The Abdus Salam
International Centre for Theoretical Physics

United Nations
Educational, Scientific
and Cultural Organization

International Atomic
Energy Agency

Conference on
Structure and Dynamics in Soft Matter and Biomolecules: From Single Molecules to Ensembles

4 – 8 June 2007

(Miramare, Trieste, Italy)

ORGANIZERS:

H.S. Chan	University of Toronto, Canada
C. Micheletti	SISSA - International School for Advanced Studies, Trieste, Italy
M.F. Thorpe	Arizona State University, Tempe, U.S.A.

PROGRAMME
ABSTRACTS of INVITED TALKS
and
TITLES of POSTER PRESENTATIONS

web-page: http://agenda.ictp.trieste.it/smr.php?1845

Strada Costiera 11, 34014 Trieste, Italy - Tel. +39 040 2240 111; Fax +39 040 224 163 - sci_info@ictp.it, www.ictp.it

PREFACE

This Conference will bring together researchers from across disciplines to provide state-of-the-art perspectives on experimental, theoretical and computational approaches to these important areas and to foster discussions on the challenges and new strategies in this field. The following problems will be discussed:

Energy landscapes in proteins and soft-condensed matter
Packing in soft matter systems
Network glasses
Intrinsically disordered proteins
Protein aggregation

Organizers:

Hue Sun CHAN *University of Toronto, Canada*

Cristian MICHELETTI *SISSA, International School for Advanced Studies, Trieste, Italy*

Michael THORPE *Arizona State University, Tempe, USA*

List of Invited Speakers:

updated 29 May 2007

G. Barkema *(Utrecht, Holland)*
P. Boolchand *(Cincinnati, USA)*
G. Chirico *(Milan, Italy)*
P. Derreumaux *(Paris, France)*
R. Esposito *(Udine, Italy)*
C. Fernandez *(Rosario, Argentina)*
G. Garcia Naumis *(UNAM, Mexico)*
Y. Goto *(Osaka, Japan)*
M. Gruebele *(U. Illinois, USA)*
M. Kilfoil *(Montreal, Canada)*
M. Kurnikova *(Pittsburgh, USA)*
A. Maritan *(Padova, Italy)*
D. Mihailovic *(Ljubljana, Slovenia)*
N. Mousseau *(Montreal, Canada)*
R. Nussinov *(Tel Aviv, Israel)*
R. Pomès *(Toronto, Canada)*
P. Salmon *(Bath, UK)*
J. Sanchez-Ruiz *(Granada, Spain)*
J.-E. Shea *(Santa Barbara, USA)*
F. Stellacci *(MIT, Cambridge, USA)*
P. Tompa *(Budapest, Hungary)*
S. Vishveshwara *(Bangalore, India)*
J. Wang *(Stony Brook, USA)*
D. Weaire *(Dublin, Ireland)*

Complete List of Participants is available via the following web-page:
http://agenda.ictp.trieste.it/smr.php?1845

PROGRAMME

(as of 29 May 2007)

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Conference on
Structure and Dynamics in Soft Matter and Biomolecules: From Single Molecules to Ensembles

4 – 8 JUNE 2007
(Miramare, Trieste, Italy)

PRELIMINARY PROGRAMME
(updated as of 29 May 2007)

ALL LECTURES WILL BE HELD AT THE
ICTP MAIN BUILDING - MAIN LECTURE HALL

Organizers / Local Organizer:
H.S. Chan, C. Micheletti and M.F. Thorpe

MONDAY, 4 JUNE 2007

08.00 – 09.15 **REGISTRATION / ADMINISTRATIVE FORMALITIES**
reception area of the Main Building

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09.15 – 09.30 **OPENING** – Welcome address

09.30 – 10.30 **M. KILFOIL** (McGill University, Montreal, Canada)
Insights into fundamental states of matter through packing problems in hard spheres, sticky spheres and M&Ms

10.30 – 11.15 **G. GARCIA NAUMIS** (UNAM, Mexico)
Rigidity as a tool to understand the role of low frequency modes in glass transition and flexible systems

11.15 – 11.40 -- *Coffee Break* –

11.40 – 12.25	**S.P. SALMON** (University of Bath, U.K.) Ordering in network glasses
12.25 – 14.00	-- *Lunch Break* --
14.00 – 15.00	**M. KURNIKOVA** (Carnegie Mellon University, Pittsburgh, U.S.A.) Native states of proteins and computational modeling of their structure and structure – function relationships
15.00 – 15.45	**G. CHIRICO** (Universita' di Milano Bicocca, Italy) Tracking single GFP proteins through unfolding pathway
15.45 – 16.10	-- *Coffee Break* --
16.10 – 16.55	**S. VISHVESHWARA** (IISC., Bangalore, India) Dynamics of protein structure networks
16.55 – 17.40	**H.S. CHAN** (University of Toronto, Canada) Cooperativity, non-cooperativity and barriers in proteins folding
18.00 onwards	**INFORMAL RECEPTION** – Main Building Terrace

TUESDAY, 5 JUNE 2007

09.00 – 10.00	**G. BARKEMA** (University of Leiden, The Netherlands) Computer simulation of structural glasses
10.00 – 10.45	**N. MOUSSEAU** (University of Montreal, Canada) From glasses to protein: simulating slow processes
10.45 – 11.10	-- *Coffee Break* --
11.10 – 11.55	**J. WANG** (SUNY, Stony Brook, U.S.A.) Protein folding and flexible binding
11.55 – 12.40	**P. TOMPA** (Hungarian Academy of Sciences, Budapest, Hungary) The role of structural disorder in protein-protein interactions
12.40 – 14.00	-- *Lunch Break* --

14.00 – 15.00	**J.M. SANCHEZ-RUIZ** (Universidad de Granada, Spain) Protein stability
15.00 – 15.45	**M. GRUEBELE** (Univ. of Illinois at Urbana-Champaign, U.S.A.) Downhill folding: evolution meets physics
15.45 – 16.10	-- *Coffee Break* --
16.10 – 16.55	**F. STELLACCI** (MIT, Cambridge, U.S.A.) Cell membrane permeation to nanoparticles
16.55 – 17.40	Round Table on Disordered Proteins and Native-state Proteins

WEDNESDAY, 6 JUNE 2007

09.00 – 10.00	**C.O. FERNANDEZ** (IBR, Rosario, Argentina) Structural biology and metallochemistry of neurodegenerative diseases: The case of α-Synuclein
10.00 – 10.45	**J.E. SHEA** (UCSB, U.S.A.) Simulations of peptide inhibitors of Amyloid-β aggregation
10.45 – 11.00	-- *Coffee Break* --
11.00 – 11.45	**P. DERREUMAUX** (IBPC/CNRS, Paris, France) Simulations of the early steps of protein aggregation
11.45 – 12.30	**R. POMES** (University of Toronto, Canada) Proline and glycine control protein self-organization into elastomeric or amyloid fibrils
12.30 – 14.15	-- *Lunch Break* --
14.15 – 15.00	**Y. GOTO** (Osaka University, Japan) Direct observation of amyloid fibril growth and propagation
15.00 – 15.45	**D. MIHAILOVIC** (Jozef Stefan Institute, Ljubljana, Slovenia) $Mo_6S_{9-x}I_x$ recognitive connectors forming molecular electronics networks

15.45 – 16.10 -- *Coffee Break* --

THURSDAY, 7 JUNE 2007

09.00 – 09.45 **R. NUSSINOV** (Tel Aviv University, Israel)
Protein folding and design: from single proteins and their building blocks to nanostructures

09.45 – 10.30 **R. ESPOSITO** (Universita' di Udine, Italy)
Conformational flexibility of β2-microglobulin:
A compromise between efficiency and aggregation risk

10.30 – 10.45 -- *Coffee Break* --

10.45 – 11.30 **A. MARITAN** (Universita' degli Studi di Padova, Italy)
Physics of proteins: a unified perspective

11.30 – 12.15 Round Table on Protein Aggregation

12.15 – 14.30 -- *Lunch Break* --

14.30 onwards **POSTER SESSION** – Main Building Poster Gallery
(plus refreshments in reception area)

FRIDAY, 8 JUNE 2007

09.00 – 09.45 **D.L. WEAIRE** (Trinity College, Dublin, Ireland)
Structure and dynamics in the physics of foams

09.45 – 10.30 **P. BOOLCHAND** (The University of Cincinnati, U.S.A.)
Network glasses, dangling ends and intermediate phases

10.30 – 10.50 -- *Coffee Break* --

10.50 – 11.35 **M. THORPE** (Arizona State University, Tempe, U.S.A.)
The flexibility window

11.35 – 12.30 Poster Highlights (4-6 brief oral presentations)

12.30 – 13.00 Informal discussion
"How scientists around the world can best interact"
+ **CLOSING SESSION**

ABSTRACTS

OF

INVITED TALKS

(in alphabetical order of Speaker as of 29 May 2007)

Computer simulation of structural glasses

G.T. Barkema,

Institute for theoretical physics,
University of Utrecht,
The Netherlands
+
Lorentz Institute,
University of Leiden,
The Netherlands

Abstract:

Structural glasses are amorphous substances that are rigid. A prototypical example of a structural glass is the material used in window panes, mostly consisting of silica (SiO2). The microscopic structure of these materials is hard to probe experimentally since the standard techniques, based on scattering, are hampered by the lack of periodicity. Computer simulations are therefore an important tool.

I will discuss various methods to generate realistic atomic configurations of structural glasses. Particular attention will be paid to the simulation of covalently bonded disordered materials, as represented by the continuous random network (CRN) model introduced more than 60 years ago by Zachariasen.

ICTP Abstract 2007

Network glasses, dangling ends and intermediate phases

P. Boolchand

Department of Electrical and Computer Engineering, University of Cincinnati, Cincinnati, OH 45221-0030

Bulk glass formation occurs over a very small part of phase space, and 'good' glasses (formed by cooling even at a slow rate ~1°C/min) select an even smaller part of that phase space. Theory and experiment suggest [1] that these sweet spots of glass formation represent Intermediate Phases consisting of rigid but stress-free networks. Calorimetric and Raman scattering experiments show that Intermediate Phases occur over a finite range of chemical compositions with sharply defined phase boundaries. Experiments also reveal that widths of Intermediate Phases collapse sharply in the presence of dangling ends [2] like one-fold coordinated halogen atoms or hydrogen or OH. We describe experiments where the near collapse of Intermediate Phases has been observed in ternary Ge-S(or Se)-I glasses. Experiments also reveal [3] that the manner in which network structure self-organizes in the narrow Intermediate Phase of these two systems are quite different, and that relative atom sizes play a role.

