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Talks

(Abstracts)
Predicting structural ensembles of intrinsically disordered proteins by multi-scale modeling

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Intrinsic Disordered proteins (IDPs) constitute as much as one third of the human genome. Several of those are associated with a variety of diseases, including cancer and neurodegenerative diseases. Unfortunately, rational drug design targeting IDPs poses serious challenges since these proteins exist as dynamic, highly flexible structural ensembles, continuously undergoing conformational conversions. We are using a variety of molecular simulation approaches, from all atom MD to coarse-grain MC and to hybrid QM/MM, in an effort at characterizing IDPs ensembles, and in particular at predicting the intriguing effects on IDPs conformations caused by disease-linked mutations and ligand binding. I will focus in this talk on proteins involved in prion and Parkinson's diseases. The relevance of combining computations with experiments for these systems will be emphasized.
The Multiscale Nature of DNA

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DNA is not only the major carrier of genetic information, but also a molecule with fascinating biotechnological possibilities, linked to its unique structure and physical properties. Modeling of DNA is a major challenge, because of its large flexibility, extreme charge density and specially because of its multi-scale nature that goes from subnanometer to the millimeter scale and from femtosecond to minutes. During my talk I will review methodological approaches developed to solve the multiscale problem and to model DNA from the nucleobase to the entire chromatin level.
Understanding the image contrast in Tunneling and Force Microscopies: From graphene to biomolecules

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We’ll review the computational tools and protocols developed in our group in order to study the mechanical and transport properties of materials, and its application to the understanding of the atomic-resolution images obtained with the scanning tunneling (STM) and the force microscope (AFM) by different experimental groups.

Firstly, we’ll focus on tuning of the electronic properties of graphene through the creation of defect [1] and edge states, looking, in particular, to the connection of graphene with metal surfaces. Combining high resolution STM experiments and DFT calculations, we have unambiguously unveiled the atomic structure of the boundary between a graphene zigzag edge and a Pt(111) step [2]. The graphene edges minimize their strain by inducing a 3-fold edge-reconstruction on the metal side, preserving an unoccupied electronic state, exclusively localized in the C-edge atoms of a particular graphene sublattice, which could be used to develop new dual-channel devices.

Metal oxides play a key role in a wide range of technological applications. While in many cases the same FM-AFM image can be explained by different models, and even different underlying tip-sample interactions, we show here that the combination of force spectroscopy (FS) measurements and first-principles simulations can provide an unambiguous identification of the tip structure and the image contrast mechanism in rutile TiO2 (110) [3] and anatase TiO2 (101) surfaces. In the case of STM, we have made a comprehensive study of the $(2\sqrt{2}x\sqrt{2})R45^\circ$ missing row reconstruction of the Cu(100) surface, using different tips and systematically varying bias voltage and tip sample distance, to explore the rich variety of image contrasts observed in the experiments [4,5]. Our results achieve a conclusive understanding of fundamental STM imaging mechanisms and provide guidelines for experimentalists to achieve chemically selective imaging by choosing appropriate imaging parameters.

Finally, we’ll present our recent work on the structure and functionality of biological systems in their native liquid environment. We’ll discuss the application of large-scale steered Molecular Dynamics simulations, based on classical potentials developed by the molecular biology community and the use of GPUs as processing units, provide insight into the protein-graphene biocompatibility, the flexibility map of human antibodies, and the hydration properties of self-assembled monolayers of single-stranded DNA and its possible use as a label-free DNA sensor.

Antibody adsorption over graphene: an atomistic MD and MF-AFM study

J.G. Vilhena, A. C. Dumitru, Elena T. Herruzo, Jesus I. Mendiesta-Moreno, Pedro A. Serena, Ricardo García, Rubén Pérez

Proteins interaction with surfaces has great technological relevance for the development of biocatalysts, implants and biosensors. Recent advances on both molecular-dynamics (MD) simulations and atomic-force-microscopy (AFM), allow studying such large systems with atomistic detail. Here we have combined MD simulations with high-resolution multi-frequency-AFM experiments to study the adsorption of the IgG antibody (150kDa) over graphene. IgG provides the majority of antibody-based immune response. Therefore studying its biocompatibility/activity over graphene is of interest to address the graphene usage as an implant material as well as to develop more sensitive immunoassays.

We have developed a protocol combining steered-MD simulations and long (>150ns) equilibration runs to address several key open questions concerning protein adsorption: the interaction mechanisms behind the adsorption, the role of the water molecules in such process, and under which conditions the protein unfolds due to the interaction with the substrate. Moreover we determine the most favorable adsorption orientation of the IgG, which in turn allows us to set up a strategy to control the IgG adsorption over graphene. Both the bioactivity and adsorption orientation statistics are in good agreement with experiments.

[1] Antibody adsorption over graphene; submitted to NanoLetters

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The Direct Simulation Monte Carlo method (DSMC) was introduced by G. Bird [1] to mimic the dynamics of the particles of a dilute gas. It is more efficient than Molecular Dynamics to study dilute systems, and has the additional advantage of allowing to exploit the possible symmetries of the state under consideration. DSMC has been used with great success to investigate the properties of dilute granular systems in rather different states. For instance, it has been used to study the distribution function of a granular gas in the homogeneous cooling state, the behavior of the energy fluctuations close to the clustering instability, the value of a new transport coefficient coupling the heat flux and the density gradient, the lack of energy partition in binary mixtures, etc. In this talk, the general ideas of DSMC will be discussed, and some results for granular fluids obtained using this method will be presented.

