICAL STAFF

- Ms. Geula Levy: Administration Assistant
- Ms. Eva Guez: Scientific Editing
- Dr. Ester Livshits: Computer and Communications Systems Administrator
- Ms. Rita Zlotnikov: Assistant systems administrator.

# CENTER COMPUTING RESOURCES

The computer facility of the Center is the principal research tool of all scientists in the center. Most of the computers are purchased by the different researchers from their personal grants. The center offers to the researchers the services of a System Manager and his assistant.

Dr. Ester Livshits, and Ms. Rita Zlotnikov are responsible for the maintenance and development of our computer services, which include both equipment of the Center, and machines used by individual groups. Computational research activities in all the groups depend heavily on the smooth functioning of the unit. This team also maintains the webpage of the center.

## NUMBER-CRUNCHING RESOURCES

There are currently over 700 computer cores, mostly Intel 64 bit machines running Linux. These are grouped in 7 distributed memory clusters, owned by the different members of the centers but managed by the System Administrator. The center has recently won a Minerva grant and purchased a strong SGI Ultra-Violate shared memory computer with 16 8-CPU nodes and 128GB shared memory.

## OTHER USER SERVICES

The disk services are based on a 10-disk RAID protected storage system, with about 1.5 Terrabyte volume. This server provides shared program access, YP authorization, home directory services and POP/IMAP mail services, printing, group website hosting etc. We also maintain four Windows domain servers with 600 GB disk space that provide active directory services, terminal services (remote desktop), such as DNS, authorization, home directory, FTP, printing, virus protection. of shared storage for the various users of Windows. In addition we have Mac-OS workstation connected to the Center Linux authorization system. All the clusters, workstations and servers are connected by switched 100Mb Ethernet with a 1Gb backbone network. Laptop owners can use the university installed wireless connection network with a 54Mb speed.

# PART IV: APPENDICES

## LIST OF VISITORS AND SEMINARS 2007-2012

Below we list the visitors and speakers in the Fritz Haber seminars during the period 2003-2007. We also mention the numbers of scientists attending the various workshops and symposiums which the center has organized in this period.

| Date | Speaker | Title |
|---|---|---|
| 4.1.07 | Dr. V. Averbukh, University of Heidelberg | Recent Advances in the Study of Interatomic Decay in Clusters |
| 8.1.07 | Dr. D. Segal, Dept of Chemistry, Columbia University | Non Equilibrium Dynamics in Spin-Bath Models |
| 11.1.07 | Dr. J. Shifman, Inst. of Life Sciences, HU | Design of Protein-Protein Interfaces |
| 15.1.-15.3.07 | Dr. A. Adesokan, UC Irvine | |
| 18.1.07 | Prof. Z. Amitay, Technion, Haifa | Multiphoton Coherent Control and Information Processing |
| 22-26.1.07 | Prof. B. Honig, Chem. & Biochem. Columbia University, New York | |
| 25.1.07 | Dr. O. Hod, Dept of Chemistry, Rice University, Houston, USA | Graphene Nanoribbons: New Players in the Field of Nanoelectronics |
| 29.1.07 | Dr. M. Nest, University of Potsdam, Germany | Correlation Quantum Dynamics of Electrons with Multi-Configurational Wave Functions |
| 1.2.07 | Ms. S. Yacoby, Physical Chemistry, HU | Auxiliary and Effective Fields in Molecular Electronic Structure |
| 22-23.2.07 | Prof. R. Hernandez, Georgia Inst. of Technology | |
| 25-26.2.07 | Prof. L. Tolbert, Georgia Inst. of Technology | |
| 11-14.3.07 | Prof. D. Leitner, Cornell University | |
| 10.4.07 | Joseph E. Subotnik, Dept of Chemistry, UC Berkeley | Local Correlation Theory: Smooth New Tricks for a Rough Problem |
| 19.4.07 | Dr. A. Heidenreich, School of Chemistry, Tel-Aviv University | Extreme Ionization of Clusters by Ultraintense Laser Pulses |
| 26.4.07 | Y. Kurzweil, Hebrew University | Quantum Memory Effects in Electron Dynamics in Metal Clusters |
| 2.5.07 | A. Cohen, The Hebrew University | Ultrafast Dynamics of Electronic States in Rare-Gas Matrix Photochemistry |
| 3.5.07 | Dr. R. Zangi, Dept of Chemistry, Columbia University, NY | When Hydrophobes Meet Electrolytes: Insights from Computer Experiments |
| 7-13.5.07 | Prof. D.J. Tobias, Dept of | Ions at the Air-Water and Membrane-Water In- |

