– XI NATIONAL CONFERENCE –

BIFI 2023

JANUARY

25th – 27th

ZARAGOZA / SPAIN

Instituto Universitario de Investigación Biocomputación y Física de Sistemas Complejos
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Foreword

Welcome to the XI National Conference BIFI 2023, held in the Institute for Biocomputation and Physics of Complex Systems (BIFI), located in Zaragoza, Spain.

The main goal of this meeting, as with our bi-annual series of National Conferences, is to provide BIFI members with a public forum where they can present their work and network with other scholars, encouraging the development of new collaborations between the various research lines and areas of the Institute as well as with external colleagues.

We are excited to announce that this year's meeting will be held in person, in the conference room of the I+D building, after a two-year hiatus caused by the unique circumstances imposed by the COVID19 pandemics.

The program comprises brief talks delivered by students and trainees, two poster sessions, and plenary lectures by the principal Investigators of most of the institute's active research lines, as well as several external contributions from other research centers in Spain, and abroad.

We anticipate that this conference will be a great opportunity for our community to reconnect, engage in stimulating and useful discussions, generate fresh concepts, and witness new partnerships emerge.

The BIFI2023 Organizing Committee
Zaragoza, 2023

Program

Wednesday, January 25th

08:30 - 08:45 **Registration.** (BIFI secretary)
08:45 - 09:00 **Opening ceremony**.

Session 1. January 25th, 09:00-11:00 h. Chair: Milagros Medina

Protein misfolding and amyloid aggregation.

09:00 - 09:30 **N. Cremades,** Novel fluorescence-based tools and applications in protein amyloid aggregation: from basic research to diagnosis. Ref. 01PI.
09:30 - 09:45 **D. Polanco,** Novel pathways of α-synuclein aggregation and toxicity through liquid-liquid phase separation. Ref. 01T.
09:45 - 10:00 **A. Carrancho,** Development and validation of a novel biomarker-based diagnostic method for Parkinson's disease. Ref. 02T.

Signal transduction and membrane protein therapies.

10:00 - 10:30 **J. García-Nafría,** Functional mechanisms of G protein-coupled receptors and their therapeutics. Ref. 02PI.

Structural Biology of neuronal membrane receptors.

10:30 - 11:00 **B. Herguedas,** Ion channel structural biology: from protein production to structure determination. Ref. 03PI.

11:00-11:30 h. Coffee Break

Session 2. January 25th, 11:30-13:30 h. Chair: Javier García-Nafría

Computational Genomics and Systems Bio-Medicine.

11:30 -12:00 **J. Sanz,** Alveolar macrophages responses to *Mycobacterium tuberculosis* infection: ontogenetic determinants and HIV-coinfection effects. Ref. 04PI.
12:00 - 12:15 **I. Marchante,** Uncovering the transcriptomic footprint of inter-individual heterogeneity in Celiac Disease. Ref. 03T.
12:15 - 12:30 **J. Bertol,** Multi-omics portrait of VirR protein function in cell wall remodeling and vesiculogenesis in *Mycobacterium tuberculosis*. Ref. 04T.

External Contribution

12:30 - 12:45 **C. Ortega-Sabater**, Untangling the impact of chromosomal instability in the progression of pediatric B-Acute Lymphoblastic Leukemia with aneuploidies through mathematical models and single-cell analyses. Ref. 05T.

Statistical-Physics Modeling of biomolecules

12:45 - 13:15 **P. Bruscolini**, Ongoing activity in the “Physical Modeling of Biomolecules” research line. Ref. 05PI.
13:15 - 13:30 **A. Sáinz-Agost**, Resonant effects in polymer translocation under transversal fields. Ref. 06T.

13:30-15:30 h. Lunch Break.

Session 3. January 25th, 15:30-17:00 h. Chair: Pierpaolo Bruscolini

Protein glycolylation and its role in disease.

15:30 - 16:00 **V. Taleb**, Structural and mechanistic insights into the cleavage of clustered O-glycan patches-containing glycoproteins by mucinases of the human gut. 06PI.

16:00 - 16:15 **A.M. González-Ramírez**, Structural basis for the synthesis of the core 1 structure by C1GalT1. Ref. 07T.

High performance and cloud computing

16:15 - 16:45 **D. Martínez / C. Gimeno**, Computing services at BIFI: Past, present and futuro. Ref. 07PI.

16:45 - 17:00 **S. Martínez-Losa del Rincón**. Quantum Technologies in the near future: The second Quantum Revolution. Ref. 08T.

17:00-17:30 h. Coffee Break.

Poster Session 1. January 25th, 17:30-19:30 h.

Thursday, January 26th

Session 4. January 26th, 09:00-11:00 h. Chair: Jesús Gonzalo-Asensio.

Invited speaker.

09:00 - 09:45 **R. Prados-Rosales,** Dynamin-like proteins are required for secretion of extracellular vesicles and virulence of *Mycobacterium tuberculosis*. Ref. 08PI.

External contribution

09:45 - 10:00 **P. Fernández,** A lipidomic approach to the understanding of Long-COVID. Ref. 09T.

Flavoenzymes: action mechanisms and biotechnology

10:00 - 10:30 **P. Ferreira**, Human Apoptosis inducing factor: recent answers to some old questions. Ref. 09PI.

10:30 - 10:45 **A. Moreno,** Repositioning drugs to inhibit MurA (UDP-N-acetylglucosamine 1-carboxyvinyltransferase UDP-N-acetylglucosamine 1-carboxyvinyltransferase), an enzyme committed to the biosynthesis of peptidoglycan in *Brucella ovis*. Ref. 10T.

10:45 - 11:00 **S. Boneta,** The use of QM/MM calculations to study the hydride transference on flavoenzymes. Ref. 11T.

11:00-11:30 h. Coffee Break

Session 5. January 26th, 11:30-13:30 h. Chair: Carlos Gracia-Lázaro

Digital Science.

11:30 - 12:00 **C.P. Llantada,** "Help us better understand our changing climate": Functions of language in Citizen Science communication. Ref. 10PI.

12:00 - 12:15 **O.M. Carciu,** Evaluative polarity in a small-scale corpus of significance statements. Ref. 12T.

12:15 - 12:30 **R. Villares,** Communicating science on Twitter conference presentations. Ref. 13T.

Data analysis, advanced visualization and technology transfer

12:30 - 13:00 **G. Ruiz**, EOSC-Synergy: Hackathon Manager, a tool for organising hackathons. Ref. 11PI.

Molecular dynamics and electronic structure

13:00 - 13:15 **C. Bouthelier-Madre**, Exact Factorization of molecular wave function, Hamiltonian dynamics and its semiclassical limits: a search for consistent hybrid systems. Ref. 14T.

13:15 - 13:30 **A. Urriolabeitia**, Mechanistic insight into the selective reduction of CO_2 catalyzed by an Ir complex and $B(C_6F_5)_3$. Ref. 15T.

13:30-15:30 h. Lunch Break.

Session 6. January 26th, 15:30-17:00 h. Chair: Marta Martínez Júlvez

Biomolecular interactions.

15:30 - 16:00 **A. Velázquez-Campoy**, 20 years of biological calorimetry at BIFI. Ref. 12PI.

16:00 - 16:15 **P.M. García Franco**, Biophysical Characterization of a zinc-dependent Human Histone Deacetylase 8 (HDAC8): A promising Therapeutic Target for Cancer. Ref. 16T.

Clinical diagnosis and drug delivery

16:15 - 16:30 **S. Hermoso**, First steps for TLB in machine learning systems: diagnosis of pancreatic cancer in a Danish population. Ref. 17T.

External contribution

16:30 - 17:00 **L.M. Esteban,** A Stepwise Algorithm for Linearly Combining Biomarkers under Youden Index Maximization. Ref. 13PI.

17:00-17:30 h. Coffee Break.

Poster Session 2. January 26th, 17:30-19:30 h.

BIFI council meeting. January 26th, 18:30 h. (BIFI members only)

Friday, January 27th

Session 7. January 27th, 09:00-11:00 h. Chair: Joaquín Sanz

Group of Theoretic and advanced modeling.

09:00 - 09:30 **P. Valgañón,** Contagion-diffusion processes with recurrent mobility patterns of distinguishable agents and control strategies. Ref. 18T.

09:30 - 09:45 **H. Pérez,** Dynamics of opinion polarization in weighted graphs. Ref. 19T.

External contribution

09:45 - 10:00 **A. Nicolas,** Assessment of the Risks of Viral Transmission in a Crowd: Combining Observations of the Interactions between Pedestrians in Daily-Life Situations and Fluid-Dynamical Simulations. Ref. 14PI.

Complex systems and networks lab.

10:00 - 10:30 **A. Aleta,** A need for a paradigm shift in healthy nutrition research. Ref. 15PI.

10:30 - 10:45 **A. de Miguel,** Exploring the integration of micro-mobility and epidemic models: d-EPR + SIR. Ref. 20T.

10:45 - 11:00 **M. Tovar,** Modelling decisions influence the impact estimates of new Tuberculosis vaccines: The case of China. Ref. 21T.

11:00-11:30 h. Coffee Break

Session 8. January 27th, 11:30-13:30 h. Chair: Pilar Catalán

Protein folding and molecular design.

11:30 - 12:00 **J. Sancho,** Molecular interactions and forces that make proteins stable: an inventory from atomistic MD simulations. Ref. 16PI.

12:00 - 12:15 **P. Bruñén,** Design and synthesis of FMN derivatives for covalent binding to *Anabaena* apoflavodoxin. Ref. 22T.

12:15 - 12:30 **J.J. Galano-Frutos,** Integrating Experiments and MD Simulations for Modeling the Structural Ensemble of a Protein Molten Globule: the *Helicobacter pylori* apoflavodoxin at acidic pH. Ref. 23T.

12:30 - 12:45 **R. Maity,** Multi-OMICs for antibacterial mode of action determination. Ref. 24T.

Genetic regulation and physiology of cyanobacteria.

12:45 - 13:15 **M. Fillat**, Regulatory networks operated by FUR (ferric uptake regulator) proteins in *Anabaena* sp. PCC7120. Ref. 17PI.

13:15 - 13:30 **J Guio**, Shedding light on novel transcriptional regulatory networks in the cyanobacterium *Anabaena* sp. PCC7120. Ref. 25T.

13:30-15:30 h. Lunch Break.

Session 9. January 27th, 15:30-16:30 h. Chair: María Fillat

Plant evolutionary and genetic biology.

15:30 - 16:00 **P. Catalán**, 20th anniversary of model grasses, study systems of evolutionary and functional diversity of monocots. Ref. 18PI

16:00 - 16:15 **M. Campos**, Unveiling the origins of the overlooked model grasses *Brachypodium stacei* and *B. hybridum*. Ref. 26T.

16:15 - 16:30 **R. Sancho**, Evolution and dynamics of the repeatome and its transposons in the temperate grass model genus *Brachypodium*. Ref. 27T.

16:30 h. Closing remarks & poster prizes.

Talks

Ref. Number: 01PI

Novel fluorescence-based tools and applications in protein amyloid aggregation: from basic research to diagnosis

Nunilo Cremades[1,2]

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A number of neurodegenerative diseases, including Alzheimer´s and Parkinson´s disease, are associated to protein amyloid aggregation, a process involving the transition from the functional, soluble state of a particular protein into misfolded, toxic oligomers and eventually insoluble fibrils with a hallmark cross-beta structure. Finding molecules with therapeutic or diagnostic potential in neurodegenerative disorders is of utter importance. However, the complexity and heterogeneity of the amyloid conformational landscape, makes amyloid aggregation a tremendously challenging target. Our lab is devoted to the development of novel fluorescence-based tools and applications for the study of the process of protein amyloid aggregation and the design of novel strategies for the diagnosis of some of these devastating diseases. In this talk, I will summarize some of our recent advances towards these aims.

