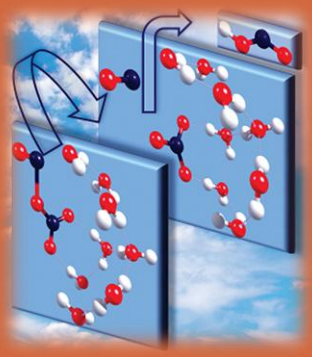
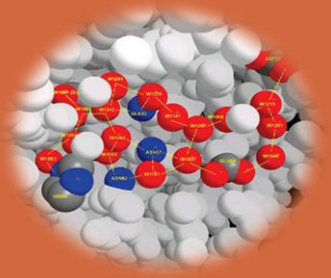
The Hebrew University of Jerusalem

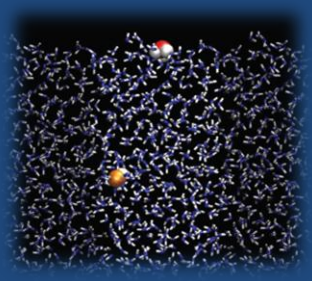
The Fritz Haber Research Center for Molecular Dynamics

Scientific Report

2010







Presented to:

The Minerva Foundation

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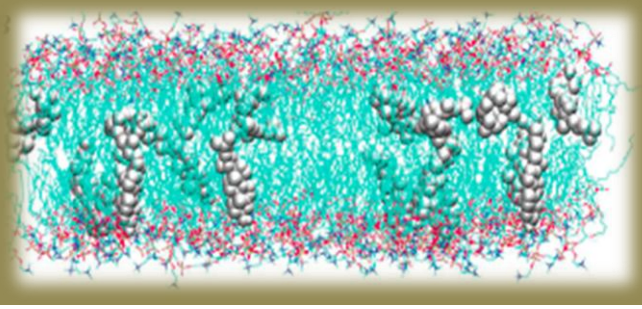

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INTRODUCTION

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 postdocs 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, proton-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 3rd 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 (Drs. Niv and Zemel 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.

RUNNING OPERATION OF THE CENTER

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

At present, there are 79 scientists active at the Center, including faculty members (9), non-faculty staff (6) long-term visitors (7), post-doctoral fellows (18) and research students (MSc (14) 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. Tova Feldman
- Dr. Gil Katz
- Dr. Ilan Dagani

- Dr. Shimshon Kallush

LONG TERM VISITING SCIENTISTS

- Prof. A. Dell-Hammerich (University of Illinois)
- Prof. F. Remacle (University of Liege)
- Prof. D. Neuhauser (UCLA)
- Prof. Hillel Tal-Ezer (Sabbatical), Academic College of Tel-Aviv Yaffo
- Dr. Shlomi Pistinner (Sabbatical), Soreq Research Center
- Dr. Naomi Rom (Sabbatical), Rafael Technologies.
- Dr. Yardena Bohbot-Raviv (Sabbatical), Biology Institute, Israel

POSTDOCTORAL FELLOWS AND RESEARCH ASSOCIATES (CURRENT)

- Dr. Saieswari Amaran
- Dr. Shu Cheng
- Dr. Helen Eisenberg
- Dr. Jennifer Galanis
- Dr. Noga Kowalsman
- Dr. Moshe Goldstein
- Dr. Rebecca S. Granot
- Dr. Chen Levi
- Dr. Esther Livshits
- Dr. Jiri Sebek
- Dr. Dorit Shemesh
- Dr. Iad Suan
- Dr. Izhar Madalassi
- Dr. Ayelet Gross
- Dr. Li-Tai Fang
- Dr. Avi Ben Shimon
- Dr. Talia Yarnitzky
- Dr. Nataly Karbachenko-Balasha

RESEARCH STUDENTS (2010)

PhD: Amshallem M; Bar L; Baratz A; Brill Y; Buchman, O; Cnaani R; Dvoris, M; Hiluf D; Gershon T; Leora M; Jacoby S; Jutkowits R; Kalman G; Klein M; Levit A; Muscatal H; Polity R; Arumugam R; Rezek Y; Rubinstein M; Sagiv L; Shinobo Ai; Shmiloviz-Ofir M.; Sukenik, S; Tzivyon U.

MSc: Bronstein A; Cyttar Y; Hirshberg B; Levy A; Moshe L; Saper G; Sagi E; Sapir L; Schafer I; Shachar A. N; Shavro M; Shudler; Wiener A; Zmiri, L.

ADMINISTRATIVE-TECHNICAL STAFF

- Ms. Geula Levy: Administration Assistant
- Ms. Eva Guez: Scientific Editing
- Mr. Michael Vilenkin: Computer and Communications Systems Administrator
- Mr. Max Tkatch: Assistant systems administrator.

INTEGRATION OF YOUNG SCIENTISTS

The integration of the young scientists (students/postdocs) at the center is done at several levels. Each student is a member of one of the research group of the center. The administration, such as stipend, registration etc is coordinated by the administrator of the center. In addition, the young researcher enjoys the computer administration services, as well as computer communications, printing, fax etc. of the center. The center supports some of the participation and travel expenses of students in conferences and summer schools in Israel and abroad. Students also give their thesis defense lectures as part of the Fritz Haber seminar schedule.

In order to enhance student involvement in the academic activities, they are charged with the scientific organization of the Fritz Haber seminar. They invite and host the speakers of this seminar (this activity is guided by Dr. Daniel Harries).

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 is requested to report to Minerva on the program, and authorize budget and activities of the Center. The Beirat convenes every second year. The last meeting was held in Jerusalem in June 2009 and included a successful international symposium on Biophysical Dynamics.

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)

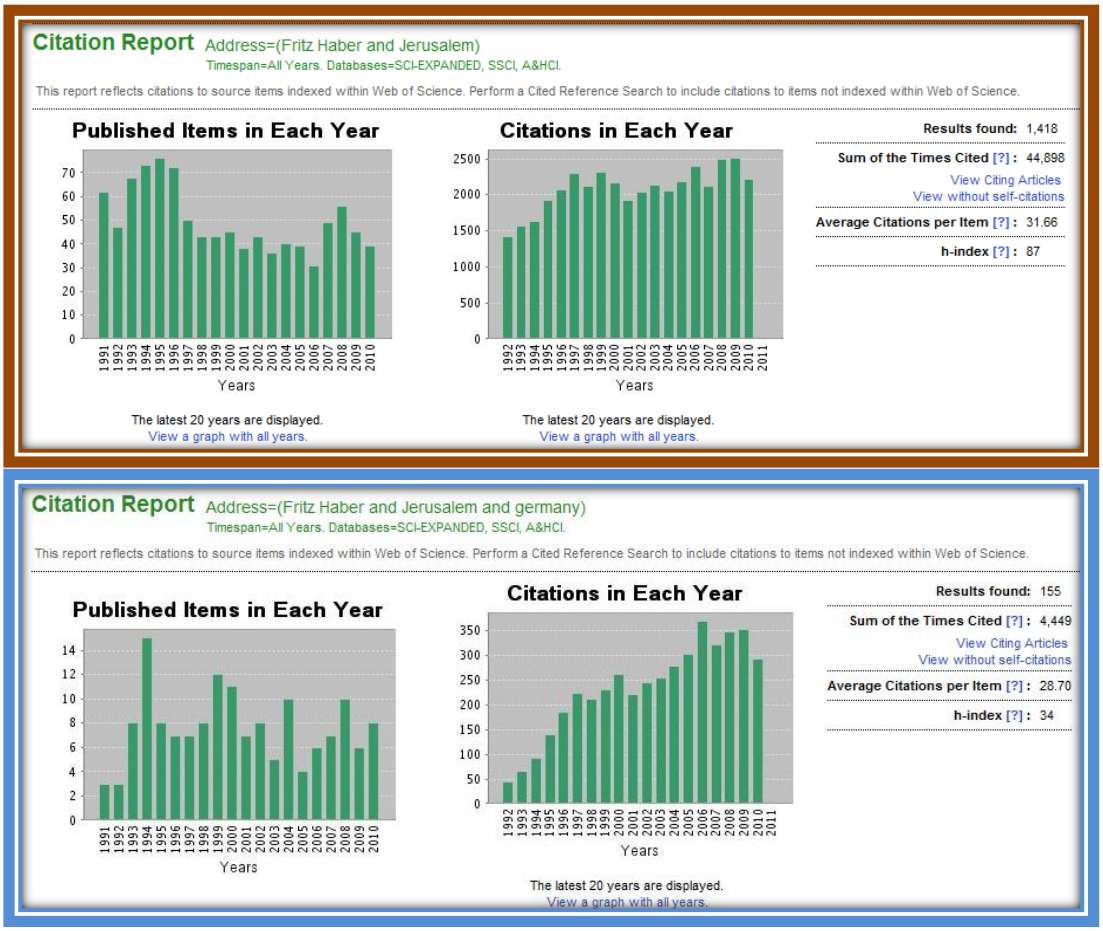

Figure 1: Top: Citation report for the Fritz Haber Center (latest 20 years). Bottom: Citation report for joint Fritz Haber center and German publications.

STATISTICS OF SCIENTIFIC IMPACT

Since its inauguration the researchers of the center have published over 1400 scientific articles in refereed journals with direct affiliation to the Fritz Haber Minerva Research Center. These articles were cited in the scientific literature nearly 45,000 times with an average of 32 citations per paper and an h-index of 87 (see Figure 1). The citation rate is 2500 per year and about 40-50 papers are published each year. The collaboration with German scientist is intense, culminating in over 150 papers which were cited over 4450 times with an average of 29 citations per item and an h-index of 34.

INDIVIDUAL RESEARCH REPORTS

NOAM AGMON

My research in the last five years involved chemical reactions and transport in solutions and in proteins. It utilized simulations, diffusion theory and experiments to study water, hydrogen bonds (HBs), proton mobility, excited-state proton transfer (ESPT), enzymatic kinetics, the green fluorescence protein (GFP), proton wires, proton antenna and single molecule diffusion.

SCIENTIFIC PROJECTS

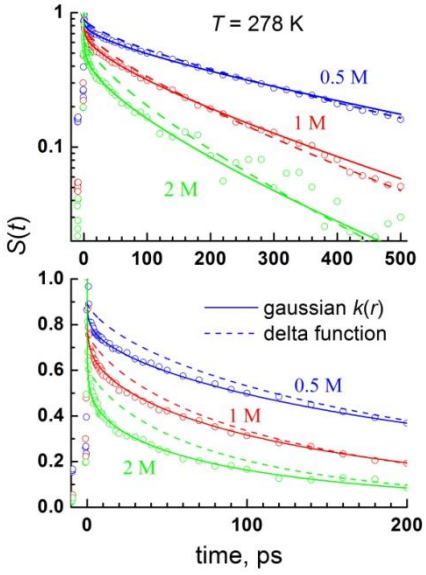

Figure 2: Time resolved decay of the IR signal from excited pyranine in its reaction with various concentrations of acetate base (indicated).

PROTON WIRES IN AQUEOUS SOLUTION

Aqueous ESPT between an excited photoacid and a high base concentration in aqueous solutions was monitored using fs time-resolved IR (Bakker, Univ. Amsterdam). The survival probability of the excited acid (circles in Figure 2) has an ultrafast component due to acid-base pairs that were connected by "water wires" already in the ground state, and a slower ps phase involving their relative diffusion.

The usual Smoluchowski theory with contact reactivity cannot fit the data (dashed lines in Figure 2), but when a distance-dependent sink-function, k(r), is utilized very good agreement with experiment is observed (bold lines in Figure 2). This k(r) exhibits an inverse temperature effect (decreasing with increasing T), suggesting quantum mechanical tunneling in a concerted multiple-PT mechanism. This suggests that as the acid and base approach each other, an intervening proton-wire is formed along which protons are shuttled in an ultrafast concerted manner. [1]

PROTON WIRES IN GFP

GFP is a natural fluorescing protein with an underlying ESPT mechanism. The photo-dissociated proton travels via Ser205 to the buried Glu222 residue. Such a short proton wire should lead to an ultrafast (fs/ps) decay of the fluorescence from the excited GFP chromophore. However, in a collaborative work with Dan Huppert (Tel-Aviv) we have shown that the fluorescence has a long tail, extending to dozens of ns. This tail is highly non-exponential showing power-law decay (Figure 3). Below 230^oK, the power-law is $t^{-1/2}$, suggesting one-dimensional diffusion of the proton within the protein. Above 230^oK, the power-law changes to a $t^{-3/2}$ decay. I have showed that this could arise from the opening of an escape route for the proton. Possible escape routes were identified in the X-ray structure of wt-GFP. These findings have motivated a project for systematic mapping of proton-wires in proteins. Results for GFP and human carbonic anhydrase are described by Ai Shinobu (below). Refs: [2, 3]

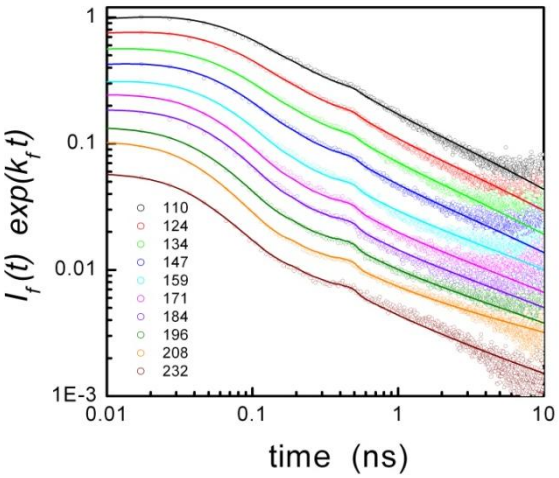

Figure 3: Time resolved fluorescence from the acidic form of wt-GFP (symbols), fitted to the solution of reversible diffusive geminate recombination in one dimension (lines).

PROTON COLLECTING ANTENNA

A two-dimensional diffusion model for a proton collecting antenna was suggested for explaining the effect of dimensionality reduction for the funneling of protons from solution and into a protein. It was solved under steady-state conditions to give an expression for the corresponding rate coefficient as a function of the geometry and fundamental rate coefficients involved in this scenario. Refs: [4]

RESIDENCE TIMES AND SINGLE MOLECULE DIFFUSION

The fluorescence signal from a dye molecule diffusing in solution through a tiny laser spot is ideally proportional to its residence time there. I have found a differential equation for calculating the mean residence time that circumvents the conventional Feynman-Kac approach. It was solved it for a spherical laser spot in arbitrary dimensionality and several experimentally relevant initial conditions. I have also determined the short- and long-time asymptotic behavior in the different dimensionalities. Refs: [5, 6]

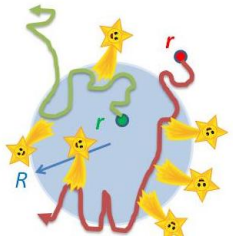

Figure 4: A dye molecule diffusing through a spherical laser spot (light blue) emits photons (yellow stars) while inside this domain. Shown are random trajectories starting outside (red) and inside (green) the domain.

FH CENTER CONTRIBUTION TO AGMON'S RESEARCH

My research in the last few years involved extensive simulations by various MD algorithms, as well as other computations. We have personal computers and a Sun computer cluster that runs Linux, all connected to the FH network. My students are not computer technicians and would not be able to maintain this system without the technical support of the Center's computer experts. They have also helped new students learn to utilize our computer system, and have installed the required software for them. On the administrative side, my research is aided by Geula Levi. Given that we have no secretaries to help us in our daily chores, this administrative help is indispensible. In addition, the FH Center organizes seminars, workshops and symposia in which my students have participated. Finally, the existence of a large and active center creates the desired atmosphere for research, allowing the students to discuss their mutual research problems and learn from the experience of others.

AGMON'S RESEARCH PLANS FOR THE NEXT TWO YEARS

After establishing the principles of proton migration in bulk water, my goal in the next few years is to shed some light on proton transport in complex environments using molecular simulations. Although I prescribe to a basic-science model-system approach, the fundamental understanding of the range of proton mobility mechanisms that can occur in various aqueous environments (from pure water, via ionic solutions, hydrophobic or hydrophilic interfaces, and porous media) is an invaluable guide for designing more efficient proton transporters, e.g. for fuel cells.

I would like first to compute the IR spectrum of protons in bulk water and reinterpret it lieu of the "special pair dance'' (see above), which is likely to have spectroscopic manifestations. Then I would like to study the effect of hydrophobic additives to water (such as tetramethylurea) on the mechanism of proton mobility. The details of this mechanism should be worked out also near the air-water interface, near hydrophobic and hydrophilic interfaces, in the water layer between planar interfaces and within microcavities. I suggest introducing "geometric correlation functions'', which can help characterize migration in complex environments. Our group will then apply MS-EVB3 to obtain their long-time behavior (only this method can currently reach such long times) and compare with (normal or anomalous) diffusion theory results.

AGMON COLLABORATIONS

1) Prof. Dan Huppert, Tel-Aviv University, Israel.
2) Prof. Gregory A. Voth, Univ. Chicago, Chicago IL, USA.
3) Prof. Huib J. Bakker, FOM Institute for Atomic and Molecular Physics, Amsterdam, Nederland. Dr. Gottfried J. Palm, Univ. Greifswald, Germany. Dr. Palm crystallized a mutant GFP, very close in structure to the wild type, and measured its 0.9 Å resolution X-ray diffraction (highest resolution to date for GFP), identifying some hydrogens as well as water molecules on the surface of the protein. The analysis of this structure by Ai Shinobu revealed existence of a HBed network of water molecules, carboxylates and threonines on

the GFP surface that may function to collect protons from solution and funnel them into the protein. Such constructions were postulated for proteins that either consume or transport protons, but thus far have not been directly observed. The joint publication made the cover page of JACS for 18 Aug. 2010.

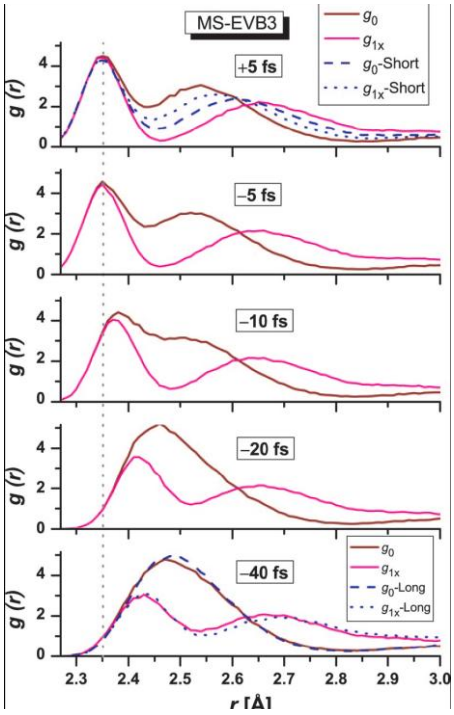

Figure 5: Averaged time resolved radial distribution function (RDF) centered on the hydronium, $g_0(r)$, and its closest first shell neighboring oxygen, $g_{1x}(r)$. With the approach to the proton hopping event ($t = 0$) both RDFs converge to the RDF of a (non-symmetric) Zundel cation - the transition structure for this process.

AGMON STUDENT REPORTS

OMER MARKOVITCH, M.SC.[1]

PROTON MOBILITY IN LIQUID WATER

Use of Multi-State Empirical Valence Bond (MS-EVB) and ab-initio Molecular Dynamics (AIMD) of a single proton in a box of water molecules, provided a first statistically significant proof that proton hops in water through a series of isomerization reactions between the "Eigen structure" (solvated H_3O^+) and the "Zundel structure", $H_5O_2^+$. (Figure 5)

During epochs devoid of proton hopping events the proton participates in a "special pair dance", Figure 6, in which the ligand closest to the H_3O^+moiety interchanges among the three 1st-shell neighbors on a timescale of ca. $40\ fs$.

We have used a long MS-EVB trajectory to perform a statistical analysis of the number of HBs to in the various solvation shells of the H_3O^+. We have established that as the protonated core is approached from the bulk water phase, hydrogen-bonds donated by it become stronger, while those accepted by it becomes weaker.

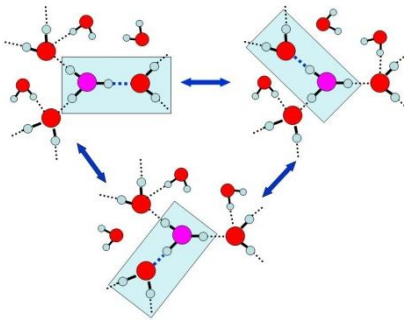

Figure 6: SP-dance within a non-symmetric Eigen complex as deduced from MS-EVB and AIMD simulations of protonated liquid water.

Thus, during proton hopping in water, the first solvation-shell of the hydronium remains intact. Also, the cleavage of an acceptor HB is very rapid, occurring as a prerequisite of the special-pair dance rather than being the rate limiting step for the actual hopping event. Refs: [7, 8]

WATER SIMULATIONS: THE HB CORRELATION FUNCTION

The kinetics of HB forming and breaking in liquid water is traditionally depicted by a (history independent) correlation function, c(t). It measures the probability that a HB that existed at time t=0 still exists at time t. By averaging an extended ensemble of water trajectories we have showed that c(t) is highly non-exponential, exhibiting the same t-3/2 tail as observed in ESPT reactions in solution. The origin of the effect is similar: diffusion influenced reversible dissociation/recombination of a geminate pair (here --

[1] Omer Markovitch has graduated and is now studying for his Ph.D. in the Weizmann Institute.

the two initially HBed water molecules). The simulated c(t) agrees quantitatively with the solution of a diffusion equation with a "back-reaction" boundary condition depicting reversible reaction. From it we obtain the rate constants for HB dissociation and its association from the bulk and determine their temperature dependence (Figure 7).

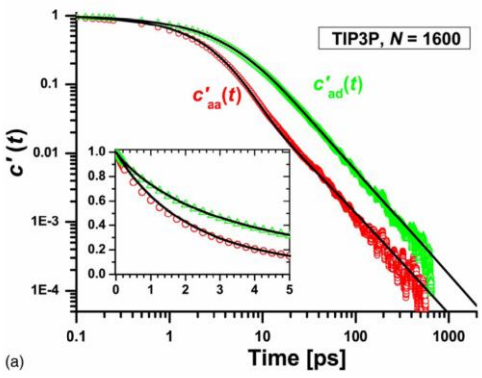

Figure 7: History independent correlation function for HBed water molecule pairs from bulk liquid water simulations. The behavior is qualitatively the same irrespective of whether the HB is defined with (red) or without (green) angular restrictions. Inset shows the short time behavior.

In a related work we have shown that acceptor and donor HBs in water are not equivalent because there is a higher probability of finding an overcoordinated oxygen atom (OCO) than the more commonly discussed bifurcated HB (BHB). As a result, the distribution of the number of acceptor HBs in water is wider than the donor HB distribution. Refs: [9, 10]

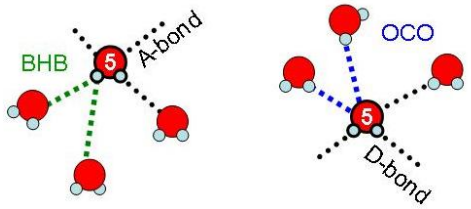

Figure 8: BHB and OCO between water molecules. Oxygen – red, hydrogen –gray.

AI SHONOBU, M.SC.

There are many proteins which consume or produce protons during their activity. Unlike electrons, protons cannot migrate within a protein through either space or its carbon-carbon bonds. It is believed that their transport requires "proton wires" of closely spaced oxygen (nitrogen, sulfur) atoms on which the proton can be transferred in a step-wise manner in a Grotthuss-like mechanism. Inside proteins, proton wires are composed out of amino acid residues' atoms and internal water molecules.

In our work, we explored those proton wires in several proteins and proposed possible roles that those wires play during the proteins' activity.

So far, we looked at 3 systems: the green fluorescent protein (GFP), which was the one investigated most thoroughly, human Carbonic Anhydrase II (CA-II) and Discosoma Red (DsRed). GFP and DsRed both belong to a family of fluorescent proteins from marine organisms and by comparing between proton wire patterns of the two systems we could learn about the origin and role of those wires.

The method we used so far was based on structural data, namely, X-ray structures of proteins taken from the Protein Data Bank (PDB). Two main computational methods were applied:

1. For the purpose of investigating proton wires in protein in a systematic manner, we built an algorithm which takes a protein X-ray structure and reports on the wiring within all the separate clusters of HBed atoms. By definition, in a given cluster there is a pathway connecting every atom to every other atom, whereas atoms outside the cluster are not connected to any atom in the cluster. A HB was defined by criteria of bond distance and angles and the search for continuous HBed chains was done by a recursive tree algorithm over all potential hydrogen bonders.
2. Another method we applied was a statistical analysis of the proton wires features which was performed on a 'library' of GFP results which was created by applying the systematic search algorithm on over a 100 X-ray structures of GFP and its mutants. The purpose of the statistical analysis was to see whether there is a connection between HB connectivity and the X-ray resolution and to see if the lack of use of dynamical tools can be compensated by averaging over a large number of systems.

The main results of this work so far are presented below.

(a) Biosynthetic wire in GFP: In GFP, a proton transfer from and to the chromophore occurs during fluorescence when the acidic proton on the phenolic oxygen dissociates. Several mechanisms for the proton pathway during and after fluorescence had been proposed and an internal proton wire connecting the chromophore to the bottom of the GFP barrel was identified in the past. This internal wire was identified by our search algorithm. In addition to the internal wire, a new cluster was also identified in GFP. The location of the cluster near the chromophore and its chemical character lead us to suggest that the newly found cluster participates in the biosynthesis of the GFP chromophore which is created by an autocyclization reaction of 3 consecutive amino acids (65-67) from the protein backbone and takes place following protein folding. We suggest that several groups from the cluster work cooperatively to assist in a dehydration reaction during chromophore biosynthesis.

(b) Proton wires in CA-II: In CA-II, a more extended wire than previously reported is identified. We find that the active site wire exits to the protein surface, and leads to Glu69 and Asp72, located on an electronegative patch on the rim of the active site cavity. One possible interpretation of this observation is that either protons or positively charged protonated buffer molecules dock in that area, from which a proton is delivered to the active site when the enzyme works in the dehydration direction.

(c) GFP proton wires statistical analysis: We applied the proton wire search algorithm to 104 X-ray structures of GFP and its mutants, creating a library of proton wire information on which we performed a statistical analysis. Examining the results, we see a clear correlation between the size/connectivity of the clusters and the water fraction in the X-ray structure. For example, looking at the total number of atoms participating in clusters in one structure vs. the water fraction of that structure, we get a linear correlation factor coefficient of 0.98. This high correlation is due to the fact that when the amount of water is small, many of the existing HBs are not identified and this cuts and shortens wires which the program can identify. The water fraction, on the other hand is highly correlated to the X-ray resolution of the structure, due to the high mobility of water oxygens.

(d) High-resolution X-ray structure: The latter work was done in collaboration with an X-ray group from Germany (Gottfried Palm, Greifswald) who has measured an X-ray structure of GFP, which has the highest resolution obtained to date (0.9Å). In this high resolution structure we were able to identify the locations of some of the hydrogen atoms. This valuable information allowed us to determine protonation states and hydrogen bonding at critical locations.

(e) Proton collecting antenna of GFP: Looking at the proton wires in the new 0.9Å resolution structure, we identify a motif which wasn't seen in previous lower resolution structures that we examined.

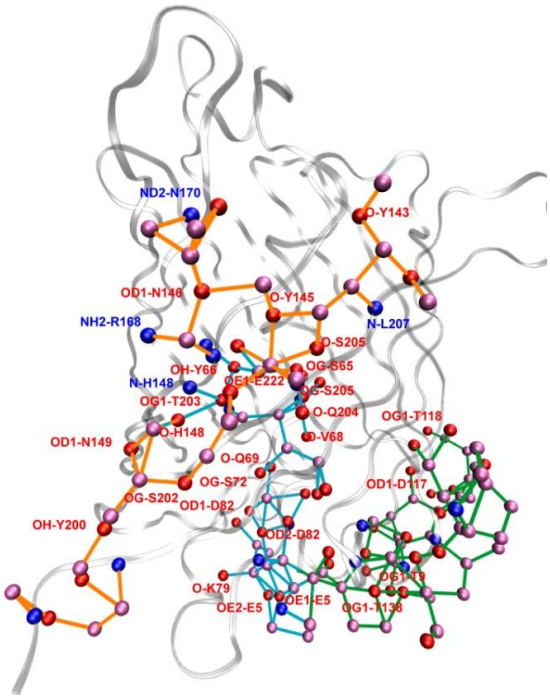

Figure 9: Active-site wire of the GFP sg11 mutant (PDB code: 2WUR). Hydrogen bonds are depicted by colored lines corresponding to their subcluster: entrance, proton collecting antenna (green), internal (cyan), and exit (orange). Atoms participating in the wire are rendered as colored spheres: red, protein oxygen; pink, water oxygen; blue, protein nitrogen.

In the high resolution structure, we see that the one dimensional internal wire inside the GFP barrel continues as a large three dimensional surface cluster. We suggest that this cluster plays the role of a proton collecting antenna of GFP. The surface cluster has a large area touching the external solution and contains polar groups (aspartates, glutamates and threonines) which create a negatively charged patch on the surface for attracting protons. This supports

the mechanism by which the proton leaves the proton interior following irradiation and a new proton is recruited from solution after the returning to the ground state.

(f) Proton wires in DsRed: DsRed is a fluorescent protein from the GFP family sharing the typical beta barrel structure. However, while GFP is monomeric, DsRed is an obligate tetramer, built as a dimer of dimers. Applying the proton wire search over DsRed, we find a wire connecting the active sites of each dimer. The wire is composed of 10 water molecules and can be used to transfer a proton between active sites. The DsRed results are very preliminary and thus we still don't have a suggestion regarding the role of this wire.