| | | |
|---|---|---|
| | Chemistry, UC Irvine, CA | terfaces |
| **14.5.07** | Prof. Steven D. Schwartz, Biophys. & Biochem. Seaver Foundation Center for Bioinformatics, Albert Einstein College of Medicie, NY | How Enzymes Catalyze Reactions in Atomic Detail |
| **17.5.07** | Prof. R. Benny Gerber, The Hebrew University | Vibrational States of Biological Molecules: Spectroscopy, Dynamics, and Potential Surfaces |
| **20-28.5.07** | Prof. P. Devlin, Oklahoma State University | |
| **29.5-1.6.07** | Prof. B. Abel, University of Göttingen | |
| **29.5-1.6.07** | Dr. E. Vöhringer-Martinez, University of Göttingen | |
| **31.5.07** | Ester Livshits, The Hebrew University | A Well-Tempered Density Functional Theory of Electrons in Molecules |
| **5-10.6.07** | Prof. Mark S. Gordon, Iowa State University and Ames Laboratory | A General Approach to Intermolecular Interactions |
| **5-10.6.07** | Dr. B. Njegic, Iowa State University and Ames Laboratory | |
| **17.6-1.7.07** | Prof. S. Adhikari, Physical Chem., Indian Assoc. for Cultivation of Science, Jadavpur, Kolkata, India | Beyond Born Oppenheimer: New Approach for Conical Intersections |
| **19-24.6.07** | Dr. M. Nest, Potsdam University, Germany | |
| **21.6.07** | Dr. Tom Young, Columbia University, NY | The Role of Active Site Water in Protein Ligand Binding |
| **23.6-1.8.07** | Dr. J. Sadlej, University of Warsaw | |
| **23.6-1.8.07** | Dr. N. Uras-Aytemiz, Suleyman Demirel University, Turkey | |
| **5.7.07** | Dr. V.B. Teif, Belarus National Acad. Of Sciences | |
| **5.7.07** | Dr. A. Dell Hammerich, Chemistry Dept., Univ. of Illnois Chicago | Defining and Characterizing Dynamic Hydrogen Bonds: An Ab Initio Molecular Dynamics Study of Aqueous Acidic Solutions and Water |
| **24.8-16.9.07** | Prof. P. Salamon, San Diego State University | |
| **26.8-31.8.07** | Safed Workshop on Cooling and Thermodynamics of Quantum Systems. Organized by Ronnie Kosloff (FH), David Tannor (WIS), and T. Mor (TECHNION). | Alicki, R. Inst. of Theoretical Physics & Astrophysics University of Gdansk, Poland; Tannor, D. Weizmann Institute, Rehovot; Dr. Mor, T. Computer Science Dept, Technion, Israel Inst. of Technology, Haifa; Andresen, B. Orsted Lab., University of Copenhagen; Boykin, Oscar P., Electrical & Computer Engineering, University of Florida; Diosi, L. Research Inst. for Particle & Nuclear Physics, Budapest; Garcia-Ripoll, J.J, Dpto. De Fisica Teorica, Facultad de CC. Fisicas, Cuidad Universitaria s/n, Madrid 28040, Spain, Universidad Complutense de Madrid; Henrich Markus, Inst. for Theoretical Physics, University of Stuttgart; Fernandez, J.M Kowalewski, LMU München; |

| | | |
|---|---|---|
| | | Ritsch, Helmut , Universitaet Innsbruck,Theoretische Physik, Austria; Roychowdhury, V.P., Dept of Electrical Engineering, UCLA; Salamon, P. Dept of Mathematics, SDSU San Diego, CA 92182; Amitay, Z., Dept of Chemistry, Technion; Averbukh, I. Weizmann Institute of Science Rehovoth; Davidson N. Weizmann Institute of Science Rehovoth; Feldmann T, Fritz Haber Center The Hebrew University of Jerusalem; Kurizki G. Weizmann Institute of Science Rehovoth; Nitzan A., School of Chemistry, Tel Aviv University; Boukobza, E. Weizmann Institute of Science Rehovoth; Elias Y. Chemistry, Technion; Weinstein Y. Chemistry, Technion |
| **2-8.9.07** | Safed Workshop on Density Functional Theory. Organized by Leeor Kronik (Weizmann), Roi Baer (FH/HUJI) and E. Rabani (Tel Aviv Univ). | Prof. EKU Gross (Berlin, Germany), Prof. S. Kuemmel (Bayreuth, Germany), Prof. R. Car (Princeton University), Prof. M. Head-Gordon (UC Berkeley), Prof. Steve Louie (UC Berkeley) |
| **6-8.9.07** | Prof. R. Car, Princeton University | |
| **6-9.9.07** | Prof. M. Head-Gordon, UC Berkeley | |
| **23.9-6.10.07** | Dr. Ch. Koch, Freie Universität Berlin | |
| **1.11.07** | Prof. M. Baer, FH, HU Jerusalem | Born-Oppenheimer Coupling Terms as Molecular Fiels |
| **15.11.07** | Ms Michael Steinberg, FH, HU Jerusalem | Structural Changes of Cytochrome c in the Gas Phase |
| **29.11.07** | Esteban Vöhringer-Martinez, Univ Göttingen & MPI Biophysical Chemistry | Dynamics of Laser Induced Phase Transitions in Water |
| **6.12.07** | Dr. Lukasz Cwiklik, Inst of Chem. & FH Center, HU Jerualem | Segregation of Inorganic Ions at Surfaces of Polar Nonqueous Liquids |
| **13.12.07** | Dr. O. Gat, Racah Inst. of Physics, HU | Rabi Oscillations on Energy Surfaces: Integrable Phase-Space Dynamics of Cavity QED |
| **16-21.12.07** | Minerva Gentner Symposium on Time dependent DFT, Quuen of Sheba Eilat Israel. Organizers:<br>Israel:<br>R. Baer (FH/HUJI),<br>E. Rabani (Tel Aviv)<br>L. Kronik (WIS)<br>Germany:<br>E. K. U. Gross (Berlin)<br>A. Goerling (Munchen) | Adhikari Satrajit, Indian Assoc. for Cultivation of Science, Kolkata, India; Argaman Nathan, NRCN, Beer Sheva, Israel; Armiento Rickard, Universitaet Bayreuth, Germany; Baer Michael, The Hebrew University of Jerusalem, Israel; Baer Roi, The Hebrew University of Jerusalem, Israel; Band Yehuda, Ben Gurion University, Beer Sheva, Israel; Bauer Dieter, Max Planck Institute for Nuclear Physics, Heidelberg, Germany; Bonacic-Koutecky Vlasta, Humboldt-Universitat zu Berlin, Germany; Buchman Omri, Hebrew University of Jerusalem, Israel; Burke Kieron, University of California, Irvine, USA; Casida Mark, Universite Joseph Forunier (Grenoble I), France; Castro Alberto, Free University of Berlin, Germany; Di Ventra Massimiliano, UCSD, La Jolla, California, USA; Dubnikova Faina, The Hebrew University of Jerusalem, Israel; Dunietz Barry D., University Of Michigan, Ann Arbor, USA; Eisenberg Helen, The Hebrew University of Jerusalem, Israel; Evers Ferdinand, Forschungszentrum Karlsruhe, Eggenstein-Leopoldshafen, Germany; Garcia-Lastra Juan Maria, Universidad del Pais Vasco, Colindres, Spain; Gershon Tamar, Hebrew University of Jerusalem, Israel; Goerling Andreas, Universitaet Erlangen-Nuernberg, Erlangen, Germany; Granot Rebecca, The Hebrew University of Jerusalem, Israel; Grimme Stefan, University of Muenster, Germany; Gross EKU, Free University Berlin, Germany; Hod Oded, Rice University, Houston, Texas, USA; Huang Patrick, Larence Livermore National Laboratory, Livermore, California, USA; Katz Gil, The |