Adiabatic piston in non-equilibrium situations: granular and molecular gases

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The steady state reached by two gases separated by an adiabatic piston will be investigated in two rather different cases. First, two vibrated granular gases will be considered. It will be shown that the system exhibits a non-equilibrium phase transition, with spontaneous symmetry breaking. Afterwards, a molecular gas with a temperature gradient generated by the walls will be discussed.
Shocks in Fluids: Is there a Theory?

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Shock fronts in dense fluids are a few molecular diameters thick and sustain large thermodynamic forces, leading to deviations from the traditional non-equilibrium phenomenology. We compare direct MD modeling with possible generalizations of Navier-Stokes and Fourier laws. The most accurate description found goes back to Maxwell.
Modeling emergent patterns in active matter: From molecular motors to microswimmer suspensions

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Active systems generate motion due to energy consumption, usually associated to their internal metabolism or to appropriate, localized, interfacial chemical reactivity. As a result, these systems are intrinsically out of equilibrium and their collective properties emerge as a balance between their direct interactions and the indirect coupling to the medium in which they displace. Therefore, a dynamical approach is required to analyze their evolution and quantify their selfassembly and ability to generate intermediate and large scale stable structures.

The modelling of such systems is challenging because of the different length scales involved. I will describe different mesoscopic approaches that capture essential features of model active systems, the capabilities and limitations.
Order N Computational Methods for Exploring Charge, Phonon and Spin Transport in Condensed Matter: Benchmarking Materials and Assessing Novel Applications

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I will present a successful computational strategy to investigate quantum (charge, phonon and spin) transport in structurally or chemically complex materials such as graphene, topological insulators, or organic matter, for which it is necessary to go beyond phenomenological approaches. The possibility to combine first principles calculations with tight-binding models, together with the development of order N algorithms which are free from any matrix inversion/diagonalization give access to the study of quantum transport phenomena in realistic models of complex materials containing up to 1 Billion atoms. Such methodologies allow direct comparison with experiments, and can hence serve as guiding tools for technology optimization, as well as new tools for discovering quantum phenomena out of reach from conventional perturbative treatments and semi-classical transport approaches.

One illustration will be the quantitative analysis on the transport properties of the damage produced during the wafer-scale production of graphene through chemical growth (CVD), or the mechanical/chemical exfoliation and chemical transfer to versatile substrates, followed by the device fabrication. Fundamental properties of charge transport in polycrystalline graphene, accounting the variability in average grain sizes and grain boundaries imperfections as observed in real samples grown by CVD will be presented, together with their relevance for device optimization and diversification of technological functionalities. Other illustrations will include thermal transport in hybrid boron nitride (BN)/graphene materials, or BN/graphene heterostructures which display fascinating physics such as the Hofstadter butterfly.

A second type of applications will focused on the study spin-orbit interaction induced by dilute ad-atom (gold, thallium) deposits on graphene. Unique phenomenon of the spin-dynamics in graphene (such as Spin Quantum Hall effect), as well as quantitative evaluation of spin precession times and spin-relaxation times as a function of charge density will be reported. Such findings will be shown to open novel perspectives for spin manipulation, contributing to the future advent of non-charge based revolutionary information processing and computing.

Using TDDFT to calculate the electronic stopping power for ions shooting through solids from first principles

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Ions shooting through materials give rise to both electronic and nuclear processes that affect their structural integrity and functionality. This kind of radiation damage is important for the nuclear, aviation and space industries, as well as for human health, in terms of particle radiotherapy. In such processes, electronic excitations, as measured by the electronic stopping power, are important in the fundamentals and in their effect. Electronic stopping is quite well understood in specific limiting situations, most prominently for simple metals, based on the theory for the homogeneous electron liquid. The understanding for other kinds of materials, especially in the low velocity regime is still very poor, with every new experiment bringing about unexpected new qualitative features. In recent years we have developed a technique for the first-principles simulation of electronic stopping power in real materials, which has been quite successfully applied to wide band-gap insulators, noble metals and semiconductors. In this talk I will briefly review the technique and its key results so far.
Molecular Dynamic Simulations of Anion/Protein Unbinding Interactions in two Similar Apoflavodoxin structures. Insights about the complex FMN-flavodoxin binding scenario.

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Abstract

The \textit{Hp}-fld is an essential protein that is being used as a target to develop new antimicrobials [1]. The binding of FMN cofactor to \textit{Helicobacter pylori}'s flavodoxin (\textit{Hp}-fld) is a very complex scenario. Some studies have been carried out about this issue, and several possible association mechanisms proposed [2-4]. Nevertheless, many aspects of that mechanisms are yet to be fully clarified as for example the roles of different anions often bound to FMN phosphate binding subsite [5,6]. In this work, we investigated from a computational point of view the anion/protein interactions of one chloride and one sulphate bound to the FMN binding pockets of the homologous apoflavodoxin structures 2BMV [5] and 1FTG [6] respectively. Molecular dynamics simulations performed for both anions (50 and 10 runs respectively). Meticulous anion/protein conformation, solvation, interaction forces and statistical analyses were carried out. The temperature factor was also evaluated. In the chloride case, on 45 of 50 runs (up to 20 ns) the anion spontaneously left its original binding site, doing so in a relatively short time and through no preferred exit route. In the other five chloride runs and for the sulphate case (up to 100 ns) the anions remained tightly bound; one very characteristic binding conformation was observed for such cases. A ‘step-by-step’ desolvation mechanism in the outgoing anion cases was observed. So, this study allows us to add new clues to the complex FMN/protein binding mechanism, and in general it could provide insights into the discovery of new small ligand as possible drugs against \textit{Hp}.

