A one-day Workshop on Protein Science

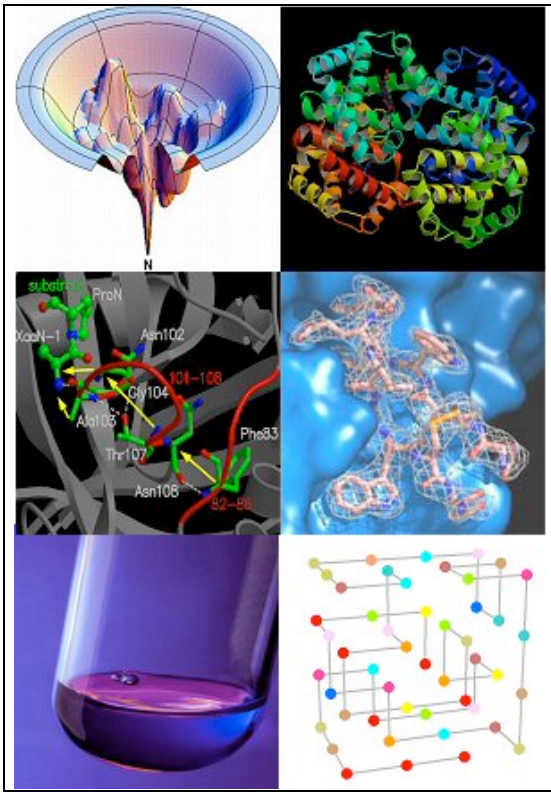
8 November 2006

10.00 -18.30h

Complexo Interdisciplinar
Universidade de Lisboa

Av. Prof. Gama Pinto 2

Understanding protein dynamics is extremely important to elucidate the relationship between structure and function in biological systems. This will be an interdisciplinary workshop bringing together scientists studying the dynamics of proteins and related molecules within different frameworks and using different experimental and computational techniques.



Invited Speakers

Miguel Castanho
Departamento de Química, U. de Lisboa

Marek Cieplak
Institute of Physics, Polish Academy of Sciences

Leonor Cruzeiro
Departamento de Física, U. do Algarve

Claudio Gomes
Instituto de Tecnologia Química e Biológica (ITQB)

Miguel Machuqueiro
Instituto de Tecnologia Química e Biológica (ITQB)

Maria João Ramos
Departamento de Química, U. do Porto

Rui Travasso
Centro de Física Teórica e Computacional, U. de Lisboa (CFTC-UL)

The participation in the workshop is **FREE**. However, please **register**: Send e-mail to Patrícia Faísca (patnev@cii.fc.ul.pt) before 5 November if you plan to attend. Please include your name and affiliation.