1. P. Boolchand, G. Lucovsky, J.C. Phillips, M.F. Thorpe, "*Self-Organization and the Physics of Glassy Networks*", Phil. Mag. 85, 3823 (2005) (article in pdf format)

2. Y. Wang , J.Wells, D.G.Georgiev, P. Boolchand, Koblar Jackson, M. Micoulaut. *Sharp Rigid to Floppy Phase Transition Induced by Dangling Ends in a Network Glass.* Phys.Rev.Lett. 87, 18, 5503 (2001) (article in pdf format).

3. F.Wang, P. Boolchand, K.A. Jackson, M. Micoulaut, "*Chemical Alloying and light-induced collapse of the intermediate phase in chalcohalide glasses*", J. Phys.: Condens. Matter 19 (2007) 226201 (article in pdf format).

Cooperativity, Non-cooperativity and Barriers in Protein Folding

Hue Sun CHAN
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and of Medical Genetics & Microbiology
University of Toronto

http://biochemistry.utoronto.ca/chan/bch.html

Many small single-domain proteins with ~ 60-100 amino acid residues undergo cooperative, switch-like folding/unfolding transitions with very low populations of intermediate, i.e., partially folded, conformations. This phenomenon is referred to as cooperative folding. For most natural proteins, cooperativity is likely an evolved trait to guard against disease-causing aggregation. From a biophysical standpoint, cooperativity is a remarkable molecular-recognition feat that has not yet been achieved by de novo experimental design. Therefore, knowing the biophysical basis of folding cooperativity is central to addressing many questions in protein folding and design and to progress in understanding diseases of misfolding. However, folding cooperativity is not readily accounted for by common notions about driving forces for folding. I will discuss how commonprotein chain models with pairwise additive interactions are insufficient to account for the folding cooperativity of natural proteins, and how models with nonadditive local-nonlocal coupling are able to rationalize cooperative folding rates that are well correlated with native topology. For even smaller proteins with ~ 40 residues such as BBL and an NTL9 fragment, our modeling investigations indicate that the difference in their apparent folding cooperativities is at least partly related to their different native topologies. The traditional formulation of folding transition states entails a macroscopic folding free energy barrier with both enthalpic and entropic components. I will explore the microscopic origins of these thermodynamic signatures in terms of conformational entropy as well as desolvation (dewetting) effects.

Intriguingly, the existence of significant enthalpic folding barriers raises fundamental questions about the validity of the funnel picture of protein folding, because such enthalpic barriers appear to imply that there are substantial uphill moves along a microscopic folding trajectory. Using results from extensive atomic simulations, I will show how the paradox can be resolved by a dramatic entropy-enthalpy compensation at the rate-limiting step of folding. In this perspective, the height of the enthalpic barrier is seen as related to the degree of cooperativity of the folding process.

References:
MacCallum, Moghaddam, Chan & Tieleman, Proc Natl Acad Sci USA 104:6206 (2007);
Knott & Chan, Proteins 65:373 (2006);
Liu & Chan, J Mol Biol 349:872 (2005); Phys Biol 2:S75 (2005);
Chan, Shimizu & Kaya, Methods Enzymol 380:350 (2004);

TRACKING SINGLE GFP PROTEINS THROUGH UNFOLDING PATHWAYS

Giuseppe Chirico

Dipartimento di Fisica, Università di Milano-Bicocca, Milano, Italia

In this report I discuss the possibility to follow conformational substates of single molecules of Green Fluorescent Protein mutants by means of fluorescence fluctuation spectroscopy. Time recording of the fluorescence signals from molecules in the native state shows that the GFP chromophore switches between the two states with a distribution of rates that is not unimodal, thereby suggesting a multiplicity of protein substates. Furthermore, under denaturing conditions, the chromophore switching rate displays different and reproducible time evolutions that are characterized by discrete unfolding times. Close to the unfolding event distinct periodic (pre-unfolding) oscillations in the fluorescence signal are also detected. The correlation that is found between native molecules switching rate values, unfolding times and pre-unfolding oscillations seems to suggest that GFPmut2 can unfold only along distinct paths that are determined by the initial folded substate of the protein.

Simulations of the early steps of protein aggregation

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More than 20 human diseases, including Alzheimer's disease and dialysis-related amyloidosis, are associated with the pathological self-assembly of soluble proteins into transient cytotoxic oligomers and amyloid fibrils. Because protein aggregation is very complex, the detailed aggregation paths and structural characterization of the intermediate species remain to be determined.

Here, we first review our current understanding of the dynamics and free energy surface of the assembly of small amyloid-forming peptides [KFFE, Abeta(16-22), Abeta(11-25), NGAIL and beta2m(83-89)] using a coarse-grained protein force field (OPEP) coupled to the activation-relaxation technique, molecular dynamics (MD) or replica exchange MD (REMD).

Next, we present REMD-OPEP simulations on the dimers of Alzheimer's peptides Abeta(1-40) and Abeta(1-42) and discuss the role of amino acids 23-28 in fibril formation.

Finally, we analyse MD-OPEP simulations of Abeta(16-22) oligomers with multiple copies of an N-methylated inhibitor.

This work was done in collaboration with Normand Mousseau (University of Montreal, Canada), Guanghong Wei (University of Shanghai, China), and Adrien Melquiond (IBPC, Paris).

CONFORMATIONAL FLEXIBILITY OF β2-MICROGLOBULIN: A COMPROMISE BETWEEN EFFICIENCY AND AGGREGATION RISK

G. Esposito - *DSTB, University of Udine - P.le Kolbe, 4 – 33100 Udine, ITALY*

The conformational flexibility of the loop region containing Trp60 is likely to play a key role in the early steps of fibrillogenesis of β2-microglobulin (β2-m), the protein responsible for dialysis related amyloidosis (DRA).
This conclusion arises from the whole body of experimental evidence obtained by comparing wild type and W60G β2-m. The interest in this single-point mutant was first stimulated by inspection of molecular dynamics trajectories at the early steps of β2-m aggregation: the intermolecular contacts captured by the simulation snapshots suggested that Trp60 should play a most relevant role together with nearby N and C-terminal residues.
The recombinant W60G mutant was expressed and its structure was shown, by NMR spectroscopy, to maintain the general wild type folding. The mutant species exhibited, however, a higher thermodynamic stability compared to wild type, and no fibril formation under mild fibrillogenic conditions, *i.e.* 20% TFE neutral aqueous solution in the presence of seeds.
In order to explain this striking result, ^{15}N relaxation measurements were performed to assess structural mobility. A lower value of the overall correlation time (τ_c) was estimated for the mutant β2-m, consistent with faster rotational dynamics with respect to wild type protein, probably due to a larger association extent of the latter. In addition, but most intriguingly, several residues in the region around Trp60 (DE loop) were observed to undergo a slow time-scale conformational exchange in wild type β2-m that proved substantially absent in W60G β2-m. Given the observed fibrillogenesis attitudes, it was argued that the "risky" conformational flexibility of the natural β2-m sequence may be a necessary compromise to enforce proper affinity with the α-chain of class I MHC, at the price of partial unfolding danger. This unavoidable condition should be eventually responsible for pathological aggregation of β2-m at non-physiological high concentrations.
Binding assay confirmed that mutant W60G has a much lower affinity for the heavy chain of MHC-I than wild type protein. Besides the loss of Trp60 indole specific interactions, also conformational rigidity should conceivably determine the observed affinity decrease.
The consistency of different lines of experimental data suggests that our interpretation of β2-m conformational plasticity may provide new insights for DRA therapies.

Structural Biology and Metallochemistry of Neurodegenerative diseases: The case of α-Synuclein

Claudio O. Fernández

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Many proteins associated with neurodegenerative diseases (PrP, APP, Aβ peptide and SOD-1) have metal binding properties. In the documented examples metal binding relates to pathogenesis via an impact on aggregation or production of oxidative damage. Thus, defining binding sites and the molecular details of complex formation may provide important and practical insights into pathogenic processes and neuronal biology. The objective of our study was to elucidate the structural features of α-Synuclein[1,2] and establish the role of metal ions in synucleinopathies at the molecular resolution currently available for other amyloidoses[3,4]. The interaction of divalent metal ions with α-synuclein were studied under physiologically relevant conditions using a battery of low and high-resolution spectroscopic techniques (CD, EPR and NMR) and chemical modification.[3,4] Protein-metal interactions were characterized at single-residue resolution by NMR. The influence of metals on inducing α-synuclein fibrillation was strongly linked to their binding properties. A comparative analysis reveals a hierarchy in protein-metal interactions, dictated by structural factors involving different domains of the protein.[1-4] The new insights into the structural basis of copper interaction with α-synuclein support a tighter link with other amyloid-related disorders such as Alzheimer's disease and prion disease, indicating that perturbations in copper metabolism may constitute a more widespread element in neurodegenerative disorders than recognized previously.

[1]Fernandez *et al*, *EMBO J.* **2004**, 23, 2039-2046.
[2] Bertoncini *et al*, *Proc Natl Acad Sci USA* **2005**, 102, 1430-1435.
[3] Rasia *et al*, *Proc Natl Acad Sci USA* **2005,** 102, 4294-4299
[4] Binolfi *et al*, *J Am Chem Soc* **2006**, 128, 9893-901

Direct Observation of Amyloid Fibril Growth and Propagation

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Amyloid fibrils form through nucleation and growth. To clarify the mechanism involved, direct observations of both processes are important (1, 2). First, seed-dependent fibril growth of β2-microglobulin (β2-m) and amyloid β peptide was visualized in real-time at the single fibril level using total internal reflection fluorescence microscopy combined with the binding of thioflavin T, an amyloid-specific fluorescence dye (3-5). Second, using atomic force microscopy, ultrasonication-induced formation of β2-m fibrils was shown, indicating that ultrasonication is useful to accelerate the nucleation process (6). Third, with the proteolytic fragment of β2-m, propagation and a transformation of fibril morphology was demonstrated (7). These direct observations indicate that template-dependent growth and structural diversity are key factors determining the structure and function of amyloid fibrils.

References

1. Ban, T. *et al.* (2006) *Acc. Chem. Res.* **39**, 663-670.
2. Chatani & Goto (2005) *Bichim. Biophys. Acta* **1753**, 64-75.
3. Ban, T. *et al.* (2003) *J. Biol. Chem.* **278**, 16462-16465.
4. Ban, T. *et al.* (2004) *J. Mol. Biol.* **344**, 757-767.
5. Ban, T. *et al.* (2006) *J. Biol. Chem.* **281**, 33677-33683.
6. Ohhashi, Y. *et al.* (2005) *J. Biol. Chem.* **280**, 32843-32848.
7. Yamaguchi, K. *et al.* (2005) *J. Mol. Biol.* **352**, 952-960.

