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Curriculum-Vitae

Born: 1970, Israel

Citizenship: Israel

Military Service: 1988–1991, Israel Defense Forces

University Studies and Diplomas:

- **B.Sc.**, 22 May 1995
  Department of Chemistry, The Hebrew University of Jerusalem
- **M.Sc.**, 7 June 1996
  Department of Chemistry, The University of Chicago
- **Ph.D.**, 27 August 1999
  Department of Chemistry, The University of Chicago
  Advisor: Stuart A. Rice, Thesis: Phase transitions in confined geometry

Honors and Fellowships:

- European Commission, Marie Curie Individual Fellowship, 2000–2001
- B.Sc. (GPA 95/100) Graduated Summa Cum Laude
  Faculty of Science, The Hebrew University of Jerusalem, 1995
- Kent prize for excellence in undergraduate studies,
  Department of Chemistry, The Hebrew University of Jerusalem, 1994
- Dean's List, Faculty of Science, The Hebrew University of Jerusalem, 1992–1993
- Dean's List, Faculty of Science, The Hebrew University of Jerusalem, 1991–1992

Employment:

- 2002–present: Research Associate in the Molecular Dynamics Group headed by Prof. Alan E. Mark, Department of Biophysical Chemistry, University of Groningen
- 2000–2001: Marie Curie Fellow of the European Community, Department of Biophysical Chemistry, University of Groningen
- 1996–1999: Research Assistant with Prof. Stuart A. Rice, Department of Chemistry, The University of Chicago
- 1995–1996: Teaching Assistant, Department of Chemistry, The University of Chicago
- 1994: Undergraduate Research Student with Prof. Jochanan Blum, Department of Chemistry, The Hebrew University of Jerusalem
- 1993: Undergraduate Research Student (summer exchange program) with Prof. Gerhard Bringmann, Department of Chemistry, University of Würzburg

Research Experience:

- Molecular Dynamics studies of the kinetics and thermodynamics of the folding process of model peptides and naturally occurring proteins.
- Computer simulations of the phase transitions and relaxation processes of condensed phase systems (colloids, dipolar soft rods, water and methanol) in confined geometries.
- Phenomenological treatment, using the Landau theory of phase transitions, of the influence of gauche conformational degrees of freedom on the phase diagram of a Langmuir monolayer.
- Computer aided drug design: Calculations of protein-inhibitor binding affinities.
- Synthesis of aromatic compounds causing cancer: The transformation from arene oxides to arene imines.
- Synthesis of complexes of chrome with biaryl compounds.

Conference Oral Presentations:

- *Freezing and melting of confined water*, 81st International Bunsen Discussion Meeting: "Interfacial Water in Chemistry and Biology", Velen, Germany, September 19–23, 2003.
- *Dynamics and thermodynamics of the helix-coil transition*, Computer simulation and theory of macromolecules, Hünfeld, Germany, May 9–10, 2003.
- *Monolayer ice - insight from confined colloids*, 17th IUPAC conference on chemical thermodynamics, Rostock, Germany, July 28 – August 2, 2002.
- *Folding of hydrophobin SC3 at hydrophilic/hydrophobic interface*, European protein folding network, Granada, Spain, February 26, 2001.
- *Free energy barrier estimation of unfolding the α-helical SP-C*, Annual meeting of proteins. The Dutch Science Organization, Lunteren, The Netherlands, December 11–12, 2000.
- *Phase transitions in confined geometry*, Midwest thermodynamics & statistical mechanics conference, Detroit, MI, May 17–18, 1999.
- *Phase transitions in a quasi-two-dimensional system*, Midwest thermodynamics & statistical mechanics conference, University of Notre Dame, IN, May 18–19, 1998.
- *Melting in Two Dimensions*, Midwest thermodynamics & statistical mechanics conference, Williams Bay, WI, May 15–16, 1997.

Teaching Experience:

- 1997–1999: Chemistry Tutor, College Tutoring Program, The University of Chicago.
- 1995–1996: Teaching Assistant for General Chemistry courses (three quarters), The University of Chicago.
- 1995: Teaching Assistant for General Chemistry courses (two semesters), The University of Illinois at Chicago.