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| | | Hebrew University of Jerusalem, Israel; Kosloff Ronnie, The Hebrew University of Jerusalem, Israel; Kraisler Eli, Tel Aviv University, Israel; Kronik Leeor, Weizmann Institute of Science, Rehovot, Israel; Krylov Anna, USC, Los Angeles, California, USA; Kuemmel Stephan, University of Bayreuth, Germany; Kurth Stefan, Freie Universitaet Berlin, Germany; Kurzweil Yair, University of California Berkeley, USA; Levy Ohad, NRCN, Israel; Livshits Ester, The Hebrew University of Jerusalem, Israel; Makmal Adi, Weizmann Institute of Science, Rehovot, Israel; Makov Guy, NRCN, Israel; Meir Yigal, Ben Gurion University, Beer Sheva, Israel; Mukhopadhyay Debasis, University of Calcuta, India; Mundt Michael, Weizmann Institute of Science, Israel; Myohanen Petri, University of Jyvaskyla, Finland; Natan Amir, Weizmann Institute of Science, Rehovot, Israel; Naveh Doron, Weizmann Institute of Science, Rehovot, Israel; Neuhauser Daniel, UCLA, Los Angeles, California, USA; Niehaus Thomas A., Bremen Center for Computational Science, Germany; Nitzan Abraham, Tel Aviv University, Israel; Pehlke Eckhard, University of Kiel, Germany; Prezhdo Oleg, University of Washington, Seattle, Washington, USA; Rabani Eran, Tel Aviv University, Israel; Rasanen Esa, Freie Universitaet Berlin, Germany; Reinhard Paul-Gerhard, Universität Erlangen/Nürnberg, Germany; Rejec Tomaz, Jozef Stefan Institute, Ljubljana, Slovenia; Rom Naomi, Rafael, Haifa, Israel; Ruggenthaler Michael, Max-Planck-Institute for Nuclear Physics, Heidelberg, Germany; Saalfrank Peter, University of Potsdam, Germany; Salzner Ulrike, Bilkent University, Ankara, Turkey; Savin Andreas, CNRS and Universite Pierre et Marie Curie, Paris, France; Schirmer Jochen, University of Heidelberg, Germany; Subotnik Joseph, Tel Aviv University, Israel; Tannor David, Weizmann Institute of Science, Rehovot, Israel; Thiele Mark, Universitaet Bayreuth, Germany; Ullrich Carsten, University of Missouri, Columbia, Missouri, USA; van Leeuwen Robert, University of Jyvaskyla, Finland; Vignale Giovanni, University of Missouri-Columbia, USA; Wang Yong, Bremen Center for Computational Materials Science, Germany; Yabana Kazuhito, University of Tsukuba, Japan; Yang Weitao, Duke University, Durham, North Carolina, USA |
| **24.12.07** | Prof. A. Krylov, Chemistry Dept., USC, LA | Adventures in Fock Space: Dyson Orbitals, Charge Transfer and Properties of Open-Shell Systems |
| **3.1.08** | Dr. R. Rohs, Columbia University, NY | The Role of DNA Structure in Protein-DNA Recognition |
| **7.1.08** | Prof. S. Malin, Colgate University, Hamilton, NY | What Are Wave Functions? |
| **24.1.08** | O. Markovitch, Inst of Chemistry & FH Center HU | Who Moved My Proton? |
| **4.2.08** | Prof. Dr. B. Abel, University of Göttingen & MPI for Biophysical Chemistry | Dynamics & Applications of Soft Liquid Beam Desorption of Biomolecules with a Laser |
| **7.2.08** | Dr. O. Furman, Dept of Molecular Genetics & Biotechnology, Hadassa Medical School, HU | Exploring the Energy Landscape of Protein-Protein Binding with Rosetta |
| **14.2.08** | D. Steinitz, Inst of Chemistry & FH Center (HU) | Crystal Reflection – A New Kind of Interferometer for Atoms |
| **18.2.08** | Prof. Dr. J. Manz, Freie Universität, Berlin | Wavepacket Dynamics Driven by Laser Pulses |
| **21.2.08** | Prof. T. Seideman, Dept of Chemistry, Northwestern | New Directions in Laser Alignment. From High Harmonic Generation to Guided Molecular As- |