Downhill Folding: evolution meets physics

Martin Gruebele

Departments of Chemistry and Physics, and Center for Biophysics and Computational Biology, University of Illinois at Urbana Champaign, Illinois 61801, USA

Proteins evolve not to fold rapidly into beautiful structures (although they often do that), but to fulfill a function. Even the (partial) unfoldedness of "natively-unfolded" proteins is directly related to function, such as enhanced binding or signal transduction.

The sometimes conflicting interplay between folding and function explains much about why proteins fold the way they do. The same sequence encodes the information necessary for protein folding and function, and the two can conflict with one another. This raises the question: how much of a protein's free energy barrier for folding is obligatory, and how much arises from energetic frustration caused by conflicts with function, or avoidance of aggregation? [1]

I present several cases of proteins re-engineered to fold nearly or completely downhill. [2],[3] Such proteins demonstrate that the physics of folding is perfectly compatible with protein folding having no significant activation barrier. Where does the barrier in most natural proteins come from, then? It has biological sources: evolution for function, and evolution against aggregation. Experiments ranging from fast kinetics to X-ray crystallography, and computational results including replica exchange molecular dynamics will be discussed. [4] The kinetic signature of downhill folding is not simply fast or nonexponential folding, but rather a smooth transition from single-exponential kinetics, to fast non-exponential and probe-dependent kinetics, and back to simpler but even faster kinetics, as the stability of the native state is increased. [2][5][6] This transition can be explained by Langevin simulations [7], which show that metastable intermediates (barriers > 3 k_BT) would require careful fine-tuning to produce a similar result.

References:

[1] M. Gruebele, "Fast protein folding: evolution meets physics," Comptes Rendus Biologies **328**, 701-712 (2005).

[2] F. Liu and M. Gruebele, "Tuning $\lambda_{6\text{-}85}$ towards downhill folding near the unfolding transition midpoint," J. Mol. Biol. available on the web (2007).

[3] H. Nguyen, M. Jäger, J. Kelly and M. Gruebele, "Engineering a β-sheet protein towards the folding speed limit," J. Phys. Chem. B **109**, 15182-15186 (2005).

[4] M. Jäger, Y. Zhang, J. Bieschke, H. Nguyen, M. Dendle, M. E. Bowman, J. P. Noel, M. Gruebele, and J. W. Kelly "The structure-function-folding relationship in a WW domain," Proc. Nat. Acad. Sci. USA **108**, 10648-10653 (2006).

[5] J. Sabelko, J. Ervin and M. Gruebele, "Observation of strange kinetics in protein folding," Proc. Nat. Acad. Sci. USA **96**, 6031-6036 (1999).

[6] W. Yang and M. Gruebele, "Folding λ at its speed limit," Biophys. J. **87**, 596-608 (2004).

[7] H. Ma and M. Gruebele, "Low barrier kinetics: dependence on observables and free energy surface," J. Comput. Chem. **27**, 125-134 (2006).

Insights into fundamental states of matter through packing problems in hard spheres, sticky spheres, and M&Ms

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Ernest Rutherford Physics Building
McGill University
3600 rue University
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CANADA

Hard spheres are used as model systems to study age-old and new packing problems. I will discuss packing of hard spheres in crystalline solids, and rich phase behaviour in terms of the entropy-driven disorder-order transition that even hard spheres exhibit. Some simple as well as sophisticated experiments are providing surprising new insights about packing in disordered solids when one deviates from spheres in shape. Deviations from hard sphere interactions, realized in experiments with colloidal systems, combined with theoretical predictions, are leading to deeper understanding of the glass and gel states of matter.

NATIVE STATES OF PROTEINS AND COMPUTATIONAL MODELING OF THEIR STRUCTURE AND STRUCTURE - FUNCTION RELATIONSHIPS

Maria Kurnikova, Chemistry Department, Carnegie Mellon University, Pittsburgh, PA 15213, USA

Proteins are main functional units of a living cell. They participate in maintaining cell structure and integrity, reception and transduction of chemical and physical signals from the environment; they function as messengers and catalyze chemical reactions; they are involved in cell reproduction and death processes. In this introductory lecture I will briefly introduce physical and chemical principles of protein structure and function. Properties of globular and membrane proteins will be discussed. Computational and theoretical approaches to protein structure prediction and protein structure-function relations will be introduced. Several examples which illustrate Molecular Modeling methodologies application to protein- ligand interaction, ion channel permeation and conformational transitions in proteins will be presented.

Physics of proteins: a unified perspective

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Globular proteins are a key component of the network of life. Over many decades, much experimental data on proteins have been gathered, yet theoretical progress has been somewhat limited. We will show that the results accumulated over the years inexorably lead to a unified framework for understanding proteins. This framework i) predicts the existence of a fixed menu of folds determined by geometry, ii) clarifies the role of the amino acid sequence in selecting the native state structure from this menu and iii) explains the generic propensity for amyloid aggregation. The experimental data and the new approach reveal an astonishing simplicity underlying the protein problem.

$Mo_6S_{9-x}I_x$ recognitive connectors forming molecular electronics networks.

Mihaela I. Ploscaru[1], S. Jenko Kokalj[1], Marko Uplaznik[1], Damjan Vengust[1,2], Dušan Turk[1], Aleš Mrzel[1], Dragan Mihailovic[1,2]*

[1]Jožef Stefan Institute and International Postgraduate School, Jamova 39, 1000 Ljubljana, Slovenia, and [2]Mo6 d.o.o., Teslova 30, 1000 Ljubljana, Slovenia.
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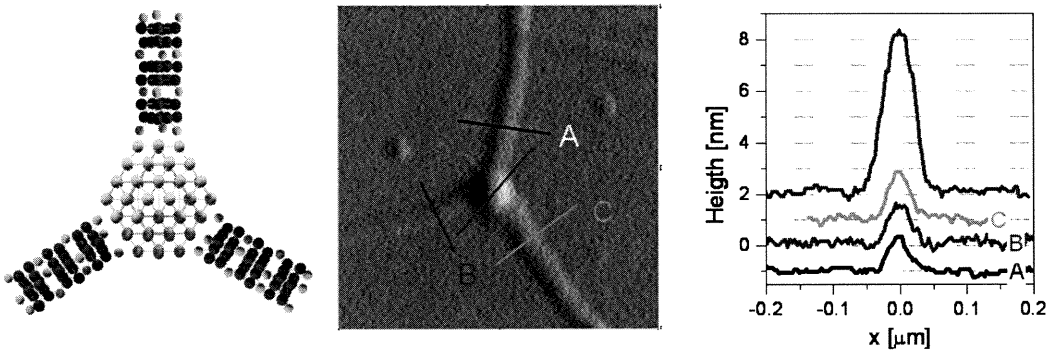
We report on the recognitive self-assembly of molecular-scale circuits using sulfur-terminated sub-nanometer diameter $Mo_6S_{9-x}I_x$ (MoSIx) molecular nanowires. We demonstrate solution-processed attachment of MoSIx nanowire leads to gold nanoparticles (GNPs) in different configurations. We further demonstrate multi-terminal branched circuits with GNPs (such as shown in the Figure), opening a self-assembly route to multiscale complex molecular-scale architectures and networks at the single-molecule level.

We also show that naked nanowires have the potential to bind thiolated proteins such as green fluorescent protein or thyroglobulin directly, thus providing a universal construct to which almost any protein or organic molecule which contains thiols could be attached.

The MoSIx nanowires have been shown to have good electrical conductivity on the nanometer scale. Experiments on electron transport suggest that correlations between electrons may need to be considered when constructing molecular scale circuits with MoSIx nanowire connectors.



From glasses to protein : simulating slow processes

Normand Mousseau
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CANADA

The simulation of slow processes that dominate the dynamics of activated materials such as glasses and proteins remains a challenge in spite of the considerable progress in computing power and algorithms. In this talk, I will discuss activated methods developed by collaborators and I as well as applications of the activation-relaxation technique (ART nouveau) to disordered materials and proteins.

This work was done in collaboration with:
GT Barkema (Utrecht),
MV Chubynsky (Montreal),
P Derreumaux (Paris),
F. El-Mellouhi (Montreal)
H Vocks (Utrecht).

Rigidity as a tool to understand the role of low frequency modes in glass transition and flexible systems

Gerardo G. Naumis
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Very recently, rigidity theory has been used as a tool to understand in a unified way physical trends in many diverse systems, like in glasses, polymers, fluids, colloids, granular material, proteins and even in computational complexity. The basic idea behind this approach is to treat bonding as a mechanical constraint. In this talk, we will show that such universality stems form the fact that rigidity theory provides a useful description of the energy landscape of flexible systems [1], and thus many thermodynamical and relaxational properties are related to it.

As an example, we discuss the case of glass transition. Although there are many theories to understand this transition, most of them just ignore a fundamental fact: all glasses have an excess of low-frequency vibrational modes. Here, the effects of flexibility and chemical composition in the variation of the glass transition temperature are obtained by using the Lindemann criteria, that relates melting temperature with atomic vibrations. Using this criteria and that low frequencies vibrations enhance in a considerable way the average quadratic displacement, we show that the consequence is a modified glass transition temperature [2]. This approach allows to obtain in a simple way the empirically modified Gibbs-DiMarzio law, which has been used in chalcogenide glasses to fit the changes in the glass transition temperature with the chemical composition. Other known relationships are also obtained, like the Tanaka law and the 2/3 law relating melting and glass transition temperatures.

Finally, we discuss the effects of flexibility in the relaxation properties. This is done by making the observation that relaxation takes place mainly due to non-linear interactions, with an energy cascade mechanism that transfers energy from high to low frequency modes, where energy is dissipated due to their quasiresonant nature. Since flexibility enhances the number of low-frequency modes, the relaxation properties are changed and stretched exponentials are observed with an exponent that depends upon the rigidity of ths system.

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Protein folding and design: from single proteins and their building blocks to nanostructures

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Nanotechnology realizes the advantages of naturally occurring biological macromolecules and their building- block nature for design. Frequently, assembly starts with the choice of a "good" molecule that is synthetically optimized towards the desired shape. By contrast, we propose starting with a pre-specified nanostructure shape, selecting candidate protein building blocks from a library and mapping them onto the shape and, finally, testing the stability of the construct. Such a shape-based, part-assembly strategy is conceptually similar to protein design through the combinatorial assembly of building blocks. If the conformational preferences of the building blocks are retained and their interactions are favorable, the nanostructure will be stable. The richness of the conformations, shapes and chemistries of the protein building blocks suggests a broad range of potential applications; at the same time, it also highlights their complexity.