FUTURE PLANS

The results so far were based solely on structural data and cannot determine whether a proton is actually transferred through those wires. In order to get one step closer to describing a plausible mechanism for proton transfer inside proteins, our next goal will be to follow the time evolution of those wires. We intend to perform MD simulations of the above mentioned proteins and more specifically:

1. Follow the time dependence of the proton wire map in GFP and DsRed by applying the proton wire search on several 'snapshots' in time during a simulation.
2. Performing free energy calculations over a specific pathway to determine the plausibility of a proton using this pathway.

Other methods that we wish to use:

1. By taking into account the pKa values of amino acid hydrogen bonding groups we'll create a score for each proton transfer step and assess the probability a proton uses a certain path.
2. Side chain rotations can be used as switches for opening/closing of pathways. Such events cannot be described in MD simulations and we'll need to manually combine the proton wire search with the possibility of multiple conformations for selected amino acids side chains.
3. When testing a proposed mechanism for proton transfer, performing point mutations at suspected critical sites can help verify our assumptions. Combining the above mentioned computational methods with experiments via collaboration with experimental groups will be a powerful tool for answering our questions.

Refs: [11, 12] (see Figure 9, our graphic on the cover).

PROFESSOR AGMON'S RECENT GROUP MEMBERS

Name	Status	Presently
Mr. Omer Markovitch	MSc	Doing PhD in Weizmann Inst
Ms. Ai Shinobu	PhD	Current
Dr. Soohyung Park	Postdoc	Postdoc in USA

ACTIVE GRANTS

Project	Period	Foundation	Total Grant
Solvation and migration of protons and hydroxide ions	2008-12	US-Israel Binational Science Foundation	$129,000
Dynamics in water and proton mobility	2009-12	Israel Science Foundation	NIS 465,000

CONFERENCE ORGANIZATION (PAST 3 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, Jan 13-17, 2008.
2	10 Gentner Symposium on "Proton Mobility in Chemical and Biological Systems". Ma`agan Village, Lake

of Galilee, Feb 7-12, 2010. Organizing committee: Noam Agmon (Chair), Shy Arkin, Klaus Gerwert and Helmut Grubmüller. This very successful and high level Minerva symposium supported German-Israel symposium, drew an international crowd from the physical chemistry and biochemistry communities.

AGMON PARTICIPATION IN EDITORIAL AND REVIEW BOARDS

The Israel Journal of Chemistry (until 2009)
PMC Biophysics

ROI BAER

The group is concentrating research efforts in two main directions:

1) Developing new approaches for extending the applicability of density functional theory (DFT) and time-dependent density functional theory.
2) Study of the spectroscopy of metallic and semiconducting nanocrystals and of carbon nanotubes, with emphasis on multiexciton generation and photovoltaics.

DENSITY FUNCTIONAL THEORY (DFT) AND TIME-DEPENDENT DFT (TDDFT)

In this venue we have made several advances:

1) First principles memory functionals for TDDFT. TDDFT is an in-principle exact theory, introduced by Runge and Gross in a seminal paper from 1984. While the theory is exact, practically all applications use adiabatic memory-less functionals. Introducing memory into TDDFT is extremely complicated dues to the symmetry requirements for Galilean covariance and causality. The functionals developed in our group (1-5) were based on known properties of memory in the homogeneous electron gas and had the required symmetries. They are, to our knowledge the only such real-time non-perturbative 3D memory functionals in existence. We applied these functionals to the study of the absorption spectra and high harmonic generation of gold clusters, where showed the effects of memory on the calculations.
   Refs: [13-18]
2) Ehrenfest molecular dynamics within real time TDDFT. We have made two studies of interesting real time dynamics. (a) We studied the energy loss of a hydrogen atom colliding with a metal surface.[19] We found that the usual friction model is not sufficient for explaining the energy loss since some is reversible (6). (b) We studied the D2 Coulomb explosion following exposure to a ultra-strong ultra-short 8fs laser pulse using TDDFT,[20] comparing to recent experiments of the Corkum group[21]. We examined results in adiabatic local density approximation (ALDA) and using a range separated hybrid. We found that these functionals are not accurate enough for quantitative account of the experimental results. (Figure 10).

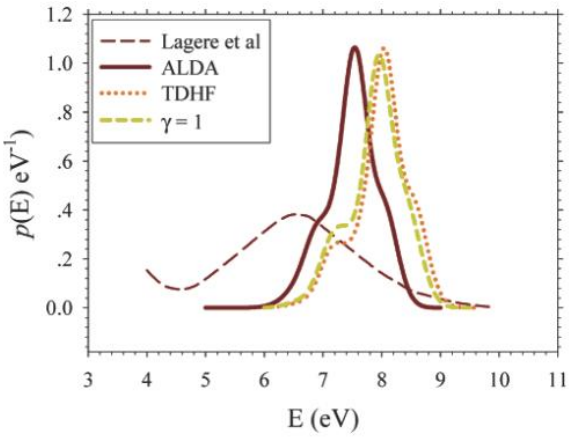

Figure 10: Kinetic energy distribution of deuterium nuclei following Coulomb explosion induced by 8.7 fs $2\times10^{15}\ W/cm^2$ laser pulse. Experiment (dashed, [21]) is compared to Ehrenfest molecular dynamics with electronic dynamics calculated using: adiabatic local density approximation (brown solid line), time-dependent Hartree-Fock (dotted) and RSH (dash-dot). [20]

3) Range-separated hybrids (RSHs). In recent years considerable effort has been invested by several groups into developing RSHs, following the works of Savin and Hirao on the subject[22-24]. Our contributions started in 2005 [25] (with Prof. Daniel Neuhauser, UCLA) when we showed how RSHs can be derived from the adiabatic connection theorem and gave several applications of the

theory. This was followed by a paper showing how range separated hybrids, when applied within DFT and TDDFT eliminate problems of spurious charge sharing between well separated systems in molecular electronics[26, 27]. And a simple RSH, the Baer-Neuhauser-Livshits (BNL) functional was developed.[25, 28] One attractive feature of the RSH is that it is an approach within the *generalized Kohn-Sham* (GKS) approach.[29, 30] This enables RSH to correct for some fundamental deficiencies of the KS theory.

4) First-principles tuning of the RSH range parameter was developed in our group ([28, 30, 31]) and subsequently shown to enable quantitative treatment of a plethora of problems previously thought to be beyond of the scope of DFT/TDDFT:
   (a) Symmetric bi-radical cations: Usual DFT is unable to describe the breaking of even the H_2^+ bond. RSH correct the situation considerably but only our first-principles tuning procedure gives a quantitative description of the asymptotics of H_2^+, He_2^+, Ne_2^+. [31] This method enabled our study of ionization molecular dynamics in water clusters[32] (see exposition of Dr. Ester Livshits below).
   (b) Charge transfer (CT) excitations (see Ms Tamar Stein exposition below); collaboration with Prof. L. Kronik (Weizmann Inst). [33, 34]
   (c) Light harvesting: in donor-acceptor-donor molecules in which thiophenes act as the donors, calculated and measured excitation energies were shown to agree. We predict from theory that by varying the number of thiophenes the energy of the lowest optical absorption can be tuned to the lower end of the optical spectrum, saturating at 1.79 eV for five thiophene rings.[35] Collaboration with Prof. Dr. S. Kümmel (Bayreuth Univ. Germany).
   (d) Ionization potentials (IPs): We found that the range-parameter tuning procedure with the BNL functional allows accurate estimation of IPs in molecules. [36] Collaboration with Prof. Ulrike Salzner (Bilkent, Turkey).
   (e) Fundamental gaps: See Ms Tamar Stein exposition below. Collaboration with Prof. Leeor Kronik (Weizmann Inst.) [37, 38]
   (f) Water cluster ionization dynamics: this system was not treatable using conventional DFT methods. Our tuned RSH approach though is excellently suited for this problem. [32] See report of postdoc Dr. Ester Livshits below.
   (g) Rydberg states have long been considered beyond the scope of TDDFT. RSHs enable improved description of Rydberg states.[24, 28] However, for Benzene for example, this description was still in significant variance with experiment (about 0.5 eV too high). We showed that the first-principles range parameter tuning procedure corrects this discrepancy and accurate description of the Benzene excitations is enabled (see Figure 11) [30].

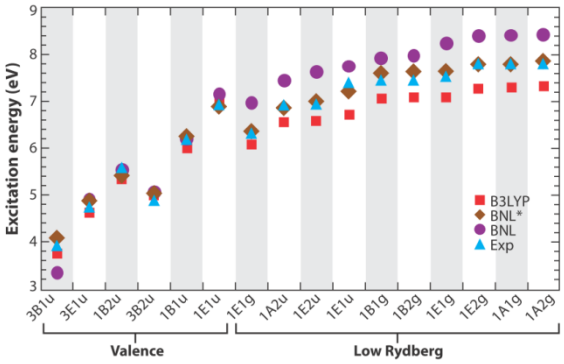

Figure 11: The TDDFT valence and low Rydberg vertical excitation energies (eV) of benzene computed using B3LYP, BNL, and first-principles range parameter tuned BNL (BNL*) compared to experimental measurements (taken from [24]). The basis set is daug-cc-pVTZ. (figure taken from [30]).

   (h) Reaction barriers in aluminum oxidation: oxygen sticking on aluminum surfaces is an activated process. Yet, practically all DFT calculations resulted in barrier-less reaction. We show that the problem is a consequence of the Hartree self-interaction in DFT, resulting in early CT from metal to O_2. Our tuned RSH approach describes such a barrier for the reaction of O_2 and Al_5. [39] Collaboration with Prof. Ronnie Kosloff at our center.

5) We have studied the connection between degeneracies in molecules and in the Kohn-Sham system describing these molecules. We showed that if there is a degeneracy in the molecule the density in the KS system in the "vicinity" of the degeneracy exhibits a "topological scar". [40]

SPECTROSCOPY OF NANOCRYSTALS AND NANOPARTICLES

In recent years we have developed a computational approach enabling to estimate the rate at which biexcitons are formed in nanocrystals and nanotubes following excitation by a photon (see Figure 12). We have shown that nanocrystals have a rather high biexciton generation rate, but currently not high enough to make them useful as efficient solar cells in the optical range of the spectrum. We have also studied, modeled and explained some of the features of the highly efficient multiple electron hole pair generation in carbon nanotube photodiodes, following recent experimental work.[41] These works are done in collaboration with Prof. Eran Rabani from Tel Aviv University. [42-45]

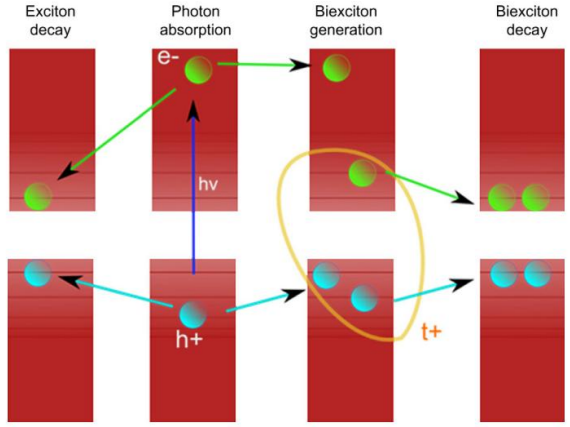

Figure 12: A sketch of the mechanism for biexciton generation in nanostructures. After photon absorption at time t=0 an exciton is formed, which decays to the band edge within $\hbar\gamma^{-1}$ by phonon emission or relaxes/transforms to a resonant biexcitonic state within $\hbar\Gamma_S^{-1}$. This then relaxes to the biexciton band edge (within $\sim\hbar\gamma^{-1}$). In the present example, the excited hole h^+ decays to a positive three-particle entity called a positive trion T^+.

COOPERATION WITH GERMAN SCIENTISTS

The German-Israel Foundation supported a colaboration with Prof. Dr. L. S. Cederbaum from Univ. Heidelberg on electron dynamics using time-dependent density functional theory. In addition, Prof. Baer has co-organized, together with Prof. Dr. Andreas Goerling (Erlangen Univ) and Prof. Dr. EKU Gross (MPI Halle) the 2007 Minerva-Gentner Symposium on time dependent density functional theory.

In the past year, a new cooperation with Prof. Dr. Stephan Kuemmel's group from Univ Bayreuth began with the purpose of studying charge transfer excitations in systems relevant for light harvesting applications using the tuned range-separated hybrid TDDFT. A joint paper, involving the Bayreuth theory group of Prof. Dr. Kuemmel, our group and the experimental group of Prof. Dr. Mukundan Thelakkat (also from Bayreuth univ) was recently submitted for publication. Prof. Dr. Kuemmel has visited our center several times in recent years. In February 2011 Prof. Baer is scheduled to visit his group in Bayreuth. Prof. Baer is scheduled to visit EKU Gross' group in MPI Halle during this trip.

I am a member of the Minerva Fellowship committee, which meets twice a year (once in Germany and once in Israel).

I accepted an invitation by Prof. Dr. Ludwig Hofacker (Muenchen Univ) to edit a special issue on time dependent DFT "Chemical Physics". I asked Prof. Dr. Stephan Kuemmel (Bayreuth Univ) and Prof. Leeor Kronik (Weizmann) to join me as guest editors.

FUTURE RESEARCH PLANS

In DFT: Our group will continue to develop and test our new concept of "tuned" range separated hybrid in DFT and TDDFT. We are currently testing many transition states (see the report of Dr. Livshits below) and we find excellent results with our approach, which is almost parameter-free (!) The method has also been found useful for describing excitations in polyacenes. We have recently found the reason for the failure of TDDFT to describe the La excitations in these systems and we can show why the tuned range separated hybrid solves the problem so well. We hope to be able to explain, using the same theory, the huge polarizability of the oligoacenes. We also plan to expand our research into strong laser-molecule interactions. Here a new approach using adiabatic functionals will be tested (based on our paper of ref. [46]). This work could serve as a basis for extending and widening our collaboration with the Bayreuth group, which has published important work on this topic. We plan to extend the work on electronic degeneracies in DFT by studying specific molecules having known conical intersections.

Spectroscopy of Nanostrctures: We are planning to study the spectroscopy of hybrid systems, such as metal-semiconductor interface in nano-systems. For this we will develop a combined approach capable of describing both the Plasmon and the exciton excitations characterizing these systems, as well as the interaction between them.

INPORTANCE OF THE CENTER FOR MY RESEARCH

The Fritz Haber center provides a unique research environment for my group. This is achieved by important technical services such as the excellent computer and communication facilities maintained by the center and not of lesser import – the scientific activities supported and organized by the center and its members. These include intriguing seminars by world class visitors, scientific meetings and workshops as well as a special atmosphere encouraging fruitful sharing of information and scientific discussions.

This combination of material and "spiritual" offerings by the center considerably inspires and enhances the scientific achievements of my group.

BAERS GROUP STUDENTS REPORTS

DR. ESTER LIVSHITS (POSTDOC)

My main research interest is related to field of density functional theory (DFT) and time-dependent density functional theory (TDDFT) especially on problems related to self-interaction errors (SIEs). In my research I use a new range separated hybrid functional developed in our group that has a correct long-range behavior and as a result can address the SIE problems DFT and TDDFT.

The functional based on splitting density functional γ[n] and the complementary exchange correlation functional $E_{XC}^{\gamma}[n]$, and put these concept to work (the more detailed explanation about the functional on can find at ref[25, 28]). A most important question in this approach is how to determine the range-separation parameter γ. It could be done in two ways: one is semi-empirical, in this case γ is density independent and found by best-fitting to experimental atomization energies and bond lengths of the molecules in the molecular data base G2(1). The second way is a tuning the range separation parameter from first principles (the tuning process is explained in details at ref [33]). The functional with semi-empirical γ will denoted here as BNL functional and functional with tuned γ will be denoted here as BNL* functional. Below I describe several of my projects.

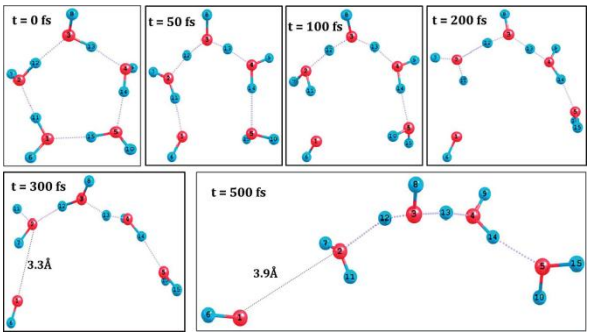

Figure 13: Snapshots of the ab initio molecular dynamics in the water pentamer cluster during the first half a picosecond after ionization. The initial configuration is a ring structure. Within less than 50 fs a proton is transferred from one of the waters to the remaining cluster creating a hydronium and a free hydroxyl radical. [32]

IONIZATION PROCESSES IN WATER CLUSTERS [32]

In this project I checked the quality of the BNL* functional for the water cation dimer and related systems, by comparing to high level wave function methods and experiments, where possible I found that our tuned range parameter BNL* functional is appropriate for describing the electronic structure and the underlying potential surface, including internal barriers, ionization energies, excited state energies and vibrational spectrum of the water dimer cation. Using our method we studied the vibrational and ionization dynamics of the water dimer and pentamer cations (see Figure 13).

The work shows that by addressing the issue of self-repulsion and using the tuning procedure it is possible to improve considerably the range of applications of DFT for systems such as the present, where charge localization is a dominant feature. Using the suggested approach, larger water systems may be accessible for study using DFT approaches.

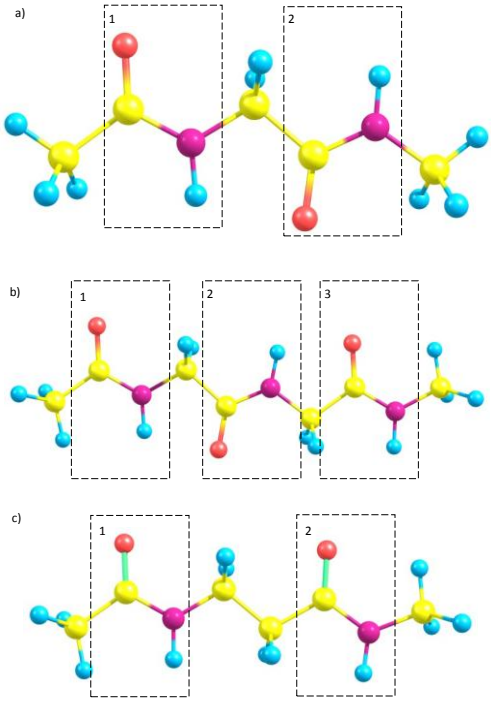

Figure 14: a) dipeptide b) tripeptide and c) β -peptide. The peptide groups are signaled by the dashed squares.

EXCITATIONS IN DI-, TRI- AND β-PEPTIDES

In this project I checked the quality of the BNL* functional to predict the excitation energies of the dipeptide, tripeptide and β-peptide molecules (Figure 14), by comparing to high level wave function method and to several TDDFT methods. Each system has several (two or three) peptide groups. I checked two types of excitations: local ($n \rightarrow \pi$) excitations internal to each peptide group and CT excitations between the peptide groups. I found that our BNL* functional is appropriate for describing excited state energies. Beside of the benchmarking of the functional I investigated the conformational dependence of the electronic spectra. I described the electronic excitations computed for the dipeptide model at the different conformations. The conformers of the dipeptide model are generated by rotation about the angles Φ and Ψ (Ramachandran angles). I am currently resuming this work and it will soon be published.

TRANSITION STATE BARRIERS

In this project I use the saddle method recently developed in our group [47] to investigate the ability of our BNL* functional to predict barrier heights for chemical reactions. Because a chemical reaction involves several species, the main problem is to decide how to tune the parameter γ. In systems involving reactants and products with very different values of γ, the path of the reaction cannot be followed using BNL*. We found that by choosing γ according to the higher energy reactants we are able to describe reaction heights to 2 kcal/mole. Our functional has but a single empirical parameter, so this is an impressive achievement.

Table 1: Best estimate barrier heights for various reactions of different types and the deviance of BNL and BNL DFT functionals (kcal).

System	Height [48]	dev BNL*	dev BNL
$H'+H_2 \leftrightarrow H'H+H$	9.6	-0.2	-4.8
$NH_2+CH_4 \leftrightarrow CH_3+NH_3$	14.5	1	-1.9
$OH+CH_4 \leftrightarrow CH_3+H_2O$	6.7	-0.8	-2.8
$ClH+H \leftrightarrow Cl+H_2$	5.6	0	-4.2
$F+H_2 \leftrightarrow FH+H$	1.8	1.5	
$O+HCl \leftrightarrow OH+Cl$	9.8	2.1	-2.6
$H+ClH \rightarrow HCl+H$	18.0	0.4	-0.2
$CH_3+FCl \rightarrow CH_3F+Cl$	7.4	-1.2	-2.2
$H+OH \rightarrow O+H_2$	10.7	1.4	-3.8
H+ON2→HO+N2	18.1	2.1	-5.0
HNC→HCN	33.1	0.4	1.6
	MAD	1.0	2.9
	MD	0.6	-2.6
	MXAD	2.1	5.0

The reactions I studied are shown in Table 1. I place the reactants as the high energy species. I compare the BNL* and BNL results to known best estimates [48]. I draw two conclusions: 1) the tuning process is essential; 2) the error is smaller for tuning by reactants than by products. This latter result can be explained by the Polanyi rule [49] stating that the electronic structure of the transition state is similar to the higher energy species.

FRITZ HABER CENTER CONTRIBUTION TO MY RESEARCH

I have been studying at the Fritz Haber Research Center for last 10 years. I started as MSc student and now I am a postdoc researcher. From my personal

experience I can assert that my professional development would be difficult (or perhaps even impossible) without the help of talented researchers and warm people who work at the Center. Among the scientific articles that I read, I often find the peer works published by the Center's groups. I realize the great contribution of our scientists to science progress in various areas from biology to physics. Beside of that, the collaboration with different research groups is magnificent that is, in my opinion, crucial for good professional study and social atmosphere. A special appreciation I want to give to the administrative staff of the Center, without their very professional and quick response my personal research and the research of any other group was impossible. I think that the strength of the Fritz Haber Center is in cooperation between the researchers, the good supported computer system and wonderful people with whom I very enjoy to work and learn. I am very proud to be an active part of one of the best theoretical chemistry research centers in the world!

MS. TAMAR STEIN (GRADUATE STUDENT)

Density functional theory (DFT) has become in the last years one of the popular and widely used method in quantum chemistry. It is formally an exact theory, its accuracy and the fact that it is relatively fast makes it very appealing for applications in variety of fields such as chemistry, condensed matter physics and biology. Time-dependent DFT (TDDFT), the extension of DFT for time-dependent problems, gives access to excited states and dynamical electronic processes, needed for molecular spectroscopy and photochemistry, intense lasers and molecular electronics. Despite the great success of DFT/TDDFT, the local and semi-local approximations for the exchange correlation functional introduce severe systematic errors when used for calculations of properties other than ground state energy, such as static or dynamical response properties. Many popular approximations to DFT often lead to unacceptably large errors or even wrong physical behavior. Much attention has been drawn in the recent years to the difficulty to describe charge transfer (CT) excitations. The inability of TDDFT within the local/semilocal approximations to qualitatively describe CT excitations is due to the fact that in the adiabatic TDDFT equations, the correct 1/R asymptotics cannot be realized. This is the first problem. TDDFT linear response equation reveals that in order to describe CT excitations there is a second condition that must be satisfied, namely that the orbital LUMO-HOMO gap $\varepsilon_L - \varepsilon_H$ must be equal to the fundamental gap $IP - EA$, where IP is the ionization potential and EA the electron affinity. In exact KS theory we have the IP theorem [50] $IP = -\varepsilon_H$. So we are left with the requirement$EA =$ ment$EA = -\varepsilon_L$. But this condition does not generally hold for KS DFT, due to the derivative discontinuity in the potential! This is the second problem in describing charge transfer excitations within TDDFT.

In my research I focus on developing methods to describe CT excitations within TDDFT. In order to achieve this, I use the BNL functional[25, 28], a RSH functional that has the correct long-range 1/r asymptotic behavior - a key issue for describing CT excitations. In RSHs, there is a free parameter, γ which, in principle is also a functional of the density[25]. We have constructed physically motivated first principles ways to tune this range separation parameter in such a way that reliable prediction of CT excitations can be made for a broad variety of molecular systems. The tuning procedure is based on the IP theorem and this condition can be used to select γ.[28] We found that in order to mitigate the derivative discontinuity, we need to use the IP theorem not only for the neutral species but also for the anionic one (where charge is located on the acceptor). This yields a first principles method that computes CT excitations to good accuracy for molecular complexes involving an aromatic donor and TCNE acceptor[33]. See Table 2.

Table 2: Comparison of theoretical excitation energies (TDB3LYP, TDBNL and TDBNL*) and experimental gas phase results for molecular complexes composed of an aromatic donor and a TCNE acceptor. Energies in eV.

Ar	B3LYP		BNL	BNL γ*			Exp[51]	
	E	F	γ=0.5	γ*	E	F	E	f
Benzene	2.1	0.03	4.4	0.33	3.8	0.03	3.59	0.02
Toluene	1.8	0.04	4.0	0.32	3.4	0.03	3.36	0.03
oXylene	1.5	~0	3.7	0.31	3.0	0.01	3.15	0.05
Naphthalene	0.9	~0	3.3	0.32	2.7	~0	2.60	0.01

We have also tested our approach for a series of coumarin dyes,[34] materials that lately draw much attention being promising candidates for dye sensi-

tized solar cells. In the coumarin dyes, the charge transfer is intra molecular, which raise the question how to apply the tuning procedure for cases were the donor and the acceptor are not different species as in the aromatic donor –TCNE acceptor example presented above. We have tested different modifications for the tuning procedure, all ab-initio physically motivated, that led to excellent results compared to recently published wave function-based results.[52]

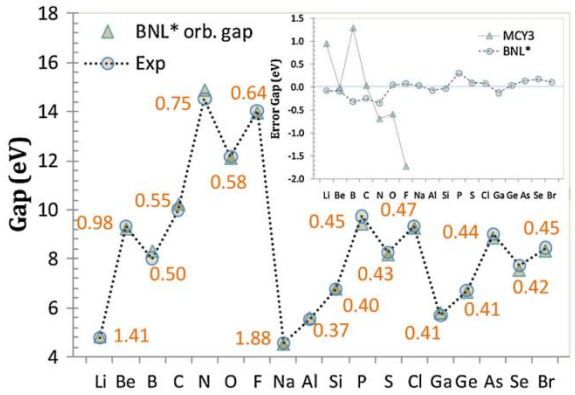

Figure 15: BNL* HOMO-LUMO gaps (aug-cc-pVTZ basis set), compared with experimental fundamental gaps. The value of the range parameter, tuned from first principles is indicated near each point. Inset: the deviation from experiment of GKS HOMO-LUMO gaps based on BNL* (this work) and MCY3[53].

In generalized KS approach, the eigenvalue gaps are shown to incorporate part of the discontinuity of the exchange-correlation potential of standard KS theory.[29] Our results on the tuning procedure for CT calculations showed that the derivative discontinuity can be made negligibly small. This is very important since it can enables calculation of band gaps which cannot be achieved with KS theory. We have tested and demonstrated the validity, accuracy, and advantages of this approach on first, second and third row atoms (shown in Figure 15) and on the oligoacene family of molecules, and a set of hydrogen-passivated silicon nanocrystals. [38]

CONTRIBUTION OF THE FRITZ HABER CENTER TO MY RESEARCH

The Fritz Haber center for molecular dynamics is a lively, vibrant and intimate center, creating an atmosphere filled with scientific creativity. The center's researchers are experts in a variety of fields of theoretical chemistry, which gives excellent opportunity to learn, and form a fertile ground for new ideas. Weekly seminars being held at the center, expose us to scientific activity from all over the world, opening doors for collaborations and exciting new discoveries. The center provides computers and resources, that have speed up significantly my research progress and enabled me to work on large systems that otherwise I wouldn't been able to work on. In addition, the center has excellent administrative staff, which helps us solve myriads of technical issues enabling us to concentrate more on our research.

PROFESSOR BAER'S RECENT GROUP MEMBERS

Name	Status	Presently
Dr. Shlomi Pistiner	Sabbatical	Soreq Nuclear Research Center
Dr. Yardena Bohbot	Sabbatical	Biological Institute, Nes Ziona
Dr. Eyal Fattal	Sabbatical	Biological Institute, Nes Ziona
Dr. Recca Granot	PhD	Senior Scientist, Dead Sea Industries Research Center
Dr. Ester Livshits	PhD	Postdoc, HUJI
Dr. Oded Hod	PhD	Senior Lecturer, School of Chemistry Tel Aviv University
Dr. Yair Kurzweil	Postdoc	Senior Researcher, Nuclear Research Center, Negev
Dr. Helen Eisenberg	Postdoc	Current
Shlomit Jacobi	PhD	Current
Yael Cytter	MSc	Current
Rotem Levi	Undergrad	2nd year student
Omri Buchman	PhD	Current
Adva Baratz	PhD	Current
Tamar Stein	PhD	Current

PROFESSOR BAER'S SCIENTIFIC COLLABORATIONS

Name	Institution
Prof. Leeor Kronik	Material, Weizmann Institute
Prof. Stephan Kuemmel	Physics, Bayreuth University, Germany
Prof. Daniel Neuhauser	Chemistry, UCLA
Prof. Eran Rabani	Chemistry, Tel Aviv University
Prof. Ulrike Salzner	Chemistry, Bilkent University
Dr. Nathan Argaman	Physics, Nuclear Research Center Negev

ACTIVE GRANTS

Project	Period	Foundation	Total Grant
Conical Intersections using Density Functional Theory	**2009-2012**	Israel Science Foundation	$230,000
Density Functional Theory With Correct Long Range Behavior	2009-2012	US-Israel Binational Science Foundation	$88,000
TDDFT	2009	Army research Lab (ARL, Washington)	$20,000
Helium diffusion in diamond	2009	Israel Atomic Energy Commission	$20,000

CONFERENCE ORGANIZATION (PAST 3 YEARS)

No.	Conference
1	The Fritz Haber Symposium on Conductance Yad Hashmona, 2007.
2	Safed Summer school on density functional theory (L. Kronik, R. Baer, E. Rabani), 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., EKU Gross (Frei Univ. Berlin) and A. Goerling (Univ Erlangen)
4	The Fritz Haber Symposium Kibbutz Tsuba, 2009.
5	Victoria Buch Symposium 2010

EDITORIAL AND REVIEW BOARDS

- Physical Chemistry Chemical Physics (2006-7)
- Minerva Fellowship Committee (2009-)
- Annual Reviews of Physical Chemistry (2010-)
- Guest editor Chemical Physics (TDDFT)
- Guest editor PCCP (molecular conductance)

AVINOAM BEN-SHAUL

Our research in recent years has dealt with biophysical phenomena and systems involving length scales which range from the molecular to the multicellular level. Until about two-three years ago, considerable effort has been devoted to the study of membrane-protein interactions. For example, with the graduate student (now Dr.) Assaf Zemel, and (the former Minerva postdoctoral fellow from Jena) Professor Sylvio May, we wrote several articles analyzing the structure, energetics, and elasticity of lipid membranes interacting with amphipathic (e.g., anti-microbial) peptides, as well as with integral peptides. With Sylvio we have also studied such phenomena like the macroion-induced phase separation in membranes due to peripherally adsorbed charged proteins. Another graduate student, (now Dr.) Yifat Brill-Karnielly has been studying the kinetics and thermodynamics of actin polymerization and filament branching in the context of cell locomotion and the lamellipodium to filopodia transition.