Ref. Number: 01T

Novel pathways of α-synuclein aggregation and toxicity through liquid-liquid phase separation

David Polanco[1,2], Pablo Gracia [1,2], María Martínez-Monge[2], Nunilo Cremades[1,2]

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α-synuclein (αS) is a small, intrinsically disordered protein whose deposition in the form of amyloid aggregates is the main hallmark of Parkinson's disease (PD), although the mechanisms that lead to in vivo αS aggregation remain unknown. Increasing evidences suggest that aberrant protein liquid-liquid phase separation (LLPS) precedes the initial nucleation of amyloid formation in intrinsically disordered proteins related to neurodegenerative diseases. Recently, we have reported that αS is able to undergo LLPS under cytomimetic conditions with other proteins and peptides containing disordered regions enriched in positively-charged residues, such as the Alzheimer's disease (AD)-related, and also amyloidogenic protein, Tau. Using state-of-the-art fluorescence microscopic and spectroscopic techniques, we have directly monitored and characterized the nucleation of amyloid aggregates in the interior of the protein droplets. Interestingly, these aggregates contain preferentially both αS and Tau, suggesting that the amyloid pathway that we reported could be a possible molecular mechanism for the in vivo formation of αS/Tau co-aggregates identified in AD and PD patients' brains. We are currently expanding our study to other physiological partners with which αS and Tau could undergo LLPS in disease conditions, opening new avenues for the study of toxic LLPS-related mechanisms in neurodegenerative diseases.

Ref. Number: 02T

Development and validation of a novel biomarker-based diagnostic method for Parkinson's disease.

Alejandra Carrancho[1], David Polanco[1], Juan Marín[3], Nunilo Cremades[1,2]

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3. Miguel Servet Hospital, University of Zaragoza.

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Parkinson's disease (PD) is an age-related neurodegenerative disorder characterized by a clinical picture that includes bradykinesia, tremor, postural instability, and motor and non-motor related symptoms. From a molecular point of view, it is defined by the accumulation and deposition of α-synuclein (α-Syn) aggregates in Lewy bodies and neurites where specific types of cell-toxic oligomers (OAS) are generated, and their presence has been reported in CSF and plasma samples. Nowadays, the diagnosis PD is primarily clinical and its differentiation from other types of parkinsonisms is complicated. We are proposing a novel technique for the early diagnosis of PD that relays on the use of potent biomarkers in biological fluid samples by combining the high affinity of certain molecules for OAS with the discriminatory power of nanobodies specifically binding to all α-Syn species. For their detection, as a proof of concept, we propose to use single-molecule fluorescence techniques to simultaneously identify signals from both fluorescently labeled molecules. Through this work, an unequivocal and earlier detection of PD could be achieved, permitting the implementation of more personalized treatments and a more detailed study of the molecular patterns associated with the disease.

Ref. Number: 02PI

Functional mechanisms of G protein-coupled receptors and their therapeutics

Javier García-Nafría[1,2]

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G protein-coupled receptors (GPCRs) are the largest family of membrane receptors in the human body, they control the function of all major organs and are also the most prolific pharmacological targets. GPCRs sense a variety of molecules (lipids, hormones, neurotransmitters…etc) and transduce the signal to the intracellular milieu by coupling to and activating heterotrimeric G-proteins. Within this talk I will present the group´s current research to understand new structural and functional mechanisms of GPCRs as well as their novel regulation. I will introduce our approach to understand drug specificity, signaling bias and oligomerization, as well as our research direction in the study of orphan receptors (GPCRs with no identified endogenous ligands). For this purpose, we use state-of-the-art cryo-electron microscopy, biophysics, biochemistry and cell assays while developing new tools and approaches in protein engineering and receptor oligomerization.

Ref. Number: 03PI

Ion channel structural biology: from protein production to structure determination

Carlos Vega Gutiérrez[1,2], Irene Sánchez Valls[1,2], **Beatriz Herguedas**[1,2]

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Structural biology of membrane proteins, and ion channels in particular, has lagged behind that of soluble proteins, with less than 8000 structures currently deposited in the *Protein Data Bank* versus more than 190,000 structures for all biological macromolecules. Still, membrane proteins play key roles in cell function, constituting 30 % of the human genes and being the target of 50 % of drugs approved in the market.
The main bottlenecks in structural biology of membrane proteins are protein expression and stabilization of membrane proteins outside the lipid bilayer. Our group is focused on the characterization of Ligand Gated Channels which bind Glutamate (iGluRs), the main excitatory neurotransmitter in the brain. Here we summarize our advances in protein production using baculovirus infection of mammalian cells, we show different strategies to solubilize membrane proteins in either detergents or lipid nanodiscs, and we present the cryo-EM data of GluA4, a Glutamate Receptor ion channel involved in neurotransmission at early stages of development.

Ref. Number: 04PI

Alveolar macrophages responses to *Mycobacterium tuberculosis* infection: ontogenetic determinants and HIV-coinfection effects

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Out of every 10 individuals infected with the pathogen *Mycobacterium tuberculosis* (*Mtb*), only less than one is roughly expected to develop tuberculosis (TB) during their lifetime. Understanding the reasons of subjects' uneven fates upon *Mtb* infection constitutes a matter of extraordinary importance wherein variation at the early phases of infection, mainly mediated by alveolar macrophages (AMs), play an increasingly acknowledged role. From an epidemiological point of view, HIV coinfection remains the single major unique source of heterogeneity in TB presentation and immune profiling. Yet, the effects of HIV-coinfection on the early responses to Mtb infection, occurring before the deployment of the adaptive responses eventually compromised in HIV+ individuals, remain largely unknown. This is in part because AMs, and their different responses to Mtb infection with respect to Bone-marrow-derived macrophages (BMDMs) are only partially understood.

In this contribution, I will cover a series of results recently achieved in our group on these matters, where we describe the transcriptional and metabolic responses of AMs to intracellular infection with Mtb *in-vitro*. First, I will describe the transcriptomics and metabolic signature of AMs, as opposed to Bone-marrow-derived macrophages (BMDMs) in the murine model, to find that the bactericidal capabilities of these cells largely depend on their ability -significantly compromised in AMs- of shifting from an oxidative phosphorylation-based metabolism to one mainly based on glycolysis. Second, I will describe the different immune responses that we have observed between HIV-TB coinfected individuals and controls, using data coming from in-vitro infected, human AMs extracted from bronco-alveolar lavages. Here, we found that not just HIV infection compromises the responses of AMs to an *in-vitro* infection with Mtb, but the only usage of anti-retroviral prophylactic therapy (ARPT) does so too.

Taken together, our results point to a relevant role of AMs in explaining the observed heterogeneity found in TB epidemiology, especially in what regards to its prevalence among HIV+ individuals as well as people living under ARPT.

Ref. Number: 03T

Uncovering the transcriptomic footprint of inter-individual heterogeneity in Celiac Disease

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Celiac disease (CeD) is an autoimmune disorder triggered by dietary gluten that is characterized by villous atrophy of the small-intestine, crypt hyperplasia and influx of intra-epithelial lymphocytes. Despite a common histological picture, the pathways leading to both pathological adaptive responses to gluten and tissue destruction/remodelling vary across CeD patients. However, the impact of the causal factors in the development of the disease, as well as their contribution to interindividual differences in presentation, progression, severity, and recovery have not been fully disentangled. A better understanding of the factors driving the heterogeneity within CeD patients is crucial to further understand disease pathogenesis and identify potential therapeutic approaches complementary to gluten-free diet (GFD), which is problematic in a significant fraction of patients.

In this study we present an exhaustive characterization of the transcriptional signature of CeD. To achieve this, we analyzed RNA-seq data from duodenal samples extracted from a panel of N=407 patients enrolled in a multi-year study at the University of Chicago, USA, distributed between controls, active CeD patients, and CeD patients under GFD. As a result, we found that age and sex are important drivers of molecular heterogeneity in CeD affected tissue, and identified a series of genes whose variation across celiac patients is larger than among controls, which makes them candidate markers for explaining CeD heterogeneity. Importantly, the activity of these markers is strongly correlated with the levels of villous atrophy and crypt hyperplasia found across patients, as well as with inferred levels of M2-polarized macrophages and CD8 T cells.

Taken together, our results offer new insights into the regulatory basis of CeD heterogeneity, that are potentially useful towards the development of personalized approaches to the management of this increasingly prevalent disease.

Ref. Number: 04T

Multi-omics portrait of VirR protein function in cell wall remodeling and vesiculogenesis in *Mycobacterium tuberculosis*

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VirR, a LytR_C domain containing protein, has been related to regulation of production of extracellular vesicles (EVs) in *Mycobacterium tuberculosis* by maintaining cell wall integrity. To test its regulatory role in vesiculogenesis, proteomic and transcriptomic profiles from a mutant strain of *M. tuberculosis* with an inactive phenotype of the VirR protein (VirR-KO) were obtained, as well as from the wild-type strain H37RV. The VirR-KO mutant, as ascertained through electron microscopy and nanoparticle tracking analysis, presented an abnormal cell wall morphology linked to higher permeability, lower virulence and an increased production of extracellular vesicles.

Transcriptomic analysis was performed on whole cell lysates from each strain revealing major differences concerning host defense and host-induced stress responses, as well as protein secretion, which partly explain the divergent virulence and secretory profiles of H37RV and the VirR-KO mutant. Furthermore, these analyses also revealed divergent expression levels for genes involved in mRNA translation, stabilization, and metabolism; thus pointing to the existence of relevant post-transcriptional regulatory mechanisms mediated by VirR. To test this hypothesis, proteomic analyses were performed on whole cell lysates and isolated extracellular vesicles from each strain, revealing largely disjoint sets of differentially expressed proteins with respect to mRNAs, further pointing to the relevance of post-transcriptional mechanisms in the regulatory role of VirR. Differential expression analysis of the proteins revealed greater differences between extracellular vesicles from different strains than between whole cell lysates, indicating a primary role for VirR in the proteomic enrichment profile of EVs.

Taken together, our results highlight a relevant regulatory role for virR that leans both on transcriptional and post-transcriptional mechanisms, which significantly mediates the amount and function of EVs secreted by *Mycobacterium tuberculosis*.

Ref. Number: 05T

Untangling the impact of chromosomal instability in the progression of pediatric B-Acute Lymphoblastic Leukemia with aneuploidies through mathematical models and single-cell analyses

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Aneuploidy, defined as the gain or loss of whole chromosomes, is a hallmark of cancer and is common in childhood B-cell acute lymphoblastic leukemia (B-ALL). Karyotype heterogeneity has been observed by single-cell analysis in aneuploid childhood B-ALL subtypes, with a major clone and a series of smaller subclones, suggesting chromosome instability (CIN).

In this work, we propose the use of an agent-based model (ABM) to characterise *in silico* the role of CIN in B-ALL progression. We build an ABM that incorporates a certain CIN probability after each cell division, allowing us to track each cellular karyotype by looking for the effects of CIN levels in tumour growth, growth rate and cell fitness. We numerically characterised the contribution of each individual chromosome to cell fitness. For this quantification we incorporated functional and structural chromosomal features that impact on chromosome missegregation rates.

Additionally, we define a chromosomal heterogeneity index using ecological and statistical measures. This work relies on molecular cytogenetics and single-cell sequencing data from primary samples, patients and PDX models.

Our results suggested that karyotype heterogeneity might be used as a prognostic factor in childhood B-ALL and showed that certain levels of CIN fuel leukemia progression, selecting stereotypic karyotypes similar to those observed in patients.

Ref. Number: 05PI

Ongoing activity in the "Physical Modeling of Biomolecules" research line

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In this talk, I will present an overview of the research activity of the three different subgroups that contribute to this line, covering both published and ongoing studies. All of them share a common approach, based on the applications of theoretical and computational methods, from the non-linear and statistical-physics fields, to different biomolecules as well as biological processes.