Proline and Glycine Control Protein Self-Organization into Elastomeric or Amyloid Fibrils

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Elastin is the polymeric extracellular matrix protein which provides extensible tissues, such as large arteries and lung alveoli, with the propensity for elastic recoil. In contrast, amyloid fibrils are a pathogenic state of proteins associated with tissue degeneration in numerous debilitating diseases, including Alzheimer's disease, transmissible spongiform encephalopathies, and type II diabetes. Although both elastin-like and amyloid-like materials result from the aggregation and self-organization of proteins into fibrils, the molecular basis of their differing physical properties is poorly understood. Here we study the structural properties of monomeric and aggregated states of a set of peptides modeled after elastin-like and amyloidogenic sequences using molecular simulations. We demonstrate that elastin-like and amyloid-like peptides are separable on the basis of peptide-peptide hydrogen bonding, polyproline II content, and backbone hydration. The comparison of similar sequences indicates that these properties are modulated by proline and glycine. Accordingly, the analysis of diverse sequences, including those of elastin, amyloids, spider silks, wheat gluten, lizard egg shells, and insect resilin, reveals a threshold in proline and glycine composition above which amyloid formation is impeded and elastomeric properties become apparent. The predictive capacity of this threshold is confirmed by the self-assembly of recombinant peptides into either amyloid or elastin-like fibrils. Our findings support a unified model of protein aggregation in which hydration and conformational disorder are fundamental requirements for elastomeric function.

Ordering in Network Glasses

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The structure of glass is a formidable problem to solve because the atomic sites are topologically disordered and the presence of two or more chemical species adds further complexity. In this talk, some new in-roads are reported that have emanated from the application of neutron diffraction methods. Specifically, it is found that the topological and chemical ordering are both described by at least two different length scales at distances greater than the nearest-neighbour. The interplay between the ordering on these length scales and the physical properties of glassy networks is discussed.

PROTEIN STABILITY

Jose M. Sanchez-Ruiz

Several important issues related with the stability of proteins will be described and discussed:

-Thermodynamic stability versus kinetic stability.
-The protein stability curve and the existence of cold denaturation.
-The structure-energetics relationships and their implications for protein design.
-The role of residual structure in protein denatured states.
-The adequacy of the two-state equilibrium model in relation with the possibility of existence of intermediate states.
-The adequacy of the two-state equilibrium model in relation with the possibility of downhill folding.
-The general implications of protein kinetic stability.
-The design of enhanced free-energy barriers for protein irrerversible denaturation.
-The existence of alternative, native or nearly-native states.

Simulations of peptide inhibitors of Amyloid-β aggregation

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Alzheimer's disease is associated with the abnormal self-assembly of the Alzheimer Amyloid-β (Aβ) peptide into aggregate structures. Both the end-product amyloid fibrils as well as smaller soluble oligomers formed in the initial stages of aggregation appear to be toxic to the cell. An attractive therapeutic approach to combat amyloid diseases lies in the development of strategies to inhibit or reverse aggregation. We consider here the 16-22 fragment of the (Aβ) peptide, the shortest sequence of Alzheimer Aβ peptides capable of forming fibrils. An N-methylated version of this peptide has recently been shown to inhibit fibrillogenesis and disassemble Aβ fibrils. We present molecular dynamics simulations of the interaction of this inhibitor peptide with small oligomers of Aβ peptides, as well as with a model fibril. Our simulations suggest that the inhibitor peptide can act on both prefibrillar and fibrillar forms of Aβ, and that the specific mechanism of inhibition depends on the structural nature of the Aβ aggregate.

Monolayer Protected Metal Nanoparticles and Cells

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Metal Nanoparticles are supramolecular assemblies of a self-assembled monolayer on a single metallic crystal. In this talk we will show that the composition and structure of the ligand shell determines profoundly the ability of these particles to interacting with cells. Nanoparticles with cell membrane permeation ability will be presented.

The role of structural disorder in protein-protein interactions

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Intrinsically disordered proteins (IDPs) have received increased attention lately, as it has become clear tat the lack of a stable 3D structure is prevalent in the proteomes of higher organisms. Structural disorder is particularly prevalent in regulatory and signaling proteins, and IDPs often carry out their functions via protein-protein interactions (PPIs). In this work we have addressed the principles of the involvement of disorder in PPIs. We have shown that short linear recognition motifs of proteins tend to fall into locally disordered regions, and such regions provide efficient switches for the rapid evolutionary adaptation of interaction networks. The actual binding regions undergo disorder-to-order transition upon binding and adopt well-defined structures in the cognate complexes. Analysis of the secondary structural preferences of these regions has led to the unexpected finding that IDPs have a strong preference for their structures attained in the bound state, which suggests that their binding motifs might presage their final, partner-induced conformations. This fine balance between order and disorder is probably indicative of the thermodynamic and kinetic fine-tuning of recognition by IDPs, which is in line with their preferential functioning in interaction networks. Our studies on PPI networks have shown that disorder is higher in proteins with multiple interactions (hubs proteins) than in proteins with a few interactions. We also have studied atomic details of the interfaces, which suggests that IDPs use a unique strategy for recognition. They present a much higher proportion of their residues for interaction than their globular counterparts, and they tend to expose their hydrophobic residues for effective interaction with their partners. Overall, these and other observations corroborate our premise that involvement in rapid and regulated PPIs has been a key element in the evolutionary advance of protein disorder.

The Flexibility Window

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Functionally interesting materials often exist in the flexibility window which lies between rigid materials (e.g. crystalline silicon) that cannot deform and flexible materials that can adopt multiple distinct conformations (e.g. polymer chains). The nature of the interatomic interactions makes some materials rigid while others are flexible. This is controlled by constraints, both equalities and inequalities, which determine the flexible and rigid regions. Graph theory methods are used to find the flexibility and geometric simulation methods are used to study the mobility.

Examples include (a) zeolites maximize their density and contain flexible pores that are useful for cracking petroleum (b) the intermediate phase in chalcogenide glasses that has unusual reversibility properties and (c) proteins and other biomolecules that have enough rigidity to define their three dimensional structure, while retaining enough flexibility to function (d) quadrupolar ordering of the corner sharing octahedra in $LaMnO_3$.

Work supported by NSF and NIH.

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Dynamics of Protein Structure Networks

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The protein structures have been represented as networks of non-covalent connections, which are weighed on the basis of the strength of interaction. It has been shown that the degree distribution profiles of structure networks are complex, ranging from a random Gaussian–like to exponential-like behaviour, depending on the strength of interaction(1). The size of the largest cluster undergoes a transition like behaviour at a critical strength of interaction, which appears to be related to the process of protein folding. The dynamics of protein structure networks have been investigated by combining the methods of molecular dynamics simulation and the structure network analysis. The network dynamics in equilibrium is investigated by simulating the protein, Methionyl t-RNA sythetase at 300K. The advantage of the network analysis in understanding the dynamics of different domains at the level of side-chain interaction will be discussed. The unfolding simulations of Lysozyme are carried at 500K and the process of unfolding has been investigated through structure networks (2). The transition from folded to unfolded states have been monitored through changes in the network of side-chain interactions. Correlations between the dynamical nature of the network and experimental findings on protein stability and folding have been observed.

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Protein Folding and Flexible Binding

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Transition state theory has been often used in protein folding. We study the effect of diffusion in protein folding dynamics. We found configurational dependent diffusion can have significant effects on the kinetics. It can shift the transition state and therefore the kinetic route or path as well as change the thermodynamic barrier height and therefore the kinetic rate. For fast folding, the effect of configurational dependent diffusion is expected to play an important role and the transition state theory should be significantly modified accordingly. Flexible molecular recognition can be very important in realizing the function and specificity in the cell. We study the flexible binding when folding and recognition are intimately coupled. We found for a particular protein interaction complex, the flexible recognition proceeds as first binding and then folding in contrast with the conventional wisdom of first folding and then binding, revealing the important underlying nature.

Structure and dynamics in the physics of foams

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Ordinary soap froth offers us an opportunity to study almost all the usual problems of structure and dynamics of condensed matter in a simple, well-defined and generally accessible system. We will outline the history of the subject as well as recent developments, which include a strong current interest in rheology.

ABSTRACTS

OF

POSTERS

(in alphabetical order of author name as of 29 May 2007)

The Effect of an Neighbouring Electric Field on the Conductance of the Gramicidin A Channel. A Brownian Dynamics Study.

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1. Abstract

The Gramicidin A is the most studied channel theoretically and experimentally. In the literature there are many works about the potential mean force that a cation experiences when passes through the channel. Despite of that, it has not been possible to reproduce correctly the experimental curves of the current as a function of the applied voltage and the ionic concentration; a difficulty we confronted too in a previous work (C. Aponte et al. (2006) Rev. Col. Fís., 38(4): 1639-1642). In those works it is generally assumed that electric field is constrained inside the channel. Here, we explore the effect of an electric field present outside the channel, due to the edge in the opening of the channel. The existence of this electric field is justified because it drives forward the cations toward and from the channel. We developed brownian dynamics simulations to calculate the current through the channel as a function of the applied voltage and the ionic concentration in the media. In addition to the effect mentioned above, we considered inside the channel the potential mean force profile obtained by Allen et al. (Allen et al., (2004) PNAS, 101(1): 117-122), the electrostatic repulsion between ions and a single-file force proportional to $1/r^9$. We explored the growth of the current caused by this external electric field and how it changes the saturation properties in the current-concentration relationship.

Downhill and two-state: Which factors may affect these scenarios of folding?

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To study "downhill" folders with marginal or no free energy barrier, we consider factors that can change the cooperativity of proteins. Structures of roughly the same size ($\simeq$ 40 amino acids) were chosen from Protein Data Bank and studied using coarse-grained C_α Go-like model with Langevin dynamics. Three types of Go-like potential are considered: a regular 10-12 form (default case), a potential which accounts for important desolvation barriers and a model with many-body interactions. Desolvation barriers increase free energy barriers for two-state folders, thus increasing the cooperativity of folding. The effect of many-body interactions is much more pronounced: free energy profiles change their shape from unimodal to bimodal, thus changing the folding scenarion from "downhill" to two-state. This result indicates the downhill proteins are deficient in many-body interactions, compared to the two-state.

Probing the Conformational Modifications of Conducting Polymer Chains by Small Angle X-Ray Scattering.