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| | University | sembly |
| **3.4.08** | M. Khasin, Inst. of Chemistry HU (Ph.D. Lecture) | Efficient Simulation of Quantum Evolution Using Dynamics Coarse-Graining |
| **10.4.08** | Prof. R. Podgornik, Inst. Jozef Stefan, Ljubljana, Slovenia | Quenched Disorder and Coulomb Interactions |
| **14.4.08** | Prof. Zhigang Shuai, Chinese Academy of Sciences, Beijing | Carrier Transports in Organic Semiconductors: Band vs. Hopping Descriptions |
| **15.5.08** | M. Assaf, Racah Inst. of Physics, Hebrew University | Noise Enhanced Persistence in Biochemical Regulator Networks with Feedback Control |
| **18-22.5.08** | 1st International Symposium on Improvised Explosives, Rosh Hanikra | |
| **22.5.08** | Prof. P. Jungwirth, Acad. of Sciences, Czech Republic, Prague | Ions at Aqueous Interfaces: From Water Surface to Hydrated Proteins |
| **26.5.08** | Prof. E. Geva, Univ. of Michigan, Ann Arbor | Vibrational Energy Relaxation and Multi-Dimensional Infrared Spectroscopy of a Vibrational Mode Strongly Coupled to its Environment |
| **3-4.6.08** | Conference in Honor of ABS's Birthday –Mishkenot Shaananim | |
| **16.6.08** | Prof. B. Dunietz, University of Michigan, Ann Arbor | Exploring Conductance Switching Properties of Molecular and Nano-Scale Devices – A Computational Approach |
| **19.6.08** | Prof. P. Brumer, Dept of Chem., University of Toronto | Laser-Induced Femtosecond Electrical Currents in Molecular Wires: From Fundamentals to Polyacetylene |
| **24.7.08** | Prof. S. Kuemmel, Physics Inst., University of Bayreuth, Germany | Quantum Mechanics Without a Wavefunction: Problems and Prospects in Density Functional Theory |
| **31.7.08** | Prof. B. Tsukerblat, Dept of Chem., BGU, Beer Sheva | Nanoscopic Cluster V15: Spin Frustration and Antisymmetric Exchange |
| **4.8.08** | Dr. L. Kronik, Dept of Materials & Interfaces, Weizmann Inst. of Science | Understanding Electronic Properties at Molecule/Inorganic-Solid Interfaces of First Principles |
| **6.11.08** | Professor Ruth M. Lynden-Bell<br>University Chemical Lab., Cambridge, UK | Towards Understanding Water: Simulations of Modified Water Models |
| **10.11.08-14.11.08** | Prof. P. Devlin, Oklahoma State Univ. | |
| **10.11.08** | Professor Thomas Weinacht<br>Physics Dept, Stony Brook University, NY | Controlling Molecular Dissociation using Strong Laser Fields |
| **12.11.08** | Professor Fillipp Furche, University of California, Irvine | Electronic Structure Calculations as a Tool in Chemistry |
| **25.11.08-29.11.08** | Professor Vladimir Feldman<br>Moscow State University, | A New Look at Radiation Chemistry of Matrix-Isolated Molecules: Modeling Primary Events in |