Another major project has been concerned with the theoretical modeling of the "electrostatic switch mechanism" involving the MARCKS protein, which is implicated in a wide variety of signal transduction processes. In this work, which has been carried out by the graduate student (now Dr.) Shelly Tzlil, (and

partly by the part time postdoc Vladimir Teif) we have analyzed the entropic and energetic-electrostatic contributions involved in the adsorption of the naturally unfolded MARCKS protein onto lipid membranes containing monovalent (PS) and tri-valet (PIP2) lipids. Taking into account lipid mobility and the details of electrostatic interactions and chain conformational entropies we have demonstrated the dramatic enrichment by charged (especially trivalent) lipids of the adsorption zone. To model this complicated system Shelly Tzlil has developed a sophisticated simulation method (extended version of the Rosenbluth sampling algorithm) enabling the simultaneous modeling of protein configurational dynamics and lipid mobility. A snapshot from this simulation, describing a coarse-grained MARCKS model adsorbing on a mixed lipid membrane is shown in Figure 16.

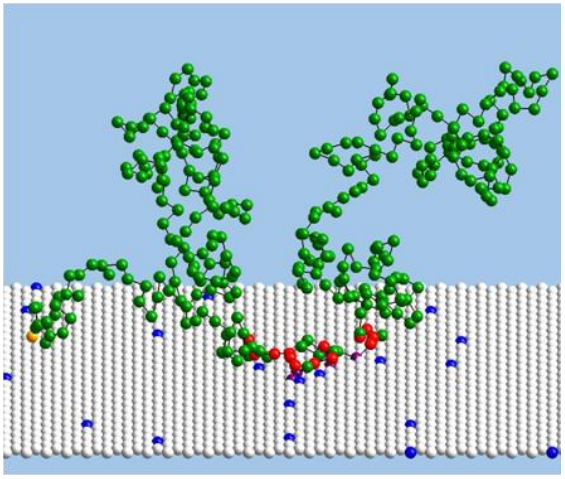

Figure 16: A typical snapshot of the MARCKS protein model, demonstrating the extended configurations of the long "tail" and "loop" domains, as distinguished from the membrane bound central basic domain. Green and red spheres represent here neutral and positively charged amino acids, respectively. The myristoyl anchor is represented by a yellow sphere. PIP2, PS and PC lipids are represented by blue, purple and white spheres, respectively.

The first part of Dr. Tzlil's PhD thesis has been concerned with the physico-chemical mechanisms of DNA packaging in the protein capsid of bacteriophages (i.e., bacterial viruses), and the inverse process of DNA injection into the cell. Our work on this topic, which has been carried out in collaboration with the group of Professor Bill Gelbart from UCLA, provided the first theory and calculation of the pressures and forces involved in the above processes. Our predicted results have shown excellent agreement with experimental studies independently published around the same time. In our work we have also predicted that increased osmotic pressure in the ambient solvent can inhibit genome ejection. This prediction has stimulated a series of experimental studies (at UCLA and elsewhere) revealing quantitative agreement with our theoretical predictions.

In recent three years our research has focused on two major directions. The first is concerned with viral structure, assembly and energetics, yet the emphasis has been shifted from bacteriophages to animal and plant viruses, primarily viruses whose genomic material is RNA. Single-stranded RNA (ssRNA) in these viruses is less densely packed than (the extremely densely packed) dsDNA in bacteriophages, yet viral RNA appears to be more compact than ssRNA in solution. In several recent papers on this topic – jointly published with professor Gelbart and his group members (see our 2008 – 2010 publication list) we have analyzed various aspects of ssRNA structure, size and energetics, in bulk solution vs. the confines of viral capsids.

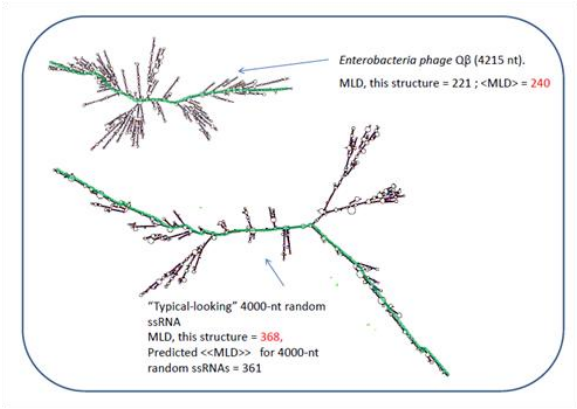

Figure 17: Secondary structures of viral and random sequences of comparable-length. The viral sequence appears more compact. The maximum ladder distances of the two structures, here colored green, indicate the paths crossing the maximal number of base pairs between any two bases of the structure.

Based on detailed analyses of hundreds of viral and non-viral RNAs secondary structures we have shown, for example, that the average ladder distance of viral RNA is consistently smaller than that of random RNAs, (Yoffe et al, PNAS 2008). Mapping the maximum ladder distance into a linear polymer model we have argued that this difference applies to the spatial

dimensions as well; see Figure 17. In a yet unpublished work we have demonstrated this viral vs. non-viral RNA disparity based on their respective radii of gyration, calculated using Kramers theorem. In another paper we have explained why the two ends of ssRNA area always necessarily close (Yoffe et al NAR, 2010). In another, more recent, article we proposed a simple model for RNA folding, explaining why the average fraction and average duplex length is asymptotically independent of sequence length (L. T. Fang et. al, submitted).

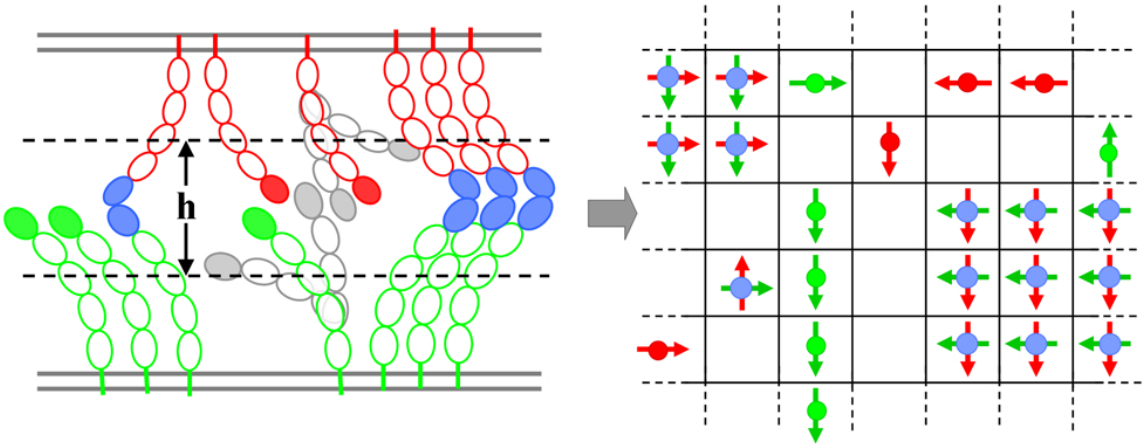

Figure 18: A. Schematic illustration of two interacting cadherin-decorated membranes. The EC1 domains are labeled by solid ellipses – green for cadherins in the lower membrane and red for those at the top layer. If apposed domains form a trans dimer they are labeled solid blue. Hollow ellipses label the EC2-EC5 domains. The grey "ghosts" molecules illustrate alternative configurations, all within the interaction shell of thickness h. B. The 2D square lattice, corresponding schematically to a top view on the interaction shell. "Top" (red) and "bottom" (green) EC1s do not interact with each other and move independently on the lattice, except when they happen to occupy the same lattice site (i.e., they are on top of each other as in A), in which case they can form a trans dimer (larger, blue, circle). The lateral (cis) interactions between the three species are described in the text.

Our second major research field in recent year is concerned with cell-cell adhesion; primarily inter-cell adhesion mediated by cadherin proteins. Cadherins are composed of several (typically five or more) ectodomains (i.e., extra-cellular domains); the outermost sub-domain, usually labeled EC1, mediates binding, by forming a trans-dimer with the EC1 of a cadherin molecule anchored to the membrane of another cell. The cells of many tissues (e.g., embryonic and epithelial tissues) are covered typically by 104-105 cadherin molecules. When two cell membranes face each other, a fraction of their respective cadherins forms trans dimers with each other, by a mechanism known a domain swapping. The number of trans dimers formed depends on the total concentration of cadherins and their binding energies. Figure 18 illustrates schematically two adhering membranes due to trans dimers formed between cadherins decorating the apposed surfaces.

The exctodomains of the adhesive molecules are connected to a trans-membrane domain, which in the cytosolic part is bound to a protein complex mediating its binding to either the actin cytoskeleton or to intermediate filaments. The cadherins are laterally mobile, and can interact with each other to form cis-dimers, either between monomeric cadherins or between trans-dimers. If the lateral interaction is strong enough they can cluster to form an intercellular "junction". We have recently proposed a model describing this process as a two-dimensional phase transition of trans-dimers, involving an intricate interplay between cis and trans interactions (Wu et al, PNAS 2010); see Figure 18.

While working on our model for junction formation we have realized that the interaction free energies between cadherins (both cis and trans interactions) are not identical to those measured in 3D solution, where direct measurements of cadherin binding affinities are measured. There is a need for a "renormalization" of the binding free energies because the entropy losses upon binding in 2D and 3D are markedly different, and the difference is sizeable com-

pared to the overall binding affinities. Qualitatively, the 2D affinities are about one half than those measured in 3D. A paper summarizing these results has recently been submitted (Wu et al, submitted). To calculate the entropic contributions we have carried out a combined Monte Carlo–Molecular Dynamics simulation of cadherin dynamics and structure (see Figure 19) and the results have been incorporated into a statistical-thermodynamic modeling scheme of junction formation.

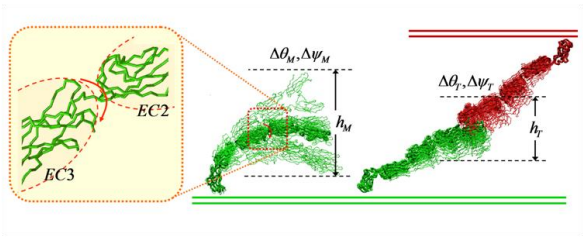

Figure 19: Monte-Carlo simulations of the flexibility of the cadherin ectodomain. The rotations of the EC5 domain with respect to the membrane plane depend on the three Euler angles, φ , ψ and θ of that domain, as shown in the upper left panel. The inter-domain hinge motion indicated by a red arrow is 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, Δψ and Δθ 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.

FUTURE PLANS

Our work in the near future will continue along the same two research directions outlined above, namely: 1) Physical chemistry of viral systems, with emphasis on genome structure, energetics, and packaging. 2) Multi-scale modeling of membrane adhesion, inter-cellular junctions, and tissue development. Several projects, in both fields are in progress, some are nearing completion. The list below outlines very briefly some of the questions of interest.

Viruses, RNA and DNA:

- Developing a theory for the 3D structure of ssRNA based on mapping the secondary structure into a tree graph and using Kramers theorem to calculate the radius of gyration.
- Using Molecular Dynamics simulations of coarse-grained RNA models to calculate the flexibilities of ss loops of different degrees (i.e., number of emanating duplexes of base pairs) and sizes. Subsequently, we shall use these results to calculate the 3D structures of viral and non-viral RNAs.
- Modeling viroids and dsDNA animal viruses.

Cadherins, cell-cell adhesion and tissue development:

- Combined Molecular Dynamics and Monte Carlo simulations of cadherin motion and dimerization in the presence and absence of calcium ions. Our preliminary calculations show, in agreement with experiment, that the rigidification of the cadherin ectodomain by calcium ions indeed plays a crucial role in mediating trans cadherin binding.
- Comprehensive statistical-thermodynamic formulation of the 3D-2D renormalization.
- Simulating multi-cell behavior, cell segregation in cell mixtures and tissue evolution.

COLLABORATION WITH GERMAN SCIENTISTS

Many years ago, I learned from Professor Kompa and his group in the Max Planck institute for quantum optics how chemical lasers work. In the 1970s we published several papers on the topics, culminating with the publication of a book “Lasers and Chemical Change” (ABS, Y. Haas, K. L. Kompa and R. D. Levine; Springer 1982). In the 1980s I have continued collaborating with professor Kompa and Dr. Frank Rebentrost from the MPI for quantum optics on several topics besides chemical lasers, e.g., multiphoton ionization and fragmentation of molecules, and the kinetics-thermodynamics of catalytic reactions on metal surfaces. In the 1980 I have also started working on the statistical thermodynamics of self-assembling and biophysical systems. Much of my work on these systems, primarily bio-membranes, membrane-protein interactions, cell-cell adhesion and actin polymerization, has been inspired, motivated and encouraged by frequent discussions with Professor Erich Sackmann from the TU Munich. I have visited him many times, including long stays during his group retreats in the ustrian-Italian Alps. We have also attended many joint meetings, including for instance his special lecture in a symposium organized for my 65th birthday in 2008 in Jerusalem, and my lecture in the big and impressive meeting in Croatia in 2009 (by the former students of Professor Sackmann to honor and

celebrate his 75th birthday. We keep close ties till these very days.

Two younger collaborators with whom I published articles in various forums are Professor Joachim Raedler from LMU-Munich, with whom we published a joint theoretical-experimental paper on the entropically-driven release of counterions during the macroscopic condensation of two oppositely charged macroions. I have especially benefited from and enjoyed very much my long lasting, and exceptionally fruitful, collaboration with Dr. Sylvio May, who started working with me as a Minerva graduate student in the mid 1990s and later as a Minerva postdoc for two years here I Jerusalem. We have published many papers together on a variety of biophysical problems. We continue collaborating, though less frequently, these days as well.

PROFESSORS BEN-SHAUL'S GROUP

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
Biopolymers Interacting with Mobile Surface Charges	2006-2010	Israel Science Foundation	~$150,000

EDITORIAL BOARDS, PRIZES

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

VICTORIA BUCH 1954-2009

Professor Buch has passed away on 21 June 2009 following a heroic struggle with a deadly cancer disease. Despite her deteriorating health condition, Victoria Buch worked relentlessly, practically up to the very last day, on finalizing her last scientific contributions. Since her scientific work as a member of the center covered almost all the review years (some of her last papers were published in 2010) we include her contributions and give here her last submitted research report.

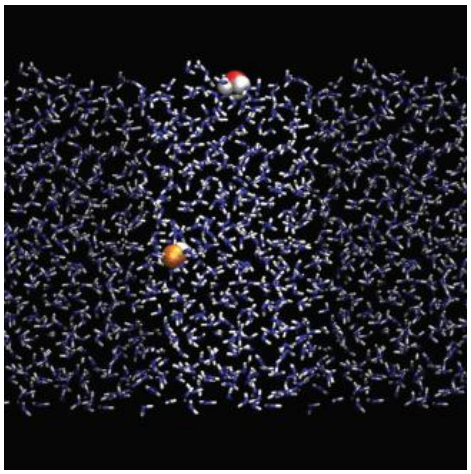

Figure 20: A typical snapshot from a molecular dynamics simulation depicting a surface bound H_3O^+ (red and white) and bulk OH^- (orange and white) in an aqueous slab (blue and white). The two neighboring periodic images of the solvent next to the unit cell are also depicted (shaded representation).

WATER SURFACE IS ACIDIC

Water autoionization reaction $2H_2O \rightarrow H_3O^- + OH^-$ is a textbook process of basic importance, resulting in pH = 7 for pure water. However, pH of pure water surface is shown to be significantly lower, the reduction being caused by proton stabilization at the surface. The evidence presented here includes ab initio and classical molecular dynamics simulations of water slabs with solvated $H3O^+$ and OH^- ions, density functional studies of $(H_2O)_{48}H^+$ clusters, and spectroscopic isotopic-exchange data for D_2O substitutional impurities at the surface and in the interior of ice nanocrystals. Because H_3O^+ does, but OH^- does not, display preference for surface sites, the H_2O surface is predicted to be acidic with pH < 4.8. For similar reasons, the strength of some weak acids, such as carbonic acid, is expected to increase at the surface. Enhanced surface acidity can have a significant impact on aqueous surface chemistry, e.g., in the atmosphere.

Based on molecular computational and experimental evidence we have shown that the surface of neat water is acidic with pH 4.8 because of a significant surface propensity of hydronium (but not hydroxide) ions. By argument analogous to our results for neat water, weak acid solutions can display enhanced surface acidity, i.e., surface pH reduction by at least 2.2 units, corresponding to ΔG_{sb}> 3 kcal/mol of hydrated protons. [Note that pKa of the acid is not necessarily reduced by the same extent, being affected additionally by ΔG_{sb} values of the neutral acid and the negative ion]. The case of carbonic acid is of particular interest. Under normal atmospheric conditions, bulk water exposed to the air acquires a pH of 5.7 because some of the dissolved CO_2 gas undergoes a reaction $CO_2 + 2\ H_2O \rightarrow H_3O^+ + HCO_3^-$. At the surface, pH will be reduced more significantly than in the bulk, because of surface propensity of hydronium ions. Enhanced acidity of water surface can have a significant impact on aqueous surface chemistry in natural atmospheric environments, cloud nucleation, thundercloud electrification, and electrochemistry (e.g., corrosion processes).

The present results contradict previous microscopic interpretation proposed for macroscopic titration experiments and zeta potential measurements on oil emulsions and gas bubbles in water, indicating negatively charged surfaces. It was proposed that this effect is caused by a substantial surface propensity of OH^- and lack thereof for $H3O^+$. The existing controversy between molecular simulations and spectroscopic experiments on one side and macroscopic measurements on the other side, cannot be fully resolved at present. Refs: [54, 55]

ELUSIVE STRUCTURE OF HCL MONOHYDRATE

The study addresses the structure of crystalline HCl monohydrate which is composed of H3O+ and Cl-. The published x-ray diffraction patterns indicate an element of disorder, the nature of which is debated in the literature. The computational investigations include searches for alternative crystal structures employing an empirical potential, and on-the-fly simulations as implemented in the density functional code QUICKSTEP employing Gaussian basis sets. The experimental work focuses on Fourier-transform infrared (FTIR) spectra of crystal nanoparticles. Simulations of FTIR spectra and of the x-ray diffraction patterns are consistent with crystal monohydrate structure composed of ferroelectric domains, joined by "boundary tissue" of antiferroelectric structure.

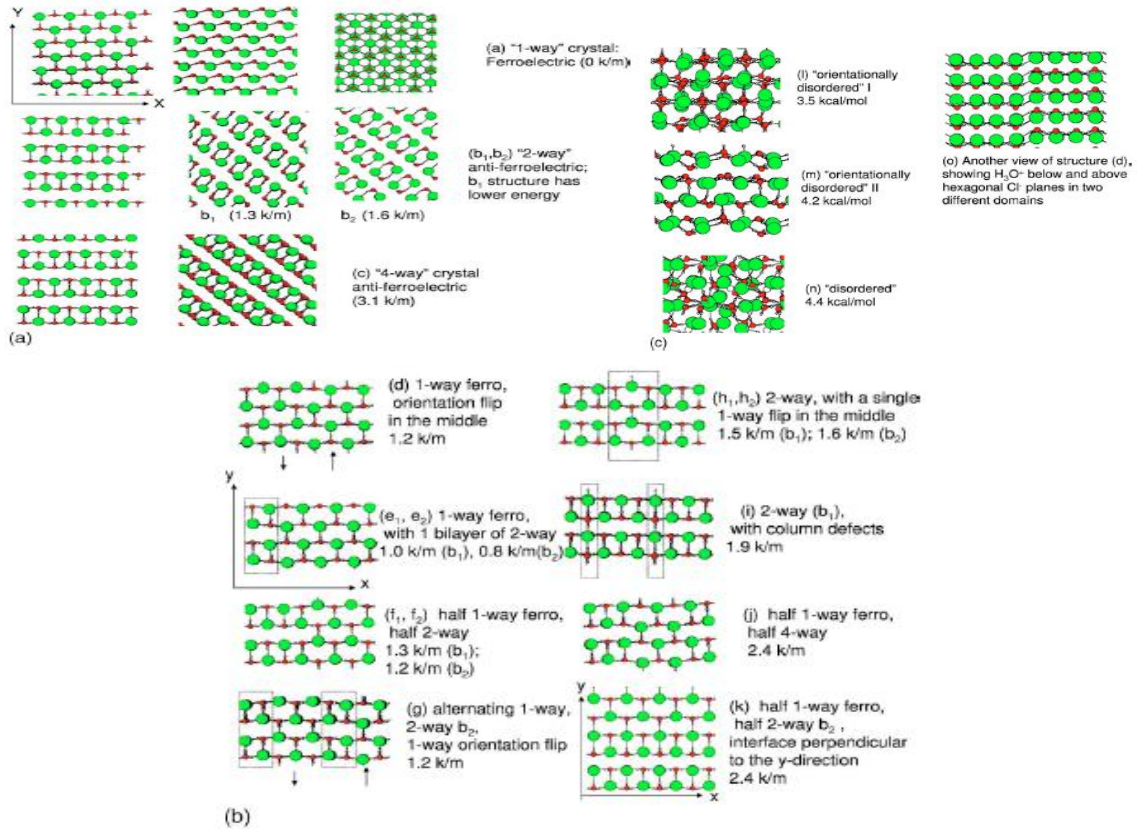

Figure 21: Monohydrate models examined in this study. Models (a),(b), (c), (i), (l), (m), and (n) employed a unit cell with 60 atoms/12 formula units. The remaining models correspond to a unit cell with 120 atoms/24 formula units. For the graphic display, the models were further expanded, using periodic boundaries. The energies are given in kcal/(mol formula units), for metallic boundary conditions which cancel the surface contributions that raise the energy of ferroelectric structures. The energy of the ferroelectric structure (a) is taken as zero. Structures (a)-(c) are shown from several different points of view. Some of the structures were obtained in the MD crystal structure search, employing an empirical potential; others were generated manually; see text. All the structures were reminimized using QUICKSTEP on the BLYP level, in the DZVP basis.

Searches for alternative crystal structures yielded a number of antiferroelectric models, with Cl^- frame similar to that derived from x-ray diffraction. Still, the best agreement between the computations and the experimental data (the diffraction patterns and the IR spectra) was obtained for the original ferroelectric structure, which thus appears to be a dominant component of the crystal. The presence of distinct hydronium orientations is proposed to be due to presence of ferroelectric domains whose dipoles cancel. Such domains commonly occur in ferroelectric substances; in absence of domains, macroscopic dipole would raise substantially the energy of the material. It is shown here that different domains can be accommodated in a continuous Cl^- frame at a modest energy cost. One of the new anti-ferroelectric models appears to serve as a boundary tissue connecting the different domains. In addition, this study revealed strikingly anharmonic vibrational dynamics of the monohydrate system. Refs: [56].

SUM FREQUENCY GENERATION SURFACE SPECTRA OF ICE, WATER, AND ACID SOLUTION INVESTIGATED BY AN EXCITON MODEL

We developed a new computational scheme for calculation of sum frequency generation (SFG) spectra, based on the exciton model for OH bonds. The scheme is applied to unified analysis of the SFG spectra in the OH-stretch region of the surfaces of ice, liquid water, and acid solution. A significant role of intermolecularly coupled collective modes is pointed out. SFG intensity amplification observed for acid solutions in the H-bonded OH-stretch region is repro-

duced qualitatively and accounted for by enhanced orientational preference “into the surface” of the H_2O bisectors within the hydronium solvation shell. Refs: [57, 58]

HCL HYDRATES AS MODEL SYSTEMS FOR PROTONATED WATER

Ab initio molecular dynamics simulations are presented of vibrational dynamics and spectra of crystal HCl hydrates. Depending on the composition, the hydrates include distinct protonated water forms, which in their equilibrium structures approximate either the Eigen ion $H_3O^+(H_2O)_{(3)}$ (in the hexahydrate) or the Zundel H_2O H^+OH_2 ion (in the di- and trihydrate). Thus, the hydrates offer the opportunity to study spectra and dynamics of distinct species of protonated water trapped in a semirigid solvating environment. The experimentally measured spectra are reproduced quite well by BLYP/DZVP-level calculations employing Fourier transform of the system dipole. The large overall width (800-1000 $cm^{(-1)}$) of structured proton bands reflects a broad range of solvating environments generated by crystal vibrations. The aqueous HCl solution was also examined in search of an objective criterion for separating the contributions of "Zundel-like" and "Eigen-like" protonated forms. It is suggested that no such criterion exists since distributions of proton-related structural properties appear continuous and unimodal. Dipole derivatives with respect to OH and OH^+ stretches in water and protonated water were also investigated to advance the understanding of the corresponding IR intensities. The effects of H bonding and solvation on the intensities were analyzed with the help of the Wannier centers' representation of electron density. Refs: [59].

AT THE WATER'S EDGE: NITRIC ACID AS A WEAK ACID

Nitric acid plays a role in many important chemical processes that happen in our environment, often at surfaces where less is known about its reactive behavior. Recent studies have shown that undissociated nitric acid is present on the surface of a nitric acid solution. Using ab initio molecular dynamics simulations (Figure 22), we show that a nitric acid molecule present on an aqueous solution surface structures and orients in a way that significantly reduces its ability to be the strong dissociating acid that it is in aqueous solution. Hydrogen bonding to surface solvating water molecules plays a key role in this altered molecular behavior. Refs: [60]

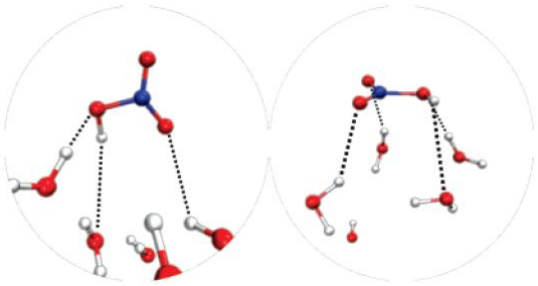

Figure 22: Snapshot of the initial configurations of surface nitric acid molecules that were used in the surface trajectories. In one trajectory, the nitric acid molecular plane, containing the three NO bonds, was initially placed perpendicular to the surface (left) and the second trajectory (right) with its molecular plane initially parallel to the water surface plane.

PROTON ORDER IN THE ICE CRYSTAL SURFACE

The physics of the ice crystal surface and its interaction with adsorbates are not only of fundamental interest but also of considerable importance to terrestrial and planetary chemistry. Yet the atomic-level structure of even the pristine ice surface at low temperature is still far from well understood. This computational study focuses on the pattern of dangling H and dangling 0 (lone pairs) atoms at the basal ice surface. Dangling atoms serve as binding sites for adsorbates capable of hydrogen-and electrostatic bonding. Extension of the well known orientational disorder ("proton disorder") of bulk crystal ice to the surface would naturally suggest a disordered dangling atom pattern; however, extensive computer simulations employing two different empirical potentials indicate significant free energy preference for a striped phase with alternating rows of dangling H and dangling O atoms, as suggested long ago by Fletcher [Fletcher NH (1992) Philos Mag 66:109-115]. The presence of striped phase domains within the basal surface is consistent with the hitherto unexplained minor fractional peaks in the helium diffraction pattern observed 10 years ago. Compared with the disordered model, the striped model yields improved agreement between computations and experimental

ppp-polarized sum frequency generation spectra. Refs: [61].

ROBERT B. GERBER

The research highlights of my group in the last 5 years are in the following areas: (1) Mechanisms and rates of atmospheric reactions; (2) Vibrational spectroscopy and conformer structures of biological molecules; (3) New molecules of the noble gases and their properties; (4) Photochemistry and photo-induced dynamics of molecules in cryogenic solids.

SCIENTIFIC PROJECTS

MECHANISMS AND RATES OF ATMOSPHERIC REACTIONS

The objective of our work in this field is to throw light, by dynamics simulations, on the presently unknown mechanisms and timescales of important atmospheric reactions. The approach we have taken involved Molecular Dynamics carried out directly for potential surfaces from suitable electronic structure methods. Several algorithmic innovations were introduced by us for relevant cases, e.g., adaptation of high-level MP2 ab initio potentials for dynamics of relatively large systems.