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Abstract:

We show that conformational modifications of conducting polymer chains play an important role in modifying the electrical and optical properties of these systems. The different routes driving these conformational modifications are identified. Specifically, we study the structure of the conducting polymer poly ethylene dioxythiophene (PEDOT) complexed with polystyrene sulfonate (PSS) in dilute solutions of water, dimethyl sulfoxide (DMSO) and glycerol, with the help of small angle X-ray scattering. The polymer chains are found to be relatively more extended in glycerol and DMSO compared to water. The SAXS investigations reveal that the solvent-assisted modifications of conducting polymer chains can improve chain organisation and charge transport, which results in an enhanced conductivity for PEDOT-PSS films processed from specific solvents such as glycerol and DMSO.

Understanding the molecular determinant of the aggregation of elastin-like peptides

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Elastin is a ubiquitous protein found in cartilage, blood vessels, and skin. It is the molecular component that endows these tissues with remarkable mechanical properties including tensile strength, plasticity, and elasticity. In addition to its fundamental biological significance, elastin is the object of considerable interest because of its remarkable physical and biophysical properties and applications of outstanding biomedical and biotechnological potential. Yet, despite the importance of this protein as a structural biopolymer, the molecular basis underlying the distinct attributes of elastin remains poorly understood. We use atomistic computer simulations to characterize the molecular processes giving rise to the structural, thermodynamic, and mechanical properties of elastin. More specifically, we use large-scale molecular dynamics simulations to investigate the spontaneous self-aggregation of elastin-like polypeptide chains with similar sequences but different aggregation properties. In particular, we examine systematically the effect of amino acid sequence, temperature, and solvent properties on the structural and dynamic properties of the chains as well as the morphology of the self-assembly.

Effect of the light absorption by hemoglobin on the efficiency of the photodynamic therapy

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Abstract: The experimental data and theoretical calculations show, that hemoglobin can be considered as a primary agent, whose photoexcitation induces cytotoxic reactions, resulting in tumors destruction without an exogenous singlet oxygen photosensitizer. In the paper different light regimes of a photodynamic therapy are analyzed. It is shown that the action spectrum for a cellular death following a laser treatment doesn't coincide to the absorption spectrum of the photosensitizer.

Effective method of a malignant tumor treatment is a photodynamic therapy (PDT). Compared to current treatments PDT offers the advantage of an effective and selective method of destroying diseased tissues without damaging surrounding healthy tissues. So potentials of a modern oncology have considerably extended with photodynamic therapy. The investigation of a mechanism of PDT action is very important problem, since for an enhancement of the treatment efficiency it is necessary to know the full sequence of reactions or, at least, the most significant of them.

Recently, it was demonstrated that PDT action spectrum didn't coincide with an absorption spectrum of photosensitizer (PS) [i]. Moreover, an irradiation of nonsensitized tumors result in a sizable necrosis formation [ii,iii]. So it is reasonable to expect that in addition to photodynamic reactions other physical-chemical processes are induced during PDT treatment.

The efficiency of PDT treatment is known to depend on the free oxygen concentration, the dose of a photosensitizer (PS) and the irradiation regime. At the same time the high oxygen consumption rate during PDT reduces significantly the oxygen pressure. It was proposed to use a photoinduced dissociation of a hemoglobin-oxygen complex to increase the free oxygen concentration. But under conditions typical of PDT, the increase of the free oxygen concentration is calculated to be no more than 2%. However, in the course of PDT treatment an acute hypoxia appears. Then the insignificant increase of the free oxygen concentration can markedly affect on the PDT efficacy.

The aim of this work is to compare the extents of the photoinduced tumor destructions with and without a singlet oxygen sensitizer and to determine a cytotoxic effect of different light absorbing components of biological tissues.

The experiments were carried out on tumor strains Pliss lymphosarcoma and sarcoma M-1 transplanted to non-purebred white rats. The Photolon photosensitizer (RUE Belmedpreparaty, Belarus) was injected at a dose 5 mg kg^{-1} intravenously. The investigations of the efficiency of PDT treatment were carried out under different optical regimes. Lasers LD680-2000 (Biospec Lab., Moscow, λ_1=671 nm) and Metalas - M (Mechatron, Moscow, λ_2=627,8 nm) were used in the experiments. First of them excited mainly the photosensitizer and the second one provided primarily an oxyhemoglobin photoexcitation. The rats were irradiated either with one laser (λ_1=671 nm or λ_2=627,8 nm) or two lasers ($\lambda_1+\lambda_2$) simultaneously. The tumor necrosis was estimated from the functional state of the tumor bloodstream with the help of the vital staining method. In more detail the method of quantitative determination of photoinduced tumor destruction efficacy was described in [iv].

It has been shown that the destructions of tumors irradiated by light with wavelengths λ_1 or λ_2 don't differ significantly. Besides the simultaneous irradiation with light $\lambda_1+\lambda_2$ (two-wavelength regime) results in a non-additive accumulation of tumors destruction. Moreover, the necrosis sizes of the sensitized and non-sensitized tumors are of the same order. In spite of the fact that only two irradiating wavelength were used, it seems reasonable to say that the action spectrum for a cellular death is not coincide to the absorption spectrum of the photosensitizer. The comparison of the experimental data and theoretical calculations demonstrated that precisely hemoglobin (both oxy- and deoxy forms) is the primary agent, which absorbs light and initiates the cytotoxic reactions leading to non-sensitized tumors destructions. But a combination of photodynamic and non-photodynamic reactions might act in an additive or synergistic manner. An unrecognized overlap of both effects might complicate the interpretation of PDT mechanism.

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Free Energy Landscape for the Random Heteropolymer with Power-Law Correlated Sequence

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Thermodynamic properties of the random heteropolymers with persistent power-law correlations in monomer sequence have been investigated. We show that this type of sequences possess proteinlike properties. In particular, we show that they can fold into stable unique three-dimensional structure (the "native" structure, in protein terminology) through two different types of pathways. One is a fast folding pathway and leads directly to the native structure. Another one, a more slower pathway, passes through the microphase separated (MPS) state and includes a number of intermediate glassy states. The scale and the magnitude of the MPS are calculated. The frozen state can be reached only by sequences with weak long-range correlations. The critical value for the correlation exponent is found, above which (strong correlations) freezing is impossible.

Coil-to-Globule Transition of Poly(*N*-isopropylacrylamide) Doped with Chiral Amino Acidic Comonomers

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The dramatic conformational change of the thermosensitive poly(*N*-isopropylacrylamide) (pNIPAAm) has motivated many investigations aimed at understanding the basic physics of coil-globule transition. By combined light scattering and circular dichroism measurements (CD), we have investigated the temperature behavior of pNIPAAm copolymerized with a 1/10 fraction of valine- or leucine-derived groups randomly positioned along the chains. The comonomers provide the pNIPAAm chains with chirality, electric charge, and increased hydrophobicity. For valine-derived copolymers, the coil-globule transition is basically unmodified with respect to pNIPAAm, whereas doping with leucine-derived groups significantly lowers the transition temperature and makes the transition discontinuous. The CD signal enables probing the collapse of the doped pNIPAAm chain around the chiral groups. Accordingly, we surmise that the globulization is promoted by micellelike intrachain clusters of leucine-derived groups, interspersed with the (more) soluble NIPAAm sequences. The formation of such crumpled coils as an intermediate state in the globularization of leucine-doped pNIPAAm could explain the discontinuous character of the transition.

THE ANALYSIS OF HUMAN LYZOZYME STRUCTURE WITH MOLECULAR DYNAMICS SIMULATION

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Abstract: The main objective of one of the research projects that we are running inside The National Research and Development Program, is the study of amyloidosis. Lysozyme is one of the proteins that form the proteic agregats. It has been determined that the human lysozyme that forms amiloid fibrils *in vivo* present some point-like mutations. Having these information as a starting point, we want to use the molecular dynamics simulation method in order to study the structure of the human lysozyme and some point-like mutations of this. In order to analyze the contribution of the hydrophobic residues to the stability of the protein, we simulated the molecular dynamics on such a mutant structure and we studied the dynamic and structural properties. The simulation was done at denaturation temperature, in water box and NPT ensemble. The mutant structures supposed to replace the isoleucine with the valine in the native human lysozyme, 1LZ1. It was been analyzed various structural and dynamic properties: RMSD, accessible surface area, dihedrals, distances between C_α atoms, hydrogen bounds.

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PROTEIN PROFILE STUDY OF CLINICAL SAMPLES: CASES OF CERVICAL AND ORAL CANCERS

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Protein profiles of serum, pap smears and tissues collected from healthy and malignant patients, were recorded using HPLC-LIF technique developed in our laboratory. Protein profiles of serum, pap smears and biopsy tissues from healthy and malignant volunteers shows significant differences in the number of peaks and relative intensities. Statistical analysis (PCA) of the data has given good discrimination between samples from normal and diseased subjects. Protein profiles of serum samples collected from healthy and oral cancer subjects were also studied using HPLC-LIF method. Serum protein profile data of normal and oral cancer were classified into two distinguishable clusters using clustering algorithms. Statistical parameters like scores of factors and Mahalanobis distance were used for the discrimination of protein profiles while using PCA. Fuzzy clustering technique has been utilized to discriminate samples with more than two classes. Serum protein profile data of normal , oral and cervical cancers were classified into three distinguishable clusters using fuzzy clustering algorithms.

Key word: Protein profile, HPLC-LIF, Oral cancer, Cervical cancer, PCA

Self-organized critical intermediate phase of elastic networks

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Some properties of covalent glasses as a function of their chemical composition can be understood using their representation as elastic networks and studying rigidity of these networks. As the mean coordination of a glass increases, the covalent network becomes more and more rigid and eventually an infinite percolating rigid cluster emerges, a phase transition known as the rigidity percolation transition. Surprisingly, recent experimental work has observed not one but two transitions, with an intermediate phase between them. The existence of this new phase is attributed to the self-organization of the network as it tries to avoid unnecessary stress. We study this self-organization using a model on the triangular lattice, in which networks avoid stress but are random otherwise. Compared to the previous work by Thorpe *et al.*, we introduce a bond-switching procedure that ensures equilibration and the absence of bias. We find an intermediate phase of a finite width in which a percolating rigid cluster exists with a probability between 0 and 1. A power-law distribution of non-percolating cluster sizes, normally observed at a single critical point in percolation transitions, is seen everywhere in the intermediate phase. We also observe a finite probability of percolation appearing and disappearing upon addition or removal of a single bond. These properties indicate that in this phase the network maintains itself in a critical state on the verge of rigidity, a signature of self-organized criticality, unusually, in a system at equilibrium.