Ref. Number: 06T

Resonant effects in polymer translocation under transversal fields

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Polymer translocation has long been a topic of interest in the field of biological physics given its relevance in both biological (protein and DNA/RNA translocation through nuclear and cell membranes) and technological processes (nanopore DNA sequencing, drug delivery) [1,2]. In this work, we simulate the translocation of a semiflexible homopolymer through an extended pore, driven by both a constant longitudinal and a time-dependent transversal end-pulled force. We find a large minimum region of the mean translocation times as function of the frequency of the transversal force that is typical of the Resonant Activation effect [3]. This minimum is present for all the rigidities of the polymer and reveals a linear relation between the optimum translocation time and the corresponding period of the driving as a function of the bending values.

References

[1] J. J. Kasianowicz, E. Brandin, D. Branton, and D. W. Deamer. *Proc. Natl. Acad. Sci. USA **93**, 13770 (1996).*

[2] M. Zwolak and M. Di Ventra, *Rev. Mod. Phys. **80**, 141 (2008).*

[3] A. Fiasconaro, J. J. Mazo, and F. Falo, Active polymer translocation in the three-dimensional domain, *Phys. Rev. E **91**, 022113 (2015).*

Ref. Number: 06PI

Structural and mechanistic insights into the cleavage of clustered O-glycan patches-containing glycoproteins by mucinases of the human gut

Víctor Taleb [#1], Qinghua Liao [#2], Yoshiki Narimatsu [#3], Ana García-García [#1], Ismael Compañón [#4], Rafael Junqueira Borges [5], Andrés Manuel González-Ramírez [1], Francisco Corzana [4], Henrik Clausen [3], Carme Rovira [6 7], Ramon Hurtado-Guerrero [1,3,8]

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Mucinases of human gut bacteria cleave peptide bonds in mucins strictly depending on the presence of neighboring O-glycans. The Akkermansia muciniphila AM0627 mucinase cleaves specifically in between contiguous (bis) O-glycans of defined truncated structures, suggesting that this enzyme may recognize clustered O-glycan patches. Here, we report the structure and molecular mechanism of AM0627 in complex with a glycopeptide containing a bis-T (Galβ1-3GalNAcα1-O-Ser/Thr) O-glycan, revealing that AM0627 recognizes both the sugar moieties and the peptide sequence. AM0627 exhibits preference for bis-T over bis-Tn (GalNAcα1-O-Ser/Thr) O-glycopeptide substrates, with the first GalNAc residue being essential for cleavage. AM0627 follows a mechanism relying on a nucleophilic water molecule and a catalytic base Glu residue. Structural comparison among mucinases identifies a conserved Tyr engaged in sugar-π interactions in both AM0627 and the Bacteroides thetaiotaomicron BT4244 mucinase as responsible for the common activity of these two mucinases with bis-T/Tn substrates. Our work illustrates how mucinases through tremendous flexibility adapt to the diversity in distribution and patterns of O-glycans on mucins.

Ref. Number: 07T

Structural basis for the synthesis of the core 1 structure by C1GalT1

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Abstract

C1GalT1 is an essential inverting glycosyltransferase responsible for synthesizing the core 1 structure, a common precursor for mucin-type O-glycans found in many glycoproteins. To date, the structure of C1GalT1 and the details of substrate recognition and catalysis remain unknown. Through biophysical and cellular studies, including X-ray crystallography of C1GalT1 complexed to a glycopeptide, we report that C1GalT1 is an obligate GT-A fold dimer that follows a S_N2 mechanism. The binding of the glycopeptides to the enzyme is mainly driven by the GalNAc moiety while the peptide sequence provides optimal kinetic and binding parameters. Interestingly, to achieve glycosylation, C1GalT1 recognizes a high-energy conformation of the α-GalNAc-Thr linkage, negligibly populated in solution. By imposing this 3D-arrangement on that fragment, characteristic of α-GalNAc-Ser peptides, C1GalT1 ensures broad glycosylation of both acceptor substrates. These findings illustrate a structural and mechanistic blueprint to explain glycosylation of multiple acceptor substrates, extending the repertoire of mechanisms adopted by glycosyltransferases.

Ref. Number: 07PI

Computing Services at BIFI: Past, Present and Future

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Our computing infrastructure has always been a key contributor to some of the most important projects, like the Spanish Supercomputing Network in HPC field or EGI Fedcloud in Cloud Computing to name some of them.

However, time passes for everything and everyone, so our infrastructure is now suffering management problems due to outdated software and hardware.

We're taking advantage of this situation by planning new ways of managing all services that we offer from the datacenter and sysadmin team, in order to deploy it as the new infrastructure arrives.

The talk proposes to give you an overview of a new managing way, tracking about monitoring and observation services, user management, use policies regarding terms of service or privacy, ways of applying for accesses or requesting support.

Also, we'll talk about this year incoming machines and infrastructures, their integration in the datacenter, performance and other improvements respect old ones.

Ref. Number: 08T

Quantum Technologies in the near future: The second Quantum Revolution

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For the first time, Quantum Technologies and Quantum Physics are available at an understanding level that anyone can use and interpret. In the early years of the 20th century, Quantum Physics theory became more and more complicated as well as refreshing. Now, it is possible to figure out how complex systems work on the nanoscale whilst, for instance, we simulate a molecule in research for a new medical drug using a Quantum Computer simulator.

From the last years of the 20th century until now, superconductive materials based on CMOS technology, took the Quantum scene to make circuits that hold the fundamental information unit, the Qubit. It is now when Quantum Computers based on this technology begin to be available to everybody, but nevertheless, there are drawbacks that we must deal with.

There is more to come and research in areas like Quantum Computation, Quantum Machine Learning. Many companies claim a Quantum Leap achievement on focused issues, but, it is still needed a complete citizen ecosystem that brings the Quantum advantages to the general audience. We present the Quantum Spain initiative, which aims to bring public use of the Quantum Computation power to every citizen, research group, and company in Spain.

Ref. Number: 08PI

Dynamin-like proteins are required for secretion of extracellular vesicles and virulence of *Mycobacterium tuberculosis*

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The secretion of extracellular vesicles (EVs) is ubiquitous in prokaryotic and eukaryotic cells. EVs are membrane-bound nanostructures actively released by cells to communicate with other cells in their environment. The content of EVs includes lipids, proteins, metabolites, and nucleic acids. *Mycobacterium tuberculosis*, the etiological agent of human tuberculosis (TB), secretes EVs in culture and during infection. *In vitro* studies have suggested that mycobacterial EVs contribute to nutrient acquisition, toxin delivery, and immune modulation. However, the importance of vesicle secretion during *M. tuberculosis* infection is unclear.

Here, we identify the dynamin-like proteins (DLP) IniA and IniC as essential factors for EV secretion and virulence of *M. tuberculosis*. Utilizing a DLP mutant we show that EVs allow *M. tuberculosis* confined within macrophages to communicate with uninfected host cells and stimulate an inflammatory response that promotes bacterial proliferation and host pathology. Importantly, IniAC are known to be induced by one of the standard antitubercular drugs, isoniazid. Using this information, we have generated a reporter strain to inform about drugs that can modulate vesicle production in M. tuberculosis.

These studies significantly advance our understanding of mycobacterial EVs biogenesis and its contribution to TB pathogenesis, as well as open the field to investigate vesiculogenesis as a druggable process in *M. tuberculosis*.

Ref. Number: 09T

A lipidomic approach to the understanding of Long-COVID

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After the COVID-19 pandemic outbreak, many scientific efforts have been put into how to control the virus propagation or how to mitigate the severity of the illness. However, for around 10-20% of the patients infected with SARS-CoV-2, the infection can lead to symptoms that persist over time. Long-COVID is defined as the persistence of physical and neuropsychiatric symptoms over a period of, at least, 12 weeks [1]. The reason why some people keep these symptoms is still unclear. Based on numerous evidences indicating that the lipid composition of host membranes is dramatically affected by COVID-19 [2], and in the fact that our endogenous antimicrobial peptides (AMPs) are sensitive to the membrane composition of pathogenic agents [3], we propose that such lipid alteration can be directly related to the Long-COVID condition. With this work, we intend to contribute with a new study to advance on the knowledge of Long-COVID. A lipidomic analysis on 152 plasma samples of patients (41 infected but asymptomatic, the rest with long-COVID symptoms) [4] has been performed. Furthermore, around 200 clinical variables have been collected. With all this information, a data mining study has been applied, unravelling a potential relationship between the lipid alteration and the sustained inflammation and activation of the immune response characteristic of the Long-COVID condition. Our results open the door to the capability of a specific lipid subset to predict Long-COVID-19 patients' outcome.

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Ref. Number: 09PI

Human Apoptosis inducing factor: recent answers to some old questions

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The Apoptosis-Inducing Factor (AIF) is a moonlighting flavoprotein involved in mitochondrial respiratory complex assembly, but also able to trigger DNA cleavage and parthanatos.

In healthy cell, AIF is anchored to the mitochondrial inner membrane and interacts with CHCHD4 (coiled-coil-helix-coiled-coil-helix domain containing 4) playing an essential role in the maintenance of mitochondrial structure and oxidative phosphorylation. Moreover, mutations in the AIFM1 gene can also compromise its pro-life functions by producing phenotypes associated with severe processes of neurodegeneration.

Upon lethal cellular stress, AIF translocates from the mitochondria to the nucleus, where upon association with other proteins, such as the endonuclease CypA and the histone H2AX, induces chromatin condensation and DNA fragmentation.

In this context, we are using a combination of biophysical, molecular and cellular biology methodologies to understand the AIF physiological role in cellular death and life, as well as its implication in neurodegenerative disorders.

Ref. Number: 10T

Repositioning drugs to inhibit MurA (UDP-N-acetylglucosamine 1-carboxyvinyltransferase UDP-N-acetylglucosamine 1-carboxyvinyltransferase), an enzyme committed to the biosynthesis of peptidoglycan in *Brucella ovis*

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Brucella ovis is a facultative intracellular bacterium that infects sheep. Enzymes committed to the cytoplasmic steps of the biosynthesis of peptidoglycan are essential to maintain the shape and rigidity of bacteria, preventing osmotic lysis. Therefore, these enzymes are potential drug targets. The UDP-N-acetylglucosamine 1-carboxyvinyltransferase of *Brucella ovis* (BoMurA, EC 2.5.1.7) is one of such enzymes. It catalyzes the transfer of enolpyruvate from phosphoenolpyruvate (PEP) to UDP-N-acetylglucosamine (UNAG) to yield UDP-N-acetyl-3-O-(1-carboxyvinyl)-alpha-D-glucosamine (EP-UNAG). We determined the kinetic parameters of BoMurA, and searched for suitable BoMurA inhibitors. We used activity-based high-throughput screening (HTS) to assess 1,240 FDA-approved compounds of a Prestwick Chemical Library®. To determine the activity of the enzyme, a solution containing BoMurA and UNAG was distributed on 96-well plates and one different Prestwick compound was added to each well. Reactions were started by adding PEP. Negative and positive controls lacked BoMurA and the Prestwick compound, respectively. We identified 121 compounds (9.8% of those included in the library) inhibiting BoMurA (activity level reduced by 25–100%). We pre-selected those reducing activity by at least 70%. These compounds were classified as tetracycline antibiotics, beta-lactam antibiotics, or as non-antibiotics. We finally selected seven compounds with high inhibitory capacity for further study.

Ref. Number: 11T

The use of QM/MM calculations to study the hydride transference on flavoenzymes

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Hybrid quantum mechanics/molecular mechanics (QM/MM) calculations are a powerful tool for studying in detail the mechanisms of hydride transferences on flavoenzymes. In this study this methodology is employed to achieve an atomic-level description of these reactions and reveal the role of individual residues during the catalyzed pathway. This information is valuable for understanding the regulatory mechanisms of flavoenzymes and for exploring the effects of known disease-associated mutations. In addition, kinetic properties are computed and compared with empirical data, providing good agreement between the theoretical and experimental results.

Here we are focus on two systems of interest. The apoptosis-inducing factor (hAIF) enzyme, which is involved in the regulation of programmed cell death in human cells. It is believed that changes in the redox balance of the cell environment can affect the conformational landscape of hAIF through the reduction of its FAD cofactor with NADH, and thus the utterly importance of understanding this process. The other enzyme is the NAD(P)H dehydrogenase (quinone 1) (NQO1), which is involved in the detoxification of a wide range of electrophilic compounds, among which we choose the dicumarol molecule as a model of study.