References

Large-scale ab-initio calculations with SIESTA-PEXSI

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The possibility of treating large systems with first-principles electronic-structure methods has opened up new research avenues in many disciplines. In particular, the SIESTA program \cite{Soler2002} has become quite popular and is increasingly being used by researchers in geosciences, biology, and engineering (apart from those in its natural habitat of materials physics and chemistry). SIESTA's efficiency stems from the use of strictly localized basis sets and from the implementation of linear-scaling algorithms which can be applied to suitable systems. A very important feature of the code is that its accuracy and cost can be tuned in a wide range, from quick exploratory calculations to highly accurate simulations matching the quality of other approaches, such as plane-wave methods.

We have implemented in the SIESTA code a new electronic-structure solver based on the Pole Expansion and Selected Inversion (PEXSI) technique \cite{Lin2013}. This approach scales at most quadratically with system size by exploiting in a general way the sparsity of the Hamiltonian and other matrices involved. It can be applied to all kinds of systems, including metals, and its accuracy is comparable to that of cubic-scaling full diagonalization. PEXSI can use large numbers of processors efficiently due to the near-perfect parallelization over poles and the good scaling of the pole-specific operations, thus enabling the treatment of very large systems in high-performance machines.

\begin{thebibliography}{99}
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Light-induced processes in finite and extended systems from TDDFT

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In this talk we will review the recent advances within density-functional and many-body based schemes to describe spectroscopic properties of complex systems with special emphasis to modelling time and spatially resolved electron spectroscopies (including transient pump-probe techniques). Pros and cons of present functionals will be highlighted and provide insight in how to overcome those limitations by merging concepts from many-body perturbation theory and time-dependent density functional theory. We will discuss some of the theoretical approaches developed in the group (and under development) for the characterisation of matter out of equilibrium, the control material processes at the electronic level and tailor material properties, and master energy and information on the nanoscale to propose new devices with capabilities. We will focus on examples linked to the efficient conversion of light into electricity or chemical fuels ("artificial photosynthesis") and the design on new nanostructured based optoelectronic devices based on inorganic nanotubes, among others. The goal of the group activities in the long-run is to provide a detailed, efficient, and at the same time accurate microscopic approach for the ab-initio description and control of the dynamics of decoherence and dissipation in quantum many-body systems.
Glycoglycerolipids are structural components of mycoplasma membranes with a fundamental role in membrane properties and stability. Their biosynthesis is mediated by glycosyltransferases (GT) which catalyze the transfer of glycosyl units from a sugar nucleotide donor to diacylglycerol. The essential function of glycolipid synthases in mycoplasma viability, and the absence of glycoglycerolipids in animal host cells make these GT enzymes a target for drug discovery by designing specific inhibitors. However, rational drug design has been hampered by the lack of structural information for any mycoplasma GT. Most of the annotated GTs in pathogenic mycoplasmas belong to family GT2 (CAZY classification [1]). We had previously shown that MG517 in Mycoplasma genitalium is a GT-A family GT2 membrane-associated glycolipid synthase [2]. We present here a series of structural models of MG517 obtained by homology modeling following a multiple-template approach. The models have been validated by mutational analysis and refined by long scale molecular dynamics simulations. Based on the models, key structure-function relationships have been identified: The N-terminal GT domain has a GT-A topology which includes a non-conserved variable region involved in acceptor substrate binding. Glu193 is proposed as the catalytic base in the GT mechanism, and Asp40, Tyr126, Tyr169, Ile170 and Tyr218 define the substrates binding site. Mutation Y169F increases the enzyme activity and significantly alters the processivity (or sequential transferase activity) of the enzyme [3]. The C-terminal region of MG517, with no sequential or structural homology to any other protein, has been partially modeled combining structure prediction servers and computational biophysics analysis. This region is predicted to be mainly composed of alpha helices where the apical one has a clear amphipathic character. The last helix is thus proposed as part of the MG517 interaction with the membrane. By means of molecular dynamics simulations, the amphipathic behavior of this helix and its association with the membrane has been validated. Overall, this is the first structural model of any GT-A glycoglycerolipid synthase and provides preliminary insights into structure and function relationships in this family of enzymes.

The revolution of genome sequencing opens the door to precision medicine

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During the last years we have witnessed an astonishing development of the high throughput technologies. This revolution has had an especial impact in the field of sequencing where the new generations of sequencers can produce enormous amounts of data at affordable prices [1]. Nowadays the bottleneck of discovery has moved from the data production phase to the data analysis and interpretation phases. New ways of understanding and addressing complex biological problems beyond the conventional approaches from the molecular biology are arising from the computational biology [2]. Computational biology scientists have now the possibility of formulating and testing hypothesis as well as querying biological systems from a systems biology perspective using genomic data on gene activity (gene expression, methylation, etc.) and/or functionality (mutational spectrum).

The impact of this genomic revolution in the field of medicine has been enormous. Thus, the concept of personalized medicine has evolved to P4 (Personalized, Predictive, Preventive and Participatory) medicine. In particular, Precision medicine needs of better ways of defining diseases by relating conventional clinical–pathological diagnostic criteria with state-of-the-art molecular profiling methodologies. A more precise diagnostic of the disease, based on the description of their molecular mechanisms would allow creating innovative diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient’s requirements [3]. To achieve this, two main problems need to be addressed from a methodological point of view: how genomic features relate among them to give rise to disease phenotypes and how different measurements of different genomic features (i.e. nucleotide variants, gene expression, methylation, etc.) can be integrated to provide more precise descriptors of disease phenotypes. Both aspects have a strong computational component. In the coming years Biocomputing will become an increasingly important component of Medicine.