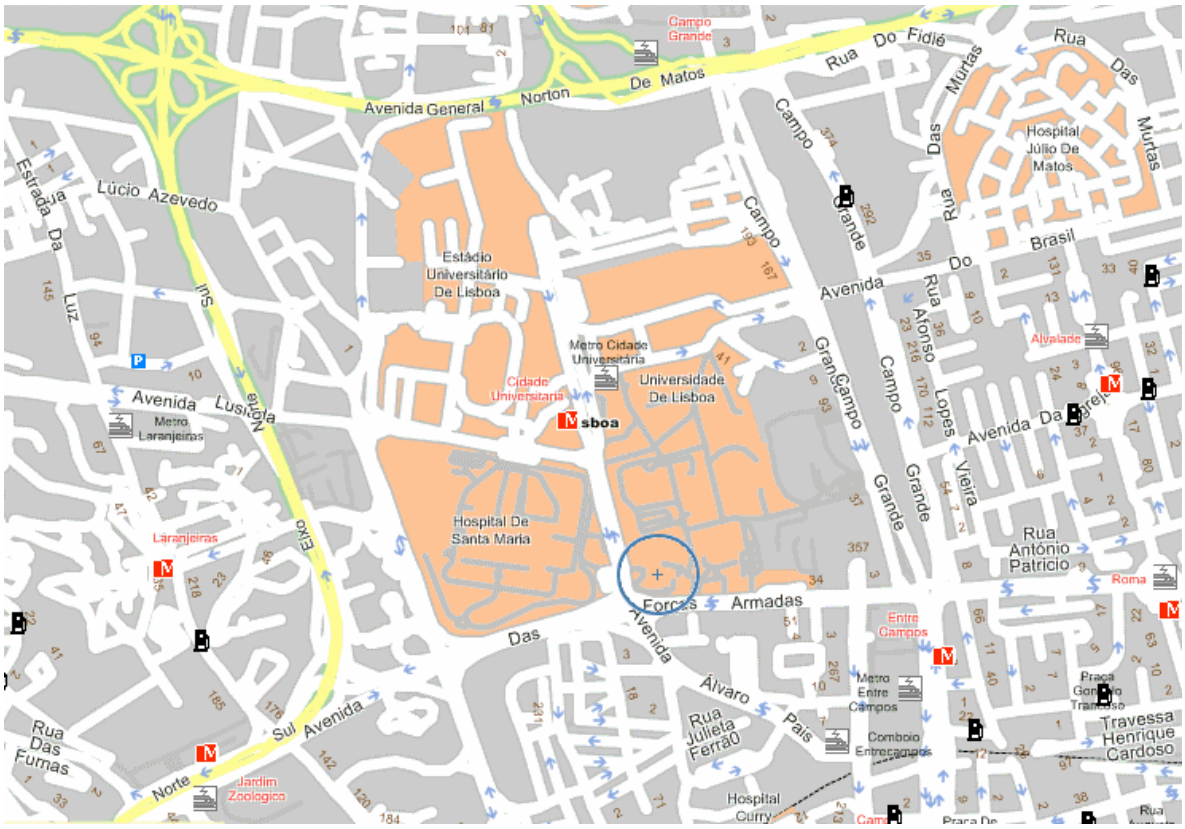
Organization:

CFTC Centro de Física Teórica e Computacional

Further details can be obtained from Patrícia Faísca, email: patnev@cii.fc.ul.pt

Location

Complexo Interdisciplinar da Universidade de Lisboa
Av. Prof. Gama Pinto 2, 1649-003 LISBOA CODEX



How to get here:

Metro: Entrecampos e Cidade Universitária.
Buses: 31, 35, 54, 701, 732, 738, 755, 768.

Program

Note: All sessions will be held at the 'Anfiteatro', which stands on the ground floor to the right of the main entrance door.

MORNING SESSION

10:00 – 11:00 **Marek Cieplak** (Institute of Physics, Polish Academy of Sciences): *Stretching to understand proteins*

11:00 - 11:40 **Miguel Machuqueiro** (ITQB, U. Nova de Lisboa):
Constant-pH Molecular Dynamics: methodology and applications

11:40 -12:00 **COFFEE BREAK**

12:00 -13:00 **Leonor Cruzeiro** (Departamento de Física, U. do Algarve):
The VES Hypothesis and protein folding and function

13:00 -14:30 **LUNCH**

AFTERNOON SESSION

14:30 -15:30 **Maria João Ramos** (Departamento de Química, U. do Porto):
Theoretical Studies of Biological Systems

15:30 -16:30 **Cláudio Gomes** (ITQB, U. Nova de Lisboa):
Protein misfolding and disease

16:30-16:50: **COFFEE BREAK**

16:50-17:50 **Miguel Castanho** (Departamento de Química, U. de Lisboa):
Why and how should peptides interact with lipid membranes?

17:50 -18:30 **Rui Travasso** (CFTC-UL):
Nucleation phenomena in protein folding: The modulating role of protein sequence

Abstracts

Stretching to understand proteins

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Mechanical stretching of single proteins has been studied experimentally for about 50 proteins yielding a variety of force patterns and peak forces. Here, we perform a theoretical survey of 7749 proteins of known native structure and map out the landscape of possible dynamical behaviours under stretching at constant speed. The model used is constructed based on the native geometry. It is solved by methods of molecular dynamics and validated by comparing the theoretical predictions to experimental results. We characterize the distribution of peak forces and on correlations with the system size and with the structure classification as characterized by the CATH scheme. We identify proteins with the biggest forces and show that they belong to few topology classes. We determine which protein segments act as mechanical clamps and show that, in most cases, they correspond to long stretches of parallel beta-strands, but other mechanisms are also possible. We then consider stretching by fluid flows. We show that unfolding induced by a uniform flow shows a richer behaviour than that in the force clamp. The dynamics of unfolding is found to depend strongly on the selection of the amino acid, usually one of the termini, which is anchored. These features offer potentially wider diagnostic tools to investigate structure of proteins compared to experiments based on the atomic force microscopy.