| | Russia | Condensed Phase |
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| **2.12.08** | Prof. Svatopluk Zeman, University of Pardubice, Czech Republic | Initiation Reactivity of the Individual Polynitro Compounds – Specification of Reaction Center |
| **4.12.08** | Prof. Nir Gov, Chemical Physics, Weizmann Inst., Rehovot | Dynamic Instability in an Expanding Cell Culture |
| **6.12.08** | Dr. Lukasz Cwiklik, Hebrew University | Segregation of Inorganic Ions at Surfaces of Polar Nonaqueous Liquids |
| **18.12.08** | Dr. Michal Sharon, Biological Chemistry, Weizmann Institute | Weighing the Evidence for Structure: Mass Spectrometry of the Degradation Machinery |
| **13.1.09** | Prof. David J. Srolovitz, Yeshiva College, NY | Why Do ZnO Nanoribbons Spontaneously Bend? |
| **29.1.09** | Dr. Emmanuel Tannenbaum, BGU, Beer-Sheva | Diploidy, Homologous Recombination Repair, and the Selective Advantage for Secual Reproduction in Unicellular Organisms |
| **4.2.09** | Prof. Igal Szleifer, Northwestern U., Chicago | Thermodynamics and Kinetics of Protein Adsorption |
| **13.2.09-19.2.09** | Prof. J. Manz, Freie Universität, Berlin | |
| **9.3.09** | Dr. Arik Landau, Chemistry Dept., USC | The Frozen Natural Orbital (FNO) Equation-of-Motion Coupled-Cluster (EOM-CC) Approach |
| **15.3.09-29.3.09** | Dr. Christiane Koch, Free Univ. Berlin | |
| **21.3.09-29.3.09** | Dr. Mamadou Ndong, Free Univ. Berlin | |
| **16.3.09** | Dr. Oleg S. Vasyutinskii, Ioffe Inst., Russian Acad. of Sci., St. Petersburg | Orbital Polarization of the Chemical Reaction Products: Experimental Determination of the Dynamical Amplitudes and Phases |
| **26.3.09** | Prof. Stephen Leone, Dept of Chemistry, UC Berkeley | X-Ray Probing of Atomic and Molecualr dynamics to the Attosecond Limit |
| **31.3.09** | Prof. Martin Zanni, Dept of Chemistry, Univ. of Wisconsin, Madison | 2-D IR Spectroscopy and Isotope Labeling Defines the Pathway of Amyloid Formation with Residue Specific Resolution |
| **23.4.09** | Dr. Mary K. Gilles, Lawrence Berkeley National Lab., Berkeley, CA | Probing Atmospheric Aerosols by Micro-Spectroscopic Methods |
| **30.4.09** | Dr. Baruch Barzel<br>Racah Inst. of Physics, HU | A Simple Simulation for a Complex Network |
| **5.5.09-19.5.09** | Prof. Brian Burrows, Staffordshire University | |
| **10.5.09** | Prof. Pavel Jungwirth, Acad. Sci. Czech Republic | Calculations of Photoionization in Water: Electrons, Cationic Holes, and Ionized DNA Bases |
| **14.5.09** | Dr. Maytal Caspary Toroker, Technion Haifa | Flux Correlation Approach to Electronic Transport through Molecular Junctions |
| **25-26.5.09** | Symposium on Interfaces<br>At Kibbutz Tzuba | Attendance and participation of the Beirat members |
| **24-29.5.09** | Prof. Dr. W. Domcke, Tech. Univ. Munchen | |

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| **24-27.5.09** | Prof. Dr. G. Meijer, Fritz Haber Insitute, Berlin | |
| **24-27.5.09** | Prof. Dr. H. Grubmüller, Max-Planck-Institut für bio-physikalische Chemie | |
| **26.5.09-1.6.09** | Prof. P. Devlin, Oklahoma State Univ. | |
| **11.6.09** | Dr. Yoav Tsori, Ben Gurion University of The Negev | Place Separation Transition in Liquids and Polymers in Electric Field Gradients |
| **3.8.09** | Prof. Ilan Benjamin Dept of Chemistry, UCSC | Water Structure at Interfaces and Chemical Reactivity |
| **15.10.09** | Dr. Jiri Vala, National University of Ireland | Topological Quantum Computing |
| **19.10.09** | Prof. Emily Allyn Weiss, Northwestern University | Chemical Control of the Optical Properties of CdSe QD-Organic Complexes |
| **28.10.09** | Prof. Daniel Harries, The Hebrew University of Jerusalem | Driving Macromolecular Self Organization by Crowding and Osmotic Stress |
| **10.11.09** | Prof. David Chandler, Dept of Chemistry, UC Berkeley | Sampling Trajectory Space to Study Rare Events and Non-Equilibrium Order - Disorder |
| **15.11.09-06.12.09** | Dr. Sergey Zybim, Caltech USA | Material simulations - cooperation with R. Kosloff |
| **30.11.09** | Prof. Erik T.J. Nibbering, Max-Born-Inst., Berlin | Ultrafast Vibrational Spectroscopy of Bimolecular Reaction Dynamics in Liquid Solution |
| **10.12.09** | Computational Chemistry Symposium In collaboration with Lis Meitner Center) | J. Sauer (Humboldt University, Berlin): C-H activation by transition metal oxides – from gas phase clusters to supported catalysts<br>D. Danovich (HU): No-pair bonding in the high spin states of metal clusters<br>T. Ansbacher (HU): Copper-Keepers – copper chaperones and their coordination number of Cu(I)<br>W.L. Jorgensen (Yale University): From water models to drug lead optimization<br>M. Amity (HU): Hydrolysis of organophosphate compounds by mutant Butyrylcholinesterase – A story of two histidines]<br>R. Politi (HU): Osmolytes modulate peptide folding<br>A. Dreuw (J.W. Goethe University, Frankfurt): Photo-initiated processes in the medium-sized organic pigments<br>T. Stein (HU): Charge transfer excitations using Time-Dependent Density Functional Theory<br>P. Schyman (HU): Brain chemistry: How does P450 catalyze the formation of neurotransmitters<br>S. Amaran (HU): The photoassociation of Mg_2<br>E.F. Sheka (Friendship University of the Russian Federation, Moscow): Fullerene-cluster amplifiers and nanophotonics of fullerene solutions<br>L. Pele (HU): Anharmonic vibrational spectroscopy calculations for biological molecules: new algorithms and applications<br>Ch. Dryzun (HU): Novel general symmetry measures |
| **24.12.09** | Prof. David J. Tannor, Weizmann Institute, Rehovot | How Did Pauli Miss It: An Exact Formulation of Quantum Mechanics with Complex Trajectories |