Double-comparative transcriptomics shows adaptive flexibility of bacterial transcriptomes

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The comparative analysis of primary transcriptomes from closely related bacteria, challenged by identical environmental perturbations, is a potentially powerful approach. To enable a double-comparative transcriptomics approach (different conditions and two different organisms) focusing on cyanobacteria, we analyzed the transcriptomes of two *Synechocystis* strains under 10 different conditions using strand-specific cDNA sequencing. We generated genome-wide transcription start site (TSS) maps, derived operon structures, 5'- and 3'-UTRs and identified 24 conserved asRNAs and 55 conserved small RNAs (sRNAs) with very similar regulation. Such sRNAs constitute a large and heterogeneous class of bacterial gene expression regulators. Much like eukaryotic microRNAs, they typically target multiple mRNAs through short seed pairing, thereby acting as global post-transcriptional regulators. However, the experimental identification of possible targets and therefore their confirmation as functional regulators of gene expression has remained laborious. We have been developing a strategy that integrates phylogenetic information to predict sRNA targets at the genomic scale and reconstructs regulatory networks upon functional enrichment and network analysis (CopraRNA [1]). Furthermore, CopraRNA precisely predicts the sRNA targets at the genomic scale and reconstructs regulatory networks upon functional enrichment and network analysis (CopraRNA [1]).

The verification of many new targets by CopraRNA, even for extensively investigated sRNAs, demonstrates its advantages and that CopraRNA-based analyses can compete with experimental target prediction approaches. Thus, these data allow the exact inference of previously unknown riboregulators and of regulatory elements for the regulons activated under conditions most important for photosynthetic growth. Remarkably, we identified a class of genes that lack a specific TSS but instead their mRNA originates from the transcription of an sRNA that clearly accumulates as a discrete and abundant transcript while also serving as the 5' UTR of the adjacent protein-coding gene. Such an sRNA/mRNA structure, that we named ‘actuation’, might constitute a means of how bacteria remodel their transcriptional network.

Understanding the molecular mechanisms of specific plant traits such as fleshy fruit development and ripening is key in future breeding programs. Regulatory small RNAs (sRNAs) have been recently discovered and become one of the most intensively studied fields in molecular biology. MicroRNAs (miRNAs) are the best characterised of the different classes of endogenous small RNAs (sRNAs) that regulate the expression of protein coding gene and they play an important role almost all metabolic pathways, such as fruit development. MicroRNAs negatively regulate the accumulation of mRNAs therefore when they are expressed in the same cells their expression profiles show an inverse correlation. There are a few examples in literature of positively correlated miRNA/target pairs, but it is not known how widespread this phenomenon is. Here, we investigated the correlation between the expression profiles of differentially expressed miRNAs and their targets during tomato fruit development using high throughput sequencing, Northern blot and RT-qPCR. We found an equal number of positively and negatively correlated miRNA/target pairs indicating that positive correlation is more frequent than previously thought. We also found that the correlation between microRNA and target expression profiles can vary between mRNAs belonging to the same gene family and even for the same target mRNA at different developmental stages. Since microRNAs always negatively regulate their targets, the high number of positively correlated microRNA/target pairs suggests that mutual exclusion could be as widespread as temporal regulation. The change of correlation during development suggests that the type of regulatory circuit directed by a microRNA can change over time and can be different for individual gene family members.
Inferred Model of the Prefrontal Cortex Activity Unveils Task-Related Cell Assemblies and Memory Replay

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Cell assemblies are thought to be the units of information representation in the brain, yet their detection from experimental data is arduous. Here, we propose to infer the effective network structure from simultaneously recorded neurons in prefrontal cortex using an inverse Ising model and to define cell assemblies as the co-activated neurons in the dynamics of the resulting abstract neural network. The inferred couplings are potentiated after wakeful experience and the resulting assemblies strongly co-activate during wakeful experience and are found to replay during subsequent sleep. Different dynamical regimes as may be observed across wakefulness and sleep can be reproduced by changing a global input parameter, providing access to rare activity fluctuations, crucial for replay. Across sessions, a variety of different network scenarios is observed, providing insight in cell assembly formation and replay.
A new Similarity Index for comparing non-sequential protein segments

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The functional elements of proteins such as catalytic sites or ligand binding pockets frequently consist of sparsely distributed amino acids rather than sequential residues. The vast majority of the available structural alignment tools are not meant for the comparison of clusters of isolated residues [1-3] and thus they are unable to perform comparisons restricted to functional elements. In addition, the metrics used to compare sequences make extensive use of evolutionary and annotated data and not only physical-chemical properties of amino acids[4-6]. Although these metrics have proven to be very useful to classify sequences into different folds without using structural data [7], they introduce an unwanted bias when it comes to the comparison of isolated amino acids and thus a new metric is needed. The aim of this study is to develop a new method for the sequence-free quantitative comparison of non-sequential protein segments on the basis of their structural and chemical features only.

An *in silico* search for glucose-methanol-choline oxidoreductases with interesting features in ten *Polyporales* genomes

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The aim of this work was to find new glucose-methanol-choline (GMC) oxidoreductases with potential biotechnological applications taking advantage of the great deal of fungal genomes currently available. In order to do so, ten fungal species were selected (*Bjerkandera adusta, Phlebia brevispora, Ganoderma sp., Fomitopsis pinicola, Phanerochaete chrysosporium, Dichomitus squalens, Ceriporiopsis subvermispora, Trametes versicolor, Rhodonia placenta* and *Wolfiporia cocos*) from the order Polyporales, which possess the ability of degrading wood and, hence, have the degradative machinery encoded in their genomes. We performed an *in silico* search through protein sequence homology using cloned enzymes (aryl-alcohol oxidases, glucose oxidases, methanol oxidases, pyranose oxidases, cellobiose dehydrogenases and pyranose dehydrogenases) from related fungi. Once the putative enzymes of each class chosen, their sequences manually curated and annotated, we: i) analyzed their evolutionary relationships by constructing gene phylograms based on their predicted protein sequences; and ii) established their duplication/reduction history during fungal evolution by investigating the number of genes of each enzyme type most probably present at every node in the species evolutionary tree (by reconciliation between our constructed gene tree and the species tree available). Moreover, we modeled almost all the GMC sequences out of the 195 found in the ten genomes using the crystallographic structures of related enzymes as templates to gain insight into their structural variation and hypothesize their probable catalytic properties.
Identification of new interacting partners of the global regulator FurA from *Anabaena* sp. PCC 7120