One of the most interesting results obtained is the demonstration that contact with a single water molecule induces ionization of (asymmetric) N_2O_4 to an ion pair $(NO^+)(N_3^-)$, which happens on a timescale of several picoseconds, and the process is accelerated to the femtosecond range for a larger number of water molecules. This result settles a significant, debated issue on the hydrolysis mechanism of NOx species. It was published as a cover article in JACS.[62]

A second highlight result in this field deals with the formation mechanism of ClNO, a major source of atomic chlorine in the atmosphere. In joint research with the experimental group of B.J. Finlayson-Pitts, it was shown that the reaction of HCl with N2O4, when taking place in contact with water, provide an efficient route for ClNO formation. A single water molecule suffices in principle to catalyze the process to an extent that this emerges as the likely dominant mechanism for ClNO formation. This result was recently published as a cover article in PNAS.[63]

Figure 23: Dynamics of ionization of (asymmetric) N_2O_4 in contact with water. (cover figure from ref. [62])

Another highlight result is on the interesting topic of photochemistry on ice particles. We studied the dynamics of photoinduced chemistry of the peroxide CH3OOH on an ice cluster, which is of atmospheric relevance. Our modeling of the process was based on the assumption that very shortly after excitation, the system converts to the electronic ground state, thus creating a vibrationally highly excited species on the ice particle. The dynamics simulations yielded the interesting and surprising result that the consequence of the excitation as to give a rise to a large sequence of chemical reactions, and to about 10 major different products, obtained on an ultrafast timescale. The result, supported by experimental evidence, substantially changes the state of knowledge and understanding of photoinduced reactions on ice,

primarily by showing that the chemistry that is involved even for a small organic peroxide is much richer than has been thought. A paper describing this result was published in PNAS.[64]

VIBRATIONAL SPECTROSCOPY AND COMFORMER STRUCTURE OF BIOLOGICAL MOLECULES

The highlights of our recent work on this topic are twofold: (a) We developed a powerful, much improved algorithm for anharmonic vibrational spectroscopy calculations of large molecules. The result is for the VSCF-PT2 (Vibrational Self-Consistent Field, corrected by second order perturbation theory), a method developed by our group, that is used in a substantial number of laboratories. The new algorithm development improves the scaling of the computational effort of VSCF-PT2 by a factor of N3 for large N, where N is the number of vibrational modes.[65] The new algorithm is already implemented in GAMESS, a major molecular suit of programs. It greatly extends the size range of molecules for which anharmonic, coupled-mode vibrational spectroscopy calculations are feasible (these now include di- and tr-peptides). The other major highlights are applications of our VSCF codes, carried out in many cases in cooperation with experimental groups, to determine structure and other properties of biological molecules. A study of the Raman spectra of PYP (Photoactive Yellow Protein), carried out in cooperation with Prof. R.A. Mathies (Berkeley) led to much improved characterization of 3 intermediate structures in the photocycle of this system.[66] A joint study with the experimental group of Prof. O. Dopfer (TU Berlin) resulted in determination of structure and interactions of protonated imidazole with water molecules,[67] and a joint paper with Profs. G. Meijer, G. von Helden and their coworkers in Berlin, led to spectroscopic characterization of different conformers of phenylalanine.[68] These studies have advanced our knowledge on the structures of conformers of biological molecules, and their spectroscopic properties.

NEW MOLECULES OF THE NOBLE GASES AND THEIR PROPERTIES

The highlight result of our work in this area in the period of the review is the discovery of “di-xenon water”, HXeOXeH and determination of its spectroscopic and energetic properties.[69] The new water molecule was obtained in a joint study, in which we cooperated with the experimental group of Prof. M. Räsänen, the leaders in this field. Our computational work predicted the stability of the species, predicted its vibrational spectroscopy by which it was identified, and investigated the nature of the chemical bonding in the molecules. HXeOXeH is to our knowledge the smallest experimentally known noble gas molecule with more than one noble gas atom. In view of the relative abundance of water in the solar system, the speculation of the possible presence of HXeOXeH in certain planetary environments is of interest.

A second result of significance in this area are our results on the lifetimes of several metastable noble-gas compounds at different temperatures. For example, we made the interesting prediction that HXeCCH, a compound of xenon and acetylene, is kinetically stable up to near room temperatures.[70] This may be relevant to potential applications of these new molecules.

PHOTOCHEMICAL DYNAMICS OF MOLECULES IN CRYOGENIC MATRICES

This research is part of the long-term project Sfb 450, in which I was a participant for the entire 12 years of its duration. The project ended in July 2010. My subproject dealt with ultrafast dynamics of dihalogens in noble gas matrices, in which our collaborators were Prof. J. Manz (Theory), and Prof. N. Schwentner (Experiment), both of FU Berlin. The highlight recent result on this was the theoretical-experimental demonstration that the process of photolysis of F2 and FCl in solid Ar is highly selective with regard to the diatomic quantum number of S (spin) and Ω, within the sub-picosecond timescale.[71] The selective ultrafast population of certain spin and Ω states opens possibilities for coherent control of photolysis in matrices [71].

CONTRIBUTION OF THE FRITZ HABER CENTER TO MY RESEARCH

The Fritz Haber Center is a highly stimulating environment for research in the theoretical and computational chemical sciences. I am sure that it helped at-

tract outstanding students and senior visitors to my group, as well as to other groups of the center. A very positive development in recent years, is that the Center now includes activities in a wide range of theoretical and computational fields: Electronic structure theory; Reaction dynamics; Statistical Mechanics; Spectroscopy; Elastic theory and macroscopic systems; New computational methods and algorithms. All this gives me the opportunity to learn and develop new ideas and lines of research.

The Fritz Haber Center was particularly important in fostering and catalyzing my contacts with research groups in Germany. This led above all to my fruitful collaborations, and in several cases, also to substantial joint grants with colleagues in Germany. I do not think these could develop without the Fritz Haber Center.

Finally, while the budget involved is relatively modest, the infrastructure provided by the Fritz Haber Center (computer system and administrative assistance, both shared by all members) functions very well and contributes to the excellence of the place. This infrastructure cannot be provided by single-investigator grants.

In summary, the overall environment provided by the center is unique worldwide and this is what makes possible the intense and fruitful research activities in theoretical and computational chemistry by the researchers of the center.

COOPERATION WITH GERMAN SCIENTISTS

COOPERATION WITH COLLEAGUES IN FU BERLIN IN THE FRAMEWORK OF SFB 450

Analysis and Control of Ultrafast Processes. I was a participant in this project from its inception, for the entire duration of the project. (It ended in July 2010). My main cooperation in this framework was with Professor Jörn Manz (Chemistry, FUB), on the ultrafast dynamics of photodissociation in noble-gas matrices. As discussed in other parts of my report, one of the most interesting issues was the role of non-adiabatic transitions in these systems, which turned out to be of major importance. Prof. Manz and I collaborated extensively on this project with Professor N. Schwentner (Physics, FUB), who's group carried out pump-probe femtosecond experiments that were interpreted by the theoretical calculations. Some of the key coworkers were Professor O. Kühn (then FUB, now Professor at Rostock), Dr. B. Schmidt (FUB, a former postdoctoral research fellow of mine in Jerusalem). Students/postdocs of my group who participate extensively, include: Dr. Masha Niv (now on the Faculty of Agriculture, HUJ); Dr. Arik Cohen (now a postdoc at UCLA); Dr. G.M. Chaban (now on the research staff of NASA – Ames Research Center, Ca., USA); Dr. Hagai Eshet. I participated in the instruction of Dr. M. Schmidt who got her doctorate at FUB, working on this project.

Towards the end of Sfb 450, we became involved in another sub-project, on control of isomerization of biological molecules by pulsed laser techniques. Work on this project continues still here, after the conclusion of Sfb 450. On this topic, we had cooperation with Prof. G. Meijer (Fritz Haber Institute) and Dr. G. van Helden, on vibrational spectroscopy of amino-acids. We have also cooperated on this topic with Professor Jörn Manz. Students and postdocs of my group who also participated in this project include: Dr. B. Brauer; Dr. I. Suwan (now lecturer at a Palestinian College); Dr. J. Sebek, and M. Shmilovitz-Ofir.

List of exchange visitors under this project: Prof. J. Manz (numerous times); Prof. N. Schwentner; Prof. M. Bargheer; Dr. M. Gühr; Dr. M. Schröder. Refs of joint publications with German collaborators in the framework of Sfb 450: [68, 71-77]

COOPERATION WITH PROFESSOR B. ABEL ON DYNAMICS OF PROCESSES ON WATER CLUSTERS

This project was a preliminary study combining experiments on water clusters and droplets by the group of Professor B. Abel, with dynamics simulations by my group here. Our focus in Jerusalem was the dynamics, using relatively high-level ab initio methods (MP2), carried out for small clusters, using DFT methods, carried out in Göttingen by Dr. E. Vöhringer-Martinez, and Prof. H. Grubmüller (MPI, Göttingen). Early joint results were published in the article below. On the basis of interesting initial results, we plan to

pursue joint funding with Prof. Abel, and extend this cooperation.

List of exchange visitors under this project: Prof. B. Abel (twice); Dr. E. Vöhringer-Martinez.

Published joint article: [78]

FUTURE RESEARCH PLANS

MECHANISMS AND DYNAMICS OF ATMOSPHERICALLY-RELEVANT REACTIONS AT SURFACES, AEROSOLS AND CLUSTERS

Both thermal and photochemical reactions will be explored. Systems include molecular reactions at water droplets, ice particles, silica surfaces, alumina surfaces and clays. Methods include dynamics simulations using directly potential surfaces from electronic structure theories (including in cases multireference treatment of multiple potentials, excited state, radicals, and hemolytic bond breaking).

This project involves extensive method development. A key person in the project is Dr. Dorit Shemesh, a senior postdoc in our group. She has dual German/Israeli citizenship. Cooperation is planned (and has begun) with the group of Professor B. Abel (Leipzig), on a theoretical-experimental basis. The group of Prof. Abel will carry out experiments with their pioneering Femtosecond-ESCA experiments on ultrafast reactions at water droplets.

The role of the **Fritz Haber Center** is of critical importance for this project, in view of the cooperation with Prof. B. Abel, and the role of Dr. Shemesh, for whom the Fritz Haber Center is an optimal working environment.

PHOTOCHEMICAL PROCESSES AND DYNAMICS OF PEPTIDES AND THEIR HYDRATES

Using novel algorithms for dynamics on systems of multiple electronic states, and including treatment of nonadiabatic transitions in the process, we propose to explore excited-state conformation transitions, H-transfer reactions and other chemical processes in small peptides and their complexes with water molecules. The objective is to understand reaction effects on peptides and proteins, and the role of water. The innovative aspect of our work is in pursuing excited-state dynamics for these systems by novel electronic structure methods combined with nuclear dynamics. Dr. Dorit Shemesh (Israel/Germany), a senior postdoc in our group, will be a leading investigator in this project. A suit of programs developed by Prof. Walther Thiel (MPI, Mülheim) will be one of the major tools. Cooperation with Prof. Thiel and his group is already under way in this, and one of his co-workers will visit here soon. We anticipate a first joint paper in this field. We are also – via Dr. Dorit Shemesh – in interaction with Prof. W. Domcke (TU München) on this topic, on which he has done pioneering electronic structure calculations, and we are cooperating with him as well. ≫ Continuation of the **Fritz Haber Center** is very important for this project.

OVERVIEW ARTICLE ON NONADIABATIC PROCESSES IN PHOTOCHEMISTRY OF MOLECULES IN MATRICES

In work done in the framework of Sfb 450, in which I participated, important progress was made on quantum and on semiclassical treatments of nonadiabatic processes in the photodissociation of small molecules in noble-gas host solids.

Prof. O. Kühn (University of Rostock) and I plan to write jointly a major review (including some new results) on the findings of the Sfb 450 research on this. The relatively simple systems that were explored seem very useful laboratories for understanding of nonadiabatic processes in condensed phases, a topic of continuing major interest. An invitation from Physics Reports is at hand.

GERBER STUDENT/POSTDOC REPORTS

DR. DORIT SHEMESH - POSTDOC

RESEARCH HIGHLIGHTS

Excitation of light and the subsequent processes are tremendously important in living organisms (e.g. vision, photosynthesis) and in the environment (e.g. absorbance of UV light by the ozone layer). However, light can also cause damage by invoking undesired

reactions. In biology, It is therefore of general interest to understand what are the primary steps of photoprotective biological function, i.e. the photostability of a certain biological system. In atmospheric chemistry, 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. In my research I model photochemical processes in a) biological systems and b) in atmospheric systems.

Irradiation of peptides and amino acids

Part of my research focuses on the mechanistic picture of photochemical processes in biological molecules and in atmospheric systems. During my postdoc with Prof. Domcke (as a Humboldt-Fellow) I started working on the photoexcitation dynamics of amino acids and small peptides. Very little is known about radiationless pathways in larger biological systems like small peptides. Spectroscopic data on these systems show that not all low energy conformers predicted by theory are available in the gas phase. [79-81] It has been suggested, that this is related to proton transfer paths in the excited states. We have investigated the excited-state potential energy surface of a low-lying conformer of the Glycine-Phenylalanine-Alanine tripeptide with a high level ab initio method named CC2.[82] The calculations reveal a potentially very efficient excited-state deactivation mechanism via conical intersections of the excited states of the indole chromophore with locally-excited and charge-transfer states of the peptide backbone. These findings suggest that the excited-state lifetime of the lowest-energy conformer of the Gly-Phe-Ala tripeptide may be too short to allow the detection of a resonant two-photon ionization signal. It is proposed that the efficient excited-state deactivation enhances the photostability of the tripeptide. Similar findings were obtained for the Trp-Gly peptide [83]. The calculations done during my postdoctoral stay with Prof. Domcke involved all calculations of deactivation pathways (i.e. by computing the associated potential energy surfaces) for biological molecules. As an example figure 1 shows a cartoon picture of the process (cover page in PCCP) [84]. An extension to this work has been done in my second postdoc with Prof. Gerber (as a Lady-Davis Fellow).[85] Here I modeled under the supervision of Prof. Benny Gerber the photoexcitation dynamics of biological molecules. All these systems are very large. Therefore excited-state dynamics with high level ab initio methods are not possible. We therefore used non-adiabatic surface hopping dynamics with the OM2 Hamiltonian implemented in the program package MNDO. From the non-adiabatic surface hopping dynamics we gained insight into the relevant excited-states, in the detailed mechanism and the timescales of the processes involved. In particular we studied the photoexcitation dynamics of two conformers of N-acetyl-phenylalanyl-amide (NAPA) with one water molecule. Experimentally, only the X conformer is observed by R2PI spectroscopy, although, the M2 conformer is also energetically accessible. Non-adiabatic photoexcitation dynamics show that for the M2 conformer, the S0 state starts to be populated already after 100 fs. In contrary for the X conformer, there is no decay to the ground state within 450 fs of simulation time. We have identified the conical intersections involved in the decay process of the M2 conformer. The simulations nicely explain the short lifetime of the M2 conformer compared to the X conformer and the experimental observations.

Irradiation of peroxides in water droplets

Other very important systems are peroxides in water droplets, which can be found in the atmosphere. Photoexcitation of peroxides in water droplets are tremendously reactive, as has been shown by a recent paper by Gerber et al [64] 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. Under the supervision of Prof. Benny Gerber I 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 solvated in a water cluster[86]. Interestingly, there exist significant differences between

both systems: The water 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 waters as a cage for the fragments and thereby prohibiting their prompt dissociation.

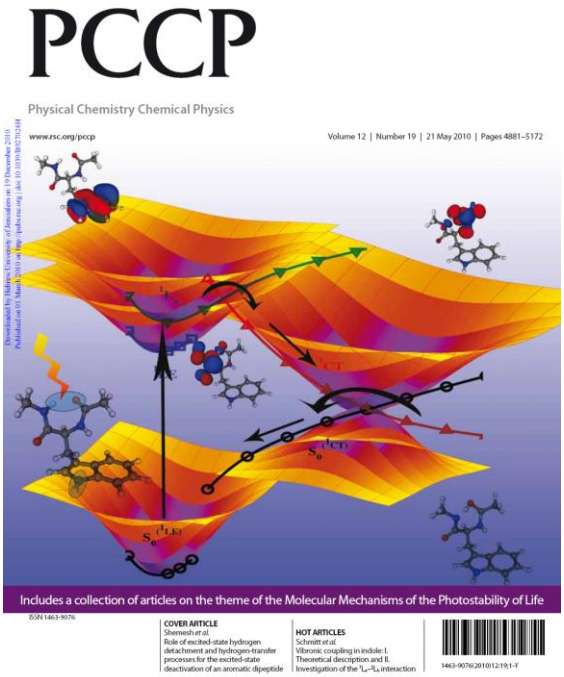

Figure 24: D. Shemesh, AL. Sobolewski, W. Domcke, Phys Chem Chem Phys, special issue on "Molecular Mechanisms of the Photostability of Life", 12 (2010) 4899, Cover page[84]

In summary, high level ab initio methods have been applied to explain the photostability of short peptides. Non-adiabatic surface hopping dynamics have been used to explain the conformer specific dynamics of small hydrated peptides. The same method has been also in applied in an atmospheric relevant system, peroxide in a water droplet. There it has been shown, that the water has a catalytic effect on the depopulation of the excited state to the ground state.

DR. D SHEMESH: CONTRIBUTION OF THE FRITZ HABER CENTER TO MY RESEARCH

I started to work at the Fritz Haber Center as a bachelor student in 1999 and finished my Ph.D. under the supervision of Prof. Benny Gerber in 2006. Since I completed my bachelor degree studies at the Hebrew University with high grades, I was permitted to continue directly to studies for a doctoral degree in the same field, without first being required to complete Master's degree studies (writing the thesis). After a postdoctoral stay of three years (2006-2009) with Prof. Domcke at the "Technische Universitaet Muenchen" in Germany, I returned to work with Prof. Benny Gerber as a postdoc. I always enjoyed and still do enjoy very much the wonderful working environment of the Fritz Haber Center. During my Ph.D. I had the opportunity to learn from distinguished teachers various classes in quantum chemistry. Such an accumulation of theoretical Professors is in my opinion outstanding and contributed significantly to my scientific career. I had a lot of vivid and stimulating discussions with the members of the Fritz Haber Center and their students. The Fritz Haber Center contributed also substantially in finding a postdoctoral position. During my Ph.D. I had the opportunity to meet excellent visiting scientist from abroad. For instance, I met Prof. Domcke during one of his visits to Israel and presented him my research. Later on, he accepted me as a postdoctoral student.

D. SHEMESH: FUTURE RESEARCH PLANS

COLLABORATION WITH PROF. DOMCKE (TECH. UNIV. MUENCHEN, GERMANY)

- The photochemistry of chiral biological molecules has been explored by calculating the excited state potential energy surface. The paper of this project is currently under preparation.

- A review article on the photochemistry of peptides will be written. The review article will discuss the emerging field of conical intersection in amino acids and peptides where I have contributed essentially.

COLLABORATION WITH PROF. SCHLAG (TECH. UNIV. MUENCHEN, GERMANY)

- Molecular dynamics simulations with/without water are performed for a set of amino acids and peptides involving tryptophan. The conformational preferences of tryptophan in these systems are investigated, hoping to understand how water affects the available phase space of an amino acid. This will contribute to understanding of folding processes in proteins.
- Charge transfer (CT) processes after ionization in peptides is surprisingly fast as found experimentally by the Schlag group (Weinkauf et al. J. Phys. Chem. 100 (1996) 18567). A thorough theoretical explanation to this effect is still missing. I have performed calculations on a model peptide, which confirms the CT model proposed by Prof. Schlag. This project approaches its final stage and will be shortly summarized as a paper.

COLLABORATION WITH PROF. THIEL (MPI, MUELHEIM, GERMANY)

Photodynamical simulations of peptides (discussed in the research achievements) will continue on different related biological systems.

COLLABORATION WITH PROF. NIZKORODOV (UC IRVINE)

The photochemistry of adsorbates on ice particles relevant for atmospheric chemistry will be studied using non-adiabatic surface-hopping molecular dynamics. Additional calculations on these systems include calculation of the UV absorption spectra of adsorbates on ice. It has been noted that most atmospheric systems show unexplained tail absorption to the red. Absorption spectra of peroxide with and without water have already been obtained. For this particular system the width of the UV spectrum can be explained by the flexibility of the torsion angle and its strong energy dependence in the excited state. Further investigation for different adsorbates on ice is planned next.

DR. JIŘÍ ŠEBEK – POSTDOC

RESEARCH HIGHLIGHTS

During my Ph.D. studies in Prague I focused on quantum-chemical computations combined with molecular dynamics. The main topic of my work was the simulation of electronic spectra of the amide group, especially in peptides, the results of which are summarized in two articles which were published in the Journal of Physical Chemistry A. I also worked on interpreting the electronic spectra of porphyrins and investigating the origin of their optical activity. The results in this area were published in the Journal of Physical Chemistry A. I am also a co-author of one article dealing with the applications of porphyrins and another dealing with molecular dynamics with restrictions derived from optical spectra. Another topic of my Ph.D. research was the simulation of the Raman optical activity spectra of small peptides (especially L-Alanyl-L-Alanine), the results were published in the Journal of Physical Chemistry A as well.

As a postdoctoral researcher in Jerusalem I have been working on several projects related to the vibrational spectroscopy, including the anharmonic corrections, which seems to be a very powerful tool for the studies of the conformations of important biomolecules, and of the dynamics of some conformational changes which play a very important role in the living systems.

One of the systems of my interest is lipids, an essential part of biomembranes. Their molecules are rich in CH2 and CH3 functional groups and the characteristic vibrations of CH stretches can be utilized in living cell imaging using Raman microscopy, while a profound understanding of the phenomena leading to the Raman signal is very useful for developing these microscopy techniques. For our calculations of the Raman spectra we used dodecane (both C12H26 and C12D26) as a model molecule for long fatty acid chains, with a similar ratio of CH2 and CH3. We have made a detailed study of CH stretching vibrations with elucidating the role of symmetric and asymmetric CH2 and CH3 stretches, including anharmonic

effects. For the estimate of spectral broadening we have made a conformer analysis. On this project we are cooperating with some experimentalists who provided us with the experimental spectra. We have reached a very good agreement with the experiment data, only several discrepancies were found, the explanations of which have been suggested. Our results are summarized in an article which is going to be submitted very soon.

I have also dealt with the conformational changes of 3-aminophenol, which can provide us with a deeper insight into some simple conformational changes due to the simplicity of this molecule and the availability of very detailed experimental data for each conformer separately. These conformers have, that is to say, a very different magnitude of the dipole moment, which enables their separation. The reaction dynamics of the conformational change was studied. During the isomerization, just one structural parameter was significantly changing, i.e. the CCOH torsion angle, which caused also the change of the dipole moment. The calculated dipole moment magnitudes were somewhat bigger than the experimental ones. However, if the dipole moment component perpendicular to the plane containing the aromatic core was omitted, a very good agreement with experiment was reached. This is in accordance with the assumption that the molecule is quantum-mechanically planar and behaves as an average of two enantiomers. On this project we have been collaborating with coworkers from Germany, especially with Professor J. Manz and some experimentalists (G. von Helden, J. Küpper).

Another project of mine is the examination of the proton exchange dynamics between two aminoacids, in our case between two glycine molecules. First, the structure of the protonated glycine dimer, (Gly)2H+, was investigated. Several structures have been previously suggested. Their energies have been calculated by different methods and there were significant differences in the results, especially for two lowest-energy conformers. In this case one of them seemed energetically preferred by B3LYP and other DFT methods and the second one by MP2. However, if the B3LYP functional was modified using van der Waals correction, the results became similar to those obtained by MP2. The MP2 minimum structure thus seems to be more probable. Also previous vibrational spectra analyses support this structure, and so we have used it for the examinations of the molecular dynamics of the proton motion. These calculations are at the very beginning at present.

J. ŠEBEK: CONTRIBUTION OF THE FRITZ HABER CENTER TO MY RESEARCH

I started to work at the Fritz Haber Center as a postdoctoral student in 2009 under the supervision of Prof. Benny Gerber. I enjoy very much the wonderful working environment of the Fritz Haber Center. Especially notable is the cooperation, endorsed by the center, with our German collaborators, which was very fruitful. Our results concerning 3-aminophenol were combined with the achievements of our colleagues from Berlin and presented together on a poster at the ACU IV Symposium - Analysis and Control of Ultrafast Photoinduced Reactions in Berlin in October 2009. At the time of this conference I could also see the equipment for the experiments related to our common topic and could participate a very interesting exposition of the experimental techniques.

J. ŠEBEK: FUTURE RESEARCH PLANS

In the coming two years I plan to pursue new directions in collaboration with J. Manz and G. von Helden, J. Küpper (Berlin), concerning the 3-aminophenol. One of our points of interest is the analysis of the vibrational spectra, including anharmonic effects using the VSCF approach for the internal coordinates, a relatively new method.

I also plan to further investigate of the anharmonic effects of hydrocarbon molecules, this time focusing on degeneracy effects. For this purpose I plan to first study butane.

Another focus of my research is on the dynamics of the proton in protonated glycine dimer.

Last but not least, I will incorporate the anharmonic methods we are developing into GAMESS, enabling the use of *ab initio* calculations. One of our challenges is to create a code for anharmonic intensities,

which has not been a part of the GAMESS package so far.

GERBER ACADEMIC ACTIVITIES, 2005-2009

1. Member of the Scientific Committee of the Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Prague (from 2005).
2. Member of the Editorial Advisory Board, Journal of Chemical Physics, 2001-2004.
3. Member of the Editorial Advisory Board, Chemical Physics (continuing).
4. Member of the Editorial Board of Computational Material Science (continuing).

RECENT AND ACTIVE GRANTS

Granting Agency	Period	Amount
DFG – SFB 450	Jan 2002 – Dec 2009	Euro 360,180
US-Israel Science Foundation (BSF)	Sept 2005 – Aug 2009	$ 81,900
Isr. Sci. Found. (ISF)	Oct 2008 – Sept 2011	NIS 516,000
Govt. Tech. Projects	Sept 2008 – Sept 2009	NIS 1,200,000
Govt. Tech. Projects DARPA (USA)	Jan 2009 – Dec 2009	$ 500,000
Govt. Tech. Projects DARPA (USA)	Jan 2010 – Dec 2010	$ 500,000

PROFESSOR GERBER'S GROUP 2010

Name	Status	Presently
Dr. Shemesh, D.	PhD	Postdoc Munich Univ.
Dr. Brauer B	Postdoc	Current member of the group
Dr. Goldstein, M.,	Postdoc	Current member of the group
Dr. Sebek, J	Postdoc	Current member of the group
Dr. Steinberg, M.	Postdoc	Current member of the group
Dr. Suwan, I.,	Visiting	Current member of the group
Cwik, Y.	Undergraduate	Current member of the group
Hirshberg, B.	MSc	Current member of the group
Kerem S	Undergraduate	Current member of the group
Knaanie, R.,	PhD	Current member of the group
Noiman M	MSc	Current member of the group
Dr. Njegic, B.	Postdoc	Current member of the group
Smilovici-Ofir, M.	PhD	Current member of the group
Pele, L.	PhD	Current member of the group
Sagiv L	PHD	Current member of the group
Shahar, A.	MSc	Current member of the group
Tsivion, E.	PhD	Current member of the group
Zmiri, L	PHD	Current member of the group

PROFESSOR GERBER GROUP MEMBERS GRADUATING SINCE 2006

Name	Graduation	Presently
Adesokan, A.A. **Student at UCI, Visiting Student at Hebrew University)**	Ph.D. (UCI, 2002)	Postdoc, Harvard Medical School
Cohen, Arik	Ph.D. (HU, 2008)	Postdoc, UCLA
Eshet, Hagai	M.Sc. (HU, 2007)	Ph.D. Student, Parrinello Group ETH, Switzerland
Goldstein, Moshe	Ph.D. (HU, 2010)	Lecturer, Jerusalem College of Technology & RBG Group
Miller, Yifat	Ph.D.	Postdoc, NIH

	(HU, 2008)	
Segev, Elad	Ph.D. (HU, 2008)	Computational Researcher, Biotech. Company
Shemesh, Dorit	Ph.D. (HU, 2003)	Senior Postdoc, RBG Group (postdoc at TU Munich)
Suwan, Iyad	Postdoc in RBG Group	Lecturer at Palestinian College & Visiting Researcher, RBG Group

AWARDS AND HONORS 2007-2010

- Foreign member of the Finnish Academy of Sciences and Letters, elected 2007.
- Elected a Finland Distinguished Professor, "FiDiPro" by the Finnish Academy of Sciences and the University of Helsinki (2010)
- Festschrift for R.B. Gerber, special issue of J. Phys. Chem., edited by A.B. McCoy, A. I. Krylov and V. Buch (2009)
- Editorial advisory board, Chemical Physics (continuing).
- Editorial board of Computational Material Science (continuing).

DANIEL HARRIES

Our main interest is in the way biologically diverse environments create conditions for macromolecules to associate and dissociate and form complexes that carry specific functions in cells. A variety of physical forces determine the outcome of such macromolecular encounters. We are particularly interested in a variety of examples where not only strong and specific interactions are important, but where the presence of many weak and often non-specific interactions is crucial as well. Such interactions include: screened electrostatics, non-specific hydrogen bonding, and entropically driven depletion forces that result from excluded volume interactions (or “crowding”).

We focus on a number of biologically relevant systems that involve internal arrangements of macromolecules or self-assembly of these, such as peptide folding and aggregation, and viral assembly. An extension of these ideas has been the surprising realization that the same forces that act on the microscopic scale are also relevant for macroscopic objects, such as granular materials, demonstrating that the governing physical principles are sometimes remarkably similar over many length scales.

Our group, was initiated almost 5 years ago, and has steadily grown, and over the past year included: one postdoctoral fellow, two PhD students, one Masters student, and an undergraduate student. Together with our collaborators in Israel and abroad, we theoretically study a wide range of phenomena that are directly linked to experiments, as detailed below. In the following, several highlighted research topics of the group are described.

MICRO-MOLECULAR CROWDING AND OSMOTIC STRESS ON PEPTIDE FOLDING AND AGGREGATION

One of our main focuses has been to elucidate how proteins and peptides are influenced by the crowded cellular environments. It is hard to imagine that this crowding by macromolecules and small solutes or “osmolytes” do not profoundly influence macromolecular interactions in the cellular environment. However, for many years and until recently, this effect has been largely ignored. The two student reports appended to this report describe our recent efforts to follow this crowding and osmolyte activity, with surprising emerging results that are changing the way we understand the osmotic action of cosolutes. Specifically, our results contrast the prevailing entropic mechanisms that have been suggested to

determine protein stability. Instead, we are seeing that even though solutes are excluded from macromolecular surfaces, the solution and its structure still play dominant roles in determining protein stability (see Figure 25).