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| **14.1.10** | Dr. Michael Khasin, Michigan State University | The spectrum of an oscillator with fluctuating mass and nanomechanical mass sensing |
| **5.2.10** | Prof. Simon Schuring, Curie Inst. France | High resolution AFM of membrane proteins in native membranes |
| **7-12.2.10** | Gentner Symposium on H+ mobility in chemical and biological systems | Noam Agmon (Jerusalem), Isaiah T. Arkin (Jerusalem), Huib J. Bakker (Amsterdam), Ernst Bamberg (MPI Frankfurt), Kankan Bhattacharyya (Kolkata), Qiang Cui (Madison)<br>Bertrand Garcia-Moreno (Baltimore), Ricard Gelabert (Barcelona), Robert B. Gennis (Urbana-Champaign), Klaus Gerwert (Ruhr-Universität Bochum), Gerrit Groenhof (MPI Göttingen), Helmut Grubmueller (MPI Göttingen)<br>Menahem Gutman (Tel Aviv), Joachim Heberle (Bielefeld)<br>Volkhard Helms (Saarbrücken), Gerhard Hummer (NIH)<br>James T. Hynes (Paris), Carola Hunte (Leeds), Dan Huppert (Tel Aviv), Wolfgang Junge (Osnabrück), Soren R Keiding (Aarhus), Amnon Kohen (Iowa City), Daniel J. Müller (Dresden), Eric T.J. Nibbering (MBI Berlin), Michael Gjedde Palmgren (Copenhagen), Forest Lucy (MPIBiophysics, Frankfurt), Ehud Pines (Ben Gurion University of the Negev), Steven D. Schwartz (New York), Kyril M. Solntsev (Georgia Tech.), Eckhard Spohr (Duisburg-Essen), Andrei Tokmakoff (MIT), Mark E. Tuckerman (New York), Gregory A. Voth (University of Utah), Ulrike Alexiev (Berlin)<br>Patrick Ayotte (Sherbrooke), José D. Faraldo-Goméz (Frankfurt am Main), Chikvaise Mari (Heidelberg), Yuri Feldman (Jerusalem), Manuela M. Pereira (Oeiras), Ai Shinobu (Jerusalem), Alexeiev Ulrike (Berlin), Evgenii S. Stoyanov (Riverside), Jessica M. J. Swanson (Salt Lake City), Pawel Swietach (Oxford), Jasper J. van Thor (London), Freier Erik (Univ Bochum, Germany), |
| **25.2.10** | Prof. James Heath, Caltech, USA | Exploring fundamental transport limits in precisely designed, nanoscales structures: applications to granular solids, thermoelectrics, and superconductors |
| **10.3.10** | Prof. Avinoam Ben Shaul, The Hebrew University | Molecular Basis of Cadherin-Mediated Cell-Cell Adhesion and Cell Sorting |
| **22.3.10** | Dr. Tsachi Livneh, Nuclear Research Center, Negev | Temperature and Pressure Dependent Raman Scattering at Resonantly Tuned Exciton States in 2H-MoS2 |
| **26.4.10** | Prof. Jacob Klein, Weizmann Institute of Science Rehovot, Israel | Hydration lubrication: exploring a new paradigm |
| **3.5.10** | Dr. Dorit Shemesh, Tech Univ Munchen and Fritz Haber Center HUJI | Photoinduced Dynamics of Biological Molecules |
| **8-11.5.10** | Victoria Buch Symposium | Dr. Lukasz Cwiklik<br>Dr. Barbara Jagoda-Cwiklik<br>Prof. Joanna Sadlej<br>Prof. Erio Tossatti<br>Prof. Paul Devlin<br>Prof. Pavel Jungwirth |