Constant-pH Molecular Dynamics: Methodology and applications

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The structure, function and dynamics of most biomolecules in solution are very dependent on pH. Until recently, computational molecular dynamics (MD) methods treat pH effects in a very approximate way, namely by selecting a representative state for each protonable site. We developed a constant-pH MD method which combines MD, Poisson-Boltzmann (PB) and Monte Carlo (MC) methodologies in a way that ensures a correct sampling of both conformation and protonation states during the simulation. Here we present an overall description of this methodology and its application to the decalysine peptide and the neuropeptide kyotorphin.

The constant pH MD method deals with the solution pH like the usual parameters of an MD simulation, allowing for changes in the protonation state of each titrable site during the simulation, where the new states can be obtained from PB calculations and MC simulation of protonation equilibrium.

The method was applied to study the pH-induced helix-coil transition of poly-lysine, a standard model system displaying strong coupling between protonation and conformation. The predicted midpoints for both the protonation and structural transitions are in excellent agreement with the experimental data.

A full conformational study of the analgesic dipeptide kyotorphin (Tyr-Arg) was also performed. The protonation of the N-terminus amine was confirmed as a key element in the dihedral (Cβ-Cα-Cα-Cβ) transition cis/trans, and the PCA analysis confirmed those two major conformation populations (the trans extended and the cis packed). The fitting of kyotorphin's conformational space to the structure of morphine resulted in a set of conformers that were able to fulfill most of the constraints for the μ-receptor. These results suggest that we cannot exclude strong similarities between the kyotorphin receptor and the structural family of opioid receptors.

These results illustrate the potential of constant-pH MD methods to study molecular processes where pH plays a central role, as those taking place in biological systems.

The VES Hypothesis and protein folding and function

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The possibility that vibrational energy transfer is a step in protein function (the VES hypothesis) was proposed in the early 1970's by McClare [1] and was taken up by Davydov in connection with a mechanism for muscle contraction [2]. Computer simulations show that vibrational energy transfer is indeed a robust way of transferring energy from the active site to other regions of a protein where the energy is needed for work [3,4]. Experiments by the group of Hamm [5] confirm the results obtained in computer simulations [3], according to which, at low temperature, vibrational excitations are self-trapped, while at biological temperatures they are localized because of static and dynamical disorder. And experiments by the group of Austin [6] show that it takes, on average, 20 ps for the Amide I excitations to be transferred from myoglobin to water. Here the VES hypothesis is applied to protein folding and, more specifically, to the problem of the structural instability of prions and other proteins associated with misfolding diseases [7].

References:

[1] C. W. F. McClare, Ann. N.Y. Acad. Sci. (1974) 227: 74.
[2] A. S. Davydov, J. Theor. Biol. (1973) 38: 559.
[3] L. Cruzeiro-Hansson and S. Takeno, Phys. Rev. E (1997) 56: 894.
[4] L. Cruzeiro, J. Chem. Phys. 123: 234909 (2005).
[5] J. Edler and P. Hamm, J. Chem. Phys. (2002) 117: 2415.
[6] R. H. Austin, A.H. Xie, L. van der Meer, B. Redlich, P.A. Lindgard, H. Frauenfelder, and D Fu, Phys. Rev. Lett. (2005) 94: 128101.
[7] L. Cruzeiro, J. Phys.: Condens. Matter 17: 7833-7844 (2005).