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FurA from the cyanobacterium *Anabaena* sp. PCC 7120 is a global regulator that controls not only the iron homeostasis but it is also involved in the nitrogen metabolism as well as in the oxidative stress response. This DNA-binding protein contains five cysteine residues, four of them arranged into two redox CXXC motifs (C101VKC104 and C141KPC144) whereas the fifth cysteine (C133) is a common feature among the cyanobacterial orthologs [1]. Since the canonical CXXC motif is indeed an essential, common signature of the active site of thiol-oxidoreductase enzymes, we prompted to evaluate the contribution of these motifs to the functionality of FurA. We have recently demonstrated, for the first time for a Fur-family member, that FurA exhibits disulfide reductase activity [2]. With the aim to identify the FurA reducing partner, GST-pull down assays carried out using crude extracts of *Anabaena* followed by MALDI-MS/MS analyses. These experiments revealed that FurA is able to interact with several potential partners in the cell. The putative N-acetylmuramoyl-L-alanine amidase All1140, the histone-like DNA-binding protein HU, another FurA molecule and the phosphoribulokinase enzyme PRK were proposed as potential FurA partners. In order to confirm all these interactions in vivo, the proteins detected by pull-down were cloned and bacterial two-hybrid (BACTH) assays were performed. As expected, FurA was confirmed to interact with another FurA monomer, with All1140 as well as with HU. However, we could not detect the interaction between FurA and PRK. Notably, FurA binding partners HU and All1140 have been previously localized in the outer membrane fraction of *Anabaena*, while FurA itself has been annotated as “cell-binding protein” in the Cyanobase and Uniprot databases. To corroborate whether FurA is present in the cell-wall fraction of the cyanobacterium, localization assays were performed using a protoplast suspension and the supernantant containing the outer membrane and the peptidoglycan fractions of *Anabaena*. Western blotting analysis showed that FurA entirely localizes in the protoplast fraction, in the cytosol of *Anabaena*. Since we were unable to find a redox partner of FurA by pull-down experiments, the ability of the regulator to interact with other cyanobacterial electron carriers such as reduced thioredoxin, plastocyanin, ferredoxin or ferredoxin-NADP+ reductase was assessed by chemical crosslinking experiments. Interestingly, a potential interaction between *Anabaena* FurA and ferredoxin was successfully detected and it will be further analyzed in future assays.


A point mutation in the sensor domain of the PhoR kinase severely impacts on *Mycobacterium tuberculosis* pathogenicity

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The *Mycobacterium tuberculosis* PhoP/PhoR two-component signal transduction system regulates well-known virulence pathways including: secretion of the major virulence factor ESAT-6 and production of immunomodulatory lipids. Consequently, mutations in phoP results in attenuation of *M. tuberculosis* [1; 2] and are indeed the founding principle for the construction of the live attenuated vaccine candidate MTBVac [3]. However, although the role of PhoP has been extensively documented, the structure-function mechanistics of PhoR remain to be elucidated. In this work, we propose a structure for PhoR based on domain structures of related proteins. Our results suggest that PhoR is a membrane protein able to auto-phosphorylate upon reception of a yet unknown environmental signal and subsequently phosphorylates its cognate transcriptional regulator PhoP.

Further, phylogenetic analyses of PhoR in related members of the *M. tuberculosis* complex indicate a G71I mutation exclusively present in *M. bovis* and *M. africanum*. This mutation lies in the putative sensor domain of PhoR and severely impacts on regulation of PhoP-dependent phenotypes. Specifically, we use *M. tuberculosis* H37Rv carrying the PhoR G71I mutation to demonstrate that mutants are unable to secrete ESAT-6 and to produce acyltrehalose-based lipids. Confirming these observations, we also demonstrate that G71I mutants show decreased mRNA expression of PhoP-regulated genes. Finally, we carry out *ex vivo* experiments of macrophage replication and virulence in mice to test the relevance of this G71I mutation. Our results demonstrate an impaired multiplication in macrophages as well as reduced virulence for SCID mice as demonstrated by longer time-to-death in mice infected with strains carrying the mutated phoR allele. Taken together, these results indicate that in addition to PhoP, its cognate sensor kinase PhoR is essential for *M. tuberculosis* virulence.