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| | | Prof. Michelle Parrinello<br>Prof. Nevin Uras |
| **17.5.10** | Dr. Yair Shokef, Weizmann Inst of Science | Ordered Models for Disordered Matter |
| **24.5.10** | Prof. Eran Rabani, Tel Aviv University | Multiexciton generation and carrier multiplication at the nanoscales |
| **31.5.10** | Dr. Ophir Flomenbom, Flomenbom BPS | Making it possible: constructing a reliable mechanism from a finite two-state trajectory |
| **7.6.10** | Prof. Rony Granek, Ben Gurion Univ. of the Negev | Protein Dynamics and Stability: Universality vs. Specificity |
| **10.6.10** | Dr. Tzahi Grunzweig, University of Otago, Dunedin, New Zealand | Deterministic Loading of a Single Atom to a Micro-Trap |
| **14.6.10** | Prof. Victor V. Volkov, University of Florence, Italy | Structural relations at phospholipid bilayer interface: heterogeneity, dynamics, and intermolecular relations |
| **5.7.10** | Prof. Michael Galperin, UCSD | Transport in State Space |
| **20-27.7.10** | Dr. Beil Fabian, Tech Univ Darmstadt | Collaboration with Prof. R. D. Levine |
| **20-31.8.10** | Prof. Peter Salamon, San Diego State University | Collaboration with Prof. R. Kosloff |
| **14.10.10** | Dr. Julia Laskin, Pacific Northwest, Nat'l Laboratory, Washington, USA | Soft-landing of Complex Ions on Surfaces |
| **6-12.11.10** | Prof. Dr. Markus Meuwly, Univ Basel | Diatomic Molecules as Spectroscopic Probes for Protein Interiors<br>Collaboration with Prof. R. B. Gerber |
| **21.11.10 - 7.12.10** | Prof. Anne McCoy, Ohio State | Solvent Induced Electron Leap-Frogging:<br>Time-Resolved Excited State Dynamics and Electron Photodetachment Studies of IBr- and IBr-…CO2 |
| **26-28.12.10** | Prof. Michael Galperin, UC San Diego | Molecular Transport Junctions |
| **30.12.10** | Dr. Dima Lukatsky, Ben-Gurion University of the Negev | Multi-scale sequence correlations shape proteome promiscuity |
| **6.1.11** | Prof. Koby Levy, Department of Structural Biology, Weizmann Institute of Science, Rehovot, Israel | |
| **10.1.11** | Prof. István Hargittai Institute of General and Analytical Chemistry, Budapest University of Technology and Economics, Budapest, Hungary | Judging Edward Teller |
| **14.2.11** | Prof. Bernhard Dick, Institute for Physical and Theoretical Chemistry, Laserspectroscopy and Photochemistry, University of Regensburg, Regensburg, Germany | Photodissociation of Nitroso Compounds Studied by Velocity Map Imaging (VMI) and 3d-REMPI-Spectroscopy |
| **17.2.11** | Prof. Joseph Subotnik, Department of Chemistry, University of Pennsylvania, Philadelphia, PA, USA | The Initial and Final States of Electron and Energy Transfer Processes: Photochemistry for Quantum Chemists |
| **24.2.11** | Prof. Robert Gordon, Depart- | Coherent Phase Control of Photoluminescence from |

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| | ment of Chemistry, University of Illinois at Chicago, Chicago, IL, USA | Gallium Arsenide |
| **14.3.11** | Prof. Sergey Nizkorodov, University of California, Irvine, CA, USA | |
| **22.3.11** | Prof. Henri Orland, Institute of Theoretical Physics, CEA-Saclay (Atomic Energy Commission), Gif-sur-Yvette, France | Dominant Pathways in Protein Folding |
| **24.3.11** | Dr. Zhenggang Lan, Max Planck Institute of Coal Research, Mülheim, Germany | The Role of Conical Intersections in Molecular Excited-State Dynamics |
| **4.4.11** | Prof. Zlatko Bacic, Department of Chemistry, Faculty of Arts & Science, New York University, New York, NY, USA | |
| **2.5.11** | Prof. Pavel Jugwirth, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague, Czech Republic | |
| **5.5.11** | Prof. Todd Martinez, Department of Chemistry, Stanford University, Stanford, CA, USA | |
| **17.5.11** | Dr. Ioannis D. Petsalakis, Theoretical & Physical Chemistry Institute (TPCI), The National Hellenic Research Foundation (NHRF), Athens, Greece | Photoinduced Electron Transfer In Chemical Sensors and Carbon Nanohybrids |
| **23.5.11** | Prof. Konstantin M. Neyman, Department of Physical Chemistry, University of Barcelona, Barcelona, Spain | |
| **17.11.11** | Prof. Eric Clot Institut Charles Gerhardt Université Montpellier 2 Montpellier, France | Computational Studies of Homogeneous Catalysis: Should we Use Dispersion Corrections? |
| **5.12.11** | Prof. Martina Havenith.Germany | Watching the dance of water in the hydration shell of ions and biomolecules in the THz frequency range |
| **15.12.11** | Mr. Ehud Tzvion Institute of Chemistry The Hebrew University of Jerusalem Jerusalem, Israel | New noble-gas molecules and their condensed phases |
| **29.12.11** | Prof. Adam Zlotnic Department of Molecular & Cellular Biochemistry Indiana University Bloomington, IN, USA | |
| **9.1.12** | Dr. Sharly Fleischer Department of Chemistry, Massachusetts Institute of Technology (MIT), Cambridge, MA, USA | Coherent Control of Molecular Rotational Motion by Intense THz Fields |
| **12.1.12** | Dr. Yardena Bohbot-Raviv Department of Applied Mathematics Division of Environmen- | |