Ref. Number: 10PI

"Help us better understand our changing climate": Functions of language in Citizen Science communication

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This presentation explores language-in-use in web-based Citizen Science (CS) communication. It aims to understand how CS discourse reflects some of the social exigences of the Open Science agenda, namely to build trust in science and to engage citizens in scientific research. Applying qualitative discourse analytical techniques to a small corpus of CS projects, this paper shows how language is mainly used for two purposes, to build credibility and trust in scientific research and to make specialised knowledge accessible to audiences with different levels of scientific literacy and interests in science. The data also show that other important functions of language in the CS projects are to express emotion and to build and maintain citizen volunteers' engagement. Correlation analyses between language functions and text types further reveal intrageneric functional variation, with specific distributions of language functions observed across the modular texts and the embedded mini texts included in the project websites. Implications for training scientists in forms of communication for public engagement in science are finally discussed.

Ref. Number: 12T

Evaluative polarity in a small-scale corpus of significance statements

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By capitalizing on the affordances of Internet technology, academic journals have added-on several digital genres to articles online (e.g. research highlights, graphical abstracts, plain language summaries, etc.). These newly emerged genres seek to promote an open research publication culture and boost public trust in science by making research results available to society at large. This paper focuses on such an emerging digital genre, the significance/impact statement published alongside open access articles on environmental issues in journals of the Royal Society of Chemistry. This short text (60-120 words) is requested by the editors of these journals at the stage of manuscript submission and provides the authors' statement in plain language of the broad-scale implications and real-world relevance of the work presented in the article it accompanies. Here I report on the language of evaluation in a small-scale corpus of 103 significance statements (10,680 tokens) published in five journals. Computational linguistics software and techniques (R Studio, 2020; WordSmith Tools 8.0, Scott, 2018) were used to extract from the corpus frequencies and collocational information. Findings describe how scientists exploit language to express evaluative polarity (negative or positive) in significance statements, which has implications on how research results are communicated to engage diverse audiences.

Ref. Number: 13T

Communicating science on Twitter conference presentations

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Technological advances and social media are currently transforming how scientific knowledge is produced, shared, and disseminated. Within the preferred digital platforms employed by scientists, Twitter has become a powerful tool to disseminate, network, and engage with both specialised and non-specialised publics. Moreover, because of COVID-19 lockdowns, instructional and informative Twitter threads have become more popular, and academic institutions have contributed to this trend by adapting spoken genres such as 3 Minute Thesis presentations and academic conferences into the Twitter thread format. From a small-scale corpus of 55 Twitter presentations, I report on the main results identified with the support of computer-assisted software. Findings focus on the rhetorical structure of Twitter presentations, the communicative strategies employed by scientists to re-contextualize and remediate scientific knowledge, and the innovation provided by Web 2.0 affordances. The pedagogical implications of this study align with current policies of open science for social impact and wider dissemination of science beyond expert publics.

Ref. Number: 11PI

EOSC-Synergy: Hackathon Manager, a tool for organising hackathons

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The European Open Science Cloud (EOSC) is an environment for hosting and processing research data to support EU science. The ambition of the EOSC is to provide European researchers, innovators, companies and citizens with a federated and open multi-disciplinary environment where they can publish, find and re-use data, tools and services for research, innovation and educational purposes.

In this context, in order to support the implementation of EOSC-relevant national initiatives, the EU funded the project EOSC-synergy to contribute to the EOSC implementation by expanding national e-infrastructures and building human capacities in EOSC. In practice this means more compute and storage available, more datasets and tools to expand avenues of research. The consortium includes relevant research infrastructures in Spain, Portugal, Germany, Poland, Czech Republic, Slovakia, Netherlands UK, and EGI.eu.

Hackathon Manager is a platform that has been created by BIFI within this project to facilitate the organisation of hackathons taking advantage of the EOSC infrastructure and accessible through the EOSC Portal.

A hackathon is a sprint-like event in which computer programmers and others involved in software development collaborate intensively on software projects with the goal of creating a functioning product by the end of the event (typically 24-48 hours).

Ref. Number: 14T

Exact Factorization of molecular wave function, Hamiltonian dynamics and its semiclassical limits: a search for consistent hybrid systems.

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Hybrid systems are the natural approximation for many body quantum systems (molecules), where the full quantum scheme is divided in two subsystems, one of those suffers a classical limit and thus its dynamics are approximated by classical dynamics (nuclei), while the other remains quantum mechanical (electrons). Some particular hybrid dynamics, as Ehrenfest's, based on Self Consistent Field approximation (the loss of entanglement between subsystems), can be written in a Hamiltonian Language, as they are just the cartesian product of classical and quantum dynamics, both of Hamiltonian nature, coupled through a common Hamiltonian function.

By means of Liouville theorem, this allows us to relate micro-dynamics with statistical dynamics. However, such dynamics turn out to be non-linear and therefore, the dynamics of the hybrid density matrix (which had been built linearly on the projectors) cannot depend exclusively on the density matrix itself. This leads to an inequivalence between Liouville's equation and von Neumann's equation.

To solve this issue, we consider another family of hybrid system: those derived without SCF. Thus, entanglement between both subsystems is still present, and the full quantum theory can be identified with Exact Factorization of the wave function. Firstly, we prove that the theory is Hamiltonian at the quantum level and identify the role of the factorization gauge. Secondly, we propose a route towards a hybrid theory that preserves such Hamiltonianity, conserving a footprint of entanglement between classical and quantum systems, that will help smoothing the inconsistencies of hybrid statistical mechanics.

Ref. Number: 15T

Mechanistic insight into the selective reduction of CO_2 catalyzed by an Ir complex and $B(C_6F_5)_3$

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The possible use of CO_2 as a cheap and abundant C_1-carbon source has been gaining attention over the last years.[1] The inert nature of CO_2 poses a considerable problem for this goal. Catalysis presents itself as one of the few promising avenues to overcome this challenge.

Many different systems have been reported to be able to reduce CO_2 to formaldehyde level with hydrosilanes, all of them requiring the presence of a Lewis acid to achieve selectivity.[2] In fact, the selectivity of these processes has been shown to depend on the metal complex / Lewis acid ratio. Additionally, with an excess of borane, the formation of methane is facilitated. However, the discussion on the operating mechanism remains open and confronting mechanisms have been proposed.

In this work, we present a theoretical study based on density functional theory (DFT) of the selective reduction of CO_2 by tertiary silanes catalyzed by $[Ir(CF_3CO_2)(\kappa^2\text{-}NSi^{Me})_2]$ and $B(C_6F_5)_3$.[3,4]

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Ref. Number: 12PI

20 years of biological calorimetry at BIFI

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Biological Calorimetry has been instrumental in elucidating key structural and functional characteristics of biological macromolecules since the 1960s. This has been possible thanks to scientific and technological advances (mainly instrumentation, experimental procedures, modelling and data analysis).

Calorimetry was occasionally used by researchers at the University of Zaragoza before the creation of BIFI. Starting in 2003, an experimental laboratory focused on Biological Calorimetry was planned and developed in parallel to the development of BIFI, which has led to establishing BIFI as a national and international reference center in Biological Calorimetry.

In this talk we will review landmarks and research projects in which Biological Calorimetry has played a fundamental role.

Ref. Number: 16T

Biophysical Characterization of a zinc-dependent Human Histone Deacetylase 8 (HDAC8): A promising Therapeutic Target for Cancer

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Epigenetics may refer to covalent modifications associated with the alteration of gene expression. These modifications are fundamental for many cellular processes which are sometimes passed on to future generations. One important posttranslational chromatin modification affecting gene expression is the acetylation status of lysine residues found in the accessible N-terminal region of core histones. Histone acetylation by histone acetyltransferases (HATs) results in the activation of the transcription mechanism whereas deacetylation by histone deacetylases (HDACs) leads to its repression. Because HDACs exert a major gene silencing role, HDACs alteration results in impaired acetylation and deacetylation which may cause the onset of numerous disorders including cancer. Therefore, HDACs have been considered as relevant drug targets. Among class I HDACs, overexpression of HDAC8 is found to be highly correlated in breast cancer, gastric carcinoma, lung cancer, among others. The discovery of a novel HDAC inhibitor as new drugs for transcription therapy and cancer chemoprevention, is imperative. In order to achieve it, our main objective is performing a comprehensive biophysical study of the structural role of zinc in HDAC8 for further experimental molecular screening procedures of chemolibraries to identify bioactive compounds which can behave as competitive/allosteric HDAC8 inhibitors.

Ref. Number: 17T

First steps for TLB in machine learning systems: diagnosis of pancreatic cancer in a Danish population

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Thermal Liquid Biopsy refers to the analysis of serum samples by differential scanning calorimetry, providing a global picture of the proteins and their interactions. The thermogram shows the difference in heat capacity between serum solution and reference buffer solution as a temperature function. Our objective is to optimize the analyses of thermogram curves to predict and diagnose pancreatic cancer subjects (n=321) and discriminate them from a control group (n=332) in a population from Denmark.

We compared a simplified model with only temperatures and a complete model adding biochemical variables (carbohydrate-antigen-19.9, chitinase-3-like-protein-1, interleukin-6, and C-reactive-protein). The predicted models were built applying machine learning algorithms based on penalized regression, including resampling techniques, categorizing continuous variables (pairs of temperatures), cross-validation, and variable selection. The complete model showed a higher area under the ROC curve (0.91 vs. 0.75; Delong test: p-value<0.001) and specificity (98% vs. 46%) than the simplified model. In contrast, the sensitivity was higher in the simplified model (86%) than in the complete model (77%).

We conclude that the addition of biochemical variables improves the models' prediction performance for the thermogram curves analysis. However, further validation in other independent cohorts of patients is necessary to confirm its applicability in clinical settings.

Ref. Number: 13PI

A Stepwise Algorithm for Linearly Combining Biomarkers under Youden Index Maximization

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Combining multiple biomarkers to provide predictive models with a greater discriminatory ability has received attention in recent years. Choosing the probability threshold that corresponds to the highest combined marker accuracy is key in disease diagnosis. In this study, we present a stepwise algorithm for linearly combining continuous biomarkers to maximize the Youden index, a statistical metric that provides an appropriate synthetic index for diagnostic accuracy. To investigate the performance of our algorithm, we analyzed a wide range of simulated scenarios and compared its performance with that of five other linear combination methods in the literature (a stepwise approach introduced by Yin and Tian, the min-max approach, logistic regression, a parametric approach under multivariate normality and a non-parametric kernel smoothing approach). The obtained results show that our proposed stepwise approach showed similar results to other algorithms in normal simulated scenarios and outperforms all other algorithms in non-normal simulated scenarios. In scenarios of biomarkers with the same means and a different covariance matrix for the diseased and non-diseased population, the min-max approach outperforms the rest. The methods were also applied on two real datasets (Duchenne muscular dystrophy and prostate cancer).

Ref. Number: 18T

Contagion-diffusion processes with recurrent mobility patterns of distinguishable agents and control strategies

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The analysis of contagion-diffusion processes in metapopulations is a powerful theoretical tool to study how mobility influences the spread of communicable diseases. Nevertheless, many metapopulation approaches use indistinguishable agents to alleviate analytical difficulties. Here, we address the impact that recurrent mobility patterns, and the spatial distribution of distinguishable agents, have on the unfolding of epidemics in large urban areas. We incorporate the distinguishable nature of agents regarding both, their residence, and their usual destination. The proposed model allows both a fast computation of the spatio-temporal pattern of the epidemic trajectory and the analytical calculation of the epidemic threshold. This threshold is found as the spectral radius of a mixing matrix encapsulating the residential distribution and commuting patterns of agents. By the end of this paper it will become clear that very subtle differences in the way we treat the system's agents will have very important consequences, in a similar way that the distinguishability of particles matters in statistical physics. We prove that the simplification of indistinguishable individuals overestimates the value of the epidemic threshold and show how the new formalism can be a powerful tool to assess control strategies aimed at increasing the epidemic threshold under scenarios of epidemiological risk.