Phylogenetic analysis of resequenced organelle genomes: the case of the Brachypodium distachyon complex chloroplasts

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Chloroplast genomes of grasses contain two single copy regions separated by two nearly identical inverted repeats, harboring in total over a hundred genes. These sequences have great value for the reconstruction of the evolutionary history of plants due to their limited size and constrained rate of change. Here we report that high throughput sequencing experiments of grasses of the Brachypodium distachyon complex (B.stacei, B.distachyon and B.hybridum) yield as a by-product sufficient reads to allow the assembly of their plastids. The chloroplasts of a total 54 ecotypes were reconstructed by first filtering chloroplast Illumina pair-end reads based on their k-mer composition, followed by genome assembly, using as reference a collection of sequenced plastids of monocot plant species. Despite the challenge of resolving both inverted repeats, we find that these plastids contain genetic polymorphisms that can help infer their evolutionary history. For instance, a 1Kb insert found in polyploid B.hybridum ABR113, also seen in B.stacei ABR114, contributes to the understanding of its hybrid origin.
Structural basis for the interaction of the FAD synthetase from the human pathogen *Streptococcus pneumoniae* with its ligands

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The pneumococcus *Streptococcus pneumoniae* is a human pathogen that causes a great number of infections (pneumonia, sinusitis, peritonitis, etc ...) and severe invasive processes (meningitis, septicaemia, etc ...), particularly in the elderly, children and immunosupressed people. Its natural habitat is the human nasopharynx and colonization can occur during the first days of life. As in most prokaryotic organisms, *Streptococcus pneumoniae* has a bifunctional FAD synthetase (FADS) responsible for the \textit{in vivo} synthesis of the cofactors flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) required to produce all its flavoenzymes and flavoproteins [1]. Despite the \textit{SpnFADS} crystallographic structure has been reported (PDB 3OP1), no additional information about interaction parameters or efficiency of its Riboflavin Kinase (RFK) and FMN Adenylyl Transferase (FMNAT) activities have been reported. Data obtained in our lab indicate that in spite of the enzyme catalyses both activities, the FMNAT requires strong reducing conditions. That fact contrasts with that described for FAD synthetase from *Corynebacterium ammoniagenes*, the member of the family so far best characterized [2,3]. Here we show a multidisciplinary analysis of the interaction of \textit{SpnFADS} with its substrates/products by using both binding equilibrium experimental methods and theoretical docking approaches.


Monte Carlo Simulations of Polymer Adsorption and Aggregation in Generalized Ensembles

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An overview is given on recent results of Monte Carlo simulations of polymer adsorption and aggregation based on a coarse-grained continuum polymer model with bending stiffness and 12-6 Lennard-Jones interactions among the monomers. As adsorbing substrate either a plane surface [1] or the curved inner wall of a spherical cage [2] with varying attraction strength is considered. By means of extensive Monte Carlo simulations in generalized ensembles (multicanonical and parallel tempering methods), rich phase diagrams in the adsorption strength-temperature plane are found, ranging from highly ordered, compact to extended, random coil structures and from desorbed to partially or even completely adsorbed conformations. These findings are identified in canonical and microcanonical [3] analyses with different energetic and structural observables such as the gyration tensor and derived universal quantities. Some special features of an adsorbing fluctuating membrane [4], allowing for a back-reaction of the polymer and substrate degrees-of-freedom, are also briefly discussed. The talk concludes with very recent results on the aggregation transition of semiflexible polymers in dependence on their bending stiffness [5]. Our data shows that the stiffness plays a key role in whether the system forms amorphous aggregates or twisted bundle structures.

References

Statistical Physics of Pure Barkhausen Noise

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We discuss a model metallic glass in which Barkhausen Noise can be studied in exquisite detail, free of thermal effects and of the rate of ramping of the magnetic field. The mechanism of the jumps in magnetic moment that cause the Barkhausen Noise can be fully understood as consecutive instabilities where an eigenvalue of the Hessian matrix hits zero, leading to a magnetization jump \(\Delta m\) which is simultaneous with a stress and energy changes \(\Delta \sigma\) and \(\Delta U\) respectively. Contrary to common belief we find no ``movements of magnetic domain boundaries'' across pinning sites, no fractal domains, no self-organized criticality and no exact scaling behaviour. We present a careful numerical analysis of the statistical properties of the phenomenon, and show that with every care taken this analysis is tricky, and easily misleading. Without a guiding theory it is almost impossible to get the right answer for the statistic of Barkhausen Noise. We therefore present an analytic theory, showing that the probability distribution function (pdf) of Barkhausen Noise is not a power law times an exponential cutoff. On the basis of the theory we explain why standard methods to extract the form of the pdf are likely to fail, as indeed happened until now.
Statistical Mechanics Model for Integer Factorization

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We proposed a new approach to solve the problem of the prime factorization, by modeling it as the problem of a ground state searching problem of statistical mechanics Hamiltonian [1]. In this model, the system size is given by the logarithm of the target composite integer N to base p, where p is any integer. We performed the replica exchange Monte Carlo simulation [2] of the model in the cases of factoring the product of two large prime numbers and roughly observed that its solving time depends almost exponentially on the system size.

Thus we consider statistical mechanics models for the problems of finding divisors in a composite integer N, focusing on a parameter \( \alpha = \frac{m}{n} \), where m is the number of prime factors included in the N, and n is the system size of the model. The number of the ground states is given by the total number of possible combinations of each prime divisor which grows with \( m! \), when \( \alpha \) is large. On the other hand, as \( \alpha \) becomes small, such as \( m=2 \), the number of the ground states drops drastically. This can be analogous to the behavior of the statistical mechanics model of NP-complete problems [3]. Hence we expect the possibility that a phase transition occurs on a small value \( \alpha = \alpha_c \), and the average computational complexity for finding a divisor increases rapidly near \( \alpha_c \) (there may be a case that the value of \( \alpha_c \) is 0).

We perform simulations in order to validate the existence of the transition, and the results are discussed in this presentation. Through the behavior of the physical quantities, we attempt to approach the average complexity class of the integer factorization problem.