This paradigm shift has, interestingly, also led us to study the formation of amyloid fibers in solution. We find that here, too, osmolytes do not seem to conform to the prevailing ideas of macromolecular crowding. Instead, osmolytes seem to affect amyloid aggregation differently than crowders (such as the polymer PEG), in that they delay the time required for fibril nucleation, but increase the amount of fibrils formed at equilibrium. Refs: [87-91]

Contribution: R. Politi, S. Sukenik, L. Sapir; in collaboration with A. Friedler (HUJ), D. Shalev (HUJ), D. Danino (Technion).

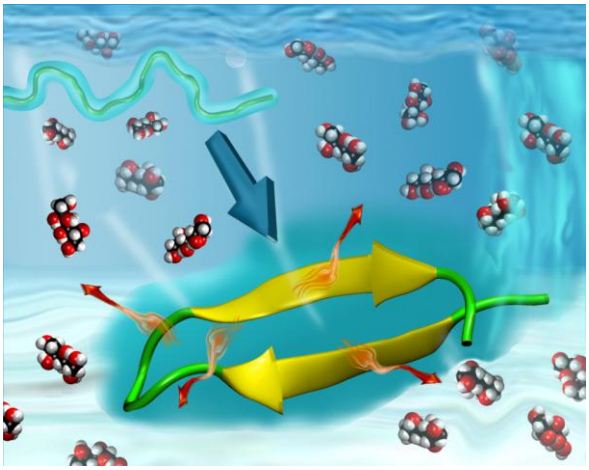

Figure 25: Schematic of a model peptide placed in stressed aqueous solution that includes osmolytes. Addition of osmolytes to solution shifts the thermodynamic equilibrium and stabilizes the peptide in its β-hairpin state. The arrows depict the most surprising point of our study, showing that this stabilization is enthalpically and rather than entropically driven. From the cover of Chem. Comm. ref [89].

DEPLETION FORCES AND CONFINEMENT EFFECTS IN VIBROFLUIDIZED GRANULAR MATERIALS

Ranging from nano- to granular-scales, control of particle assembly can be achieved by limiting the available free space, for example by increasing the concentration of particles (crowding) or through their restriction to 2D environments. It is unclear, however, if self-assembly principles governing thermally equilibrated molecules can also apply to mechanically excited macroscopic particles in nonequilibrium steady-state.

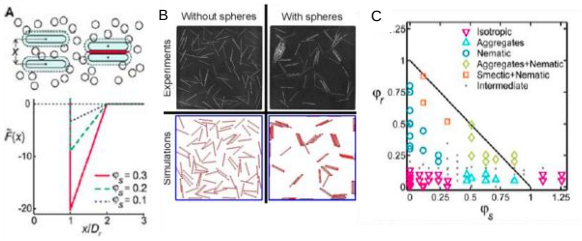

Figure 26: Attractive depletion interactions between hard rods in the presence of sphere crowders favor rod binding and suppress rod slip. Diagrams in A depict the area that rods exclude from spheres (dashed regions) and excluded area overlap (dark shaded regions) when two rods are less than one sphere diameter apart, shown for rod ''binding'' (A). The free energy gain is greater when there is more overlap that "releases" excluded volume. The experimental realization of this depletion force is seen as clustering of rods when spheres are introduced to rod mixtures (panel B, top, spheres not shown for clarity). The same patterning is achieved in 2D Monte Carlo simulations of hard rods and spheres (Panel B bottom). Panel C shows the wide variety of patterning that is found for different possible combinations of rod and sphere densities.

We have shown that low densities of vibrofluidized steel rods, when crowded by high densities of spheres and confined to quasi-2D planes, can self-assemble into linear polymer-like structures. Our 2D Monte Carlo simulations show similar finite sized aggregates in thermally equilibrated binary mixtures. Using theory and simulations, we have been able to demonstrate how depletion interactions create oriented ''binding'' forces between rigid rods to form these ''living polymers.'' Unlike rod–sphere mixtures in 3D that can demonstrate well-defined equilibrium phases in coexistence, our mixtures confined to 2D lack these transitions because lower dimensionality favors the formation of linear aggregates, thus suppressing a true phase transition. The qualitative and quantitative agreement between equilibrium and granular patterning for these mixtures suggests that entropy maximization is the determining driving force for bundling. Furthermore, this study uncovers a previously unknown patterning behavior at both the granular and nanoscales, and may provide insights into the role of crowding at interfaces in molecular assembly (see Figure 26).

Moreover, we have found that rods assemble and disassemble to form nematic phases. Interestingly,

we have been able to find elastic constants for these systems that would correspond to the appropriate continuum "Frank free energy" that describes molecular nematics. The method relies on analyzing defects in the container to infer the cost of creating such defects in terms of splay and bend contribution to the free-energy (See Figure 27).

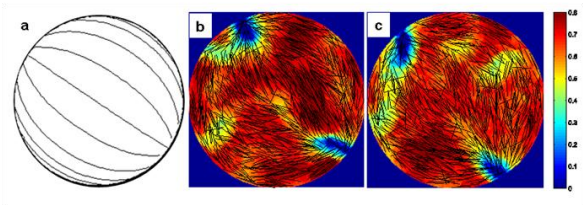

Figure 27: Patterning in a confined geometry. a) The free energy minimum derived by mean field theory. Fluctuations to the solution seen in: (b) equilibrium Monte Carlo simulations of hard rods and (c) granular experiments of vibrated steel needles. In (b,c), individual rods are shown in black, while the color maps the local orientational ordering and highlights the location of the two defects (blue).

Contribution: J. Galanis; in collaboration with R. Nossal (NIH), W. Losert (UMD).

Refs: [92, 93]

MEMBRANE INTERACTIONS AND PROPERTIES OF LIPID BILAYERS

We have been probing the interactions of macromolecules at the lipid membrane interface. The material properties of lipids, as well as protein-lipid interactions, govern the interactions and consequent assembly of these multi-component mixtures. The study of such complex systems requires the development of new computational tools that are based on statistical thermodynamics, as detailed in the following two examples.

MEMBRANE DEFORMATIONS AND LIPID DEMIXING UPON BAR PROTEIN DOMAIN ADSORPTION

Many proteins participating in cellular signaling processes contain BAR domains that have been implicated in membrane shaping. While the BAR domains have been shown to form dimers that are suggested to sense or induce significant curvatures on cell membranes, the underlying mechanisms are not well understood.

To address such processes quantitatively, we have introduced a dynamic mean-field scheme that allows self-consistent calculations of the equilibrium state of membrane-protein complexes after such lateral reorganization of the membrane components, and serves to probe kinetic details of the process. Applicable to membranes with heterogeneous compositions containing several types of lipids, this comprehensive method accounts for mobile salt ions and charged macromolecules in three dimensions, elastic energies of the membrane, as well as for lateral demixing of charged and net-neutral lipids in the membrane plane. In our model, the mobility of membrane components is governed by the diffusion-like Cahn-Hilliard equation, while the local electrochemical potential is based on nonlinear Poisson-Boltzmann theory. We have tested this method, and have demonstrated that protein and lipid diffusion in the membrane plane are coupled through the extent of lipid headgroup charge, as also seen in experiments (see Figure 28).

We then applied this new formalism to investigate such mechanisms of protein-membrane interactions, and have studied complexes of single Amphiphysin BAR domains interacting with large patches of lipid membrane bilayers of heterogeneous compositions. Our results suggest that a single BAR dimer is capable of stabilizing a significantly curved membrane, but we predict that such deformations will occur only for membrane patches that have the inherent propensity for high curvature, reflected in the tendency to create local distortions that closely matches the curvature of the BAR dimer itself. Such favorable preconditioning for BAR-membrane interaction may be the result of perturbations such as local lipid demixing induced by the interaction, or of a prior insertion of the BAR domain's amphiphatic N-helix.

However, our simulations indicate that in itself, local segregation of charged lipids under the influence of an adsorbing Amphiphysin BAR domain dimer cannot produce high enough asymmetry between bilayer leaflets. In the absence of additional energetic contributions that favor membrane asymmetry, upon BAR adsorption the membrane will remain nearly flat

relative to the undulation expected from thermal fluctuations. Thus, we conclude that the N-helix insertions have a critical mechanistic role in the local perturbation and in curving of the membrane, which is then stabilized by the electrostatic interaction with the BAR dimer.

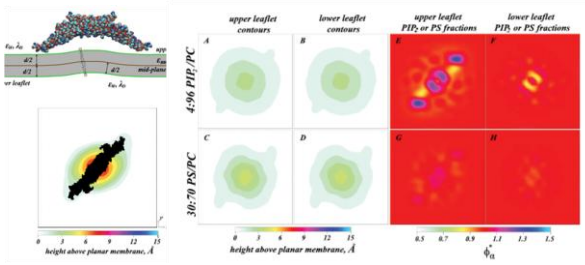

Figure 28: BAR domain adsorbed to lipid membranes causing elastic deformation and lipid segregation, as derived in our mean-field calculations.

CHOLESTEROL ORDERING IN LIPID MEMBRANES

An essential component of mammalian cell membranes, cholesterol is known to be critical for membrane organization, dynamics, and function. The nonuniform distribution of cholesterol between cellular organelles, lipid membrane compartments, and even between leaflets of the same bilayer, highlights cholesterol's role in influencing the biophysical properties of a fluid lipid matrix and in the stabilization and function of membrane proteins through specific interactions. The great variability found in the concentration of cholesterol among various cells and between the plasma membrane and the variety of membranes of other cellular organelles underscores the importance of tightly regulated cholesterol content for proper function at the subcellular level. In fact, inborn errors of cholesterol synthesis lead to major developmental abnormalities, and conversely, an excess of cholesterol is widely acknowledged as detrimental.

We performed molecular dynamics (MD) simulations of hydrated bilayers containing mixtures of dimyristoylphosphatidylcholine (DMPC) and cholesterol at various ratios, to study the effect of cholesterol concentration on its orientation, and to characterize the link between cholesterol tilt and overall phospholipid membrane organization. The simulations show a substantial probability for cholesterol molecules to transiently orient perpendicular to the bilayer normal, and suggest that cholesterol tilt may be an important factor for inducing membrane ordering. In particular, we find that as cholesterol concentration increases (1-40% cholesterol) the average cholesterol orientation changes in a manner strongly (anti)correlated with the variation in membrane thickness. Furthermore, cholesterol orientation is found to be determined by the aligning force exerted by other cholesterol molecules, see Figure 29. To quantify this aligning field, we analyzed cholesterol orientation using, to our knowledge, the first estimates of the cholesterol tilt modulus □ from MD simulations. Our calculations suggest that the aligning field that determines □ is indeed strongly linked to sterol composition. This empirical parameter should therefore become a useful quantitative measure to describe cholesterol interaction with other lipids in bilayers, particularly in various coarse-grained force fields.

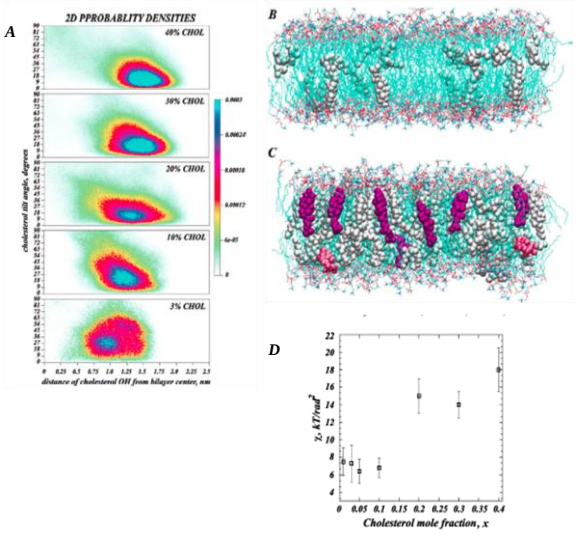

Figure 29: Cholesterol in membranes transition from a broad orientational distribution at low cholesterol mole fractions to a narrow one at high cholesterol fractions. This change in orientation can be seen in the probability distributions in A as a function of depth in the membrane and tilt angle, and also in the simulation snapshots in panels B (low cholesterol content of 3%) and D (high cholesterol content of 30%). These orientational changes can be translated to a stronger tilt modulus for high cholesterol content membranes. This modulus is shown in panel D to transition sharply to a higher value at the concentration regime for which the lipid membrane undergoes a first order transition from lipid disordered to lipid ordered phases.

Collaboration with Harel Weinstein and George Khelashvili, Weill Medical College of Cornell University, NY, Georg Pabst (Graz). Refs: [94-97]

D. HARRIES: HOW THE CENTER HAS CONTRIBUTED TO MY RESEARCH

My group's work relies heavily on computation, and therefore on computational resources and their maintenance. I can firmly attest that most of our work would have been impossible to achieve without the knowhow of the dedicated IT team at the Fritz Haber center. Since the establishment of my group, we have acquired and integrated a high performance computer cluster (joint with FH member Dr. Masha Niv) that performs the core of all our calculations. The integration of this cluster, and proper configuration with software and computation libraries, is a crucial step that was only possible due to this team. In addition, the center harbors important academic and intellectual relationships between its members. These interactions form a critical mass of theoretical knowhow that promotes knowledge transfer between faculty, students, and vice versa. This special environment would be lost without the existence of the center.

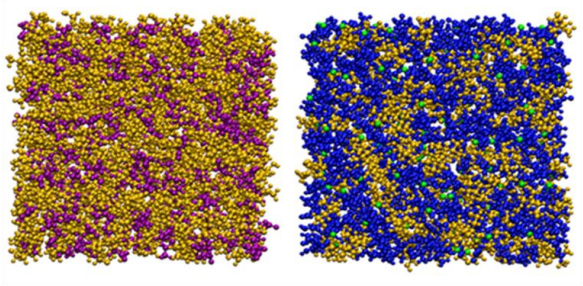

Figure 30: Choline-acetate (left) and Choline-chloride (yellow-green) – urea (blue) mixture (right) as seen in simulation snapshot. Extended structures are seen, indicating clustering of the different components in the low-melting temperature salt mixture.

D. HARRIES: FUTURE RESEARCH PLANS

Beyond the continued research in the directions detailed above, we have pursued a new exciting emerging field in the past year. Together with several groups around Europe, we are investigating ionic liquids as possible solutes for directed self-assembly of macromolecules. With our experimental partners, we are searching for new understanding of the way ionic liquids interact with protein, biopolymers, lipids, carbohydrates, and other biological macromolecules.

With the group of Werner Kunz (Regensburg) we are planning to further study Deep Eutectic Solvents (DES). These mixtures are formed from two (or more) materials that are solid are room temperature, but form a molten solution when mixed. Particularly striking are mixtures of choline salts with urea or sugar. Preliminary simulations already indicate that DES are in fact themselves self assembling fluids, with strong internal structure (see Figure 30). The main goal in this research is to tailor such solvents to enable assembly of macromolecules in nontoxic solvent-tunable environments that can highlight interactions that are modified with respect to more conventional solvents. Computer simulations can help predict the properties of these new solvents as well as their phase transition properties.

D. HARRIES: STUDENT REPORTS

REGINA POLITI, GRADUATE (PHD) STUDENT

RESEARCH HIGHLIGHTS

Living cells have developed multiple strategies to ensure that correct protein folding occurs even under substantial environmental stresses. Among the most widely employed methods to counteract external osmotic pressure is the use of small cosolutes called osmolytes.[98, 99] The exact mechanism of macromolecular stabilization by osmolytes is still largely unknown, but it has been recognized that solutes stabilizing the native state of proteins (protective osmolytes) tend to be preferentially excluded from protein-water interfaces. [100-102]

In my research I focus on the effects of various molecularly small osmolytes on the stability of peptides and proteins. We use a model 16-residue peptide that can fold to a β-hairpin structure. In aqueous solutions and at neutral pH, this peptide folds in an endothermic, entropically driven process.[103-105] As I detail here, my studies of the mechanism of action of added osmolytes have revealed some surprising departures from the prevailing paradigms on how excluded cosolutes affect protein and peptide folding.

Molecular crowding due to excluded volume interactions has been widely invoked to explain how osmolytes can drive protein stability. For example, it was shown that high fractional volume occupancy of crowding agents, such as soluble polymers, significantly shifts the non-native to folded thermodynamic equilibrium toward the more compact native states.[106, 107] This effect was shown to be related to the restriction of protein conformations to allow larger free volume for osmolytes, thereby destabilizing the unfolded state with respect to the native conformation.[108, 109]

Surprisingly, we have found that in contrast to the crowding mechanism, polyol and sugar osmolytes act to drive further folding primarily through diminishing the enthalpic loss with concomitant reduction in the favorable entropic gain for folding. The traditional molecular crowding mechanisms, which are based on steric interactions and are entropic in nature, do not usually consider the possibility of enthalpic contributions that may be mediated by the aqueous solution. My study shows that these mechanisms should be revisited, and that additional contributions to the stabilizing free energy are of fundamental importance.

I use a combined theoretic-simulation and experimental approach to probe the changes in peptide folding upon osmolyte addition. Using circular dichroism (CD) spectroscopy I have been able to determine the free energy of folding, $\boldsymbol{\Delta G^{0}_{D\rightarrow N}}$, of the model peptide in the presence and absence of different concentrations of polyols and carbohydrates, acting as small molecular osmolytes. I experimentally studied a range of osmolytes that differ not only in the number of hydroxyl groups (varying from 3 for glycerol to 8 for trehalose) but also in structure (isomers).[89] To further investigate the origins of smaller enthalpic loss in the presence of sugar osmolytes I further used Molecular Dynamics (MD) simulation of unfolded and folded peptide states in pure water and in the presence of osmolytes.

Experimentally, we find that that for all osmolytes tested, $\boldsymbol{\Delta\Delta G_{D\rightarrow N}}$ (defined as the difference between $\boldsymbol{\Delta G^{0}_{D\rightarrow N}}$ measured in water and its value obtained in the presence of osmolytes) varies linearly with Osmolal concentration (Figure 1a). Furthermore, while all osmolytes tested enhance β-hairpin stability, the variation in $\Delta\Delta G$ generally grows with osmolyte size. Using the Wyman linkage (or the Gibbs adsorption isotherm), the linearity of folding free energy with osmolyte concentration implies a constant change in the number of solute-excluding water molecules (preferential hydration) upon folding, ΔN_W.[91, 110] The evaluated ΔN_W for each osmolyte (table in Figure 31) further reveals that ΔN_W grows approximately linearly with partial molar volume inside of each group, polyols and carbohydrates. This observation is consistent with the fact that larger osmolytes are more strongly excluded from the peptide surface.

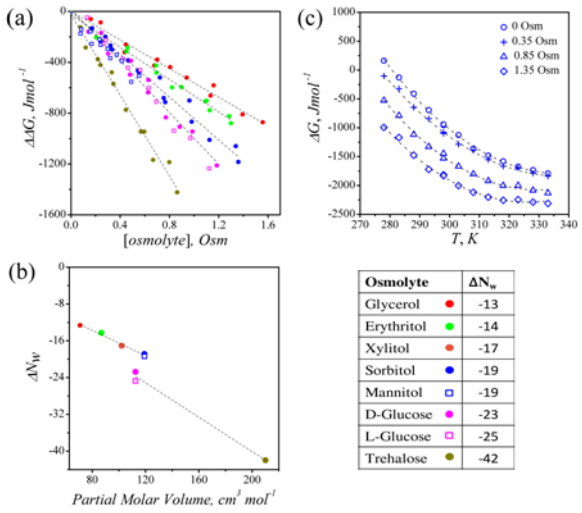

Figure 31: Effect of osmolytes on β-hairpin stability. a) Folding free energy, $\Delta\Delta G_{D\rightarrow N}$, versus osmolyte concentration at T=298K for different polyols and sugars. b) Preferential hydration upon folding, ΔN_W, versus osmolyte partial molar volume. Dashed lines are guides to the eye. c) Peptide folding free energy, , versus temperature, T, at different sorbitol concentrations.

Figure 31c shows the variation of folding free energy ΔG with temperature, used to dissect $\Delta\Delta G$ into enthalpic and entropic contributions. These values allow to determine ΔH, ΔS and ΔC_p for folding at T=298K, summarized in Table 1. While in the absence of osmolytes the β-hairpin conformation is entropically stabilized and folding is endothermic, for water-osmolyte mixtures β-hairpin stability increased in the presence of osmolytes, primarily due to a decreased enthalpy loss. Remarkably, the favorable entropy for folding in water is diminished by added solutes, a mechanism that cannot be explained by steric crowding.

Analysis of a variety of thermodynamic parameters from our MD simulations emphasized the key role of hydrogen bonds in increasing peptide stability in the presence of the osmolyte sorbitol. Figure 32a shows the difference between folded and unfolded conformations in total number of hydrogen bonds in peptide environment with respect to the bulk, plotted as a function of the distance from any peptide atom. Figure 32a indicates that during peptide folding, the environment in fact losses hydrogen bonds, both in pure water, and in the presence of sorbitol, but that in the presence of sorbitol the loss is smaller. Figure 32b shows the difference in the number of internal peptide hydrogen bonds between folded and unfolded states, evaluated for the peptide immersed in pure water and in aqueous sorbitol solution. The number of internal peptide hydrogen bonds is larger in the presence of sorbitol than in pure water.

I further dissected the number of internal peptide hydrogen bonds found in simulations into backbone-backbone and "other" hydrogen bonds. While there is almost no difference in the number of other hydrogen bonds in pure water and in the presence of sorbitol, the number of backbone-backbone hydrogen bonds is larger in the presence of sorbitol. When weighting not only the numbers but also the strength of hydrogen bonds using the empirical function established by Espinosa et al[111], a significant effect of sorbitol in the solution becomes evident. Figure 3 shows the energies of each interaction evaluated in pure water and in the presence of sorbitol. The strongest hydrogen bonds were formed between water and peptide. These hydrogen bonds are much stronger than peptide sorbitol hydrogen bonds, suggesting a molecular origin for sorbitol exclusion. There is no significant difference in the estimated energies between folded and unfolded states except for peptide-peptide hydrogen bonds. The small number of internal peptide hydrogen bonds that can be created in unfolded state as well as the fact that these hydrogen bonds are relatively weak can explain the advantage of folding in pure water as well as in the presence of sorbitol. Stronger peptide-water hydrogen bonds are created around folded than unfolded state in pure water as well as in the presence of sorbitol.

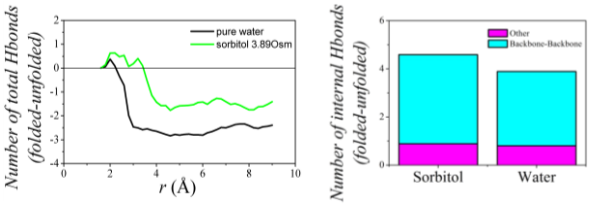

Figure 32: Difference between folded and unfolded states in the number of hydrogen bonds in pure water and in the presence of sorbitol. a) Hydrogen bonds in the peptide environment calculated with respect to the bulk are plotted as a function of the distance from any peptide atom. The hydrogen bonds in peptide environment taken into account are the water-water, water-sorbitol, water-peptide, sorbitol-sorbitol and sorbitol-peptide hydrogen bonds. b) Number of internal peptide hydrogen bonds.

In general there is a loss in the number of hydrogen bonds as a result of folding. Parts of these hydrogen bonds are peptide-water hydrogen bonds that are the strongest hydrogen bonds formed. To compensate for the loss of these hydrogen bonds as a result of folding there is an increase in the number of internal peptide hydrogen bonds, significant improvement of their strength, as well as creation of stronger hydrogen bonds between peptide and water. Water-water, water-peptide, and peptide-peptide hydrogen bonds are stronger in the presence of sorbitol than corresponding hydrogen bonds in pure water. The water molecules released upon folding in the presence of sorbitol create hydrogen bonds that are stronger than hydrogen bonds created in pure water. Every water-water and water-peptide hydrogen bond created in the presence of sorbitol gains an additional 0.5kJ/mol.

Combining the information from experimental and computational analysis, I found that the excluded osmolytes tested cause peptides to preferentially adopt a more compact (folded) structure relative to more extended (unfolded) conformations. By folding, the peptides create a more ordered, enthalpically favored, environment. Understanding the role of osmolytes in regulation will not only allow to predict the action of osmolytes on macromolecular interactions, but will also provide insights on how osmolytes may be involved in pathologies or their prevention. Refs: [87, 89, 90]

R. POLITI: FUTURE PLANS

Osmolytes have been shown to inhibit or accelerate peptide aggregation into amyloid fibers (see my list of publications ref.1), but there is a lack of biophysical information regarding the way osmolytes affect aggregation. We have been using CD spectroscopy, Thioflavin T fluorescence assay, and cryo-TEM microscopy to evaluate the influence of osmolytes on the aggregation of our convenient model peptide. In the nearest future, using MD simulations I will follow peptide states and conditions that promote aggregation *versus* those that promote proper (monomeric) folding.

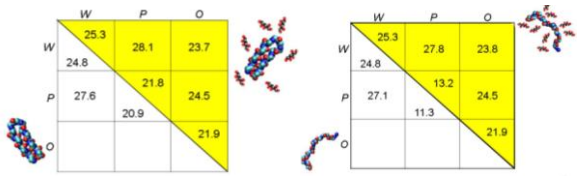

Figure 33: Average energies of each hydrogen bond taken into account in pure water (white triangle) and in the presence of sorbitol (yellow triangle) in a) folded and b)unfolded states. The energies are in kJ/mol.

R. POLITI: CONTRIBUTION OF THE FRITZ HABER CENTER TO MY RESEARCH

Being a part of the Fritz Haber center provides an excellent environment for the transfer of knowledge between generations of scientists and is known as a place that brings together theoretical scientists from across the physical and chemical disciplines. This encourages intense exchange of thoughts and ideas. I do believe that in order to profoundly learn and develop investigative abilities, the most important thing is not only the mediating teacher but also the tools and facilities available in the center. The center provides computational resources and IT administrators that facilitate the complex simulations we perform in our studies. These facilities allow us to concentrate on the science and make our scientific endevors possible.

LIEL SAPIR, MSC STUDENT

RESEARCH

Stabilizing osmolytes are naturally occurring molecularly small solutes that are used by many organisms to counteract harsh environmental stresses. Such harsh conditions include dehydration and freezing that diminish available hydration and can seriously damage biomolecules. Some osmolytes, known as protective osmolytes, are known to stabilize proteins and peptides by shifting the folding equilibrium towards the native state.[106, 107] Protective osmolytes include many types of solutes, including polyols and sugars. Of these solutes, trehalose is one of the best known for its significant effect. The thermodynamic basis for osmolyte action is described in terms of their preferential interactions; however, the molecular mechanism has not yet been resolved. My main objective in this research is to identify the molecular mechanism underlying this protein stabilizing effect.

Most osmolytes are able to form hydrogen bonds with surrounding molecules. This ability affects the water hydrogen bond network, and many protective osmolytes have been shown to strengthen the hydrogen bonds between water molecules. In addition, they cause the tetrahedral arrangement of water molecules to be less ordered. Since water have a pivotal role in protein folding, this effect on water bulk properties must play a role in the stabilization effect.

In the case of trehalose, the hydrogen bonding ability not only affects water structure but also promotes extensive concentration dependent aggregation of trehalose molecules, which may impact trehalose's role as a protective cosolute to biomacromolecules. To study the self-association of trehalose in aqueous solutions over a wide concentration range, we used molecular dynamics (MD) simulations, as well as vapor pressure osmometry. We have found that the cluster size increase with concentration (Figure 34), and that at concentrations of 1.5-2.2 m the solutions reach the percolation threshold. Experimentally however, trehalose solutions showed positive deviations from ideal van't Hoff's law that grew with concentration. We have linked these observations in a simple equation of state that accounts for the repulsive excluded volume interactions between trehalose

molecules, as well as attractions reflected in sugar clustering. We find that simulations result in reasonable representations of the solution equation of state. However, in contrast to experiments, the balance between the repulsive and attractive trehalose-trehalose interactions in simulations results in a slightly negative deviation from ideality, probably due to the moderately over aggregative nature of the force fields used.

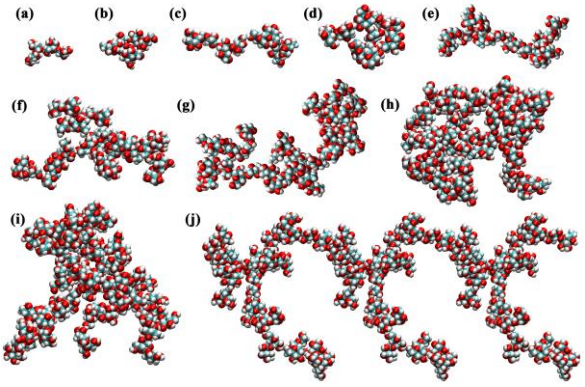

Figure 34: (a-i) Trehalose molecules bind through hydrogen bonds with each other, thereby forming clusters in solution. The clusters grow with trehalose concentration. (j) A percolating cluster.

To follow the effect of osmolytes on macromolecular interactions, we explored the conformational landscape of a 16 amino acid model peptide, known to form a β-hairpin fold in solution. The peptide state is probed under several solution conditions: in pure water, and in aqueous solutions of two prominent protective osmolytes (glucose and trehalose). The peptide state is followed using MD and replica exchange (REMD) simulations, and compared with results from NMR spectroscopy. Our MD results demonstrate how the addition of protective osmolytes to solution alters the peptide's conformational landscape (Figure 35). The REMD simulations, though much more demanding in terms of computer resources and time, allow for better sampling of the protein conformational ensemble. Thus, one can thoroughly examine the effect of glucose and trehalose on the protein free energy landscape, namely to dissect the effect of these cosolutes to different thermodynamic contributions, and to discern between the effect on the native and non-native structures. We find that the thermodynamic stabilities observed in simulations correspond to experimentally determined thermodynamic parameters. Refs: [88, 90]

L SAPIR: FUTURE PLANS

In the upcoming years, we plan to develop computational tools for the simulation of macromolecules in realistic cellular environments that contain osmolytes. The results from the REMD simulations of the model peptide will allow us to determine the effect of the cosolutes on the relative stability of each conformation of the peptide. This data, together with other thermodynamic parameters available in the literature, is crucial in the development of implicit solvent models. Simulations of macromolecules with such implicit solvent will be faster than the current available methods (such as MD and REMD), and will thus facilitate the computational exploration of macromolecules within realistically natural environments in acceptable time-scales.