Ref. Number: 19T

Dynamics of opinion polarization in weighted graphs

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Opinion polarization has become widespread in modern societies. Its emergence is usually linked to the advent of social networks, which can generate echo chambers that isolate people from opposing perspectives. However, real-world relationships are not solely dependent on one's opinion about certain issues, but also on friendship, kinship, professional ties and the like, usually featuring cross-cutting interactions whose effect on one's opinion lies on the importance assigned to the other's point of view.

To take these facts into account, we adapt an opinion model previously applied to temporal graphs [1] to static, weighted graphs. In our model, agents always interact with the same set of neighbors, being influenced by their opinions and giving more importance to like-minded individuals by means of the weights.

We find that polarization is indeed possible under this formalism in a wide parameter range and network structures. Depending on the parameters, agent's environment can vary from high heterogeneity (multiple cross-cutting relationships) to low heterogeneity (high homophily). Moreover, some polarized configurations generated over a certain range of parameters mimic those obtained in surveys about typically polarized issues like LGTBQ+ rights or other partisan topics, which allows us to classify multiple issues based on the inferred optimal parameters.

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Ref. Number: 14PI

Assessment of the Risks of Viral Transmission in a Crowd: Combining Observations of the Interactions between Pedestrians in Daily-Life Situations and Fluid-Dynamical Simulations

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The broad patterns of contacts in a population may not be sufficient to inform detailed epidemiological models, in particular if they aim to be applied to a specific situation. Instead of these contact rates, we show that detailed field-data about pedestrian interactions in given settings (in particular, outdoors in the frame of our study) can be collected empirically. These empirical data are used to build a detailed network of interactions in the crowd and, by combining it with spatially resolved models of viral transmission via respiratory droplets, to infer the risks of new infections raised in each situation [**1**]. Recently, we have improved these coarse-grained models to better anchor them in Computational Fluid Dynamical (CFD) simulations of the propagation of droplets during breathing (**Figure 1**) and talking, which affords a more accurate study of the spatial dependence of transmission [**2**], which notably highlights the importance of relative air flows on transmission risks. Finally, these modelling efforts have allowed us to assess the mitigation efficiency of redesigning strategies, for instance switching from two-way foot traffic to one-way foot traffic.

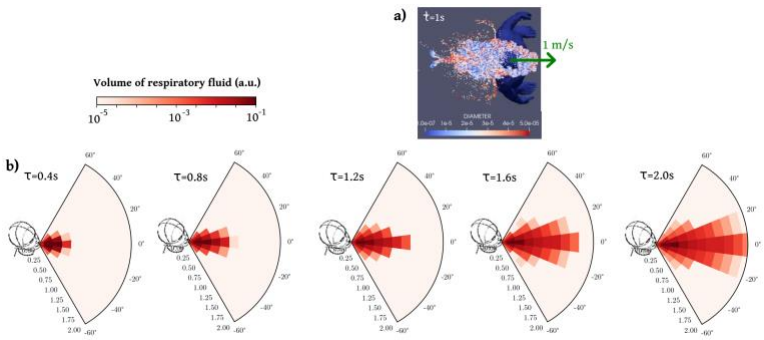

Figure 1: Propagation of respiratory droplets during breathing. (a) Microscopic CFD simulations, (b) Coarse-grained spatio-temporal model derived from these data.

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Ref. Number: 15PI

A need for a paradigm shift in healthy nutrition research

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Humanity is facing a triple dilemma: to produce more food, ensure its nutritional adequacy, and avoid the unjustified expansion of cultivated lands at the expense of the native environment. But these complex issues cannot be solved in isolation. This project is a summary of the steps we have taken to tackle this problem from a complex systems perspective, accounting for trade-offs and synergies that cannot emerge if studied in isolation.

The links between social and environmental dynamics are complex and vary substantially from place to place and through time. Because of constraints in data availability, analytical methods, and a lack of understanding of how social and environmental objectives interact, there is no workable model that allows the optimization of food production while minimizing environmental and societal costs. Similarly, understanding the population's dietary patterns and their impact on health requires many different sources of information that interact with each other. Nutritional epidemiology faces enormous challenges posed by measurement error and related consequences such as unknown confounders, and the inability to address complex exposures.

In this project, we focus on vegetable oils as a case study. We study a large array of problems, ranging from our current knowledge of food composition and its data gaps, the public debate on vegetable oils in social media, the controversial role of Nutri-score, or the environmental and socio-economic impacts of palm oil production in Indonesia. All these systems, and many others, interact with each other and play a major role in the pursuit of the Sustainable Development Goals (SDGs), including reducing poverty, inequality, and hunger, improving health and education, while also meeting climate, biodiversity, and ecosystem goals.

Ref. Number: 20T

Exploring the integration of micro-mobility and epidemic models: d-EPR + SIR

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The availability of massive data from GPS and mobile phone carriers has enabled us to gain novel insights into human mobility, including the revelation of two main classes of individuals: returners and explorers. The first ones move primarily among very few locations, while the second ones exploit several more locations. The Exploration and Preferential Return (EPR) family of models covers some of the main features that real mobility data has revealed, including this exploration-returning dichotomy. In particular, the d-EPR model incorporates real spatial structure and the gravity model of mobility, so that some 'relevance' or attractiveness metric is considered whenever individuals explore new locations.

On the other hand, in the epidemic modeling literature, many works have considered the role of human mobility in disease spreading well as the spatial pattern of propagation under different frameworks. The metapopulation approach, for instance, has been fruitful in that sense, offering new tools and insights on the interplay of disease spreading and mobility. However, mobility is modeled in these approaches not based on the individual but through population/flow-based theoretical/data-driven schemes.

Until now, the integration of this type of micro-mobility model with epidemic models is something that has been barely explored and thus we consider that it deserves exhaustive analysis. In this project, we try to fill this gap and consider the integration of epidemic spreading models with mobility models based on the individual, as the aforementioned d-EPR model. We aim to uncover the interplay of these micro-founded mobility patterns on the spreading of disease and in turn see whether individuals experience a differential impact depending on their mobility profiles (explorers vs. returners).

Ref. Number: 21T

Modelling decisions influence the impact estimates of new Tuberculosis vaccines: The case of China.

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Two-thirds of new Tuberculosis (TB) cases worldwide were located in eight high-burden countries last year, being China the third in number of cases. The slow descent in TB burden, along with the rise of Multidrug-resistant strains of Mycobacterium tuberculosis, seriously threatens TB control and claims for new tools to effectively fight TB and meet the elimination target set by the End TB strategy in 2035.

There are several candidates for Tuberculosis vaccines under development which might help accomplishing those objectives, and that are going through phase 2b in the development pipeline. The impact of those vaccines on a general population needs to be addressed using spreading models, given the lack of correlates of protection in TB.

Unfortunately, modelling decisions do have an impact on the impact estimations, which should be addressed to provide a robust impact forecast. To this end, meaningful descriptions of vaccines emanating from RCTs, and a good understanding of modeling bias are needed.

In this work, we studied the effect of modelling decisions over the impact of new tuberculosis vaccines in China, targeting adolescents or elder people, according to varying vaccine descriptions that represent reasonable mechanisms of action related to the three routes to active TB.

Ref. Number: 16PI

Molecular interactions and forces that make proteins stable: an inventory from atomistic MD simulations

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We know that most proteins adopt in physiological conditions a folded, compact conformation that performs useful biological functions. Although the molecular players of the folding equilibrium and the physical forces operating on them are perfectly identified, their relative contribution to stabilize the folded conformation is not clear at all. We have recently shown that key thermodynamic quantities, such as ΔH_{fol} and ΔCp_{fol}, can be computed from MD simulations. Our analysis of ΔH_{fol} energy partitions obtained from the simulations of four proteins whose ΔH_{fol} and ΔCp_{fol} have been calculated within error reveals a highly consistent energy pattern. From the molecular point of view internal Protein-Protein and Solvent-Solvent interactions are similarly stabilizing, while Protein-Solvent interactions are strongly destabilizing. From the point of view of elementary interactions, van der Waals is most important. Coulombic interactions are also stabilizing although their contribution is much more protein dependent. In contrast, Bonded interactions are destabilizing, indicating that the native state is strained. On the other hand, our analysis shows that the negative sign of the heat capacity change of folding is determined by Protein-Solvent interactions or, from the other perspective, by coulombic interactions. We will put numbers to all these contributions and connect them to simple protein properties such as protein length or changes in solvent exposure.

Ref. Numbers: 22T

Design and synthesis of FMN derivatives for covalent binding to *Anabaena* apoflavodoxin

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Many flavoproteins are involved in vital metabolic transformations, which are of high biotechnological relevance and play essential biological roles in small organisms and humans. Flavodoxins are electron- transfer flavoproteins that contain one molecule of non-covalently bound flavin mononucleotide as the redox component.

This flavoprotein is subject to dissociation equilibrium and influenced by solution conditions, which may result in cofactor dissociation, leading to destabilization of the protein moiety and to irreversible loss of its catalytic activity.

In order to develop a new strategy for the rational increase of flavoproteins´ conformational stability, we have been focused on getting variants of the Anabaena flavodoxin bearing covalently bound catalytically active FMN; for which we have synthesized two FMN derivatives which contain electrophilic and reactive groups.

Suitable flavodoxin variants have also been designed, expressed and purified. We have performed a brief computational study to confirm that these compounds are suitable to establish covalent links with new flavodoxin mutants and that the links are compatible with maintaining the native orientation of the isoalloxacin moiety relative to the apoprotein.

Currently, we are carrying out experiments to find the best conditions to achieve such covalent binding of FMN derivatives through nucleophilic residues strategically located near the active center.

Ref. Number: 23T

Integrating Experiments and MD Simulations for Modeling the Structural Ensemble of a Protein Molten Globule: the *Helicobacter pylori* apoflavodoxin at acidic pH

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We present an integrative atomistic modeling of the Molten Globule (MG) structure (ensemble) formed at acidic pH by the apoflavodoxin from the human pathogen *Helicobacter pylori* (*Hp*). MG is a compact, non-native conformation of proteins that plays a central role in the mechanism of protein folding. MG has been showed to be relevant for cell functions and related to the onset of misfolding diseases. However, high-resolution structural models have been elusive due to inherent experimental difficulties, thus none have yet been obtained, hampering a better understanding of the roles of these conformations in protein folding and misfolding. In this work we address an experimental φ-analysis to derive experimental equilibrium φ-values of native and 55 mutants of *Hp* apoFld, which are used in biased molecular dynamics simulations to bring the native conformation into an MG ensemble. Subsequent refinement steps are carried out based on experimental structural data (e.g. hydrodynamic radius and circular dichroism (CD) spectrum, ^{1}H-NMR, near-UV CD spectral features and solvent-accessible surface area change upon unfolding), and a final reliable atomistic model of the *Hp* apoFld MG ensemble is released, which is now available at the PDB-Dev database (Code: PDBDev_00000112).

Ref. Number: 24T

Multi-OMICs for antibacterial mode of action determination

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Antimicrobial resistance (AMR) poses a significant global threat of profound proportions with an estimated death of nearly 5 million every year. The development of new ideally narrow-spectrum antibiotics for "Priority pathogens" like *Helicobacter pylori* is one of the key factors along with the development of socioeconomic indicators, international cooperation, vaccines and diagnostics facility. Though the necessity of identifying the mode of action can be debated, a molecular-level understanding is of immense benefit for future drug development. Recent developments in OMICs technique can provide a molecular-level view of drug-induced changes in the cellular process. While large-scale omics data are becoming more accessible, and multi-omics studies are becoming much more frequent—real multi-omics integration and data filtering remains very challenging for bacterial systems. *In vivo* understanding of drug target and off-target interaction can provide the necessary information to filter OMICs data. In order to deconvolute the cellular target of the compounds of interest, we have used Proteome Integral Solubility Alteration (PISA). In this study, we have used data from PISA experiment to filter differential expression data from proteomics and transcriptomics to understand the most influenced pathways. Finally, we have validated the expression of these pathways by metabolomics data to obtain the big picture in the cellular response to drugs.