Theoretical Studies of Biological Systems

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This talk is aimed at providing an overview of the research performed on biological systems, presently carried out at the Theoretical and Computational Chemistry Research Group in Porto. The research projects presented here are diverse, focussing on several computational strategies with drug design in mind, namely computational genomics [1]; DNA adsorption onto Si(100) surfaces [2]; the atomic level understanding on disease-related enzymatic mechanisms and inhibition [3]; computational alanine-scanning mutagenesis of protein-protein interfacial residues [4]; molecular docking using total flexibility of ligand and receptor [5]; and, obviously, drug design as such [6].

References:

[1] Marques AT, Antunes A, Fernandes PA, Ramos MJ, BMC Genomics 7, 202 (2006)
[2] Santos HR, Ujaque G, Ramos MJ, Gomes JA, J Comput Chem. 27, 1892 (2006)
[3] Cerqueira, NMFSA, Fernandes, PA, Eriksson, LA, Ramos, MJ, Biophys J 90, 2109 (2006)
[4] Moreira, IS, Fernandes, PA, Ramos, MJ, Proteins 63, 811 (2006)
[5] Sousa, SF, Fernandes, PA, Ramos, MJ, Proteins 65, 15 (2006)
[6] Sharma RK, Pande V, Ramos MJ, Inoue J, Otsuka M., J Med Chem 49, 3595 (2006)

Protein misfolding and disease

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Protein misfolding in the cellular environment is an event which may result from adverse cellular and physiologic factors or from genetic defects. Missense variations, which account for over half of the known gene lesions in human genetic disorders often have structural consequences, affecting protein folding or the stability of a given fold. In some pathologies, misfolded protein conformations accumulate in the cell, overloading or bypassing the protein quality control system, generating functional deficiency. One of the themes of my laboratory is the study of the conformational, structural and functional properties of clinical variants of proteins implied in conformational diseases. We are currently studying those involved in the neurodegenerative disorder Friedreich's ataxia and on the metabolic pathology glutaric aciduria. In this talk I will review basic concepts of cellular protein folding and some of our recent data which also illustrates our experimental strategy which comprises biophysical, biochemical and cell biology methodologies.

Why and how should peptides interact with lipid membranes?

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Cells in living organisms are regulated by chemical and physical stimuli from their environment. Often, ligands interact with membrane receptors to trigger responses and Sargent and Schwyzer conceived a model to describe this process, 'membrane catalysis'. There is a notion that the physical organization of membranes can control the response of cells by speeding up reactions. The work at the Molecular Biophysics Lab (Faculdade de Ciencias, Univ. Lisboa) is related to several aspects of the 'membrane catalysis' model and how it can be exploited to unravel the details of membrane mediated ligand receptor interactions. We examine the possible effects that ligand concentration causes in the 'membrane catalysis' and develop methodologies to determine the partition constant. The role of in-depth location and orientation of ligands is explored using spectroscopic techniques. The use of these methodologies will be exemplified with studies where the role of membranes in the mechanism of action of HIV fusion inhibitors enfuvirtide and T1249, and the analgesic peptide Kyotorphin are elucidated.

Nucleation phenomena in protein folding: The modulating role of protein sequence

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For the vast majority of naturally occurring, small, single domain proteins folding is often described as a two-state process that lacks detectable intermediates. This observation has often been rationalized on the basis of a nucleation mechanism for protein folding whose basic premise is the idea that after completion of a specific set of contacts forming the so-called folding nucleus the native state is achieved promptly. Here we propose a methodology to identify folding nuclei in small lattice polymers and apply it to the study of protein molecules with chain length N=48. To investigate the extent to which protein topology is a robust determinant of the nucleation mechanism we compare the nucleation scenario of a native-centric model with that of a sequence specific model sharing the same native fold. To evaluate the impact of the sequence's finer details in the nucleation mechanism we consider the folding of two non-homologous sequences. We conclude that in a sequence-specific model the folding nucleus is, to some extent, formed by the most stable contacts in the protein and that the less stable linkages in the folding nucleus are solely determined by the fold's topology. We have also found that independently of protein sequence the folding nucleus performs the same `topological' function. This unifying feature of the nucleation mechanism results from the residues forming the folding nucleus being distributed along the protein chain in a similar and well-defined manner that is determined by the fold's topological features.

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