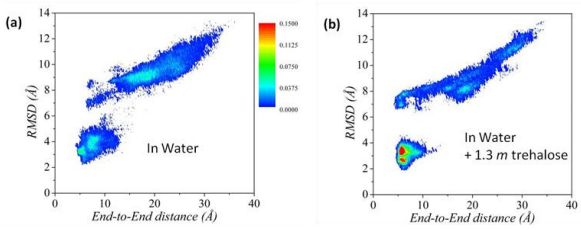

Figure 35: The probability density distribution of the peptide conformations with respect to two structural parameters: the root-mean-square-deviation (RMSD) and the distance between α -carbons of first and last amino acids in the peptide (end-to-end distance). These probability density distributions are easily interpreted in terms of free energy. The distribution is shown for the peptide in (a) pure water, and (b) 1.3 molal trehalose aqueous solution, as seen in MD simulations. The folding effect is seen in larger probability of the folded state in the presence of trehalose.

Protective osmolytes have also been shown to effect nucleic acids (RNA and DNA). Many osmolytes have been shown to destabilize the secondary structure of RNA, while their effect on the tertiary structure was either stabilizing or destabilizing. We plan to employ the methodologies we use with protein molecules to the study of osmolytes effect on RNA sequences. We have already started with MD simulations of a model 12-nucleotide RNA sequence, which show that trehalose and glucose alter the RNA's conformational free energy landscape.

L SAPIR: THE CONTRIBUTION OF THE FRITZ HABER CENTER TO MY RESEARCH

The resources provided by the Fritz Haber Center have been indispensable for the success of my research. My project is based on advanced simulation methodologies that require extensive computational resources. The system administrator group of the center is of outmost importance for the maintenance and operation of our computation cluster. For being able to run our simulations, the cluster requires continuous work by skilled professionals, with specific knowledge about the hardware and software. Furthermore, the new computing cluster sponsored by Minerva provides additional resources for our simulations, facilitating results to be accumulated in realistic times.

D. HARRIES: COOPERATIONS AND COLLABORATIONS

We recently established collaboration with Werner Kunz (Univ of Regensburg) on Ionic liquids and deep eutectic mixtures as new solvents for macromolecules and self assembly, as detailed above.

Other 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)

D. HARRIES: CONFERENCE ORGANIZATION

- Biophysics mini-symposium (14 Feb 2007, Heb. Univ., with Drs. U. Raviv and A. Friedler).
- From Macromolecular to Cell Biophysics (June 3-4, 2008, Mishkanot, Jerusalem with D. Andelman and W. M Gelbart).
- Biomolecular simulations (2009, Safed, with M. Niv, D.T. Major, and K. Levy).
- Liposomes in Jerusalem honoring Chezy Barenholz (2011, Maale Hahamisha, member of organizing committee).

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, MSc student, Dean's prize 2007, 2008, 2009.

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

RESEARCH

Existence of quantum phenomena is well established in small isolated systems. The central challenge in molecular dynamics is to unravel the origin of such phenomena also in large and complex systems. The difficulty stems from the fact that the quantum phenomena are hidden by inherent averaging in such systems. We have approached this endeavor by four converging research efforts:

- Quantum Thermodynamics
- Coherent Control
- Open system dynamics
- Ultracold molecules

In addition we have an applied research effort devoted to public safety: defense against improvised explosives.

QUANTUM THERMODYNAMICS

A crucial moment in the development of quantum mechanics is when Einstein employed thermodynamical arguments to obtain the relation between energy and frequency. Quantum thermodynamics is engaged in the opposite direction, establishing the laws of thermodynamics starting from quantum mechanics. Our recent effort in this field was the study of quantum refrigerators with the focus on the third law of thermodynamics; approaching the absolute zero temperature. To address these issues, we follow the tradition of thermodynamics constructing models of quantum heat engines and refrigerators. The main issues that were addressed are:

- What are the restrictions imposed by the working medium?
- What are the conditions for optimizing the cooling power when $T_C \to 0$?
- Is there a minimum temperature above the absolute zero?

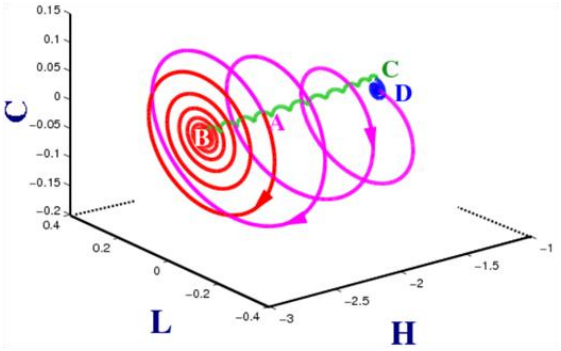

Figure 36: Typical optimal cooling cycle trajectory with linear scheduling shown in the quantum thermodynamical variables energy $\hat{H}$, Lagrangian $\hat{L}$ and correlation $\hat{C}$. Point A represents the beginning of the hot *isochore*. Point B represents the beginning of the demagnetization *adiabat*. Point C represents the beginning of the cold *isochore*. Point D represents the beginning of the magnetization *adiabat*. Notice the big difference between the demagnetization and magnetization adiabats.

These issues were addressed by a reverse Otto cycle (Figure 36) with working medium consisting of interacting spins or harmonic oscillators. We found that the quantum analogy to friction is the inability to follow adiabatically the instantaneous energy levels of the changing Hamiltonian of the working medium. This friction has a quantum origin in that the Hamiltonian does not commute with itself at different times. We were able to identify a series of frictionless solutions which were used to define the scaling of the cooling power when $T_C \to 0$.

These studies shed new light on the third law of thermodynamics. Refs: [112-117]

OPTIMAL CONTROL THEORY

A closed quantum system is defined as completely controllable if an arbitrary unitary transformation can be executed 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 time-scale of the transformation?
- Can the noise be exploited to carry out a non unitary task?

Complete controllability requires that the effect of noise is suppressed for an arbitrary transformation. We were able to show that for large quantum systems, generic noise in the controls dominates for a

typical class of target transformations i.e. complete controllability is destroyed by the noise. But the noise can also be beneficial coupling to the bath can purify the state which is equivalent to cooling [118, 119] allowing tasks such as tracking a reference noiseless state or a quantum version of a governor preserving a quantum state.

CONTOL UNDER DISSIPATIVE CONDITIONS

In an excitation by weak electromagnetic field of an isolated molecule, a control objective is rigorously only frequency dependent. This means that phase control of the pulse cannot improve the objective beyond the best frequency selection. Once the molecule is put in a dissipative environment a new time scale emerges. We have demonstrated that the dissipation allows achieving coherent control of branching ratios in the excited state. The influence of the environment is modeled by the stochastic surrogate Hamiltonian. For sufficient relaxation we find significant control in weak field depending on the chirp rate. The observed control is rationalized by a timing argument caused by a focused wavepacket. The initial non adiabatic crossing is enhanced by the chirp. This is followed by energy relaxation which stabilizes the state by having an energy lower than the crossing point [120].

ULTRA COLD MOLECULES

STUDY OF PHOTOASSOCIATION

The total number of molecules produced in a pulsed photoassociation of ultracold atoms is a crucial link between theory and experiment. A calculation based on first principles can determine the experimental feasibility of a pulsed photoassociation scheme. The calculation method considers an initial thermal ensemble of atoms. The absolute number of molecules in the calculation agree to within experimental error for photoassociation with picosecond pulses for a thermal ensemble of rubidium or cesium atoms in ultracold conditions [121].

OPTIMAL CONTROL THEORY FOR COLD MOLECULES

We have developed control schemes to enhance molecular production in ultracold photoassociation.

The idea is to generate a flux toward short interatomic distances. We are collaborating with the experimental group of P.L. Gould in studying new coherent control schemes using nanosecond shaped pulses.[122]

Using ideas from control theory we have developed pump-probe spectroscopy to study pair correlations that determine the many-body dynamics in weakly interacting, dilute ultracold gases. A suitably chosen, short laser pulse depletes the pair density locally, creating a hole in the electronic ground state. The dynamics of this nonstationary pair density is monitored by a time-delayed probe pulse. The resulting transient signal allows us to spectrally decompose the hole and to map out the pair correlation function. [123]

OPEN SYSTEM DYNAMICS

CAN QUANTUM SYSTEMS BE SIMULATED: SURROGATE DYNAMICS

We explore the fundamental issue of our ability to simulate quantum dynamics using a classical computer. This is the inverse question asked in constructing a quantum computer. It is well established that complexity in simulating a quantum system grows out of bounds when the number of particles involved increases. Typically the numerical effort grows exponentially with the number of degrees of freedom. A scheme to simulate the evolution of a restricted set of observables of a quantum system was developed. Focusing on a simulation of a restricted set allows to drastically reduce the cost of the simulation. This reduction is the result of replacing the original unitary dynamics by a special open-system evolution. This open-system evolution can be interpreted as a process of weak measurement of the distinguished observables performed on the evolving system of interest. A time-scale separation allows the unitary dynamics of the observables to be efficiently simulated by the open-system dynamics on the interme-

diate time scale. The simulation employs unraveling of the corresponding master equations into pure-state evolutions, governed by the stochastic nonlinear Schrödinger equation. The stochastic pure-state evolution can be simulated efficiently using a representation of the state in the time-dependent basis of the generalized coherent states, associated with the spectrum generating algebra. [124-126]

SURROGATE HAMILTONIAN

The surrogate Hamiltonian is a general scheme to simulate the many body quantum dynamics composed of a primary system coupled to a bath. The method has been based on a representative bath Hamiltonian composed of two-level systems that is able to mimic the true system-bath dynamics up to a prescribed time. The original surrogate Hamiltonian method was limited to short time dynamics since the size of the Hilbert space required to obtain convergence grows exponentially with time. By randomly swapping bath modes with a secondary thermal reservoir, the method can simulate quantum dynamics of the primary system from short times to thermal equilibrium (see Figure 37). By averaging a small number of realizations converged values of the system observables are obtained avoiding the exponential increase in resources.[127]

This system bath simulation method is non-Markovian. In addition, the system and bath are initially correlated. Moreover, it is the only method that is consistent with an external driving field. We have employed the method to study weak field control and hot injection.[120, 128]

FUTURE RESEARCH PLANS

Quantum phenomena will constitute my main research efforts. The field of quantum thermodynamics has emerged into the limelight. We will therefore increase our efforts in studying quantum refrigerators. We will add to our agenda continuously driven quantum refrigerators and quantum absorption refrigerators, refrigerators driven by heat or noise.

We intend to study molecular ultrafast spectroscopy under dissipative conditions. We will collaborate with Professor D. Miller now 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 explicitly time dependent Hamiltonian.[129] We want to extend this study to nonlinear problems such as the Gross-Pitayevsky equation. In addition we want to adopt the program to optimal control problems.

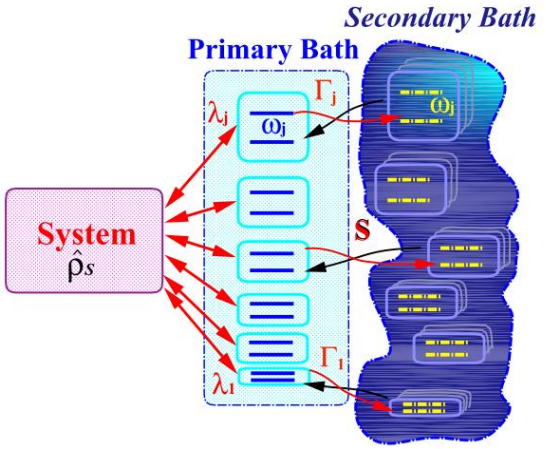

Figure 37: Flowchart of energy currents in the Surrogate Hamiltonian method between the primary system, the primary bath and the secondary bath. The system and the primary bath are coupled via the Hamiltonian interaction represented by the interaction λ_j. The primary bath and the secondary bath interact via the swap operation $\hat{S}$.

We are also currently in the middle of an experimental-theoretical collaboration on two-photon photo-association of Mg atoms with the group of Zohar Amitay in the Technion and Christiane Koch in Kassel. This is a first step in a general scheme to control binary reactions. We are also collaborating with the group of Phil Gould in the University of Connecticut on control experiments on photo-association of Rb atoms.

CONTRIBUTION OF THE FH CENTER TO MY RESEARCH

The Fritz Haber center for molecular dynamics has always been my scientific home. The center is a vibrant community of researches in diverse fields of molecular dynamics. Whenever a scientific question emerges there has always been a local expert to resolve the issue and lead to further insight.

The constant inflow of guest to the center from Germany and other countries means that we can contribute to the broader scientific community. As a result we maintained our status of one of the major theoretical centers in molecular dynamics. In addition the center has supplied basic services of a friendly administration which is able to deal with our visitors and students. A crucial theme for theory is up to date computer service in the ability to incorporate the latest hardware and software. 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. In addition we have been working with the experimental groups of Professor A. G. Woeste in Berlin and Matthias Weidemueller in Heidelberg.

ACTIVE GRANTS FOR PROFESSOR KOSLOFF

Granting Agency	Period	Amount
Niedersachsen	2007-10	€ 112,500
D.F.G	2007-10	€ 137,500
Homeland security	2008-10	$ 96,000
Quantum Computing	2008-09	$ 25,500
ISF	2007-10	₪ 500,000
Government Grant	2007-10	₪ 1,200,000

GERMAN COLLABORATIONS

Name	Affiliation	Field
Prof. Dr. Cederbaum. L.	University of Heidelberg	Quantum Many Body Dynamics
Prof. Dr. Freund, H.-J.	FH, MPG, Berlin	Photodissociation on Surfaces
Prof. Dr. Hasselbrink, E.	Univ. of Duisburg- Essen	Oxygen Dissociation on Surfaces
Prof. Dr. Hoffmann, K.-H.	University of Chemnitz	Quantum Thermodynamics
Prof. Dr. Klüner, Th.	Theoretical Chemistry, University of Oldenburg	Coherent Control and Surface Reactions
Dr. Koch, Ch.	FU Berlin	Coherent Control / Cold Molecules
Dr. Nest. M.	TU, Munich	Many Body Quantum Mechanics
Dr. Poschinger, U.	University of Freiburg	Cold Molecules
Prof. Dr. Tieman, A.	University of Hannover	Cold Molecules
Prof. Dr. Weidenmüller, H.-A.	University of Heidelberg	Cold Molecules
Prof. Dr. Wester, R.	University of Freiburg	Cold Molecules
Prof. Dr. Wöste, L.	FU Berlin	Coherent Control / Cold Molecules

RAPHAEL D. LEVINE

The work described herein is with the cooperating German investigators: Eleftherios Goulielmakis, Reinhard Kienberger, Ferenc Krausz, Karl L. Kompa and Matthias Lezius of the Max-Planck-Institut für Quantenoptik, Garching, Rainer Weinkauf of the Heinrich-Heine-Universität Düsseldorf, Mathias Nest at TU München, and, very recently, Marc Vrakking of the Max-Born-Institut, Berlin.

Françoise Remacle of the Université de Liège has been an active partner in this work

The Fritz Haber Research Center has provided not only the stimulating atmosphere and the right physical environment but also the encouragement needed for this extensive cooperation.

Direct financial support for the work reported herein was provided primarily by the James Franck German-Israel Binational Program. This support made the work possible and it is gratefully acknowledged.

On a more modest level this cooperation was also supported by GIF, the German-Israel Foundation and by the FP7 FET project MOLOC.

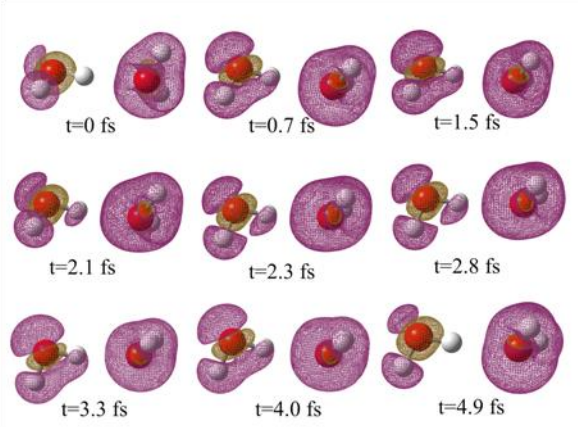

Figure 38: Ultrafast charge migration in the water dimer. The molecule is asymmetric where one water molecule donates and the other accepts the hydrogen bond. Therefore the initial fast ionization can have the charge localized on one moiety. The dynamics is computed in a many electron picture so that the other electrons are able to respond to the non-stationary (and hence moving) charge density. Violet: positive density; Golden: negative density, isocontour value: 0.004 Å-3. Adapted from ref [130].

ULTRAFAST QUANTUM DYNAMICS OF ELECTRONS IN HIGH FIELDS

Our earliest paper directly on this topic is “An Electronic Time Scale in Chemistry”, [131]. Important earlier work on charge directed reactivity was done in collaboration with E W Schlag and R Weinkauf. A very recent example is given in the abstract Figure 38. Accordingly, we only report on three directions that are currently in progress. One, is the description of the motion of the nuclei, possibly during and then after the pulse. The issue is if one can have control over the chemistry by controlling the nature of the electronic wavepacket that is excited. The usual way of thinking is not quite applicable because the motion is coherently over several electronic states, each one with its own potential. Therefore the simpler view, as given by the Hellmann-Feynman theorem, that the force on the nuclei is the derivative of the potential is not quite applicable. A detailed technical report on this point is available .

The second direction attempts to address the issue of probing the coherent electronic motion that can be pumped by an ultrafast pulse. We have first investigated this in a paper “Probing Ultrafast Purely Electronic Charge Migration in Small Peptides” [132] published in the EW Schlag festschrift. This used an ultrafast photoelectron spectroscopy induced by a 100as soft X-ray pulse that is available in the Krausz group and elsewhere. In collaboration with Eleftherios Goulielmakis of the MPQ we are now looking for what one could do to probe the motion in a molecule called 2-phenylethyl-N,N-dimethylamine (PENNA). This is a simple bichromophoric system so that the electronic wave packet can initially be localized at either the ‘N end’ or the ‘phenyl end’ of the molecule. Much data about the fast electronic spectros-

copy of PENNA has been collected by Rainer Weinkauf and we have used it earlier in a joint publication about optically induced logic [133]. Now the purpose is to use PENNA to experimentally demonstrate electronic motion in a larger molecule. The theoretical situation is clear as shown in the figure below that plots the dipole moment along the molecular axis for a wavepacket localized initially at either end. The time scale for charge migration, about 15 fs, makes PENNA a suitable candidate. A PPT presentation about this work, which was used as an invited talk of the ACS and invited plenary presentations is available upon request.

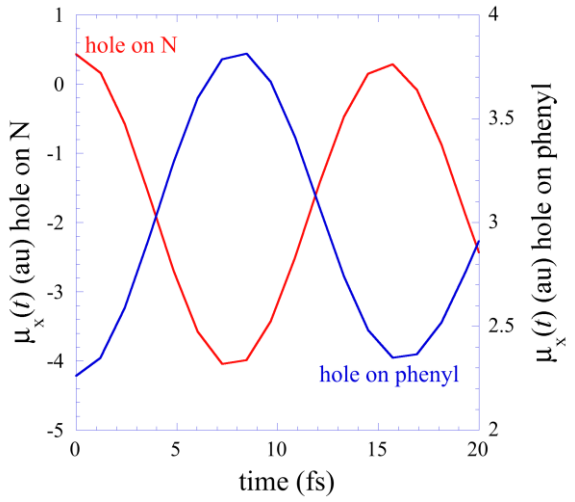

Figure 39: Time evolving dipole moment following initial ionization. Computed using a many electron basis.

The third direction results from our preliminary work on the generation of high harmonics. We concluded that unlike the impression given in the attoscience literature, there is considerable distortion of the molecule during the high field ionization. We have performed computations on several molecules, LiH, N_2 and PENNA, all of which confirm the extensive Stark mixing of unperturbed levels by the laser field. The results for LiH have just been accepted for publication in the Physical Review.

For the 2011-2012 project years we propose to make additional progress on all three topics as outlined above and to bring to fruition our new work on ABCU, (C10H19N), in collaboration with Marc Vrakking. A joint paper on stereodynamics of non equilibrium electronic excitation in ABCU has just been submitted for publication.

COLLABORATION WITH GERMAN SCIENTISTS

- Prof. K. Rademann and Dr. W. Christen of the Humboldt University of Berlin are my co-PI's in a shortly to end GIF proposal "Matter Under Extreme Conditions". I have visited them in Berlin and Dr. Christen has visited Jerusalem several times.
- Prof. T. Halfmann and Dr. F. Beil of TU Darmstadt are my coworkers in an ongoing project on molecular logic by optical excitation. They have both visited us in Jerusalem and my graduate student has spent time in Darmstadt. A joint paper has just been accepted by Physical Review Letters. We plan to continue with a joint effort on finite state logic machines.
- Prof. R. Weinkauf of the University of Düsseldorf is a long-term coworker on charge directed processes. Our 2006 joint paper on an all optical full adder on a single molecule driven by charge reorganization has been selected by the road map of information technology, ITRS, as a most promising new idea for 2007. As discussed in the scientific report, this project is still very much active.
- Prof. R. Waser and Dr. S. Karthaeuser of Forschungszentrum Jülich are my coworkers for several years in electrical addressing of single molecules. We have met several times both in Jülich and in Jerusalem and our next meeting is planned for March 2011 near Aachen.
- Prof. F. Krausz and Dr. E. Goulielmakis, Dr. R. Kienberger and Dr. M. Lezius of the MPQ Garching are my coworkers in a project on the ultrafast excitation of molecules. I have chosen to center my scientific report around this theme.
- Prof. K. L. Kompa of the MPQ Garching is a very long term coworker. Most recently we have joined forces on the subject of implementing a finite state logic machine by fs optical excitation. This initial effort is being continued by several other groups.
- Prof. M. Vrakking of the MBI Berlin has recently started a cooperation with us on ultrafast optical addressing of molecular logic. We are preparing for publication a joint paper on ABCU and we have just submitted a joint pre-proposal to the EU.

- Prof. M. Nest of the TU Munich is my coworker in a theoretical project on the ultrafast excitation of molecules. He has visited the Center several times.

PROFESSOR LEVINE'S GROUP 2008-2010

Name	Status	Presently
Dr. Haya Kornweitz	Collab.	Ariel University Center
Dr. Tamar Raz	Collab.	Jerusalem College of Technology
Dr. Menashe Rajuan	PhD	Hi-Tech company
Dr. Dan Steinitz	PhD	Jerusalem College of Technology
Dr. Ayelet Gross	PhD	Hi-Tech company
Michael Klein	PhD	Current
BenZion Harel Muskatel	PhD	Current
Sawsan Salameh	PhD	HUJI medical school
Noa Richke	MSc	Hi-Tech company
Harel Muskatel	PhD	Current
Dawit Hiluf	PhD	Current
Arumugam Rameshkumar	PhD	Current
Dr. Ganga Periyasamy	Postdoc	
Dr. Nataly Kravchenko-Balasha	Postdoc	

RECENT AND ACTIVE GRANTS

Granting Agency	Period	Amount
German Israel Foundation	2007-10	Euro 70,000
James Franck	2008-10	$130,000
EU	2008 –2011	Euro 219,000

MASHA Y. NIV

My overall scientific goal is to deepen our understanding of molecular recognition and to enable rational design of signal-modulating agents, which in turn can be used for studying signaling mechanisms in the cell. I draw on my training in theoretical physical chemistry and my subsequent experience in computational biomedicine to gain novel insights into ligand-protein and protein-protein interactions and ligand-induced dynamics in members of two key protein families, ***protein kinases (PKs)*** and ***G-protein-coupled receptors (GPCRs)***.

I took the position of **Lecturer (and later Senior Lecturer) at the Hebrew University** in 2007 and currently focus on PKs involved in cancer and diabetes—the two great challenges in human health research—and on the bitter-taste receptor subfamily of GPCRs.

TARGETING KINASE-SPECIFIC INACTIVE OR INTERMEDIATE CONFORMATIONS

This is one way to enhance the specificity of kinase inhibitors, rather than the active conformation, which is conserved among kinases. To capture non-active conformations that may be stabilized by novel and specific inhibitors, we need to explore the conformational changes that occur during the inactivation process. The 3D spatial resolution of dynamic processes is currently not tractable by experimental methods. Therefore, we used MD simulations in combination with statistical analysis to extract the most important motions occurring upon an inactivating dephosphorylation event in an emerging prostate cancer drug target, PKB. We established the correct protonation state of a histidine residue that stabilizes the interactions in the active form of the kinase (Figure 40), and found supporting evidence for a particular order of events during the active-inactive transition[134].

NATURAL COARSE GRAINING

Extending the simulation beyond the nano/microsecond timescales is one of the greatest challenges in computational biology today. One way of expediting the simulations is by reducing the number of degrees of freedom by coarse-graining the investigated structures, but the optimal way to coarse-grain a structure is not trivial. Our idea is to obtain ***a "natural" coarse-graining by identifying subregions*** in proteins that move as semi-rigid blocks (or "beads").

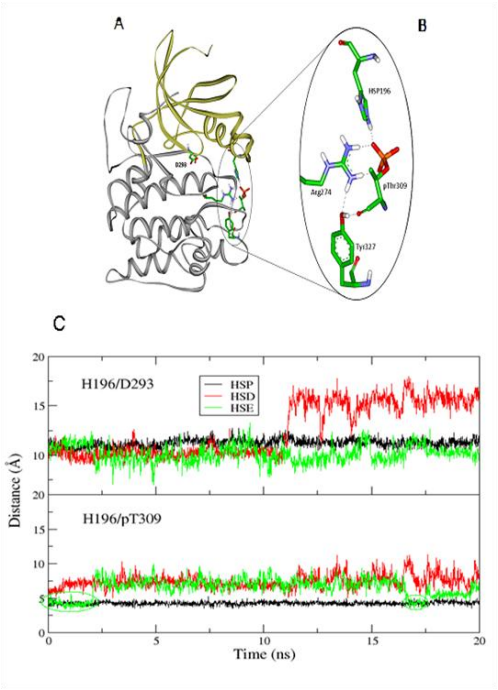

Figure 40: HIS196 is doubly protonated based on MD results Residues stabilizing pThr309 in the Akt complex. (A) Representative illustration of pT309-binding residues (colored by atom type) and hydrogen bonds (shown by dotted gray lines) of Akt complex with His 196 in the doubly protonated state. The phosphate group on T309 is shown in orange. The N-lobe and the C-lobe are shown in gold and gray ribbons, respectively. (B) The shortest heavy atom distances of the two residue pairs H196/D293 and H196/pT309 are calculated for Akt complex, with three protonation states of His 196, i.e., HSP (black lines), HSD (red lines) and HSE (green lines). From Cheng and Niv [134]

During her MSc studies in my lab, Marina Shudler used Normal Modes Analysis of PKs to identify motionally correlated regions and cluster them, in order to decompose PKs into semi-rigid subdomains. The BlockMaster technique we developed was validated against several test cases of independent proteins with known subdomains and was applied to identify similarities and differences between kinase subfamilies and between active and inactive conformations (MSc thesis 2009 and ref [135]). Extension and further applications of BlockMaster are currently being carried out by another MSc student in my lab, Morin Shavro.

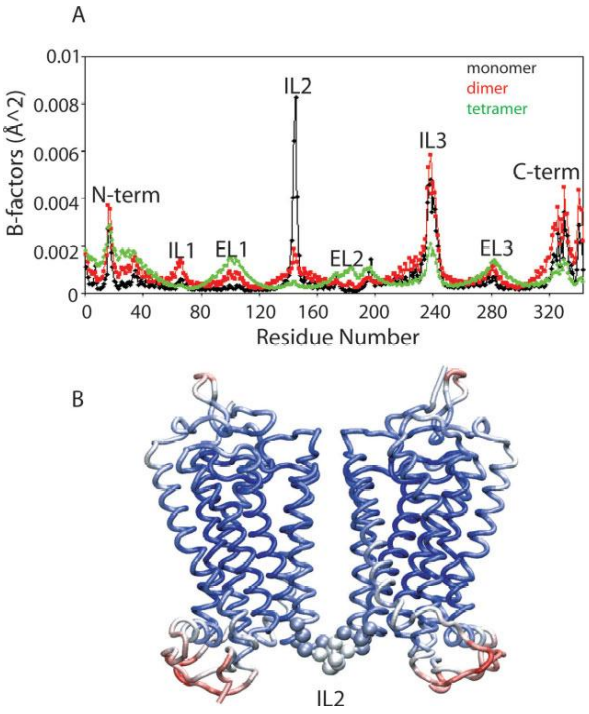

Figure 41: Oligomerization affects the internal motions of GPCRs: (A) Calculated B-factors for the first 50 lowest normal modes of rhodopsin monomer, dimer, and tetramer. (B) Vertical view of protomers A and B colored by the fluctuations calculated for the dimer, ranging from red (high fluctuations) to blue (no fluctuations). From ref. [136].

MODULATING ACTIVITY OF KINASES BY DISRUPTING THEIR INTERACTIONS WITH OTHER PROTEINS

Another approach to ***selectively modulating activity of kinases is by disrupting their specific interactions with other proteins***, rather than targeting the ATP-binding site which is common to all kinases. We contributed to this unorthodox approach early on (patents [137-139] and publications [140, 141]) and are continuing to extend, apply and promote this idea (refs [142-145] and ongoing work of Drs. Tali Yarnitzky and Avi Ben Shimon in my lab). We design peptides that mimic either the kinase or the substrate. Optimization of such lead inhibitory peptides requires structural information about peptide-protein

interactions. Computational prediction of peptide-protein structures ("peptide docking") is challenging due to peptides flexibility. We continue to develop an anchor-driven flexible peptide docking approach (see [146] and Figure 41) to identify and incorporate additional anchoring points.