Ref. Number: 17PI

Regulatory networks operated by FUR (ferric uptake regulator) proteins in *Anabaena* sp. PCC7120.

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The genome of *Anabaena* sp. PCC7120 encodes three FUR paralogs named FurA (ferric uptake regulator), FurB/Zur (zinc uptake regulator) and FurC/PerR (Peroxide stress regulator). Initially, these proteins were described as regulators involved in the acclimation of metal deficiency (FurA and FurB/Zur) and the response to peroxide (FurC/PerR).

However, functional characterization of these proteins evidenced that their activity goes beyond the control of metal and redox homeostasis, since they are also engaged in the modulation of photosynthesis, nitrogen metabolism and different stress responses.

At this moment, our group is involved in the identification of novel metabolic processes which may be regulated direct or indirectly by the FUR family, including biofilm formation and the control of new transcriptional regulators in this cyanobacterium.

Ref. Number: 25T

Shedding light on novel transcriptional regulatory networks in the cyanobacterium *Anabaena* sp. PCC 7120

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One of the main mechanisms that makes it possible for cyanobacteria to adapt to different environmental conditions is the regulation of gene expression. This process is mainly performed by transcriptional regulators, two-component systems and sigma factors. In the cyanobacterium *Anabaena* sp. PCC 7120, FUR (Ferric Uptake Regulator) proteins are a family of global regulators which control a wide set of cellular processes, ranging from photosynthesis to nitrogen metabolism. Many of the genes belonging to these functional categories are directly regulated, but some others seem to be indirectly regulated.

In this work we have identified nearly 30 genes with regulatory functions directly regulated by FUR proteins, which indicates that FUR paralogues are cornerstones of novel regulatory networks in cyanobacteria. Besides, we have found that several members of these networks are also regulated by the global nitrogen regulator NtcA, suggesting that these networks could be involved in orchestrating responses to nitrogen deficiency. Finally, as the role of these newly discovered targets of FUR proteins are unknown, CRISPR-Cpf1 based genome edition has been used to create markerless deletion mutants of some of these uncharacterized transcriptional regulators and they have been overexpressed as recombinant proteins in order to describe its function.

Ref. Number: 18PI

20th anniversary of model grasses, study systems of evolutionary and functional diversity of monocots

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Model grasses are extraordinary study systems for monocots. *Brachypodium distachyon* was suggested as a model grass species 20 years ago, but ongoing research now spans the entire genus. Dysploidy, recurrent allopolyploidisation, and extended reticulation have made this genus an ideal model to identify the known and unknown diploid progenitor genomes of its polyploid species. Sympatric speciation of diploid *B. stacei* involved wide-genome divergence and significant differential expressions of signaling pathway genes (DEGs) between arid- and humid-adapted populations. Pangenomic and coalescence-dated analyses detected multiple and bidirectional origins for the allotetraploid *B. hybridum*, reflecting a gradual polyploid genome evolution. The progenitor subgenomes of *B. hybridum* did not show evidence of homeologous exchange bias (HEB) or DEGs in different tissues and conditions. Drought response genes, strongly induced in both subgenomes, probably contributed to its local adaptation to arid habitats. Loliinae temperate species encompass key economic grasses used as fodder, pasture, or turf. Comparative phylogenetic analyses of genes and repetitive elements have uncovered the evolutionary history of this tribe and the impact of hybridization at deep and shallow nodes. The study of fescues and their endophytic *Epichloë* fungi is revealing their potential coevolution and the holobiont responses to abiotic and biotic stress.

Ref. Number: 26T

Unveiling the origins of the overlooked model grasses *Brachypodium stacei* and *B. hybridum*

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The diploid *Brachypodium stacei* and its allotetraploid derivative *B. hybridum* belong to the *Brachypodium* polyploid model complex. These species are distributed spontaneously in a wide circum-Mediterranean range. *B. stacei* and *B. hybridum* have been investigated at population genomics, evolutionary, and ecological levels. We have reconstructed the first phylogeography of *B. stacei* using 29774 SNPs filtered from RADseq sequences (39 individuals, 17 populations). Genomic structure and diversity, and coalescence-based phylogenetic analyses detected 6 main lineages [Mallorca, Greece, Canary Islands, Israel, Jaen, S Spain – Mahgreb] that separated 0.22 Ma from the common ancestor. Ecological niche models discriminated between three climatic groups. Our results suggest that the phylogeography of *B. stacei* populations was driven by long-distance dispersal events and adaptation to local climates. The evolutionary history of *B. hybridum* was inferred independently for its two subgenomes [*B.distachyon*-type (D) and *B.stacei*-type (S)] from 47 resequenced individuals. Analysis of both subgenomes recovered three separate lineages, an ancestral West Mediterranean group, and two recently evolved West+ and East Mediterranean groups, detecting a new origin for this allotetraploid plant. We found different levels of ancestral and recent genomic admixture at the chromosomal level in both subgenomes, although with low levels of heterozygosity in these individuals.

Ref. Number: 27T

Evolution and dynamics of the repeatome and its transposons in the temperate grass model genus *Brachypodium*

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The repeatome, consisting of repetitive elements, is the predominant fraction of the eukaryotic nuclear genome. We have studied the abundance, distribution and phylogenetic signal of the repeat types in *Brachypodium*, with a special interest in transposons (TEs). We analyzed genomic sequences (reads) and whole genomes in several species (annuals, perennials) and cytotypes (diploids, polyploids) of this model grass genus. The size of the monoploid genome (1Cx) was highly correlated with the abundance of repetitive elements. The tetraploid *B. mexicanum* showed the largest 1Cx size (923 Mbp) and abundance of repetitive elements (561 Mbp) (61%), followed by hexaploid *B. boissieri* (450; 155; 34%) and diploid *B. sylvaticum* (519; 160; 31%). Retrotransposons of the *Gypsy* superfamily (*Retand*, *Tekay*) were the main contributors to the increase in genome size. Phylogenetic signals were detected for the repetitive elements of the most divergent *Brachypodium* species. *Brachypodium* taxa showed three alternative scenarios of repeatome and TE dynamics with respect to the "polyploid shock hypothesis", (1) exacerbated increase of repeatome (*B. mexicanum*) as a consequence of TE bursts, (2) equivalent amount to that of progenitor species (*B hybridum*) through balanced composition, and (3) considerable reduction of repeatome (core perennials) to avoid potential genic damage of jumping TEs.

Posters

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Formulaic language for responding to new digital demands in Crowdfunding Science

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When researchers use crowdfunding platforms to get their projects funded, they tend to rely on formulaicity of the language to communicate scientific contents clearly and effectively. Despite the growing attention to emerging digital genres in the past decades, to the best of my knowledge, there are not known many research studies of formulaic language and phraseology in relation to emerging genres of public communication of science on the Internet, such as the case of science crowdfunding proposals. Therefore, examining phraseology in this digital genre can help us understand its main structural patterns and discourse functions and derive pedagogical implications for training scientists in this form of communication. Using a corpus of science crowdfunding projects from Experiment.com, this poster seeks to offer an empirical description of the recurring phraseology taking a lexical bundle approach (Biber et al., 1999) and examine its structural patterns and functional variability. The data show a high presence of lexical bundles that are typical of conversational language and whose main functions are to create proximity with the audiences when informing them about scientific matters and, above all to persuade them, specifically to prompt donation.

Thermal unfolding analysis of DNA G-Quadruplex structures.

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G-Quadruplexes are secondary, non-canonical RNA/DNA structures, formed by guanine-rich sequences assembled into four-stranded helical structures arranged as 3 to 5 layers of planes of Guanine tetrads stabilized by positive ions, such as K^+ or Na^+. These structures are key players in several biological processes [1, 2], such as the regulation of gene transcription and shortening of the telomeric region, between others.

Although a lot of work has been done regarding the mechanical unfolding of these structures, their thermal denaturation landscape has yet to be fully understood. In this work we study a series of GROMACS simulations of these structures at different temperatures to reveal the underlying free energy landscape. We took advantage of dimensionality reduction techniques such as PCA and tICA to project the trajectories into a lesser dimensionality space. The reduced data was encoded into a Markovian complex network which, in combination with a stochastic steepest descent algorithm able to identify the free energy minima, revealed the main conformations of these structures and the connections between them.

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How to persuade a wide Internet audience to donate money for a research project: A rhetorical and multimodal analysis of science crowdfunding videos

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Science funding from national institutions is in decline, and ever more scientists are turning to online crowdfunding to fund their research projects (Mehlenbacher, 2019). Given the potential of audiovisual communication in science popularisation, crowdfunding campaigns promoted through a short video are more likely to be successful (Doyle et al., 2017). The genre of scientific crowdfunding videos is an example of how the advent of digital technologies is facilitating the participation of society in the advancement of science (Luzón and Pérez-Llantada, 2019, 2022). Creating a persuasive video, however, challenges scientists to exploit the semiotic affordances available to achieve their communicative purpose. In this talk, I will provide some guidelines on how to create a persuasive video for a scientific crowdfunding campaign. These guidelines are based on an exploratory study of 50 videos linked to successful crowdfunding campaigns from Experiment.com. Drawing on classical rhetoric (Pullman, 2013) and multimodal genre analysis (Bateman, 2014), I have examined the visual and verbal rhetorical strategies that scientists use to convince a broad internet audience to drive donations for a scientific cause. The findings show the importance of building a prepared and passionate researcher identity and engaging the audience emotionally with the scientific project.

Drug discovery for inhibiting *Bacteroides fragilis* toxin isoform 3

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Bacteroides fragilis is identified as the leading anaerobe in bloodstream infections and intra-abdominal abscesses. Several studies have demonstrated that enterotoxigenic strains (ETBF) of *B. fragilis* may arise and elicit diarrhea, anaerobic bacteremia, inflammatory bowel disease, and colorectal cancer. ETBF's only recognized specific virulence factor is a zinc-dependent metallopeptidase called *B. fragilis* toxin (BFT), which damages the intestinal mucosa and triggers disease-related signaling mechanisms.

We have focused on one of the naturally occurring BFT isoforms, BFT-3, and managed to repurpose several approved drugs as BFT-3 inhibitors through a combination of biophysical, biochemical, structural, and cellular techniques. In contrast to canonical inhibitors, which target the active site of mature enzymes, these effectors bind to a distal allosteric site in the proBFT-3 zymogen structure, which stabilizes a partially unstructured, zinc-free enzyme conformation by shifting a zinc dependent disorder-to-order equilibrium. This yields proBTF-3 incompetent for autoactivation, thus ablating hydrolytic activity of the mature toxin.

Once inhibitors against BFT-3 have been identified *in vitro*, bacterial growth inhibition assays have been carried out with strains of *B. fragilis*, as well as studies in an infection animal model (*Galleria mellonella* larvae), confirming that these compounds have an inhibitory effect in *in vivo* models limiting ETBF pathogenicity.

Soludisc: an improved nanodisc for the study of membrane proteins

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Membrane proteins (MPs) are the target for 60% of the FDA drugs, however their study is hindered by the lack of technologies to extract them from the membrane while keeping them in their native local environment. Studies to determine local lipidic environment of a particular MP or the isolation of weak MP complexes is currently not feasible (e.g. determining the MP:MP interactome). Our aim is to obtain a protein nanodisc that can extract MP (and MP complexes) from lipidic bilayers mildly and maintaining their native lipid bilayer. For this purpose, we are optimizing solubilizing protocols and performing protein engineering on a protein which we termed "Soludisc". We have purified the Soludisc to confirm that it can solubilize DOPS lipid vesicles without detergent, but also whole insect cells. Negative stain electron microscopy shows the protein forms a disc-shaped structure and we have been able to extract a human dopamine receptor in such nanodiscs. Although in early days, if successful, the Soludisc will generate an enabling technology for the study of MPs including the isolation of weak MP complexes, the characterization of the MP:MP interactome and the improved isolation of MPs for their *in vitro* study and drug development campaigns.