References

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- Prof. Herman J.C. Berendsen
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Peer-Reviewed Publications

16. Ronen Zangi and Alan E. Mark
Thermodynamic stability of the helix-coil transition
in preparation (2003)

15. Ronen Zangi, Alan E. Mark and Jan B. F. N. Engberts
Physisorption of hydroxyl ions from aqueous solution to a hydrophobic surface
in preparation (2003)

14. Ronen Zangi and Alan E. Mark
Electrofreezing of confined water
J. Chem. Phys. to be submitted (2003)

13. Ronen Zangi and Stuart A. Rice
Instantaneous normal modes and cooperative dynamics
in a quasi-two-dimensional system of particles
Phys. Rev. E submitted (2003)

12. Ronen Zangi and Stuart A. Rice
Cooperative dynamics in two-dimensions
Phys. Rev. Lett. submitted (2003)

11. Alessandra Villa, Ronen Zangi, Gilles Pieffet and Alan E. Mark
Sampling and convergence in free energy calculations of protein-ligand interactions:
The binding of triphenoxypyridine derivatives to Factor Xa and Trypsin
J. Computer-Aided Molecular Design in press (2003)

10. Ronen Zangi and Stuart A. Rice
Freezing transition and correlated motion in a quasi-two dimensional colloid suspension
Phys. Rev. E in press (2003)

9. Ronen Zangi and Alan E. Mark
Bilayer ice and alternate liquid phases of confined water
J. Chem. Phys. **119**, *1694-1700 (2003)*

8. Ronen Zangi and Alan E. Mark
Monolayer ice
Phys. Rev. Lett. **91**, *025502 (2003)*

7. Ronen Zangi and Stuart A. Rice
The effect of gauche molecular conformations on the phase diagram of a Langmuir monolayer
Langmuir **19**, *5949-5955 (2003)*

6. Ronen Zangi, Marcel L. de Vocht, George T. Robillard and Alan E. Mark
Molecular Dynamics Study of the Folding of Hydrophobin SC3 at a Hydrophilic/Hydrophobic Interface
Biophys. J. **83**, *112-124 (2002)*

5. Ronen Zangi, Helena Kovacs, Wilfred F. van Gunsteren, Jan Johansson and Alan E. Mark
Free energy barrier estimation of unfolding the α-helical surfactant-associated polypeptide C
PROTEINS: Structure, Function and Genetics **43**, *395-402 (2001)*

4. Ronen Zangi and Stuart A. Rice
Hexagonal to square lattice conversion in bilayer systems
Phys. Rev. E **61**, *671-681 (2000)*

3. Ronen Zangi and Stuart A. Rice
   Nature of the transition from two- to three-dimensional ordering in a confined colloidal suspension
   Phys. Rev. E **61**, *660–670 (2000)*

2. Ronen Zangi and Stuart A. Rice
   Phase transitions in a quasi-two-dimensional system
   Phys. Rev. E **58**, *7529–7544 (1998)*

1. Nina Bazanov-Katz, Ronen Zangi and Jochanan Blum
   Further studies on heterocyclic arene imines. Preparation of 1a,9b-dihydroazirino[f][1,7]phenanthroline, 3b,4a-dihydroazirino[2,3]phenaleno[1,9-g,h]quinoline and 1a,13b-dihydrodibenzo[1,2:6,7]phenazino[1,2-b]azirine
   J. Heterocyclic Chem. **33**, *1703–1705 (1996)*

Review Articles

1. Ronen Zangi and Alan E. Mark
   Water confined to a slab geometry: Molecular Dynamics studies
   J. Physics: Condensed Matter invited contribution (2004)

Scientific Accomplishments

Dynamics and thermodynamics in two-dimensions

The character and degree of ordering present in a system is dependent on its spatial dimension; in one and two dimensional systems thermal fluctuations can completely destroy long range order of certain types. Thus, there are situations where the behavior of a system with a reduced dimensionality is qualitatively different from that in higher dimensions. For example, the nature of the melting transition in two dimensions is believed to be different than that in three dimensions. We found [2] that in a quasi-two dimensional system, melting occur via two first order phase transitions; first the solid phase transform to the hexatic and then the hexatic phase transform to the liquid phase. These findings are consistent with experimental observations of the melting behavior of a quasi-two dimensional colloid suspension.