BITTER TASTE RECEPTORS

Similar to PKs, ***GPCRs*** constitute a major family of signal-transduction proteins. These transmembrane proteins are activated by diverse ligands, including odorants, fatty acids, peptides and neurotransmitters. Recent advances in GPCR crystallography provide excellent opportunities for structure-based computational research ([147, 148]). As part of the Institute of Biochemistry, Food and Nutrition, we are particularly interested in the signaling of GPCRs that mediate flavor perception. Bitterness of food, recognized by a family of 25 bitter-taste receptors, plays a key role in food palatability. One of the most intriguing questions in the field of bitterness is: ***how can a few bitter taste receptors recognize hundreds of dissimilar bitter molecules****?* In fact, to begin answering this question, one must first compile information on the identity and chemical structures of the bitter molecules. However, such information is only partially available to the public. Ayana Wiener, a MSc student in my lab, is using text- and data-mining techniques to rectify this situation by compiling a database of chemical structures of all compounds known to be bitter. Ayana has already compiled structures of 400 molecules, which has enabled us to analyze their physicochemical properties (poster presented at the European Chemoreception Research Organization meeting, Sept. 2010). The database, BitterDB, will become publicly available and searchable by fields such as molecular weight, solubility, association with a particular receptor, etc.

To study the molecular determinants of **bitter molecules** recognition by their receptors, we established collaboration with Prof. Meyerhof's group at the German Institute of Nutrition, one of the leading experimental labs in the field. We found that exchanging two residues between hTAS2R46, activated by strychnine, and hTAS2R31, activated by aristolochic acid, was sufficient to invert agonist selectivity[149]. Anat Levit, a PhD student in my lab, is using molecular modeling and ligand-docking techniques to predict and compare the binding pockets in several bitter taste receptors (joint posters and work in progress).

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. We have used Normal Mode Analysis to investigate the effect of oligomerization on rhodopsin monomers (Figure 41) and to propose the most feasible transition from inactive to active tetramer conformation [136]. To elucidate the role of dimerization in signaling, dimerization-deficient, but otherwise intact receptors are needed. We established collaboration with Prof. Ponimaskin's lab in Germany, through which we were able to obtain GPCRs with reduced dimerization ability by re-engineering the predicted interface residues (two joint manuscripts in preparation).

These studies have pointed to electrostatic interactions between GPCR loops as important players determining the GPCR monomer affinities for each other (collaboration with Prof. Ponimaskin). We are also exploring the role of electrostatics in determining affinity and specificity of hormone-activated GPCRs and their respective hormones (Aizen, Kowalsman, Niv and Levavi-Sivan, in preparation).

Taken together, these research projects represent opportunities to promote our understanding, and in some cases to enable modification of cell signaling, by using computational tools. The computational approaches range from sequence-based conservation analysis to molecular dynamics simulations; in many cases development of special computational protocols (for example – anchor-driven flexible peptide docking or 'natural' coarse-graining) is inspired by challenges imposed by the biological systems of interest.

CONTRIBUTION OF FH CENTER TO THE RESEARCH

The Fritz Haber Center provides us with invaluable support by physically hosting and, most importantly, maintaining our High Performance Computer 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. Cheng and Niv, 2010 and manuscripts that are currently in preparation) heavily relies on the excellent technical support at Fritz Haber Center for carrying out MD simulations, docking, virtual screening and other computationally-heavy tasks.

In addition, the Fritz Haber Center provided financial support for the international conference on Biomolecular Simulations and Modeling which was co-organized by Dr. Daniel Harries and myself together with scientists from other academic institutions. The conference was very successful, with about 10 international speakers, including Dr. Martin Zacharias from Germany, and close to 100 participants in total.

RESEARCH PLANS

We plan to continue, expand and enhance our research on bitter taste molecules and bitter taste recognition. In close cooperation with the experimental lab of Professor Meyerhof (German Institute of Nutrition) we will study the structural details of bitter taste recognition, and rationally design selective bitter taste inhibitors. We expect at least two joint publications with the Meyerhof lab in high impact journals after finalizing current work in our collaborating labs on two representative bitter taste receptors. We submitted a trilateral research proposal to the DFG, with Prof. Meyerhof (Germany) and Dr. Karaman (Palestine), and a decision is expected within a few months. The database of bitter tastants, BitterDB, has been compiled by Ayana Wiener in my lab. Ayana is exploring the chemical properties of the bitter tastants with the goal of bitterness prediction. BitterDB is expected to go online in the next year, requiring expert technical support of the sys/admin team at the Fritz Haber Center.

We plan to continue studying the protein/protein recognition in GPCRs. In particular, our joint work with Prof. Ponimaskin (Germany) has resulted in identification of dimeric interfaces in serotonin homodimers, and provided testable hypotheses for the role of intracellular loops in serotonin heterodimers. These results will be published within the next year paving the way for further collaborative studies of serotonin receptors signaling.

Further collaborative studies with the German partner laboratories planned for the next two years include ongoing work on protein kinase dynamics and modulators design and further method development for knowledge-based prediction of peptide/protein complex structures.

COOPERATION WITH GERMANY

PROF. WOLFGANG MEYERHOF AND DR. MAIK BEHRENS FROM DIFE

I collaborate with Prof. Wolfgang Meyerhof and Dr. Maik Behrens from DIFE (Deutsche Institut für Ernährungsforschung Potsdam-Rehbrücke). Several joint posters were presented in international conferences, publication: [148, 149], and additional publications are expected within 1-2 years.

Exchange visits: I visited DIFE on several occasions: August 2008, February 2010 (together with my PHD student Anat Levit); August 2010. Next visit to DIFE is planned for the summer of 2011.

PROF. EVGENI PONIMASKIN (HANNOVER)

Collaboration and a joint grant (Niedersachsen-Israel Research grant, 1/1/2008-1/1/2012) with Prof. Evgeni Ponimaskin (Prof. Ponimaskin recently moved from Gottingen University to University of Hannover). Joint posters were presented and two joint manuscripts are currently in preparation.

Exchange visits: Prof. Ponimaskin visited my lab on 3 occasions (May 08, March 09 and May 10). I visited Prof. Ponimaskin in Hannover on Aug 2010. Next visit is planned for the summer of 2011.

DFG SPONSORED COLLABORATION WITH AL QUDS UNIVERSITY

Following a successful pre-proposal, we submitted to DFG a trilateral proposal together with Profs. Rafik Karaman and Hatem Hejaz from Al Quds University in Jerusalem.

STUDENT REPORTS FROM DR. NIV GROUP

DR. NOGA KOWALSMAN, POSTDOC

I am a postdoc at the lab of Dr. Masha Niv since January 2009, which I joined following my PhD at the Weizmann Institute of Science under the supervision of Dr. Miriam Eisenstein and the late Prof. Ephraim Katchalski-Katzir. My PhD on the subject of protein-protein docking, a computational approach for modeling protein complexes, included development of computational post-scan tools for identification of hits in docking runs results and their analysis (publications [150-152]) as well as cooperation with experimental labs in order to better understand and characterize the interactions of two protein kinases with their binding partners. In Niv lab I am working on two major projects involving protein-protein interactions of G-protein coupled receptors (GPCRs): (A) dimerization of serotonin receptors and (B) interaction between gonadotropins (GtHs) and their receptors.

SEROTONIN RECEPTORS DIMERIZATION

This project is in collaboration with the group of Prof. Dr. Evgeni Ponimaskin from the center of physiology in Hannover Medical School, Germany and is funded by the Niedersachsen-Israeli Research cooperation fund.

Serotonin (5HT) is one of the oldest signaling molecules from an evolutionary perspective, which activates serotonin receptors, a subfamily of GPCR receptors. In normal physiology, it takes part in developmental, cardiovascular, gastrointestinal, and endocrine function, sensory perception, and behaviors such as aggression, appetite, sex, mood, and memory. Irregular activation of serotonin was found in pathological conditions such as Alzheimer's disease, anxiety disorders and more. Thus it is of vast importance to elucidate the mechanisms by which the serotonin and its receptors work. There are several classes of 5HT receptors of which 5HT1A, 5HT2 and 5HT7 are the major classes.

Prof. Ponimaskin's lab has shown by FRET (Förster resonance energy transfer) that the 5HT1A receptors homodimerize. In order to understand how dimerization of serotonin receptors impacts their activity and regulation, we decided to create dimerization-impaired, but otherwise functional, mutants. I constructed structural 3D models of 5HT1A receptor using several GPCR templates and built models of a dimer complex based on a putative Rhodopsin dimer structure, in accordance with experimental results for other GPCR dimers and following previous work on GPCR dimerization in the Niv lab. I analyzed this model and suggested mutations that may disrupt dimerization. These mutations were tested in the lab of Prof. Ponimaskin and several mutations in transmembrane four (TM4) were found to interfere with dimerization. These findings supported TM4 as part of the dimerization interface for the 5HT1A receptors, and were introduced as constraints in subsequent implicit membrane simulations of 5HT1A homodimers. The iterative computational/experimental procedure provides an optimized model of the complex, which is used to further modify the homodimerization capability of the receptors.

The work on the homodimerization of 5HT1A receptors was presented in the 13th Israeli Bioinformatics Symposium in 2009 and The 8th Congress of The Israel Association for Medicinal Chemistry in 2010, and a joint manuscript is currently in preparation.

In addition to homodimerization, heterodimerization of serotonin receptors has important physiological consequences. We used sequence analysis and electrostatics calculations to rationalize the differences in heterodimerization affinities of different serotonin receptors subtypes, which were observed experimentally in Ponimaskin's lab (joint manuscript in preparation). Our results identified the molecular determinants that dictate heterodimerization affinities. These predictions are being tested via continued collaboration with the Ponimaskin lab.

THE INTERACTION BETWEEN GONADOTROPINS AND THEIR RECEPTORS

This project is in collaboration with the group of Prof. Berta Levavi-Sivan from the Animal Sciences department in the Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, Israel.

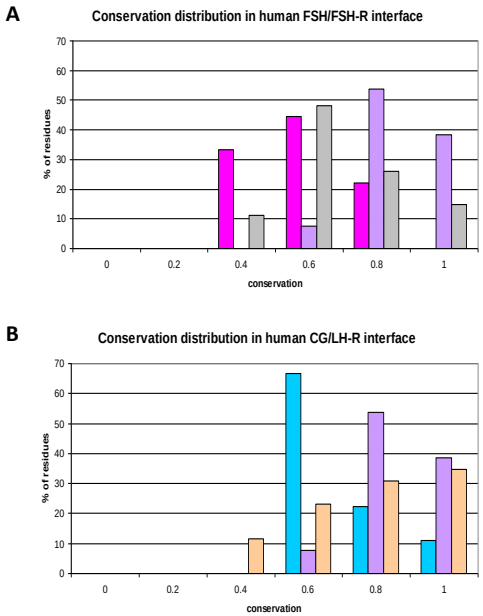

Figure 42: Distribution of interface contacts conservation using human sequences as reference. (A) Shows the distribution of conservation for the contacts in FSHβ alpha and FSH-R (magenta, purple and gray respectively) and (B) shows the distribution of for LHβ/CGβ, alpha and LH-R (light blue, purple and peach respectively). On the X- axis the conservation value that ranges from 0 to 1 (1 most conserved). The height of each bin reflects the % of interface contacts having those conservation values out of the total number of interface contacts for each unit (Y- axis).

The gonadotropins (GtHs), namely luteinizing hormone (LH) or chorionic gonadotropin (CG) and follicle-stimulating hormone (FSH) are major hormones of reproduction and directly control many aspects of gonadal development. GtHs constitute two subunits, α and β, where the α subunit is common to all the GtHs from the same species. GtHs bind and activate the GtH receptors (GtH-R), members of the GPCR family. The binding of the hormone to the receptor occurs at the large extra-cellular N-domain that is connected to the GPCR 7 transmembrane bundle via a long linker.

Details of GtHs function and their binding to their receptors is extremely important in diverse fields, from In-Vitro Fertilization (IVF) to fish farming (aquaculture). Prof. Levavi-Sivan's lab has explored the binding of GtHs from various species to GtH receptors from human and multiple fish species, using luciferase reporter gene assay, to investigate the co-development of hormones and receptors and identify cross reactivity.

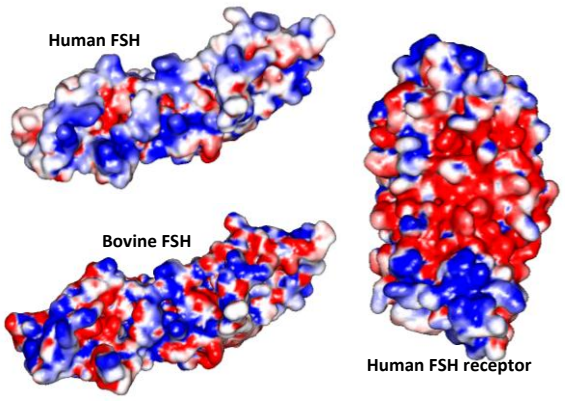

Figure 43: Better fitting between the electrostatic potential in the interface of human FSH and FSH-R. The Electrostatic potential on the surface of human and bovine FSH and human FSH-R is shown on surface representation of the molecules. The electrostatic potential scales from -3 (red) to 3 (blue) kT/E.

Indeed, a particular pattern of intra and inter species cross reactivity was found. I constructed 3D models of the hormones and receptors from several species, in order to provide structure and sequence-based explanation for the experimental results. To my knowledge, these are the first models of GtHs and GtH-R for fish. Analysis of the interface residue conservation (see Figure 42) revealed that the interface in the α subunit is more conserved than in the β subunit. This is in agreement with the fact that the α subunit is common to LH, CG and FSH, therefore mutations in this unit provoke a change in interactions with all the GtH receptors. Additionally, we find that the interface residues of the LH receptor are more conserved than of the FSH receptor. This implies more intricate co-evolution of the FSH and FSH receptor and is in agreement with the cross reactivity results from Levavi-Sivan lab. Interestingly, human and bovine FSH sequence similarities for the α and β subunits (excluding the signal peptide) are 87% and 98% respectively, and none of the receptor interface residues differ. We hypothesized that the indirect effect of the electrostatic potential may explain the experimentally observed impaired activation of the human FSH by the bovine hormone. I calculated the electrostatic potential of the proteins (Figure 43) and indeed showed that the interface of human FSH has more positive charge than the interface of bovine FSH, better fitting the negatively charged interface of the FSH receptor.

This work was presented at the 2nd annual conference of the Nutrigenomics and Functional Foods Research Center and at the annual Israel Biophysical Society Meeting in 2010, Rehovot, Israel, and a joint manuscript is currently in preparation.

CONTRIBUTION OF THE FRITZ HABER CENTER TO MY WORK

The Fritz Haber center holds the main computer cluster I use in my work. This computer cluster needs careful and constant management. The cluster provides ground for the Discovery Studio (DS) package, a program for viewing and modification of macromolecules, which I use on a daily basis. In addition I use this computer for developing short programs and long simulation runs (e.g. refinement and molecular dynamics in implicit membrane solvent using CHARMM) that are part of my work. The center provides the system administration support by setting the DS program and managing the queuing and parallelization of all simulation runs as well as efficiently solving any technical problems that arise related to storage, back-up etc.

ANAT LEVIT, PHD STUDENT

I joined the Niv lab in 2008, after completion of MSc degree in human genetics at the Tel-Aviv University Faculty of Medicine in 2006. My PhD thesis is focused on "specificity determinants in GPCR subtypes", and is under the supervision of Dr. Masha Niv and Prof. Rina Meidan (department of Animal Sciences, the Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University).

In this computational work we aim to gain insight into ligand-receptor interactions which govern small molecule binding in the TM cavity of G-protein coupled receptors (GPCRs). To this aim, we chose to focus on two GPCR subtype families, representing two distinct cases: (1) the family of human bitter taste receptors, which are activated by a broad spectrum of chemically diverse ligands, all leading to the same signaling outcome, and (2) the highly similar human Prokineticin receptors, activation of which by the same cognate ligands results in diverse signaling outcomes.

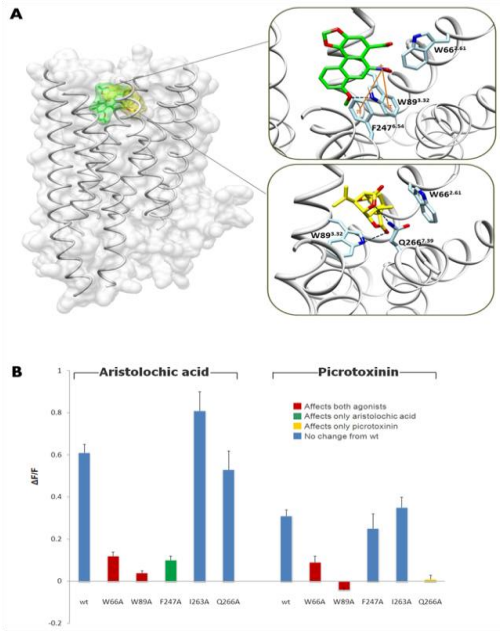

Figure 44: (A) Overall location of two hTAS2R14 agonists - aristolochic acid (green sticks) and picrotoxinin (yellow sticks) within the receptor, following docking to the main hTAS2R14 binding site using CDOCKER. Indication of intermolecular interactions observed between each ligand and receptor residues (light blue sticks) is shown in the inserts. Hydrogen bonds are shown as dashed black lines. π-cation interactions are shown as orange lines. (B) Functional calcium imaging of hTAS2R14 point-mutants. Amino acid exchanges were introduced by site-directed mutagenesis to alanine. The activations of the resulting receptor mutants were compared to wildtype hTAS2R14 (wt) using two different agonists, aristolochic acid and picrotoxinin at concentrations close to their EC50-values (1μM for aristolochic acid and 30μM for picrotoxinin). For functional expression the receptor constructs were transiently transfected into HEK 293T-Gα16gust44 cells and after 24h loaded with calcium-sensitive dye and challenged with agonists. Changes in fluorescence (ΔF/F, y-axis) upon agonist application were monitored using a fluorometric imaging plate reader (FLIPR).

STRUCTURE-FUNCTION STUDIES OF BITTER TASTE RECEPTORS

Bitter taste perception in humans is mediated by 25 GPCRs of the hTAS2R gene family. One of the main questions in bitter-taste research is how just 25 receptors can detect thousands of structurally diverse bitter compounds. The pharmacological properties of hTAS2Rs are characterized by several important features: a rather broad tuning, exemplified by the fact that many bitter receptors are activated by chemically dissimilar compounds, but discriminate even among similar bitter compounds with high accuracy; the affinity for bitter agonists is rather low (micromo-

lar range) compared with other GPCR-ligand interactions; all TAS2Rs share the same downstream signaling cascade.

The structural basis for the hTAS2Rs' unique feature of allocating numerous chemically diverse low affinity agonists is the focus of our collaborative study with the Meyerhof lab at the German Institute of Human Nutrition, Potsdam-Rehbruecke, Germany, one of the world leading experimental labs in the field of taste receptors.

The general objective of this project is to elucidate the interactions between bitter tastants and bitter taste receptors in order to improve the molecular understanding of bitterness and provide ways to modulate activity of bitter taste receptors.

A detailed study on the structure-function-relationship of hTAS2R46 and closely related receptors, revealed a transmembrane binding pocket which is involved in agonist interaction. Moreover, this study showed that a number of receptor positions interacting with bitter agonists have been shown in other, unrelated GPCRs to be important for ligand interactions as well. Additionally, the results demonstrated that even though hTAS2R46 is one of the most broadly tuned bitter taste receptors, it possesses a single binding pocket that accommodates structurally diverse agonists (Brockhoff et al. PNAS 2010; Levit et al, submitted).

To elucidate the sites of interaction between the broadly-tuned hTAS2R14 and its different agonists, we applied an iterative combination of computational tools with mutagenesis and functional assays. We generated an all-atom 3D model of the receptor, and predicted putative binding sites in the receptor cavities by an energy-based method. This was followed by computational docking of the ligand to the receptor model, and evaluation of the predicted specific interactions. We then designed model-based mutations. Functional assays on wild-type vs. mutant constructs confirmed the in-silico predicted interactions and corroborated the main predicted binding site, situated inside the trans-membrane bundle (Figure 44). This site is analogous in position to previously identified binding pockets of other bitter taste receptors, such as hTAS2R46. However, hTAS2R14 exhibits striking differences upon mutagenesis. Most intriguingly, hTAS2R14 activation appears to be less affected by amino acid exchanges in positions shown in other bitter taste receptors to result in complete loss-of-function, and is highly affected by mutagenesis of other positions in this cavity. Also, we observed ligand-specific subsites within the main binding cavity. These results begin to shed some light on the structural differences between the different hTAS2Rs and provide experimentally supported models of binding pockets that will be used for identification of additional potential binders ("structure-based virtual screening"). In summary, the interconnection of homology modeling and in-silico binding site prediction and ligands docking, with receptor mutagenesis and functional assays effectively enhanced receptor characterization.

This method is currently being applied to investigation of molecular recognition by the third broadly-tuned bitter taste receptor – hTAS2R10, in collaboration with the German partner.

PROKINETICIN RECEPTORS

An inverse situation in terms of number of cognate ligands and signaling outcome occurs in the receptors for mammalian prokineticins (PK1 and PK2), two novel highly similar secreted proteins of about 80 residues in lengt0h. PKs serve as the cognate ligands for two highly similar GPCRs termed PK receptors (PKR1 and PKR2). Located in different chromosomes, these two receptors share 85% sequence identity, which is an extremely high value among known GPCR subtypes. The receptors' ability to couple to different G proteins leads to diverse biological actions following activation. For example, cAMP accumulation through Gs coupling leads to vasodilation of endothelial cells, while receptor coupling to Gi causes activation of the ERK1/2 and Akt pathways which in turn induce increased cell proliferation.

Better understanding of the PK system can generate tools which will affect diverse areas such as development, immune response and endocrine function. The molecular details of PK receptor interactions with their ligands and downstream signaling partners, as well as the molecular basis of differential signaling remain to be resolved.

To be able to dissect signaling of the two hPKRs, an inhibitor or an activator selective for one of them is of great value. The endogenous ligands of hPRKs are small proteins that bind to the extracellular regions of the receptors. However, several synthetic small molecular antagonists were reported. We hypothesized that these small molecules will occupy a pocket within the transmembrane bundle similar to other GPCRs, including the bitter taste receptors discussed above. We aim to investigate whether there is innate diversity in the composition of the TM bundle binding site of hPKRs, which may be exploited for design of novel selective binders (either agonists or antagonists) of hPKRs. We generated 3D models of both subtypes, and identified the location of a potential small molecule-TM bundle binding cavity using an energy-based method. We then performed molecular docking of the small molecules (both activating and non-activating) that were reported in the literature to this binding site. We analyzed the binding patterns of activating vs. non-activating compounds, to elucidate the ligand-receptor interactions used by the activating compounds. Particular hydrogen-bonding pattern was found to be essential in virtually all activating compounds, but not in non-activating compounds. Overall, the interacting residues are located in positions which have been shown to be involved in such interactions in numerous rhodopsin-like family members, thus reinforcing our computational predictions and lending support to the concept that all rhodopsin-like GPCRs share a common small molecule binding pocket inside the TM cavity, regardless of the nature of their cognate ligand. The sites and the chemical features that we showed to be required for activation, were used to extract back the known active molecules as well as additional molecules from the drug bank database which are therefore predicted to be active as well. Our results indicate that the binding mode explored by the so far reported PKR binders engage only residues fully conserved among the two subtypes. We are therefore exploring additional regions related to differential signaling, see Future Plans.

CONTRIBUTION OF THE FRITZ HABER CENTER

The entire computational work described above could not have been carried out without our computational resources which are maintained by the Fritz-Haber center. The center provides excellent computational support and administration which is of the outmost importance when performing large scale calculation such as required in these projects.

FUTURE PLANS

Bitter taste receptors - specific ligand-receptor interactions of hTAS2R14 identified using computational docking studies will be translated into structural constraints which will be applied in virtual screening to identify novel hTAS2R14 binders. Through this computational study we expect to identify agonists, thus expanding the range of known hTAS2R14 activating compounds, and antagonists, which are a much sought-after tool in both the food and pharmaceutical industries. In the long run, such compounds may be able to eliminate the aversive taste of medicine and foods and should therefore result in better patient compliance in taking medicines, as well as increased consumer acceptance of healthy, but bitter vegetables and fruits. Such inhibitors will also serve as valuable tools for basic research, since selective inhibitors of bitter taste receptor will enable to shed light on the interplay between these different receptor subtypes both in taste recognition and in other tissues (such as gut and lung) where these receptors were recently, and somewhat surprisingly, shown to be expressed.

Prokineticin receptors - through a comparative evaluation of hPKR1 and hPKR2 binding cavities, we will determine possible differences in these allosteric binding sites. We aim to find, via virtual screening into non-identical sites in the receptors, compounds that will differentially bind to either hPKR1 or hPKR2. These compounds will be tested in the lab of Prof. Meidan. In addition, we will further explore intracellular regions of the receptors for differences that may explain differential signaling and target these positions for selective inhibitors design.

DR. NIV GROUP MEMBERS

Name	status	Presently
Marina Shudler	MSc	PHD student in Weizmann Inst.
Mor Rubinstein	PhD	Volcani Institute
Dr. Shu Cheng	Postdoc	PostDoc in Université de Technologie de Compiègne, France
Yonatan Aizner	undergrad	MSc student at HUJI
Inbal Sela	project student	PhD student in Bar Ilan University
Anat Levit	PhD	Current
Dr. Noga Kowalsman	Postdoc	Current
Morin Shavro	MSc	Current
Ayana Wiener	MSc	Current
Dr. Avi Ben Shimon	Postdoc	Current
Dr. Talia Yarnitzky	Postdoc	Current

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

September 2009, Initiator and co-organizer of "Biomolecular Modeling and Simulations" conference, Safed, Israel, which was partially co-funded by Fritz Haber Center.

ASSAF ZEMEL

RESEARCH ACTIVITY

Recent research has shown that the mechanical properties of the cellular microenvironment play an important role in the determination of many fundamental cellular properties and processes. For example, the elastic rigidity of the extracellular matrix has been shown to govern the size, shape and internal structure of cells. A very influential recent study[153] showed that the rigidity of the surroundings can direct the lineage specification of stem cell differentiation. Cells plated on substrates of varying rigidities that mimicked that of brain, muscle and bone, adopted the shape and differentiated state of the corresponding tissue-cell types (Figure 45A). It is now understood that the ability of cells to sense mechanical properties of their environment results from the traction forces they exert into the surroundings. In the past few years we have developed a general theoretical framework for studying the active interplay of forces between cells and their environment, see [154-159]. We study how the elastic stresses generated in the cytoskeleton govern various mechanical processes in the cell; as well as how they give rise to elastic interactions of cells. This is used to investigate the role of cell-cell elastic interactions in the alignment and patterning of cells. In addition, we study on the molecular level how ensembles of motor proteins, cytoskeletal filaments and other associated proteins produce self-organization, movements and forces in the cell.

CELL SHAPE, MATRIX RIGIDITY AND THE POLARIZATION OF STRESS-FIBERS IN CELLS

In the past year we published two papers that focused on the mechano-sensitivity of stem cells [154, 158]. This work has been done in collaboration with Dr. Florian Rehfeldt from the University of Göttingen, Prof. Dennis Discher and co workers at the University of Pennsylvania, and Prof. Samuel Safran at the Weizmann Institute. Ref. [154] was covered by a News and Views report in Nature Physics. These papers revealed several generic consequences of force-balance in cell-matrix interaction. It is empirically known that cells spread better and generate larger forces when plated on more rigid substrates. Ref. 9, proposed a simple elastic model that predicts the correct functional dependence of cell size and force on the matrix rigidity. In addition, our model allowed us to predict the orientational order parameter of acto-myosin stress-fibers in the cell, as a function of the cell shape and matrix rigidity.

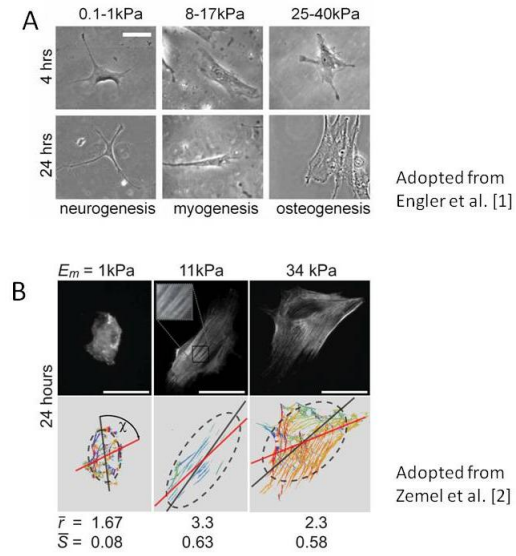

Figure 45: Human mesenchymal stem cells grown on substrates of varying rigidities. Panel A, shows the distinct cell morphologies that were obtained on the respective substartes, and Panel B, shows our analysis of the orientational distribution of the acto-myosin stress-fibers in the cytoskeleton; see text and Refs. [153] and [154] for details.

These force-producing elements of the cytoskeleton (see Figure 45B) have been shown to play an important role in the mechano-sensitivity of cells. Consistent with our collaborators' experiments on stem cells, we found that: (i) for moderate rigidity of the surroundings, stress-fibers polarize parallel to the long axis of the cell. (ii) the alignment increases with the aspect ratio of the cell; (iii) the orientational order parameter depends non-monotonically on the matrix rigidity, attaining a maximum for moderate rigidity of the matrix that is comparable to that of the cell. The model also predicts the effect of the anisotropy of cell spreading on the alignment of stress-fibers in cells (2). These findings unravel a fundamental and general relation between the cell shape, matrix rigidity and the polarization of stress-fibers in the cytoskeleton. We believe that this coupling plays a central role in the eventual determination of cell size and shape. Thus our findings provide important physical insight into the mechanical mechanisms involved in the mechano-sensitivity of stem cell differentiation.