References:

Phase Transition in 3d Heisenberg Spin Glasses with Strong Random Anisotropies, through a Multi-GPU Parallelization

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We characterize the phase diagram of anisotropic Heisenberg spin glasses, finding both the spin and the chiral glass transition. We remark the presence of strong finite-size effects on the chiral sector. We find a unique phase transition for the chiral and spin glass sector, in the Universality class of Ising spin glasses. We focus on keeping finite-size effects under control, and we stress that they are important to understand experiments. Thanks to large GPU clusters we have been able to thermalize cubic lattices with up to $64^3$ spins, over a vast range of temperatures.
A global approach to design high speed complex digital systems

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Designing high speed complex digital systems, with respect to the costs and the time to market, requires a multidisciplinary team of experts supported by a methodology and by a state of the art tools. The design of a complex systems dedicated to physics computation, including 256 Virtex 7 FPGA's connected in a 3D torus matrix, has been developed by using a huge set of Mentor Graphics® tools.

High speed digital connections, thermal and mechanical constraints have been managed concurrently starting from the feasibility analysis to the validation tests on a virtual prototype. In our presentation we will describe the methodology used to design PCB's, motherboard and mechanical staff. Finally we will also show few snapshot of the process including Schematic Entry, Layout, Signal & Power Integrity Analysis, Thermal simulations and report of tests run during the validation phase.
Interplay between awareness and epidemic spreading in networks

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We present the analysis of the interrelation between two processes accounting for the spreading of an epidemics, and the information awareness to prevent its infection, on top of multiplex networks [1]. This scenario is representative of an epidemic process spreading on a network of persistent real contacts, and a cyclic information awareness process diffusing in the network of virtual social contacts between the same individuals. The topology corresponds to a multiplex network where two diffusive processes are interacting affecting each other [2]. In a multiplex network, there are different classes of links, which are assigned to different layers, in this case, the layer of physical contacts where the epidemics spreads, and the layer of virtual contacts where the awareness of the epidemics is propagated. Moreover, every individual belongs to all the layers, thus making this kind of networks different from other structures such as colored graphs or interconnected networks [3]. A tensorial mathematical formalism for multiplex networks can be found in [4].

The analysis of this dynamics using Monte Carlo simulations and a Microscopic Markov Chain Approach (MMCA) [5] reveals the phase diagram of the incidence of the epidemics, and allows capturing the evolution of the epidemic threshold depending on the topological structure of the multiplex and the interrelation with the awareness process. Interestingly, the critical point for the onset of the epidemics has a critical value (meta-critical point) defined by the awareness dynamics and the topology of the virtual network, from which the onset increases and the epidemics incidence decreases.

Quantum Navigation and Ranking in Complex Networks

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Complex networks are formal frameworks capturing the interdependencies between the elements of large systems and databases. This formalism allows to use network navigation methods to rank the importance that each constituent has on the global organization of the system. A key example is Pagerank navigation which is at the core of the most used search engine of the World Wide Web. Inspired in this classical algorithm, we define a quantum navigation method providing a unique ranking of the elements of a network. We analyze the convergence of quantum navigation to the stationary rank of networks and show that quantumness decreases the number of navigation steps before convergence. In addition, we show that quantum navigation allows to solve degeneracies found in classical ranks. By implementing the quantum algorithm in real networks, we confirm these improvements and show that quantum coherence unveils new hierarchical features about the global organization of complex systems.
Community Detection in Quantum Systems

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Determining community structure in interacting systems, ranging from technological to social, from biological to chemical, is a topic of central importance in the study of networks. Extending this concept to apply to quantum systems represents an open challenge and a crucial missing component towards a theory of complex networks based on quantum mechanics. This talk will cover the work primarily in which accomplishes this goal by introducing methods for identifying the community structure of a network governed by quantum dynamics. We found that community structure is relevant for a host of problems commonly faced in quantum physics, and moreover that the state-of-the art methods used to detect communities in complex networks fail to give meaningful results in these cases. We overcome these limitation and present methods to detect communities in quantum systems. To illustrate our approach we turn to a host of examples, including a naturally occurring light-harvesting network, where from first principles we determine a consistent community structure. In certain regimes the communities we determine agree with a partitioning currently done by hand in the quantum chemistry literature. In other regimes, we uncover an improved community structure. Our approach rely on the definition of distances between clusters using two quantum properties: coherent transport and fidelity of the evolved state with the initial one. We define the optimal community structure using a modified modularity function. Merging concepts from quantum physics and complex network theory \cite{1} is providing a bidirectional bridge of relevant analysis tools to address networks in both disciplines. Although this work focuses on extending the concept of community detection to apply to quantum systems, it also opens the door for the application of quantum techniques to determine community structure and other key properties of traditional complex networks. However, our objective here was only to create methods that enable one to determine communities in quantum systems, wherein and as already mentioned, the existing techniques to detect communities in complex networks fail to give meaningful results.

Dynamics of interacting epidemics

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Contagion phenomena are driven by dynamical principles that can be recognized in many fields of social and medical sciences; from epidemiology to innovation and marketing. Focusing on epidemiological models, the influence of the topological properties of the networks on disease incidence has been exhaustively addressed, as well as the relevance of the main dynamical assumptions underlying each precise model. However, nowadays the need to go beyond the scheme one pathogen-one network is recurrently mentioned as a necessary step towards the understanding spreading of certain interdependent infectious agents. In this work we introduce a new model to describe the dynamics of a couple of diseases whose spreading parameters depend for each disease and individual on her state –infected or susceptible– with respect to the conjugate infection. Our model supposes an initial approach to this problem that is able to offer, simultaneously, either a dynamical description of the non-stationary temporal evolution of an epidemic process and an analytical derivation of epidemic thresholds. Our model adequately foresees the appearance of regions in the parameter space in which, for each disease, the appearance of epidemic outbreaks are conditionally subjected to the prevalence levels of the other disease. Dependences on network sizes and topologies for epidemic thresholds have been exhaustively characterized. Our model predicts atypical behaviors at this particular for diseases interacting according to an absolute crossed immunity scheme, when spreading over highly correlated networks (i.e. two competing strains of the same pathogen). Finite, not vanishing epidemic thresholds appear in this particular scenario, even over scale free networks at the thermodynamic limit. Finally, we show that the model, after a proper fitting of the dynamical parameters, is able to qualitatively reproduce the temporal evolution of a couple of diseases whose interaction is a well known fact: tuberculosis and AIDS, in a region in which the association of these two diseases comes being a major public health problem during the last twenty years: the republic of South Africa.
Impact evaluation of novel anti tuberculosis vaccines.