Competition between the amplitude of the thermal fluctuations in the lateral and transverse directions, in a system of densely packed particles confined between parallel plates only a few particle diameters apart, can induce buckling transitions to phases with no counterparts in three dimensions. We found [3] a series of buckled phases, corresponding to phases with maximum volume density, that interpolate between the structures of two dimensional and three dimensional crystals in a confined space.

When, in the vicinity of a phase transition, the correlation length of the density-density correlation function is large relative to the range of intermolecular interactions, it is believed that the specific form of the interactions between the particles, and consequently the system Hamiltonian, plays a minor role in determining the character of that phase transition. This notion underlies the introduction of universality classes and the prediction that the character of transitions that belong to the same universality class is the same. We investigated [4] the hexagonal to square lattice conversion in bilayer systems. The results show that this conversion is potential dependent. For a system of particles that interact through pair potential that include an attractive well, the hexagonal to square lattice transition is first order and direct, while for a system with hard core colloid-colloid interactions there are two degenerate stable intermediate phases, linear and zigzag rhombic, that are separated from the square lattice by strong first order transitions, and from the hexagonal lattice by either weak first order or

by second order transitions.

Single particle motion in a condensed phase is affected by interactions with many other particles. However, at short and long times the many-body problem simplifies to a one-body dynamics that is deterministic and stochastic, respectively. As a result, the distribution of the single particle displacement in each of these two limiting time regimes has a Gaussian form. Deviations from the Gaussian distribution that occur at intermediate times in three-dimensional systems are very small. However, the situation in two-dimensions is different and strong deviations were observed experimentally in the liquid phase. We reported results from molecular dynamics simulations [10,12] indicating that the deviation of the single particle displacement distribution from Gaussian form is a characteristic that is common to all phases of a system confined to two-dimensional geometry (liquid, hexatic and solid). We also showed that these deviations, which intensify with increasing density and/or decreasing temperature, are a consequence of correlated particle motion and are related to the emergence of a third dynamical relaxation mode at intermediate time regime. In further studies we showed [13] that this collective motion is generated by superpositions of instantaneous normal mode vibrations along diffusive paths. The diffusive paths are along the directions with strong bond orientation correlation, and start to grow in amplitude rapidly on entry into the hexatic phase. The results reveal a strong relationship between the average time at which the cooperative dynamics of the system is maximum and the average value of the squared frequency for which the spectrum of the normal modes (the real and the imaginary parts) is maximum.

Water under confinement and at a hydrophobic interface

Experimental studies indicate that confinement of many liquids to films thinner than 4–6 molecular layers promote solidification. We reported [8] results of molecular dynamics simulations that predict a first order transition from a monolayer of liquid water to a monolayer of ice at a temperature of 300 K and standard pressure. In addition to cooling and lateral compression, it is shown that freezing can be induced by simply increasing the distance between the confining parallel plates. Since a slab geometry is incompatible with a tetrahedral arrangement of the sp^3 hybridized oxygen of water, a monolayer of water can only freeze under ambient conditions when it is coupled to a linear buckling transition. By exploiting an ordered out-of-plane displacement of the molecules in the buckled phase the distortion of

hydrogen bonds is minimized. The in-plane symmetry of the oxygen atoms then becomes rhombic with ordered hydrogen positions. The order-disorder phase transitions that we found could explain the anomalous behavior of the Young's modulus of thin films of water observed experimentally. We conducted further studies on the behavior of bilayer of liquid water [9]. The results reveal qualitatively the same behavior; observation of freezing at ambient conditions. The stability regions of the confined ice phases are restricted to a small regions of plate separation, H. This can be explained by the ability of the structure of the confined ice phases to achieve an optimal distance of hydrogen bonds only for a small range of H. Above and below the stability region of the ice bilayer we observed [9] two bilayer phases of liquid water that differ in the local ordering at the level of the second shell of nearest neighbors and in the density profile normal to the plane, yielding two liquid phases with different densities. These results suggest the intriguing possibility of a liquid-liquid transition of water, confined to a bilayer, at regions where the ice bilayer is unstable with respect to either of the liquid phases. Above the film thickness of a bilayer, the degree of which the solid phase is enhanced due to confinement is insufficient to freeze liquid water at ambient conditions. However, the action of an external electric-field can induce freezing. We found [14] that under the action of an electric-field in the lateral direction, water confined to 3–8 layers can freeze. At thickness that corresponds to a trilayer of liquid water, there is a crossover of the structure of the confined ice from rhombic to hexagonal.