Structure characterization of Calcium-Permeable AMPA Receptors

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AMPA receptors (AMPARs) are ligand-gated cation channels located in post-synaptic neurons which belong to the family of ionotropic glutamate receptors (iGluRs). They are responsible for fast excitatory neurotransmission in the brain and they are involved in synaptic plasticity. AMPARs are tetramers composed of different combinations of four subunits (GluA1-GluA4). Subunit composition impacts all aspects of AMPAR function, from pharmacology to receptor trafficking, kinetics and cation permeability. GluA2-containing AMPARs are calcium-impermeable, while GluA2-lacking receptors are calcium permeable and less abundant. Cryo-electron microscopy (cryo-EM) has provided crucial information about the action mechanism of GluA2-containing AMPARs, while structures of GluA2-lacking receptors are currently not available. Therefore, we are focusing on the structure characterization of GluA4 homomers. We have developed a method to obtain large amounts of homotetramers solubilized in detergents in a pure, homogeneous and stable state in order to prepare cryo-EM grids. We have collected cryo-EM data of GluA4 in different functional states and we have obtained a preliminary cryo-EM map of GluA4 in the resting state. We are also analysing the effect of lipids in receptor's architecture using nanodiscs. Here we present our results with GluA4 nanodiscs using two different strategies: protein nanodiscs (MSP) and co-polymer based nanodiscs (SMALPs and DIBMALPs).

Designing more stable proteins for biotechnological and biomedical use

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Protein stability is worth being taken into account when they are going to be used for *ex vivo* or in biomedicine applications. Studying the stability of proteins in any situation and condition is important to understand their function and the processes they are involved in. Stability against thermal denaturation (thermostability) has been widely studied for protein characterization and knowledge.

Another feature of proteins is their ability to be modified in some regions without affecting their function. Site directed mutagenesis has made it possible to carry out mutations in proteins in order to increase their stability (e.g. thermal stability) without changing their function. The Protposer server is based on this concept. Through calculations, it identifies stabilizing mutations for any protein that is sent as a PDB file to the server.

We plan to use Protposer to predict possible stabilizing mutations for 6 different proteins of biomedical or biotechnological interest, and we will introduce the found mutations through site directed mutagenesis. Then, we will combine the best ones to try to obtain mutant proteins with greater thermostability and, therefore, greater applicability.

Targeting MeCP2 protein as a therapeutical tool.

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As the field of epigenetics is rapidly growing, the efforts in elucidating its transcription regulation mechanisms are being focused not only on the molecules that create the epigenetic marks (such as DNA methylation) but also the readers that transform those signals into an actual regulation of gene expression and cellular differentiation or development.
Methyl-CpG Binding Protein 2 (MeCP2) is an intrinsically disordered protein (IDP) which acts as an epigenetic reader. Thanks to its structural and functional plasticity MeCP2 is able to bind DNA, discriminate among different epigenetic marks and recruit activators or repressors of gene expression.

MeCP2 has been traditionally linked to neurodevelopmental disorders such as Rett or MeCP2-duplication syndromes, produced by a dysfunction or upregulation of MeCP2 protein, respectively. Recent studies describe also an upregulation of MeCP2 in tumoral digestive pathologies, related to tumor progression, and treatment resistance.

Our goal is to target MeCP2 function using small compounds selected from a high throughput screening based thermal shift assay (TSA)that are able to activate or inhibit its function in order to provide an specific treatment or all the MeCP2-related pathologies, and then functionally test them at a cellular model level.

The FAD synthase from *Mycobacterium tuberculosis*: improving overexpression, purification and functional and structural characterization

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Mycobacterium tuberculosis is a pathogenic bacterium responsible for the largest number of tuberculosis cases. Its DNA contains the *ribF* gene that encodes for a bifunctional FAD synthase (MtFADS) involved in FMN and FAD biosynthesis and homeostasis, being a potential target for the discovery of antimicrobials. MtFADS is envisaged to fold in two structural domains; riboflavin kinase (RFK) where riboflavin (RF) is transformed into FMN, and FMN adenylyl transferase (FMNAT) where FAD is synthetized from FMN. The homogeneous purification of MtFADS was achieved before from cultures of *E. coli* containing the pHAT2-MtFADS plasmid. However, most sobre-expressed MtFADS resulted insoluble and lacked FMNAT enzymatic activity. Here, we have evaluated different solubilization conditions from *E. coli* crude extracts, using buffers containing detergents, such as Tween-20 or Triton X-100, dithiothreitol, or urea. Additionally, expression of soluble active protein in crude extracts has been assessed by SDS-PAGE and Western, while thin layer chromatography has been used to assess RFK and FMNAT activities. In parallel, bioinformatics tools are being used to identify potential differential characteristics of MtFADS in homologues from other sources, as well as for the identification of *M. tuberculosis* flavoproteins which might act as drug activators or de-activators.

Effects of CsgA Curli protein expression in mammalian cells

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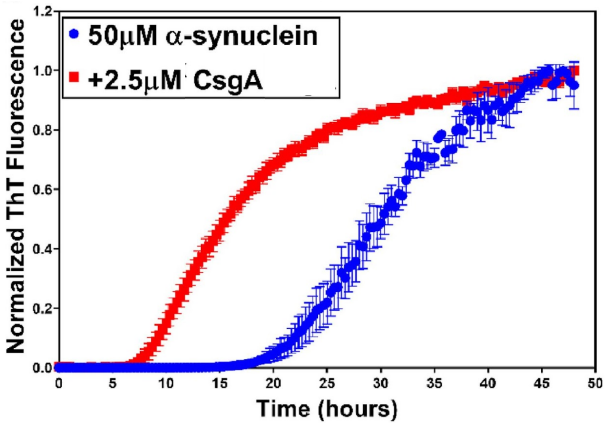
The protein CsgA is the major component of Curli fibrillar structures in bacteria biofilms. it is well known that Curli can form amyloid like structures and promote the aggregation of other amyloid protein as alpha synuclein and Aβ amyloid peptide. Recent studies have been showed that Curli CsgA protein can cross the blood barrier traveling across the gut-brain axis and promotes the aggregation of alpha synuclein in mouses as animal models. It is not well known how CsgA protein can drive the aggregation of alpha synuclein in these cells, but in presence of CsgA protein the aggregation rate of alpha synuclein is increased.



In this work we studied the effect of CsgA protein expression fussed to GFP in living cells. Using FRAP experiments we show that this protein undergoes aggregation and co-localization with the autophagy adaptor protein SQSTM1. We also study the effects of expression of this protein in the autophagy mechanism in cells using different autophagy markers such as LC3, Beclin and SQSTM1 proteins. Our result suggests that expression of CsgA curli protein promotes the accumulation of autophagosomes inside the cells which leads in autophagy miss regulation and promotes cell death.

Discovery of new drugs against pancreatic cancer using the MeCP2 protein as a therapeutic target

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During the generation and development of a tumor, there are different molecular marks that accumulate aberrantly in the genome, causing changes in the expression of genes and in the normal functioning of cells. It has been shown that certain proteins, such as the transcriptional regulator MeCP2, are responsible for reading these marks and pathogenetically blocking the expression of certain genes, thus promoting tumor development. Therefore, MeCP2 could be a promoter in the progression of pancreatic ductal adenocarcinoma (PDAC) due to its markedly different expression in tumor tissues and its ability to induce proliferation, migration and invasion of pancreatic cancer cells. The aim of this study is to evaluate MeCP2 as a potential therapeutic target against PDAC and to study the antitumor activity of compounds capable of interacting with MeCP2. For this purpose, cytotoxicity assays will be carried out in two tumor cell lines (PANC1 and Mia PaCa2) and the non-tumor cell line HPDE. Also, MeCP2 expression will be analyzed in these cell lines and in samples of healthy human and tumor tissue. In conclusion, inhibition of MeCP2, a major epigenetic mark reader, could lead to improved prognosis of pancreatic cancer patients by reversing aberrant transcription patterns.

Pirepred: Variant Calling Towards Personalized Medicine

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The current improvement of sequencing techniques has made whole exome sequencing a reality for the near future of health systems. However, novel variants still pose a challenge for the interpretation of their pathogenicity. In this work, we present PirePred, a tool for the interpretation of variants related to the heel prick test, with better *in silico* metapredictions than similar purpose platforms and additional information about the structural context of the variant. PirePred means not only an advance in newborn screening programs but also towards personalized medicine, as the method can be extended to the whole human genome. However, some issues need to be taken into account for this purpose, such as the automation of the annotations of the genome, the handling of different reference genome and protein sequences, and the possible bias existing in large clinical genomic databases. Nevertheless, the application of Protposer for genetic screening after an anomalous heel prick test is nowadays a reality.

Novel metabolic networks linked to Zur (FurB) regulation in *Anabaena* sp. PCC7120

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The nitrogen-fixing cyanobacteria *Anabaena* sp. PCC7120 contains three FUR paralogs: FurA (ferric uptake regulator), FurB/Zur (zinc uptake regulator) and PerR (peroxide stress regulator). Besides their established role in metal homeostasis, they engage in the modulation of photosynthesis, nitrogen metabolism and different stress responses. Previous works show that the regulon of FurB consists in genes involved in the adaptation to zinc deficiency and oxidative damage prevention [1,2].

In this study, differential expression analysis of RNA-seq sheds light into potential metabolic networks linked to FurB. Deletion of the *zur* gene caused significative changes in the transcription of 406 genes, of which 166 were annotated. In addition to those previously identified as FurB targets [1], we found genes involved in photosynthesis, regulatory functions, nitrogen metabolism, transposition, cell wall, transporters and carbon metabolism. The presence of putative FurB boxes and its ability to bind to the promoter region of potential target genes were analyzed. A considerable number of genes with altered transcription were involved in carbohydrate metabolism, including enzymes potentially involved in biofilm formation, a process which we found to be affected by FurB deregulation. Furthermore, we observed that the level of FurB expression slightly affects the frequency of heterocyst formation.

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Optimizing the BacMam system for AMPA receptors production.

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Membrane protein structural biology remains unkown ground with yet few structures being currently available. While production of soluble proteins is straightforward, overexpression of membrane proteins remains a harsh challenge. The complex requirements of membrane protein biogenesis, as well as protein folding, localization and post-translational modifications, usually require the use of eukaryotic systems for expression, turning out into low recombinant protein yields. These difficulties can result in high cost for protein expression, thus improving the efficiency of the process is important. To counter these challenges, the BacMam System has emerged as a powerful tool.

The BacMam system is a technique for recombinant production of eukaryotic proteins that uses insect viruses (baculoviruses) for gene delivery in mammalian cells. This system efficiently infects primary mammalian cell lines and provides higher protein expression levels than classical transient transfection methods, making it suitable for protein production in sufficient quantities to support structural studies. Here, we have generated a new pAceMam plasmid which allows tracking virus production. Moreover, we have established infection procedures for both attachment and in suspension cultures of mammalian cell lines, enabling the over-expression and purification of AMPA receptors for Cryo-EM studies.

Effect of Iron and carbon sources on *in-vitro* transcriptional responses to growth arrest of *Mycobacterium tuberculosis*

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The establishment of *Mycobacterium tuberculosis* (Mtb) long-term infection *in vivo* depends on several factors, one of which is the availability of key nutrients such as iron (Fe), and long chain fatty acids (LCFA). The relation between Fe deprivation inside and outside the granuloma, and the capacity of Mtb to accumulate lipids and persist in the absence of growth is only partly understood. In this context, current knowledge of how Mtb modifies its lipid composition and gene expression profile in response to growth arrest, depending on iron and lipids availability is scarce. To shed light on these matters, in this work we compare genome-wide transcriptomic profiles of Mtb at exponential and stationary growth phases using cultures with glycerol – dextrose, glycerol, and LCFA as the carbon sources, in the presence or absence of iron. We focused on comparing i) Fe effects on response to growth arrest with either glycerol – dextrose or glycerol as the main carbon sources for the bacteria; and ii) the effect of shifting from glycerol and dextrose as main carbon sources to LCFA in presence of Fe. As a result, we found that transcriptomic responses to growth arrest are enhanced when culture conditions incorporate nutrient cues characteristic of the phagosomal environment such as low levels of iron and high availability of LCFAs. Effects of low iron levels and LCFA on responses to growth arrest are significantly correlated and impact key pathways to bacterial survival upon phagocytosis such as energy production and stress responses, suggesting a convergent signaling dynamics of these cues towards the dormant phenotype.