MOLECULAR DYNAMICS SIMULATIONS OF PROTEINS AND PEPTIDES: FROM FOLDING TO DRUG DESIGN

Authors: Giorgio Colombo, Giulia Morra and Massimiliano Meli

Molecular recognition and spontaneous self-assembly are at the basis of the organization of all biomolecular systems. In the case of proteins and peptides, the information needed to control these processes is encoded in the sequence. This determines the form, simmetry and structural features of the interacting partners that in the end regulate the properties of biochemical pathways. Understanding the correlations between sequence structure and dynamics in proteins and peptides at an atomistic level of resolution still represents one of the grand challenges of modern biological chemistry. In this context, computer simulations represent a valuable approach to understand recognition and spontaneous self-organization (folding, aggregation and assembly of complexes), processes that cannot be directly observed experimentally.

Herein, examples illustrating the extent to which simulations can be used to understand these phenomena will presented. I will cover 1) the problem of peptide-receptor recognition and the use of the information obtained for the design of new drug-like molecules and 2) the study of the effects of different single point mutations on the self-organization properties of designed amyloidogenic peptide sequences.

Effect of buffers and solvents on the structure and aggregation of the *Sulfolobus solfataricus* acylphosphatase

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The acylphosphatase from *Sulfolobus solfataricus* (Sso AcP) adopts, like other acylphosphatases, a ferredoxin-like βαββαβ sandwich domain, but interestingly possesses an unstructured fragment of 13 residues at the N-terminus that appears to be critical in the aggregation process. To promote aggregation aqueous solutions with 20-25% (v/v) of trifluoroethanol (TFE) in acetate buffer are commonly used, and prefibrillar native-like aggregates are obtained as shown by Chiti et al[1,2]. Previously in our laboratory the Sso AcP structure was solved by NMR[3] dissolving the protein in phosphate buffer, an environment that seems to be protective against aggregation. In the present study we focused our attention on the role of different buffers, phosphate and acetate, in the presence and in the absence of 20% TFE. Preliminary measurements reveal that the structure is maintained in its native-like form in both buffers, either in the presence and in the absence of TFE, whereas different $^{1}H/^{2}H$ exchange behaviours of backbone amides are observed in the various experimental conditions.

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Desolvation Effects in Folding: Rates and Topology

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May 3, 2007

As a protein folds, water molecules must be excluded from the hydrophobic core, and thus desolvation barriers between the protein's constituent groups must be crossed before the final folded configuration can be reached. Previous research on continuum Go-like protein models has demonstrated that pairwise-additive desolvation potentials lead to more thermodynamically and kinetically cooperative folding/unfolding transitions (Z. Liu, H. S. Chan, Phys. Biol. **2** (2005) S75S85). The present work focuses on the role of this elementary desolvation potential in improving predictions of the folding rate as well as shedding light on the well-known topology-folding rate relationship (K.W. Plaxco, K. T. Simons, D. Baker (1998) J. Mol. Biol. **277**, 985994) of small single-domain proteins (where topology in this context refers to the structure of nonlocal contacts between residues). Experimentally determined folding rates of ensembles of "two-state" proteins span approximately 5 orders of magnitude, which has not been reproducible in simulations. Adding a desolvation barrier to the potential energy yields a significant increase in the span of simulated folding rates, from 2 orders of magnitude without solvation to 4-5 orders of magnitude (a range comparable to experiment). This corresponds to a 2-fold increase in the range of activation free energy barrier heights $\Delta G^{\ddagger}$ in accordance with simple transition state theory; possible scenarios for why the barrier heights should experience such a significant change will be discussed. Additionally, comparisons between topologically relevant parameters in models with and without desolvation barriers and their predictive power for folding rates and transition state properties (such as the activation conformational entropy $\Delta S^{\ddagger}$ as measured in S. Wallin, H. S. Chan J. Phys.: Condens. Matter **18** (2006) S307S328) will be made.

fd/M13 viruses: from single-molecule flexibility to mesoscale chirality ?

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The *fd* and M13 bacteriophages are rod-like, semiflexible polyelectrolytes, with large aspect ratio. At high concentration, water suspensions of *fd* and M13 exhibit a chiral nematic phase, wherein virions are preferentially aligned along an axis, which rotates in space forming a left-handed helix, with a pitch of the order of 10-100 μm.[1] The microscopic origin of this chirality is not obvious; fluctuations in the virus shape have been suggested as the responsible.[2,3] To explore this possibility, we have coupled a Monte Carlo sampling of configurations of the virus, described as a worm-like biopolymer, to a mean-field model for its orientational distribution in the chiral nematic phase. Some information on the elasticity of the virus has been provided by recent experiments of single-molecule stretching.[4] From our analysis, the extremely strong twisting ability of individual virus configurations emerges, which is however washed out by the simultaneous presence, in a sample, of contributions of opposite handedness. Due to the lack of a complete characterization of the elasticity of the virus, only a qualitative comparison between theoretical predictions and experimental results is possible.

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Scoring predictive models using a reduced representation of proteins: model and energy definition

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Reduced representations of proteins have been playing a keyrole in the study of protein folding. Many such models are available, with different representation detail. Although the usefulness of many such models for structural bioinformatics applications has been demonstrated in recent years, there are few, if any, intermediate resolution models endowed with an energy model capable, for instance, of detecting native or native-like structures among decoy sets.

In this work[1] we present a discrete empirical potential for a reduced protein model termed here PC2CA, because it employs a PseudoCovalent structure with only 2 Centers of interactions per Amino acid, suitable for protein model quality assessment.

All protein structures in the set top500H have been converted in reduced form. The distribution of pseudobonds, pseudoangle, pseudodihedrals and distances between centers of interactions have been converted into potentials of mean force. A suitable reference distribution has been defined for non-bonded interactions which takes into account excluded volume effects and protein finite size.

The correlation between adjacent main chain pseudodihedrals has been converted in an additional energetic term which is able to account for cooperative effects in secondary structure elements. Local energy surface exploration is performed in order to increase the robustness of the energy function.

The model and the energy definition proposed have been tested on all the multiple decoys' sets in the Decoys'R'us database. The energetic model is able to recognize, for almost all sets, native-like structures (RMSD less than 2.0). These results and those obtained in the blind CASP7 quality assessment experiment suggest that the model compares well with scoring potentials with finer granularity and could be useful for fast exploration of conformational space.

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AGENT-BASED APPROACH FOR MODELLING MOLECULAR SELF-ORGANIZATION

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If we consider chemical systems, such as the crystal structure [1] or the supramolecular assembly [2] of an ensemble of molecule, a common question will arise: given N molecules, what is the lowest-energy organized structure that they can form?
This problem can be solved with the decomposition of the system in N *agents*. An agent is a system capable of exchanging information with other agents and its environment, taking decisions and performing autonomous actions.
The agent-based technique, previously used to study social phenomena, was first applied to a chemical system by Troisi et al.[3]. This technique allows a system of rigid shapes to evolve to the lowest-energy ordered structure on a 2-D lattice following a combination of stochastic, deterministic and adaptive rules with less computational effort than comparable Monte Carlo simulations.
The aim of our research is to extend the model to the study of the multiscale assembly of realistic systems [1, 2].

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Inhibition of α-synuclein fibrillation by dopamine is mediated by the ^{125}YEMPS^{129} C-terminal region and by E83 in the NAC region

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Abstract

The role of dopamine in α-synuclein (AS) fibrillization is under intense study for the implications of both molecules and their interactions on the mechanism of dopaminergic neuronal loss in Parkinson's disease. Several studies have shown that AS interaction with dopamine either through formation of covalent (1,2) or non-covalent (3) interactions, lead to disruption of amyloid fibril formation and accumulation of prefibrillar aggregates *in vitro*. Here we use computational methods to analyze the ability of AS conformations to bind non-covalently dopamine and two of its derivatives, protonated-dopamine and dopaminochrome. The calculations show that dopamine binds to the C-terminal region including the stretch Y125-S129, which has been previously identified by *in vitro* experimental data (3). The binding is characterized by specific structural determinants of this region and it involves mostly hydrophobic interactions between the ligand ring and the protein, accompanied by rather unspecific H-bonding interactions. In addition, dopamine forms water-mediated H-bonding interactions with E83 side chain, which therefore emerges as a key residue for binding in the NAC region. To prove these findings, the fibrillation of mutants which abolish the H-bonding functionalities of E83 and of the selected residues at the C-terminal (E83A, E126A, S129A and the triple mutant E83A/E126A/S129A) were investigated *in vitro* in the presence and absence of dopamine relative to the wild type protein. ThT fluorescence assay, SDS-PAGE gel, circular dichroism and electron microscopy assay demonstrate that dopamine is much less effective in blocking the fibrillization of the E83A-containing mutants than the wild type, thus confirming the central role of this residue in dopamine binding.

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Anthrax Lethal Factor Investigated by Molecular Simulations

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The anthrax disease is caused by the lethal toxin, a protein aggregate which contains the zinc-based hydrolase lethal factor. Here, we investigate the structural of the Michaelis complex with an optimized substrate by a plethora of computational methods, including density functional theory, molecular dynamics and coarse grained calculations. Our calculations suggest that the nucleophile agent is a Zn-bound water molecule, and that the presence of second shell ligands is indeed crucial for tuning structure and energetics of the metal site, consistently with previous studies. The substrate in the active site groove is mainly stabilized by electrostatic interactions, yet its scissile bonds are only mildly polarized by the protein frame. In addition, our calculations provide a consistent picture in which helix alpha-19, which is present in the solid state structure of antrax lethal factor (PDB code: 1JKY), assumes a coil conformation in aqueous solution. Finally, it is suggested that that the large scale motions of the enzyme do not play an important role for the enzymatic function, as it has been found for other proteases.

On the oligomeric state of DJ-1 protein and its mutants associated with Parkinson's Disease: a combined computational and *in vitro* study

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Mutations in the DJ-1 protein are present in patients suffering from familiar Parkinson's disease (PD) [1,2].

Here we use computational methods and biological assays to investigate the relationship between DJ-1 missense mutations and the protein oligomeric state. Molecular dynamics (MD) calculations suggest that:

(i) the structure of DJ-1 wild-type (WT) in aqueous solution, in both oxidized and reduced forms, is similar to the crystal structure of the reduced form [3,4];

(ii) the PD-causing M26I variant is structurally similar to the WT, consistent with the experimental evidence showing the protein is a dimer as WT ([5-7] and in this work);

(iii) R98Q is structurally similar to the WT, consistent with the fact that this is a physiological variant [8];

(iv) the L166P monomer rapidly evolves towards a conformation significantly different than WT, suggesting a change in the ability to oligomerize [3,4].