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Even though tuberculosis is still one of the deadliest infectious diseases over the world, in the last thirty years there have been few pharmacological advances in the topic. More precisely, the main preventive weapon against the disease -the BCG vaccine, only effective against the infectious tuberculosis forms on children- is already 90 years old. For that reason, the development of a new vaccine, aimed at outperforming BCG is a major priority for public health organisms worldwide, and more than 15 independent research teams are nowadays developing new vaccine candidates. The properties of these novel drugs will be revealed within the next decade, once the clinic trials related to the vaccine development process come to an end. Among these candidates, there are vaccines of very different kinds, which make it very likely that the age of the populations on which vaccination is feasible, safe and effective will be different among the diverse new vaccines. For that reason, it is of utmost importance the development of new epidemiological models able to describe, as reliably as possible, the dependence of the disease's dynamics not only on the age of single individuals, but also on the demographic structure of the overall population. In this work, we introduce a new epidemiological model in which a number of factors related to the demographic structure of the population, such as its temporary evolution and the heterogeneity of the contact patterns among individuals of different ages, have been taken into account. Applying our model to evaluate the impact of an eventual vaccination campaign focused on a specific age group, we find out that a vaccination strategy focused on teenagers (15-20 years old) has a greater impact than other strategies focused on any other age group. Our results indicate that the adoption of certain classical oversimplifying hypothesis in what regards the age structure of the population and its mixing patterns introduces systematic biases that nowadays can be and must be eliminated from the models.
Brownian Dynamics Simulation of Cytoskeletal Networks: the Mechano-sensing Process

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The actin cytoskeleton network is the dominant structure of eukaryotic cells. It is highly dynamic and plays a central role in a wide range of mechanical and biological functions. Cytoskeleton is composed mainly of actin filaments (F-actin) resulting from the self-assembly of monomeric actin (G-actin) and cross-linked by actin cross-linking proteins (ACPs) whose nature and concentration determine the morphological and rheological properties of the network [1].

These actin filaments are reversibly coupled to membrane proteins and in conjunction with motor proteins from the myosin family, are able to generate contractile force during cell migration. By this mechanism, cells sense the rigidity of their environment and adapt their activity to it [2].

Here, we present a 3-D Brownian dynamics (BD) computational model in which actin monomers polymerize and become cross-linked by ACPs. The dynamic behaviour of molecular motors is also included [3]. In this simulation, actin monomers, filaments, ACPs, and motors experience thermal motion and interact with each other with binding probabilities and defined potentials. Displacements are governed by the Langevin equation, and positions of all elements are updated using the Euler integration scheme.

Mechano-sensing properties of active networks are investigated by evaluating the contraction and the generated stress in response to different extracellular stiffness. Our results reveal, as found in recent literature, that acto-myosin units themselves may act as rigidity sensors [4]. The magnitude and rate of stress generation increased with stress until saturation and followed a Hill force-velocity relationship.

This model has the potential to provide new insight into various biological processes such as cell migration and cytoskeletal remodelling, and can be further refined for investigating actin related phenomena.

Contact-based social contagion in multiplex networks

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We present a theoretical framework for the study of epidemic-like social contagion in large scale social systems. We consider the most general setting in which different communication platforms or categories form multiplex networks. Specifically, we propose a contact-based information spreading model, and show that the critical point of the multiplex system associated with the active phase is determined by the layer whose contact probability matrix has the largest eigenvalue. Finally, we also show that when the system through which information is disseminating is inherently multiplex, working with the graph that results from the aggregation of the different layers is inaccurate.
Heterogeneous resource allocation can change social hierarchy in public goods games.

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Nowadays one of the key elements of our societies is the interaction between groups of individuals to achieve a common objective. From a theoretical point of view, the problem has been approached with the tools offered by evolutionary game theory and defined as public goods games (PGG). Here we present a modification of the classical PGG on networks where players are allowed to distribute their investments unevenly, allocating more resources to profitable games and less in unfavorable ones. We show that with this modification an uneven distribution of the wealth naturally emerges reproducing the so-called Pareto principle. In addition, the analysis of the structure of the most productive environments highlights their organization as the backbone of the network. Our results shed light on the large-scale organization of social and economical systems and give a simple framework for the emergence of features present in real economic scenarios.
Irreversibility in the transition to cooperation in complex networks

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In the framework of the evolutionary dynamics of the Prisoner’s Dilemma game on complex networks, we investigate the possibility that the average level of cooperation shows hysteresis under quasi-static variations of a model parameter (the “temptation to defect”). Under the “discrete replicator” strategy updating rule, for both Erdős–Rényi and Barabási–Albert graphs we observe cooperation hysteresis cycles provided one reaches tipping point values of the parameter; otherwise, perfect reversibility is obtained. The selective fixation of cooperation at certain nodes and its organization in cooperator clusters, that are surrounded by fluctuating strategists, allows the rationalization of the “lagging behind” behavior observed.