In general, it is believed that the close approach of an ion from aqueous solution to the interface with a low dielectric constant is an energetically unfavorable process. In contrast, we found [15] that hydroxyl ions physically adsorb at the interface of water and a hard hydrophobic wall. The driving force for this phenomenon is the preferential orientation of the water molecules in the first two layers from the interface. This is consistent with many experimental studies, mainly measurements of electrophoretic mobility of oil droplets immersed in water, that indicate accumulation of substantial negative charge at the interface with hydrophobic medium.

Free energy barrier of the unfolding process of peptides

Free energy barrier of an activated process can be estimated using the measured reaction rate by applying Eyring's theory. Protein folding and unfolding processes are commonly characterized by NMR studies. However, the time resolution of NMR measurements is slower

than many relaxation processes of peptides and proteins. Therefore, it is important to know whether transition state theory can be applied to folding or unfolding process for which a two-state model is inferred by NMR observations. We showed [5] that such treatment can lead to severe overestimation of the free energy barrier. This is because folding and unfolding mechanisms can involve multiple barriers, with similar heights, on the multidimensional free energy surface. In this case, intermediates will not accumulate to substantial concentration and will not be easily detected by current experimental techniques.

Folding mechanism of surface active proteins at a hydrophilic/hydrophobic interface

Certain proteins, while soluble in aqueous solution, self-assemble at hydrophilic/hydrophobic interfaces into amphiphatic membranes. Experimental studies indicate that the self-assembly process is accompanied by a large increase in the β-sheet content. We showed [6] that fully extended fungal protein (86 amino acid residues) undergoes fast ($\sim$100 ns) folding at a water/hexane interface to an elongated planar structure with extensive β-sheet secondary elements. Nevertheless, simulations in each of the bulk solvents result in a mainly unstructured globular protein. The dramatic enhancement in secondary structure (kinetic and thermodynamic) cast light on the role interfaces between phases with large differences in polarity can have on the folding process. The partitioning of the side-chain residues to one of the two phases can serve as a strong driving force to initiate secondary structure formation. In addition, the interactions of the side-chains with the heterogenous environment at an interface can also stabilize configurations that otherwise would not occur in a homogenous solution.

The effect of chain flexibility on the phase diagram of a Langmuir monolayer

For simplicity the extant theoretical analyses of the Langmuir monolayer phase diagram ignore gauche molecular conformations, thereby treating the amphiphile molecules as rigid rods. However, experimental and simulation studies indicated that the gauche conformational degrees of freedom of long chain amphiphile molecules assembled in a dense Langmuir monolayer play an important role in determining the structures of the several phases that the monolayer supports. We extended [7] the Landau-type theory formulated by Kaganer and Loginov to account for the influence of the conformational degrees of freedom of a long chain amphiphile molecule on the phase diagram of a Langmuir monolayer. The effect of the gauche conformations is to modify the coefficients of the primary order parameters in

the free energy expansion and thereby to change the location of the phase transition lines. For transitions that are induced by a change in the surface pressure, the tilting transitions, we obtain a shift of the transition lines to lower surface pressure. For transitions that are induced by lowering the temperature, the crystallization transitions, we suggest, given some restrictions on the magnitude of the coefficients of the coupling terms, that the transition lines shift to lower temperature.

Free energy calculations of protein-ligand interactions

Estimating differences in free energy is central to the process of rational molecular design. In this project we evaluated [11], using molecular dynamics simulation technique, the relative binding affinities of a set of 10 inhibitors to two serine proteases, factor Xa and trypsin, that share sequence and structural homology. The inhibitors studied represent a great challenge for explicit free energy calculations at the atomic level. The mutations from one compound to another involve up to 19 atoms, the creation and annihilation of net charge and several alternate binding modes. Nevertheless, we demonstrated that it is possible to obtain converged results ($\pm$ 5–10 kJ/mol) even for such complex multi-atom mutations by simulating on a nanosecond time scale. This is achieved by using soft-core potentials to facilitate the creation and deletion of atoms and by a careful choice of mutation pathway. The results show that given modest computational resources explicit free energy calculations can be successfully applied to realistic problems in drug design.