Our combined computational and experimental approach was next used to identify a mutant (R28A) that, in contrast to L166P, destabilizes the dimer subunit-subunit interface without significantly changing secondary structure elements.

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A Comparative analysis of Viral Ion Channel Proteins on

Dynamic and Structure of cell-Membrane using X-ray Reflectivity

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We have investigated the effect of the transmembrane domain of three viral ion channel proteins on the lipid bilayer structure and dynamic by X-ray reflectivity and scattering from oriented planar bilayers. The proteins show a similar effect on the lipid bilayer structural parameters: an increase in the lipid bilayer hydrophobic core, a decrease in the amplitude of the vertical density profile and a systematic change in the ordering of the acyl chains as a function of protein-to-lipid ratio. These results are discussed in a comparative view.

Possible functional roles of exposed sulfhydryl groups in malted and unmalted African millet Seed (*Eluesine Coracana*) β-amylase

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Abstract

The behavior of exposed sulfhydryl groups of β-amylase from malted and unmalted African finger millet seed was investigated for their possible functional roles by chemical modification studies using 5,5'-dithiobis-(2-nitro-benzoic acid) (DTNB). The enzyme was inhibited by the sulphurhydyl reagent. The chemical modification revealed that there were three sulfhydryl and four sulfhydryl in β-Amylase from both unmalted and malted seed respectively each having one exposed sulfhydryl group performing different roles and were essential for catalytic activity. The data show a distinction between the *in situ* β-amylase and *de novo* β-Amylase in malted seed. The β-Amylase was oxidatively dimerized by subjecting it to 0.3 M potassium ferricyanide in 3.0 M urea. The dimerized enzyme was inactive. The exposed sulfhydryl groups was involved in the dimerization in β-amylase from malted seed possibly in zymogen formation

COMPARATIVE STUDIES ON THERMODYNAMIC ACTIVATION DATA BETWEEN MALTED AND UNMALTED AFRICAN FINGER MILLET SEED (*ELUESINE CORACANA*) β-AMYLASE

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Abstract

The effect of 4-days malting on the thermo-activation thermodynamic data of β-amylase from African finger millet (*Eluesine coracana*) seed was determined and compared with that of the β-amylase purified from unmalted seed. The results showed that the relative importance of enthalpic ($\Delta H^{\neq}$) and entropic activation between malted and unmalted was different. The activation energy for catalysis of unmalted *Eluesine coracana* β-amylase was 2.00kcal/mol. The free energy change ($\Delta G^{\neq}$), enthalpy change ($\Delta H^{\neq}$) and entropy change ($\Delta S^{\neq}$) for activation at 50° C (optimum temperature) were 15.60kcal/mol, 1.36kcal/mol and –45.60 e.u. (entropy unit) respectively. The activation energy for catalysis of malted *Eluesine coracana* β-amylase was 7.54kcal/mol. The free energy change ($\Delta G^{\neq}$), enthalpy change ($\Delta H^{\neq}$) and entropy change ($\Delta S^{\neq}$) for activation at 50° C were 15.60kcal/mol, 6.90 kcal/mol and –24.96 e.u respectively. The purified β-amylase from malted seed at 90° C had an half life of 5.87 min with free energy of inactivation of 22.928 kcal/mol, enthalpy 14.640 kcal/mol and entropy -22.83 e.u. The results indicated that malted seed β-amylase reaction is enthalpy driven and unmalted seed β-amylase reaction is entropy driven to activation complex. The thermoactiavtion data both for malted and unmalted shows that the reaction is bisubstrate with a unimolecular rate determining step. The thermodynamic data of inactivation suggest that the enzyme is less stable at higher temperatures.

Refolding upon force quench and pathways of mechanical and thermal unfolding of proteins

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Single molecule AFM experiments have generated mechanical folding trajectories for polyproteins starting from initially stretched conformations. Refolding, monitored by the end-to-end distance, occurs in distinct multiple stages [1]. Inspired by these experiments we have probed the folding dynamics of protein ubiquitin (Ub) using a coarse-grained model. We show that the dependence of refolding times on quench force follows the Bell formula. The locationtransition state along the reaction coordinate, given by end-to-end distance, was determined. Our result is consistent with the experiments on Ub. Our simulations describe, at a molecular level, the distinct mechanisms of relaxation and refolding of Ub after muscle stretching. The mechanical and thermal unfolding pathways of Ub have been studied and compared with experiments in detail [2].

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Transportation, Nesting and Activation of Molecules on Material Surfaces

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We discuss novel methodologies of molecular manipulation, nesting and activation at the nanoscale that were developed and tested by molecular dynamics simulations in our group.

First, we show that polar molecules can be dragged on the surfaces of semiconducting carbon nanotubes by polar liquids flowing inside [1]. This phenomenon is caused by fluctuating Coulombic forces generated by the molecules of the flowing polar liquid. The molecules on the surfaces are transported with the speed that is 0.6-0.8 times that of the water flowing inside the tube.

Second, we present a methodology of designing selective nesting sites for inorganic, organic and biological molecules on material surfaces [2]. The idea is to optimally modify material surfaces by atomistic doping and binding of short charged ligands to them in such a way that the created local electric fields form selective molecular traps. We demonstrate this method on GFP protein selectively attached to modified graphene layer in water.

Finally, we briefly discuss the possibilities for activation of molecules on material surfaces. As an example, we show how we can control the activity of organic catalyst on the surfaces of twisted nanotubes [3].

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Mechanism of fibril formation of short peptides

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The mechanism of oligomerization of Alzheimers A16-22 peptides is studied by the all-atom simulations with the GROMOS96 force field 43a1 in explicit water. The time to get three peptides into an anti-parallel arrangement was found to be 200 ns. This value was estimated directly from the kinetic data as well as from the free energy landscape theory using the "liquid crystal" order parameter P2 as a reaction coordinate. The routes to the ordered state of the tetramer (N=4), pentamer (N=5) and hexamer (N=6) were studied by adding one peptide to the preformed anti-parallel conformations of (N-1) peptides. Dihedral angle principal component analysis is employed to study the conformations of peptides in detail. Our results suggest that the size of the critical nucleus of A16-22 peptides is larger than 6. Importantly, our study reveals that the oligomer growth obeys the two-stage "dock-lock" mechanism [1]. We have also developed a toy lattice model [2] to further support this mechanism.

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Molecular Dynamics of Liquid Crystals-A Dielectric Study.

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Dielectric studies of the liquid crystals are important as they provide information about the molecular structures, intermolecular interactions and molecular dynamics of samples Dielectric relaxation studies provides one of the few techniques for finding the nature of molecular reorientation taking place in the liquid crystal samples.

In the present work we have reported dielectric relaxation behaviour of some liquid crystals of different types .The FLC like Felix -16/100, CS1016, and nematic mixture-24 have been studied for dielectric permittivity with the variation of frequency, and temperature. The relaxation time and other related properties have also been discussed to understand the different molecular process, going on in these systems.

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Investigation of some properties of biomimetic membranes based on the lipid impregnated nitroacetate-cellulose ultra-filter.

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Abstract:

Biomimetic membranes (BMM) are specific class of artificial membranes fabricated to imitate some important properties intrinsic to natural membranes such as selective transport of different substances through them, their electric polarization, etc

The purpose of this study is to investigate the main properties of such BMM based on Millipore® nitroacetate-cellulose ultra-filter impregnated with several organic acids and lipides by impedance measurements in a wide temperature interval, and their stability, as well.

The BMM were prepared by impregnation the ultra-filters with different pore diameters using the solutions of oleic acid butyl ester, ovum/egg lecithin, and lauric acid butyl ester. The impregnation of BMM was carried out under different condition (temperature, pH and concentration of solutions, etc)

Analysis of the data obtained in this investigation allows to work out some recommendations aimed increasing the stability and life-time of BMM, and sensitivity of the electrochemical system too.

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Protein sequence-structure relationship: a MD- based method to discriminate between sequences folding to the same structure.

In this work a method for evaluating the fitness of a protein sequence to a given fold is introduced, based on the comparison of two vectors, of which one contains information on both sequence and structure, and the other represents the structure alone. Te sequence-structure vector *e* derives from an energy decomposition method applied to an all-atom MD simulation of a native protein, in order to identify those amino acid interactions mainly responsible for its enthalpic stabilization. Average non bonded interactions between amino acids pairs calculated during dynamics are used to build a symmetric matrix which is then diagonalized. The profile of the first eigenvector (*e*) contains essential chemical and topological information on residues involved in stabilizing contacts (i.e. sequence and structure). The same diagonalization procedure is applied to the C alpha- C alpha contact map of the native structure, yielding a principal eigenvector (*c*) which contains only essential information on the native topology. These two vectors are compared by means of a Pearson's correlation coefficient.

The analysis may shed light on the determinants of the adaptability of a certain sequence to a certain geometry. This idea has been tested on three folds. For each fold a set of 10 sequences has been considered, namely a wild type sequence and 9 single point mutants, for which changes in the thermal stability were experimentally measured. In all cases a higher similarity between (*e*) and (*c*) corresponds to the more stable variants. In other words, similarity between energy matrix and contact map correlates with experimental stabilization of the protein induced by mutation. An extension of the analysis to diverse sequences within a protein family might shed light on protein evolution.

Complex between triple helix of collagen and double helix of DNA in aqueous solution

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Abstract

We demonstrate in this paper that one example of a biologically important and molecular self-assembling complex system is a collagen–DNA ordered aggregate which spontaneously forms in aqueous solutions. Interaction between the collagen and the DNA leads to destruction of the hydration shell of the triple helix and stabilization of the double helix structure. From a molecular biology point of view this nano-scale self-assembling superstructure could increase the stability of DNA against the nucleases during collagen diseases and the growth of collagen fibrils in the presence of DNA.

The living cell exists as a result of processes that generate complex, multi-component, functional structures by self-assembly. Molecular self-assembly is a process in which molecules (or part of molecules) spontaneously form ordered aggregates and involves no human intervention. The interactions involved usually are non-covalent (such as metal–ligand bonds, hydrogen bonds, or van der Waals' forces–hydrophobic interactions) [1]. We demonstrate in this paper that one example of the biologically important and molecular self-assembling complex system is a collagen–DNA ordered aggregate, spontaneously formed in aqueous solutions.