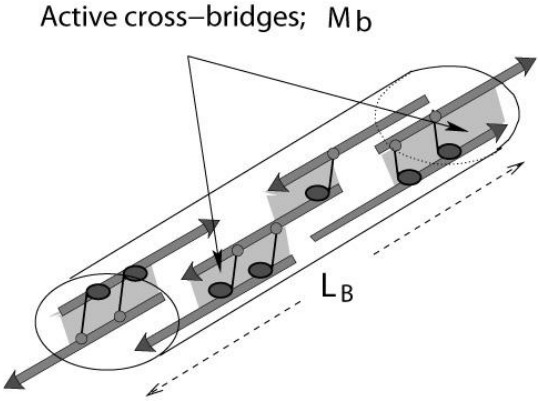

Figure 46: Schematic illustration of a cross-linked bundle of cytoskeleton filaments powered by molecular motors. M_b is the number of active overlap regions between filaments indicated by gray shading; L_B is the bundle length.

SLIDING DYNAMICS AND POLARITY SORTING OF ACTIN AND MICROTUBULE BUNDLES

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. 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 Figure 46. To theoretically explore the effects of these interactions on the self-organization and dynamics of

the filaments 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 [160, 161]. 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.

FUTURE RESEARCH PLANS

Our research on the mechano-sensitivity of stem cells provided a solid basis for extending our investigation of the physics of cell adhesion. In April 2009 I was invited by Prof. Christoph Schmidt and Dr. Florian Rehfeldt to the department of Physics at Göttingen to tighten our collaborative research. An important challenge that arises from our joint study is to develop a model for the dynamics of cell shape acquisition. Figure 45A shows that the shape that stem cells adopt changes non-monotonically with the matrix rigidity; on both the soft and hard substrates the cells assume symmetric structures, while on the substrate of intermediate rigidity they elongate (quantification of this is found in [153]). We hypothesize that this phenomenon is related to the symmetry characteristics of the elastic stresses that develop in the cell during cell spreading. Based on these considerations we have recently developed a 1D model that correctly predicts the dynamics of cell spreading on differently rigid substrates. Our goal is to extend this to 2D spreading and to account for important elements in the dynamics of cell shape acquisition. In addition, we are developing a numerical algorithm that will allow us to predict the dynamics of stress-fiber polarization in the cell. This will allow us to account for several simultaneous mechanical processes that take place during cell adhesion, including the redistribution of focal adhesions at the cell periphery, the polarization of stress-fibers in the cell, and the changes in cell shape.

These processes are studied experimentally in the group of Dr. Florian Rehfeldt for various cell types and in different mechanical conditions and we are applying for a joint grant to fund this collaborative research.

In addition, the research in our group is advancing in two other directions.

We develop an energetic formalism for studying cell-cell elastic interactions. Earlier studies have shown that in many cases of interest cell orientation can be predicted by simple considerations of force-balance [162, 163]; it has been shown that minimization of the elastic energy that results from the cells' mechanical activity reveals correct predictions about cell orientations. These ideas are being extended and will be applied to phenomena that have not yet been studied. For example, we shall study the recent experimental observation that the tendency of cells to self-associate decreases with the matrix rigidity. In addition, in collaboration with Dr. Ralf Kemkemer, at the Max Planck Institute for metals research in Stuttgart, we plan to study the spontaneous alignment of cells in differently shaped domains as well as the alignment of cells next to boundaries and in response to external loads.

Finally, we also continue our study of self-organization in the cytoskeleton on the molecular level. Thus far our simulations did not account for the presence of external forces that may oppose the collective activity of the molecular motors. However, in many cases of interest the motion exerted by the molecular motors is opposed by the elastic resistance of the lipid cell membrane. In the next years we plan to extend our simulations to include the effects of external forces, to generalize the simulations to 2D

geometries and to study specific systems of biological interest.

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

CONTRIBUTION OF FRITZ HABER CENTER TO MY RESEARCH

The numerical work in the above projects is carried out with the indispensible help of Michael Vilenkin and Max Tkach - the system administrators of the Fritz Haber center. They have helped us in the purchase and assembly of the group's computer cluster; and they professionally maintain the system and provide useful advice to our group members whenever it is needed.

GRANTS

Israel Science Foundation: $210,000, 2010-2013.

GROUP MEMBERS

- Leora Moshe – Ph. D student (2009)
- Roni Jutkowits - Ph. D student (2010)
- Einat Sagi – M.Sc student (2010)
- Avinoam Bronstein M. Sc. Student (2010)
- Nimrod Ben-Shalom, undergraduate physics student
- Maayan Sagi, undergraduate physics student.

RECENT PUBLICATIONS FROM FH CENTER (2008-2010)

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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COOPERATION WITH SCIENTISTS IN GERMANY

The researchers of the Fritz Haber center have a long history of steady and close collaboration with scientists from Germany. This is best reflected in joint research and papers, co-authored by German and Fritz Haber center researchers. Details of the collaboration in the recent years can be found in the personal report of each of the principal researchers and their students above (names, projects and research achievements). Here we will discuss only more “global” aspects of the collaboration.

Over the past 20 years 155 papers co-authored by researchers of the center and scientists from Germany were published (out of a total of 1420 publications), accumulating over 4450 citations with an average of 29 citations per item and an h-index of 34. One of these papers, a review, was cited over 530 times (principal author was R. Kosloff from the center and among the 13 authors there are two scientists from different German research groups). Furthermore, a total of 8 of these papers obtained over 100 citations.

More recently, in the past 4 years, 31 such joint papers were published (out of a total of 180 papers published by the members of the center in this period). The average annual publication rate with German scientists is 11%. In the past 4 years the rate is considerably higher around 17%.

Summarizing this data, we find that historically the center has induced prolific and scientifically strong joint research between its members and many scientists from Germany and that this collaboration rate is growing on the average in more recent years.

Collaboration is reflected of course not only in joint papers and research. Indeed, personal ties and meetings and participation in Israeli-German scientific events and forums are highly indicative as well. The number of visits of German scientists to the center or to activities organized by members of the center in the period 2007-2010 exceeded 60 and the number of visits of researchers from the center to Germany in that period was 17.

In the past 7 years, 3 different Gentner Symposia were organized or co-organized by members of the center (Ben-Shaul, Baer and Agmon). These Minerva funded symposia, brought dozens of students and professors from Germany to meet Israeli researchers as well as other renowned scientists from all over the world and contributed significantly to strengthen the collaboration and joint research between the two counties. The center has organized and supported dozens of scientific conferences with significant participation of scientists and students from Germany. The conferences of just recent years are listed in the appendix to this report. Professor Kosloff and later on Professor Baer have participated actively in the Minerva Fellowship committee which meets twice a year, once in Germany and once in Israel.

RESEARCH PLAN FOR THE NEXT 2 YEARS

SUMMARY OF INDIVIDUAL PLANS

Agmon group: studying proton transport in complex environments using molecular simulations, focusing on new proton mobility mechanisms that can occur in various ionic solutions, hydrophobic or hydrophilic interfaces, and porous media. Reinterpret the IR spectrum of protons in bulk water in lieu of the "special pair dance'' (see detailed report).

Baer Group: In DFT: Developing and testing our new concept of “tuned” range separated hybrid in DFT and TDDFT: applications for transition states; description of excitations in oligoacenes. Strong laser-molecule interactions based on a new approach (ref. [46]). Charge transfer excitations for light harvesting systems. The charge-transfer and strong laser-molecule interactions will form the basis for widening and extending the cooperation with Prof. Dr. Stephan Kuemmel’s Bayreuth group in Germany. Finally, we plan to study the spectroscopy of hybrid metal-semiconductor Nanostrctures.

Ben-Shaul’s group: 1) Physical chemistry of viral systems, with emphasis on genome structure, energetics, and packaging. 2) Multi-scale modeling of membrane adhesion, inter-cellular junctions, and tissue development.

Gerber group: mechanisms and dynamics of atmospherically relevant reactions at surfaces, aerosols and clusters (with Prof. B. Abel (Leipzig)); photochemical processes and dynamics of peptides and their hydrates (with Prof. Walther Thiel, MPI Mülheim); review of the work done in the framework of Sfb 450, namely nonadiabatic processes in photochemistry of molecules in matrices (with Prof. O. Kühn Univ Rostock).

Harries Group: Ionic liquids as possible solutes for directed self-assembly of macromolecules. With the group of Prof. Werner Kunz (Regensburg) we are planning to study Deep Eutectic Solvents (DES), in particular mixtures of choline salts with urea or sugar.

Kosloff group: Continuously driven quantum refrigerators and quantum absorption refrigerators; molecular ultrafast spectroscopy under dissipative conditions on weak field coherent control (with Prof. D. Miller in Hamburg); algorithms for simulating quantum dynamics from first principles using explicitly time dependent Hamiltonians in the nonlinear regime, such as the Gross-Pitayevsky equation; two-photon photo-association of Mg atoms (collaborating with Prof. Zohar Amitay Technion and Profs Christiane Koch in Kassel).

Niv group: research bitter taste molecules and bitter taste recognition (with Prof. Meyerhof in German Institute of Nutrition); protein/protein recognition in GPCRs (joint work with Prof. Ponimaskin Germany). Further collaborative studies with the German partner laboratories planned for the next two years include ongoing work on protein kinase dynamics and modulators design and further method development for knowledge-based prediction of peptide/protein complex structures.

Zemel group: Develop a model for the dynamics of cell shape acquisition (with Prof. Christoph Schmidt and Dr. Florian Rehfeldt, Physics/Göttingen); Developing an energetic formalism for studying cell-cell elastic interactions; self-organization in the cytoskeleton on the molecular level, extending our simulations to include external forces and 2D geometries in systems of biological interest; spontaneous alignment of cells in differently shaped domains and next to boundaries in response to external loads (collaboration: Dr. Ralf Kemkemer, at the Max Planck Institute for metals research in Stuttgart).

FUTURE RESEARCH DIRECTIONS

The recent research groups joining the center expanded its domain of activity into new fields of soft matter, protein and macromolecular dynamics and cell dynamics – largely biophysical topics. We feel that the next recruit must be made in fields related to solar energy or green energy, where considerable scientific activity is developing worldwide. Some activity in this direction is already developing in the

center, namely, solar cells based on multiexciton generation in nanosystems and the study of charge-transfer excitations with impact on light harvesting applications (see Baer's report), the center is looking to further increase activity along this venue. Thus, the center is pushing a new candidate through the academic appointment channels of the university with expertise in many-body electronic and heat conduction aspects of molecular systems, surfaces, interfaces and junctions. This candidate, who currently holds an assistant professor position in a leading university in the USA, has agreed to join the faculty and the center if offered and will significantly contribute to this direction (the candidacy of this scientist has been approved in beginning of January 2011 by the institute of Chemistry and is now under approval stages of the higher committees of the university).

Another aspect of solar energy affecting storage, transportability and dispatchability, is the conversion of solar energy into chemical energy by producing stable energy-rich molecules from highly abundant energy-poor ones. The water or carbon dioxide "splitting" is an example. Such projects involve heterogeneous photocatalysis. In our center and the chemistry institute there is ample theoretical (Kosloff, Gerber, Baer) and experimental (Banin, Asscher) expertise for studying such processes. This topic holds a potential for fruitful collaboration with German scientists, based on existing ties (Kosloff and Freund in Berlin or Klüner in Oldenburg). The center will attempt to bootstrap research in this direction within the next 2 years.

COLLABORATION WITH GERMAN SCIENTISTS

Going over the research plans of the members of the center above, it is evident that the young members of the center (Harries, Niv and Zemel) are planning to develop strong research collaborations with German scientists. The center is determined to assist these attempts by funding mutual visits, especially of students from both sides and by funding meetings and workshops organized by these young faculty members.

SCIENTIFIC TECHNICAL STAFF

In recent years, the help offered by the university in the form of scientific technical staff has deteriorated or more precisely almost disappeared. While the university partially supports a programmer in the capacity of a systems administrator, it is not of the caliber we need and remote from what we had about 10 years ago. Formerly, our technical staff was headed by a PhD staff scientist, a theoretical chemist. Now, we have a mere programmer at our disposal. Recently we have decided to push for renewed support in our research. We have located an outstanding candidate for this role of scientific management of our computer facility: Dr. Ester Livshits who was a student in Baer's group, is an excellent quantum chemist with strong background in scientific programming and high performance computing. Recently Dr. Livshits agreed to take over the scientific administration of the Fritz Haber computer facility and is scheduled to start working in this capacity by mid February 2011. Dr. Livshits will oversee not only system administration services but more importantly offer scientific computational advice, will maintain and enhance our scientific software and support our parallel computation capability. She will help students in computer programming and running complex implementations. We will endorse her active participation in the research of various groups of the center, contributing her strong expertise in quantum chemistry. The University is not able to fully support this important development. In this respect, the continued operation of the Fritz Haber center is crucial, as its funding will be used to partially complement the relatively meager funding of the university for this purpose.

PERSPECTIVE: ADDED VALUE FOR RESEARCH AND COLLABORATION

Fritz Haber is an organic center. No, I don't mean an "organic chemistry" center (God forbid…) What I mean is that the Fritz Haber center is like a "living organism". That students and postdocs, Israeli and foreign, all packed together in the same geographical location with their professors, enjoy an inspiring and scientifically fertilizing environment. This is a result of the many visitors, the seminars and the broad scope of research the center offers. The center endorses a

truly “togetherness” feeling among its researchers, young and mature. The wide range of scientific fields covered by the groups of the center leads to a fruitful exchange of ideas; discussions and debates are forever ongoing in the center, spawning scientific friendships, fertilizing research. Close collaborations are a direct result of the physical and organizational unity offered by the center. Collaborations once started during studentship often last well beyond this period, for example, the collaborations of Todd Martinez and Michal Ben Nun, of Roi Baer and Eran Rabani and of Anna Krylov and Pavel Jungwirth. Needless to say, the excellent atmosphere in the center is a source of attraction for students and postdocs near and far.

The added value in a continuation of the center is in its diverse and unique vibrant character as a scientific educator and research producer, proved excellence in research and its potential for developing collaborations with German groups. Indeed, the existing ties of the center with leading German scientists as well as the funding opportunities help the younger members of the center to develop their own collaboration with German labs.

FINANCIAL CAPITAL FUNDS AND EXPENDITURES 2008-2010

This report was prepared by the authority for research and development of the University (ref. No. 030.7618(4),(5),(6)). Annual details appear in Appendix 4.

INCOME IN EURO:

Years	2008	2009	2010
Total capital funds:	**1,237,813**	**1,390,389**	**1,579,817**
Return on capital funds %:	3.6%	3.6%	2.6%
Return on capital funds :	44,561	54,985	40,059
Matching by the university :	44,561	54,985	40,059
Balance from previous year (*)	*0*	*0*	*25,233*
Total Budget of MC of 3 years:	**89,122**	**109,970**	**105,351**

EXPENDITURES IN EURO	2008	2009	2010
1.Salaries			
1.1.Administrative	41,098	40,661	46,616
1.2.Scholarships/Academic positions	7,401	11,175	11,100
2.Exchange of Scientists/Travel Costs:	7,533	6,017	5,654
3.Workshops/Symposia:	5,648	1,974	6,877
4.Operational costs,material,equipment:	23,759	26,611	18,836
5.Various expenses:	3,683	112	0
6.List of expenses out of the matching budget if other than 1-5 and /or if in-kind:	0	0	0
Total	**89,122**	**86,550**	**89,083**
Balance:	***0***	***23,420***	***16,268***

(*)The balance from previous years includes currency fluctuations

Structure of the 3-year budget:

- About 3/4 of the budget is invested in the services offered by the center to the research groups: 48% salaries of the administrative and technical staff and 26% operational costs materials and equipment renewal/repair.
- 1/4 of the budget is invested in sponsored scientific activities such as scholarships (11%), exchange and travel (7%) and funding workshops, and scientific meetings (6%),

NOTE: The relatively large drop in income in year 2010 is unclear. We are trying to get explanations for this from the university authorities.

APPENDICES

APPENDIX 1: PAST FRITZ HABER STUDENTS WHO ARE ACADEMIC FACULTY

1. Roger Alimi, Nuclear Research center, Soreq
2. Roi Baer, The Hebrew University of Jerusalem
3. Zlatko Bacic, New York University, NY
4. Rob Bisseling, Utrecht University, The Netherlands
5. Yardena Bohbot, Biology Institute, Nes Ziona
6. Eric C. Brown, Loyola University, Chicago, IL, USA
7. Victoria Buch, The Hebrew University
8. Galina M. Chaban, Senior Researcher, NASA Ames Research Center, CA
9. David Charutz, Nuclear Research center, Soreq
10. Ron Elber, The Hebrew University, Cornell University, University of Texas in Austin, USA
11. Eyal Fattal, Biology Institute, Nes Ziona
12. Moshe Feldman, Jerusalem College of Technology
13. Eric Fredj, Jerusalem College of Technology
14. Alberto Garcia-Vela – CSIC, Madrid, Spain
15. Eitan Geva, University of Michigan in Ann Arbor, USA
16. Daniel Harries, The Hebrew University of Jerusalem
17. Jeremy Harvey, University of Bristol, UK
18. Oded Hod, Tel Aviv University
19. Solvejg Jørgensen, University of Copenhagen, Denmark
20. Pavel Jungwirth, Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Prague – Recently elected member of Czech Academy of Sciences
21. Shimshon Kallush, Ort Bruda College, Carmiel
22. Sabre Kais, Purdue University, Idiana, USA
23. Christiane Koch, Free University Berlin, University of Kassel, Germany
24. Viatcheslav Kokoouline, University of Central Florida, USA
25. Anna I Krylov, University of Southern California, USA
26. Yair Kurzweil, Nuclear Research Center, Negev
27. Daniel Lidar, University of Toronto, University of Southern California, USA
28. Jan Lundell, Nanoscience Center, University of Jyväskylä, Finland
29. Susan Gregurick, Senior Staff, DOE Research Funding Agency, Washington DC, USA
30. Maureen I. McCarthy, Pacific Northwest Labs, Wa, USA (Recently: Head of R&D, Homeland Security Office, Washington DC)
31. Todd Martinez, Stanford University, (previously University of Illinois at Urbana Champagne), USA
32. Sylvio May, North Dakota State University, USA
33. Ann B McCoy, Ohio State University, USA
34. Masha Y Niv, The Hebrew University of Jerusalem
35. Jose P Palao, La Laguna Universidad, Spain
36. Eran Rabani, Tel Aviv University
37. Tamar Raz, Jerusalem College of Engineering
38. A. Roitberg, University of Florida, Gainesville, USA
39. Burkhard Schmidt, ZIB and Applied Maths, Freie Universität, Berlin, Germany
40. Igal Szleifer, Purdue University, Northwestern University, USA
41. Naftali Tishby, The Hebrew University of Jerusalem
42. Jiri Valla, National University, Ireland
43. Nevin Uras-Aytemiz, Süleyman Demirel University, Turkey
44. Birgitta Whaley, University of California, Berkeley, USA
45. Assaf Zemel, The Hebrew University of Jerusalem

APPENDIX 2: RECENT CONFERENCES SUPPORTED BY FRITZ HABER (2007-2010)

SAFED WORKSHOP: QUANTUM THERMODYNAMICS

Professor Kosloff was on the organizing committee of this workshop which was held at the Hotel Merkazi in Safed, September 17-19, 2006.

TAIWAN-ISRAEL BINATIONAL MEETING: DYNAMICS ON MANY LENGTH/TIME SCALES

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

FH SYMPOSIUM: CONDUCTION IN MOLECULAR SYSTEMS

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: 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 Roi 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/BIOLOGICAL SYSTEMS

Professor Noam Agmon (member of the organizing committee) - 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 IMPROVIZED 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.

FH SYMPOSIUM: INTERFACES

Professor Roi Baer organizer May 25-26, 2009.

BIOMOLECULAR MODELING AND SIMULATION

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

COMPUTATIONAL CHEMISTRY SYMPOSIUM

Organizers: Dr. Avital Shurki and Prof. 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.

SYMPOSIUM IN MEMORY OF VICTORIA BUCH

Organizer: Professor Roi Baer. May 10, 2010.

APPENDIX 3: LIST OF RECENT VISITORS AND SEMINARS (2007-2010)

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 Chemistry, UC Irvine, CA	Ions at the Air-Water and Membrane-Water Interfaces
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-	Prof. P. Devlin, Oklahoma	

28.5.07	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: Israel: R. Baer (FH/HUJI), E. Rabani (Tel Aviv) L. Kronik (WIS) Germany: E. K. U. Gross (Berlin) 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 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; Saal-

		frank 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 University	New Directions in Laser Alignment. From High Harmonic Generation to Guided Molecular Assembly
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 Shaana-	

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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 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 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 Moscow State University, Russia	A New Look at Radiation Chemistry of Matrix-Isolated Molecules: Modeling Primary Events in Condensed Phase
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-	Dr. Christiane Koch, Free Univ.	

29.3.09	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 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 At Kibbutz Tzuba	Attendance and participation of the Beirat members
24-29.5.09	Prof. Dr. W. Domcke, Tech. Univ. Munchen	
24-27.5.09	Prof. Dr. G. Meijer, Fritz Haber Insitute, Berlin	
24-27.5.09	Prof. Dr. H. Grubmüller, Max-Planck-Institut für biophysikalische 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	J. Sauer (Humboldt University, Berlin): C-H activation by transition metal oxides – from gas phase clusters to sup-

	Meitner Center)	ported catalysts D. Danovich (HU): No-pair bonding in the high spin states of metal clusters T. Ansbacher (HU): Copper-Keepers – copper chaperones and their coordination number of Cu(I) W.L. Jorgensen (Yale University): From water models to drug lead optimization M. Amity (HU): Hydrolysis of organophosphate compounds by mutant Butyrylcholinesterase – A story of two histidines] R. Politi (HU): Osmolytes modulate peptide folding A. Dreuw (J.W. Goethe University, Frankfurt): Photo-initiated processes in the medium-sized organic pigments T. Stein (HU): Charge transfer excitations using Time-Dependent Density Functional Theory P. Schyman (HU): Brain chemistry: How does P450 catalyze the formation of neurotransmitters S. Amaran (HU): The photoassociation of Mg_2 E.F. Sheka (Friendship University of the Russian Federation, Moscow): Fullerene-cluster amplifiers and nanophotonics of fullerene solutions L. Pele (HU): Anharmonic vibrational spectroscopy calculations for biological molecules: new algorithms and applications 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
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) 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) Menahem Gutman (Tel Aviv), Joachim Heberle (Bielefeld) Volkhard Helms (Saarbrücken), Gerhard Hummer (NIH) 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) 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 Swie-

		tach (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 Dr. Barbara Jagoda-Cwiklik Prof. Joanna Sadlej Prof. Erio Tossatti Prof. Paul Devlin Prof. Pavel Jungwirth Prof. Michelle Parrinello 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	Collaboration with Prof. R. B. Gerber
21.11.10 - 7.12.10	Prof. Anne McCoy, Ohio State	Solvent Induced Electron Leap-Frogging: 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

APPENDIX 4: DETAILS FOR FINANCIAL YEARS 2008-10

The data given here was compiled by the authority for research and development of the Hebrew University.

DETAILS FOR YEAR 2008

1.Salaries	**Expenses**
1.1.Administrative:	
Geula Levy ,Administrator ,100% Position,11/07-9/08	**41,098**
1.2.Scholarships:	
1. Tamar Gershon	2,911
2. Yair Rezek	4,490
Total	**7,401**
2.Exchange of Scientists/Travel Costs:	
1.Dr.C. Koch from Germany to Israel	888
2.Prof. Jose Palao from Spain to Israel	294
3.Dr.Michael Kamboumes from USA to Israel	55
4.Dr. Esteban Vöhringer-Martinez from Germany to Israel	55
5.Prof.Anna Krylov from USA to Israel	88
6.Dr.Andritoss Saban from France to Israel	88
7.Prof. Dr. J. Manz from Germany to Israel	96
8.Prof.Tamar Seidemann from Usa to Israel	192
9.Prof. Dr. B. Abel from Germany to Israel	713
10.Prof.Ronnie Kosloff from Israel to Germany	1,008
11.Prof.Ronnie Kosloff from Israel to Germany	745
12.Prof.Martin Head-Gordon from USA to Gemany	141
13.Prof.S.Kuemmel from Germany to Israel	142
14.Prof.Remo Rohs from USA to Israel	91
15.Prof.Tamar Seidemann from USA to Israel	83
16.Prof.Audrey Hammerich from USA to Israel	821
17.Prof.Ronnie Kosloff from Israel to Germany	1,208
18.Prof.Roi Baer from Israel to Germany	825
Total	**7,533**
3.Workshops/Symposia:	
1.Nano Conference in Israel	242
2.The Minerva-Gentner Symposium on Time-Dependent Density Functional Theory and Applications. Eilat,Israel.	514
3.From Macromolecular to Cell Biophys-ics,Jerusalem.	2,512

4.Lectures (several times a month,lectures given by researchers from different countries take place in the Minerva Center.)	2,380
Total	**5,648**
4.Operational costs,material,equipment:	
1.Powerware System(partial expenses)	1,613
2.Michael Vilenkin,System Manager ,30% Position (expenses including course in Linux for 2,800 euro)	4,461
3.Max Tkach ,Assistant System Manger,50% position. (expenses including course in Linux for 1,653 euro)	4,916
4.A System for information storage(Fas 270 Appliance ,partial expenses)	7,364
5.Others (small amount)	5,405
Total	**23,759**
5.Various expenses:	**3,683**
Total Expenses	**89,122**

DETAILS FOR YEAR 2009

1.Salaries	**Expenses**
1.1.Administrative:	
1.Geula Levy ,Administrator ,100% Position,10/08-9/09	38,251
2.Michael Vilenkin,System Manager ,30% Position,10/08-9/09	2,410
Total	**40,661**
1.2.Scholarships:	
1.Eli Levy	1,071
2.Regina Politi	6,151
3.Ehud Tsivion	3,953
Total	**11,175**
2.Exchange of Scientists/Travel Costs:	
1.Prof.Wolfgang Domcke from Germany to Israel	922
2.Prof.Stephan Kuemmel from Germany to Israel	88
3.Prof.Gerard Meijer from Germany to Israel	702
4.Prof.Helmut.Grubmuller from Germany to Israel	316
5.Prof. Nimrod Moiseyev from Israel (Technion)	142
6.Prof. Roi Baer from Israel to Germany	310
7.Prof. Roi Baer from Israel to Germany	1,074
8.Prof. Ronnie Kosloff from Israel to Germany	1,161
9.Prof. Ronnie Kosloff from Israel to Germany	906
10.Symposium on Interfaces :"The Fritz Haber Center for Molecular Dynam-	396

ics"	
(in Kibbutz Tzuba,Israel)	
Total	**6,017**
3.Workshops/Symposia:	
1.Meeting with Prof.Ruth M.Lynden from England to Israel	29
2.Meeting with Prof. Tenenbaum from USA to Israel	25
3.Lectures (a few times a month,lectures given by researchers from different countries take place in the Minerva Center.)	1,173
4.An order to The 74th Meeting of the Israel Chemical Society	268
5.Symposium on Interfaces (in Kibbutz Tzuba,Israel)	220
6.Nano Conference in Israel	259
Total	**1,974**
4.Operational costs,material,equipment:	
1.Max Tkach ,Assistant System Manger,50% position.	8,510
2.Software	2,176
3.Computers	4,543
4.Workstation	3,016
5.Fritz Haber Prize,Symposium on Interfaces in Kibbutz Tzuba,Israel.	2,575
6.Others (small amount)	5,791
Total	**26,611**
5.Various expenses:	**112**
Total Expenses	**86,550**

DETAILS FOR YEAR 2010

1.Salaries	**Expenses**
1.1.Administrative:	
1.Geula Levy ,Administrator ,100% Position,10/09-9/10	41,575
2.Michael Vilenkin,System Manager ,10/09-9/10	1,906
3.Eva Guez ,Secretary,30% Position ,11/09-9/10	3,135
Total	**46,616**
1.2.Scholarships:	
1.Liat Pele-Bar	6,993
2.Omri Buchman	4,107
Total	**11,100**
2.Exchange of Scientists/Travel Costs:	
1.Prof.David Chandler from USA to Israel	245
2.Pro.Barry Honig from USA to Israel	122

3.Prof.William Jorgensen from USA to Israel	123
4.Prof.Andreas Dreuw from Germany to Israel	123
5.Prof.Ronnie Kosloff from Israel to Germany	2,543
6.Prof.Ronnie Kosloff from Israel to Germany	1,277
7.Prof.Roi Baer from Israel to Germany	523
8.Yair Rezek from Israel to Germany	698
Total	**5,654**
3.Workshops/Symposia:	
1.Biomolecular Modeling and Simulations in Safed	2,461
2.Symposium in Memory of Victoria Buch	2,773
3.Granot Rebecca, participation in the conference Ics 2010	108
4.Stein Tamar, participation in the conference Ics 2010	108
5.Prof.Michael Galperin from USA to Israel	120
6.Prof.Daniel Neuhauser from USA to Israel	120
7.Prof.David Chandeler from USA to Israel	137
8.Prof.Peter Solomon from USA to Israel	117
9.Lectures (a few times a month,lectures given by researchers from different countries take place in the Minerva Center.)	806
10.Computational Chemistry Symposium	127
Total	**6,877**
4.Operational costs,material,equipment:	
1.Max Tkach ,Assistant System Manager	5,144
2.A uninterruptable power supply system	1,337
3.Laptop	1,602
4.Computers parts	1,380
5.Altix Xe System-X86.Pto(partial expenses)	2,986
6.Others (small amount)	6,387
Total	**18,836**
5.Various expenses:	**0**
Total Expenses	**89,083**

APPENDIX 5: REFERENCES

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