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| | tal Sciences Israel Institute for Biological Research (IIBR) Ness-Ziona, Israel | |
| **23.1.12** | Prof. Robert J. Levis Dep. of Chemistry, Chairman Center for Advanced Photonics Research, Director Temple University Philadelphia, PA, USA | Strong Field Chemistry in Complex Systems: From Filament-Based Raman Spectroscopy to Measuring Protein Structure With Laser Vaporization |
| **2.2.12** | Dr. Waldemar Kulig Institute of Chemistry & Fritz-Haber Center The Hebrew University of Jerusalem | Looking for a proton transfer mode in aqueous solution – a novel approach for calculating the IR spectrum |
| **9.2.12** | Prof. Daniel M. Neumark Department of Chemistry University of California Berkeley, CA, USA | Ultrafast x-ray science in the femtosecond and attosecond regime |
| **1.3.12** | Prof. Richard H. Henchman Interdisciplinary Biocenter, Univ. of Manchester, UK | Defining Hydrogen Bonds to Determine the Structure and Dynamics of Water |
| **11-14.3.12** | Prof. Rudolf Podgornik Dept of Physics, Univ. of Ljubljana, Dept of Theor. Physics, Jozef Stefan Inst., Slovenia | Protein-DNA Interactions Determine the Shapes of DNA toroids Condensed in Virus Capsids |
| **19.3.12** | Prof. Anna I. Krylov Dept of Chemistry, USC | Quantum Chemistry Behind Bioimaging: Insights from Ab Initio Studies of Fluorescent Proteins and Their Chromophores |
| **26.3.12** | Dr. Ajaykumar Gopal Dept of Chem & Biochem, UCLA | Visualizing Large RNA Molecules in Solution |
| **2.4.12** | Dr. Noa Marom Inst for Computational Engineering & Science, Univ. of Texas at Austin | Electronic Structure of Dye-Sensitized TiO2 Clusters from Many-Body Perturbation Theory |
| **4.4.12** | Prof. Iwao Ohmine Director General, Inst for Molecular Science, Okazaki, Japan | Water Dynamics: Fluctuation, Reactions and Phase Transitions |
| **6.3.12-6.4.12** | Dr. Gopal Ajaykumar, UCLA | Collaboration Prof. Avinoam Ben-Shaul |
| **15.4.12** | Prof. Christoph F. Schmidt 3rd Inst of Phys&Biophys. Georg-August Univ. Göttingen | The Unconventional Gear Box of the Mitotic Yeast Kinesin-5 Cin8 |
| **19.4.12** | Prof. Dieter Hoffmann Max Planck Inst f. History of Science, Berlin | Quanten Physics in Haber's Institute |
| **1.5.12** | Prof. Oleg Gang Center for Functional Nanomaterials, Brookhaven Nat. Lab. Upton, NY | Nanoscale Self-Assembly Guided by DNA: Structures, Transformations and Rationally Designed Materials |
| **10.5.12** | Guy Cohen School of Chemistry, Tel Aviv University | Strongly Correlated Electron Dynamics Under Nonequilibrium Conditions |
| **24.5.12** | Dr. Eyal Fattal Appl. Math. Dept, Israel Inst. for Biol. Res., Ness-Ziona | Lagrangian Stochastic Modeling of Pollutant Dispersion in the Turbulent Atmospheric Boundary Layer – Application to Urban Areas |
| **7.6.12** | Prof. Evgueni E. Nesterov | Thin-Film Materials with Extended Electronic Delocali- |

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| | Dept of Chemistry, Louisiana State Univ., Baton Rouge | zation: From Molecular Design to Practical Devices |
| **6-16.2.12** | Prof. Sylvio May, Department of Physics, N. Dakota State University, USA | Collaboration with Avinoam Ben-Shaul |
| **21.6.12** | Prof. Dan Davidov<br>Racah Inst of Physics HU | Infrared Surface Plasmon Resonance, Guided Waves and Spectroscopic Determination of Changes of Optical Constants and Morphology of Life Cells Upon Drug Injection |
| **8-31.7.12** | Prof. Brian Burrows, Dept. of Computing, Engineering and Technology, Staffordshire University, UK | |
| **28.7-3.8.12** | Prof. Cambel Colin | Collaboration with Prof. R. D. Levine |
| **1-10.9.12** | Prof. Daniel Neuhauser, Dept of Chemistry and Biochemistry, University of California, USA | Collaboration with Prof. R. Baer |
| **2-7.9.12** | Batsheva de Rothschild Seminar on "Laser Control of Chemical Reactions: Toward Deciphering Mechanisms and Understanding the Theoretical and Experimental Limits" | Ronnie Kosloff (HUJI), David Tannor (WIS), Yaron Silberberg (WIS), Tobias Brixner, Joshua Jortner (TAU), Phil Bucksbaum (Stanford), Kenji Ohmori (IMS), Nirit Dudovich (WIS), Daniel Strasser (HUJI), Nimrod Moiseyev (Technion), Tobias Brixner (Wuerzburg), Thomas Baumert (Kassel), Robert Levis (Temple), Marcos Dantus (Michigan State), Henrik Stapelfeldt (Aarhus), Tom Weinacht (Stonybrook), Ilya Averbukh (Weizmann), Yehiam Prior (WIS), Moshe Shapiro (U. British Columbia), Ben Sussman (NRC Ottowa), Chris Meier (U. of Toulouse), Paul Brumer (U. of Toronto), Marcus Motzkus (Heidelberg), Sandy Ruhman (HUJI), Dwayne Miller (MPI Hamburg), Roseanne Sension (U. Michigan), Regina de Vivie Riedle (Munich), Zohar Amitay (Technion), Christiane Koch (Kassel), Herschel Rabitz (Princeton) |

# LIST OF PUBLICATIONS 2008-2012

## NOAM AGMON

1. O. Markovitch and N. Agmon, "The distribution of acceptor and donor hydrogen-bonds in bulk liquid water", Mol. Phys. 106, 485-495 (2008).
2. O. Markovitch and N. Agmon, "Reversible geminate recombination of hydrogen-bonded water molecule pair", J. Chem. Phys. 129, 084505 (2008).
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