Collagen is the major structural protein in mammals. Collagen is a useful molecule to pattern because of its fibrillar assembly and organization in vivo and in vitro, an ability to form liquid crystalline mesophases, and its structural influence on a wide range of biomaterials and tissue architectures ranging from fibrous connective tissues and bone to mesh-like basement membranes [2]. Collagen triple helix consists of three polyproline-II like chains wrapped around a common axis [3]. Collagen triple helix in aqueous solution presents as a stiff, rod-like structure, about 300 nm (280 nm) in length and 1.5 nm in diameter [4,5]. According to the DSC [5,6], low-temperature calorimetry and NMR data [7,8] the stabilization of collagen and the enormously large enthalpy of disruption of its structure are mainly the result of an extensive hydrogen bounding network inside the triple helix and in the hydration shell of molecule. According to high-resolution X-ray diffraction analysis each triple helix is surrounded by a cylinder of hydration, with an extensive hydrogen bounding network between water molecules and peptide acceptor groups [3].

With respect to the role of the bound water on the energetic and stabilization of the native macromolecule conformations in aqueous media, the triple helix of collagen and the double helix of DNA have many common features. The DNA double helix in aqueous solution is stabilized by H-bonds between complementary base pairs (A=T, G≡C), stacking interactions along the helix axis and interactions with the surrounding water layers. This bound water in the multi-layer hydration shell of the double helix [9] plays an important role in the duplex stability [10]. The model for ds-DNA in diluted aqueous solution is a worm-like chain. This chain represents the behavior intermediate between the rigid rod (like collagen) and the random coil, thus taking into account the local stiffness but long-range flexibility of the double helix [9]. The worm-like chain is defined by its contour length L (measured along

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WAKO-SAITO-MUNOZ-EATON MODEL OF PROTEIN FOLDING: KINETICS, MUTATIONS, MECHANICAL UNFOLDING

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We consider a simplified model of protein folding, with binary degrees of freedom, whose equilibrium thermodynamics is exactly solvable [1].
The kinetics is studied by means of computer simulations and a semi-analytical approach [2]. Equilibration rates show good agreement with the experimental ones for the WW domain of protein PIN1 and for the B domain of protein A, wild type and mutants [3]. The relationship between the logarithm of the equilibration rate and the absolute contact order is studied for model structures and is found to be almost perfectly linear within definite classes [4].
The model is then generalized with the inclusion of an external force, and the mechanical unfolding of protein domains and RNA fragments is studied [5]. In the case of the 27th Ig domain of titin, considering both dynamic loading and force clamp protocols, we verify theoretical expectations for unfolding forces and times and obtain an unfolding force of 0.3 nm, which compares well with the experimental value 0.25 nm reported by Fernandez and coworkers. Using the WW domain of protein PIN1 we show that the generalized Jarzynski equality is satisfied. Finally, we compute the unfolding and refolding work distributions for RNA fragments, which show a good qualitative agreement with experimental results and satisfy Crooks' theorem.

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Diffusion limited unbinding of small petides from PDZ domains

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PDZ domains are typical examples of binding motifs mediating the formation of protein-protein assemblies in many different cells. A quantitative characterization of the mechanisms intertwining structure, chemistry and dynamics with the PDZ function represent a challenge in molecular biology. Here we investigated the influence of native state topology on the thermodynamics and the dissociation kinetics for a complex PDZ-peptide via Molecular Dynamics simulations based on a coarse-grained description of PDZ domains.

Our native-centric approach neglects chemical details but incorporates the basic structural information to reproduce the protein functional dynamics as it couples to binding. We found that at physiological temperatures the unbinding of a peptide from the PDZ domain becomes increasingly diffusive rather than thermally activated, as a consequence of the significant reduction of the free energy barrier with temperature. In turn, this results in a significant slowing down of the process of up to two orders of magnitude with respect to the naive Arrhenius extrapolation from low temperature calculations.

Finally, a detailed analysis of a typical unbinding event based on the rupture times of single peptide-PDZ contacts allows to shed further light on the dissociation mechanism and to elaborate a coherent picture of the relation between function and dynamics in PDZ domains.

Anharmonicity and self-similarity of the free energy landscape of protein G

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The near-native free energy landscape of protein G is investigated through 0.4μs-long atomistic molecular dynamics simulations in explicit solvent. A theoretical and computational framework is used to assess the time-dependence of salient thermodynamical features. While the quasi-harmonic character of the free energy is found to degrade in a few ns, the slow modes display a very mild dependence on the trajectory duration. This property originates from a striking self-similarity of the free energy landscape embodied by the consistency of the principal directions of the local minima, where the system dwells for several ns, and of the virtual jumps connecting them.

Proline and Glycine Control Protein Self-Organization into Elastomeric or Amyloid Fibrils

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Elastin is the polymeric extracellular matrix protein which provides extensible tissues, such as large arteries and lung alveoli, with the propensity for elastic recoil. In contrast, amyloid fibrils are a pathogenic state of proteins associated with tissue degeneration in numerous debilitating diseases, including Alzheimer's disease, transmissible spongiform encephelopathies, and type II diabetes. Although both elastin-like and amyloid-like materials result from the aggregation and self-organization of proteins into fibrils, the molecular basis of their differing physical properties is poorly understood. Here we study the structural properties of monomeric and aggregated states of a set of peptides modeled after elastin-like and amyloidogenic sequences using molecular simulations. We demonstrate that elastin-like and amyloid-like peptides are separable on the basis of peptide-peptide hydrogen bonding, polyproline II content, and backbone hydration. The comparison of similar sequences indicates that these properties are modulated by proline and glycine. Accordingly, the analysis of diverse sequences, including those of elastin, amyloids, spider silks, wheat gluten, lizard egg shells, and insect resilin, reveals a threshold in proline and glycine composition above which amyloid formation is impeded and elastomeric properties become apparent. The predictive capacity of this threshold is confirmed by the self-assembly of recombinant peptides into either amyloid or elastin-like fibrils. Our findings support a unified model of protein aggregation in which hydration and conformational disorder are fundamental requirements for elastomeric function.

MULTI-FEATURE PROTEIN OPTIMIZATION USING SEQUENCE-STATISTICS-FOCUSED IN-VITRO EVOLUTION.

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Many efforts have been devoted to extract useful information from sequence alignments. Results have not always been conclusive. We have addressed the problem, first assuming that a consensus analysis may have evolutionary noise, and on the other hand, assuming that conservation may be related to the optimization of several features. Our results show that a sequence-statistics-focused in-vitro evolution procedure may lead to mutant proteins with increased thermodynamic stability in some cases, improved catalytic activity in others, or even higher kinetic stability. Sequencing of some of the mutants and a statistical analysis of the different mutations against the measured properties of each mutant may allow us, in a last step, to rationally generate a mutant with multi-feature optimization.

End-to-end distributions and intra-chain diffusion coefficients of disordered polypeptides measured by tryptophan triplet state lifetime and fluorescence resonance energy transfer.

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Quenching of the triplet state of tryptophan by cysteine after nanosecond UV excitation has provided a new tool for measuring the rate of forming a specific intramolecular contact in disordered polypeptides and denatured proteins. Peptides having the sequence $C(AGQ)_jW$ (j = 1-9) have been previously studied by means of this technique and by computer simulations. Here, we report measurements of the triplet state lifetime in water and denaturant solutions for two peptides having similar sequences with j = 4, in which three glutamines are replaced with glutamates in order to increase peptide solubility and the glycines are replaced with glutamines. We measured the triplet state lifetimes for different solvent viscosities in order to extract both the equilibrium probability of forming an end-to-end contact and the diffusion-limited rate of contact formation. Fluorescence Resonance Energy Transfer (FRET) measurements were performed on the same peptides using tryptophan as donor and Dinitrophenil (DNP)-maleimide reacted with cysteine as acceptor. FRET efficiencies and equilibrium contact probabilities were fitted simultaneously with different chain models: freely jointed chain, wormlike chain and the more general Domb-Gillis-Wilmers model. From the fitting we selected a rather narrow family of end-to-end distributions consistent with the experimental data and using these distributions we extracted root mean square end-to-end distances and intrachain diffusion coefficients for the peptides in different conditions of solvent and pH.

Agglomeration of protein-mediated chromatin loops

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Abstract:

Protein-mediated chromatin looping is believed to be a major organizing principle in the large-scale structure of the genome. We propose a mechanism for the self-agglomeration of chromatin loops: The competition between the gain in protein-DNA binding free energy and an entropy loss due to chromatin looping is argued to result in an effective attraction between loops. A mean-field description can be solved analytically via a mapping to a restricted random-graph ensemble. It shows the emergence of loop clusters containing a finite fraction of all loops. If the entropy loss due to a single loop is high enough, this transition is found to be of first order. Using numerical simulations, we show how to go beyond the mean-field description towards a more realistic modeling.

Dynamics of Intramolecular Contact Formation in Islet Amyloid Polypeptide (IAPP)

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Measuring the dynamical properties of unfolded chains in solution, and in particular of amyloid forming peptides, is of key importance to understand the first elementary steps in folding, misfolding and aggregation. Human islet amyloid polypeptide (hIAPP) is co-secreted with insulin in the beta-cells of the pancreas and forms amyloid deposits in type II Diabetes. In aqueous solution, before converting to its more stable multimeric fibrillar state, the monomer appears to be unstructured.

We use tryptophan triplet quenching by cystine to measure the rates of intramolecular end-to-end contact formation in hIAPP and in rIAPP (the non aggregating rat variant). Rates are measured in varying solvent conditions, from conditions in which hIAPP is a soluble unstructured monomer to conditions in which aggregation begins. Contact formation involves large scale motions which depend on the balance between attractive and repulsive interactions among amino acids in the chain and among amino acids and the solvent. Changing the solvent affects both the average size of the chain and its dynamical properties. Viscosity dependent measurements on rIAPP allow extracting these two terms from the observed rates, revealing interesting changes in the end-to-end distance distribution as a function of denaturant concentration and temperature, and in the diffusion properties of the chain. We compare such results to the case of hIAPP and to previously well characterized model peptides, $C(AGQ)_nW$.

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OF

POSTER

PRESENTATIONS

(in alphabetical order of author name as of 29 May 2007)

Conference on
Structure and Dynamics in Soft Matter and Biomolecules: From Single Molecules to Ensembles

4 – 8 June 2007
Trieste - Italy

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BADASYAN, Artem
Downhill and two-state. Which factors may affect these scenarios of folding?

BAGCHI, Debjani
Probing the conformational modifications of conducting polymer chains by small angle x-ray scattering

BAUD, Stéphanie
Understanding the molecular determinant of the aggregation of elastin-like peptides

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