Structural and biochemical characterization of the interaction between a novel type of Proteasome-Associated CHAperone and the archaeal 20S proteasome

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Chaperones (Hsp's) are key players in protein homeostasis. They prevent aggregation reactions and assist in holding nascent polypeptides or disabled protein prior to their destruction by the proteasome, the principal molecular machine for the regulated degradation of intracellular proteins. In eukaryotes, the connection between chaperones and the 20S proteasome core particle (CP) is ensured by a 19S regulatory particle (RP) that is responsible of substrate recognition and translocation to the 20S catalytic chamber using an ATP dependent mechanochemical process. Archaea represent a third kingdom of life with close evolutionary relationships with eukaryotes. Archaea lack Hsp90 and Hsp100 chaperones and Hsp70 homologues are absent from all the thermophilic and hyperthermophilic species suggesting that **archaeal chaperone machinery is likely to display some unique features.** It is known that archaea possess a eukaryotic-like proteasome composed of a simpler 20S proteolytic core (CP) and a AAA-ATPase unfoldase complex called PAN. Here, we structurally and biochemically characterize, in addition to reporting a **cryoelectron microscopy structure of a novel type of Proteasome-Associated CHAperone (PACHA) interacting with the archaeal 20S proteasome using an ATP independent mechanochemical process.**

How to efficiently analyze protein unfolding and stability events in MD trajectories?

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Molecular Dynamics (MD) is currently one of the most versatile and reliable modeling approaches to study biological systems. It has been shown to be a very useful and complementary tool to wet-lab experiments, to help elucidate kinetics, dynamics and/or thermodynamics associated to a variety of biological phenomena. The steady growth of High Performance Computing (HPC) resources and force fields' accuracy has allowed to extend the applicability of this method to higher time and length scales, with the possibility of using it even in a massive manner. In this respect, fast, reliable and relevant analyses of MD trajectories turn out needed and crucial to better exploit such potentialities. In this work, we show *ad-hoc*, semi-automated analysis methods of MD trajectories implemented for studying protein unfolding and stability events. At the same time, we show thermodynamic parameters —from used force fields— found to be sensitive and robust to identify relevant structural-dynamics phenomena associated to protein folding, which will be also of help to apply simpler —and maybe more reliable— analyses on MD trajectories of protein systems.

Two-level response to oxidative stress of FurC:Zn in *Anabaena* sp. PCC7120. Characterization of metal binding sites and oligomerization properties of the regulator.

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Metal and redox homeostasis in cyanobacteria is tightly controlled to preserve the photosynthetic machinery from mismetallation and minimize cell damage. FurC works as the PerR (peroxide response) paralog in *Anabaena* sp. PCC7120. Despite lacking the typical CXXC motifs present in FUR proteins, FurC contains a tightly bound zinc per subunit and binds zinc and manganese in a second metal-binding site. Oligomerization analyses of FurC:Zn evidence the existence of different oligomeric states ranging from dimers to octamers. Formation of tetramers and higher oligomeric forms occurs upon oxidation of thiols of FurC dimers by H_2O_2 or diamide and can be reversed by 1,4-dithiothreitol (DTT). Irreversible inactivation of FurC occurs by metal catalyzed oxidation promoted by ferrous iron. However, inactivation upon oxidation with H_2O_2 in the absence of iron was reverted by addition of DTT. Molecular modelling of FurC:Zn dimers and tetramers obtained using AlphaFold Colab and SWISSMODEL allowed to infer the residues forming both metal-binding sites and propose the involvement of Cys86 in reversible tetramer formation. These results reveal the existence of two levels of inactivation of FurC:Zn of *Anabaena* sp. PCC7120: the irreversible metal catalyzed oxidation and a reversible one through disulfide-formed FurC:Zn tetramers that may be specific for cyanobacteria.

Exploring possible new dysfunctions of alpha-synuclein in the nucleus

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Parkinson's disease is a neurodegenerative disorder whose symptoms include tremors, impairment of voluntary movements and rigid muscles, among others. The main hallmark of this disease is the formation and accumulation of amyloid aggregates composed of α-synuclein (αSyn) in the so-called Lewy bodies. αSyn is a protein that was initially discovered to be located in the nucleus, although much of the attention has been focused on the roles of the protein and their aggregation in the cytosol of the neuronal cells. However, the role of alpha-synuclein in the nucleus under physiological and pathological conditions has been recently again highlighted based on new experimental evidence, although it remains still unknown. Our group has recently discovered that αSyn protein interacts with other intrinsically disordered proteins (IDP) enriched in positively charged residues leading to the formation of biomolecular condensates, also referred to as protein droplets, through a liquid-to-liquid phase separation (LLPS) process. We are proposing that αSyn interacts with histone proteins leading to aberrant LLPS, which can lead to a depletion of functional histones and then chromosome instability in neurons and also toxic protein aggregation inside the phase-separated condensates.

Fur of the anaerobe *Clostridioides difficile* is a thiol-based oxidation sensing transcriptional regulator modulated by thioredoxin

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Clostridioides difficile is an anaerobic pathogen that produces gastrointestinal diseases. Iron is essential for this microorganism so it has developed mechanisms to cope with iron limitation. However, as high iron is lethal for *C. difficile*, iron uptake is tightly controlled by the ferric uptake regulator Fur. *C. difficile* mutants lacking the *fur* gene, apart of showing altered control of iron incorporation systems, are sensitive to oxidative stress, have host colonization defect and are less toxigenic, although Fur does not directly regulate pathogenesis or oxidative stress response genes.

By studying *C. difficile* Fur binding to the promoter regions of genes involved in iron metabolism, we describe a thiol-based redox switch mechanism, which controls Fur ability to bind to DNA in its iron-free form. We show that *C. difficile* Fur DNA binding is specific under reducing conditions and it is hindered by metal ions. We also show that some cysteine residue/s sense oxidant conditions leading to reversible oligomerization by disulphide bond formation and concomitant loss of Fur DNA-binding ability. Reduced thioredoxin reverts Fur oligomerization, which recovers its ability to bind to target promoters. Taken together, our results unveil an additional Fur-mediated mechanism of *C. difficile* adaptation to low iron environments.

Assembly of Riboflavin kinase to Pyridoxine 5'-phosphate oxidase as a preliminary step in the potential channeling of FMN

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The crucial role of riboflavin (RF) in cell metabolism is linked to its conversion into the flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) cofactors, which ensure the functionality of hundreds of different flavoenzymes in all living beings. In mammals and yeast, FMN and FAD are synthesized from RF by to independent enzymes, being the conversion of RF into FMN the major limiting step in FAD biosynthesis. Therefore, the human riboflavin kinase (*Hs*RFK), which catalyzes the biosynthesis of the FMN, must be a key element to produce the FAD cofactor and for the human flavoproteome homeostasis. Previous data exploring the regulatory mechanisms of *Hs*RFK activity showed the complex holding both products is kinetically the most stable, being FMN-release the rate-limiting step [1]. These data envisaged that interaction with its client apo-proteins might favor FMN release, in agreement with the necessity to synchronize cofactor biosynthesis with cofactor assembly to client apo-proteins. In this context, the possibility of direct assemblage of *Hs*RFK to client protein pyridoxine-5'-phosphate oxidase (PNPOx) has been here assessed. Preliminary biophysical studies, using both experimental (steady-state, fast-kinetics, calorimetry, …) and computational approaches (molecular dynamics and docking simulations) suggest protein-protein interaction, envisaging the potential channeling of FMN.

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Unveiling the role of the Ferric Uptake Regulator FurA from *Anabaena* sp. PCC 7120 in biofilm formation

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Cyanobacteria are photosynthetic prokaryotic microorganisms that are able to fix atmospheric nitrogen and CO_2, having therefore an enormous ecological and economic importance. Understanding biofilm formation in these organisms is of interest given the numerous biotechnological applications of cyanobacterial biofilms in the protection against environmental stresses or biorremediation.
FUR (ferric uptake regulator) proteins are metalloregulators present in most prokaryotes. The cyanobacterium *Anabaena* sp. PCC 7120 contains three FUR paralogues: FurA, FurB and FurC. FurA is a global regulator, essential for this cyanobacterium. FurA controls the expression of more than 100 genes not only involved in the control of iron homeostasis, but also in other processes such as photosynthesis, heterocyst differentiation and oxidative stress response. Our previous studies found that FurA was also involved in biofilm formation.
For this reason, in this work we have created a strain of *Anabaena* that overexpresses FurA. The analysis of biofilm formation and exopolysaccharide biosynthesis in this strain unveiled that FurA plays an important role in biofilm production in *Anabaena* sp. PCC 7120. These results shed new light on the understanding of biofilm formation in cyanobacteria, laying the foundations for future studies aimed at implementing biotechnological applications of biofilm formation in cyanobacteria.

Zinc implication on structural stability of metal-dependent LpxC

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Bacterial infections caused by multi-drug-resistant (MDR) gram-negative pathogens have become a serious threat to public health and novel antibiotics must be identified. The enzyme LpxC (UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase) is a zinc-dependent deacetylase, broadly conserved in all gram-negative bacteria and has no sequence homology with other deacetylases. LpxC catalyzes the second and committed step in the biosynthesis of lipid A, the membrane anchor of lipopolysaccharides (LPS), essential for bacterial viability.

Zinc is required for structural stability and protein functions, but needs to be tightly controlled through different mechanism; in fact, an excess of zinc may also be deleterious for protein stability.

In order to study the effects of zinc on LpxC stability (structural role), we employed biophysical techniques including Differential Scanning Fluorimetry (DSF) and Differential Scanning Calorimetry (DSC), recording thermal denaturation spectra in presence and absence of zinc.

The current study reveals a substantial decrease of the midpoint temperature of the unfolding transition (Tm) upon zinc removal by ethylenediaminetetraacetic acid (EDTA), but no relevant changes were observed at different concentrations of the cation.

Taking these structural data into account, the next step is to assess whether zinc has a crucial effect on the LpxC enzymatic activity.

Optimization of the expression and purification of the human flavoprotein ALR in its long and functional mitochondrial form

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A wide variety of diseases, including myopathies, diabetes mellitus, and neurodegenerative diseases, are associated with alterations of the oxidative phosphorylation system (OXPHOS) and mitochondrial metabolism [1].

An important group of these diseases is related to defects in the machinery for importing proteins into the intermembrane space (IMS). In humans, one pathway for importing soluble proteins with conserved cysteine sequence motifs (CXnC) depends on the chaperone CHCHD4 and ALR (augmenter of liver regeneration) [2].

ALR is a flavoprotein, and in its mitochondrial homodimer form binds CHCHD4 to reoxidize it and accepting two electrons which are then transfered to two CytC molecules or O_2.

The great significance of CHCHD4-ALR-pair in mitochondrial biogenesis is evidenced by pathogenic mutations in ALR that cause a rare genetic mitochondrial myopathy with systemic involvement [3]. Given its implication in mitochondrial diseases, the AIF/CHCHD4/ALR import /folding pathway emerges as therapeutic target.

For its study, it is necessary to obtain the functional oxidized ALR form, which can be complex due to the few previous studies as well as its quaternary organization and redox reactivity through its disulfide motifs. Therefore, our goal is to fine-tune the overexpression, production and purification of functional ALR.

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TLBscore in premenopausal women to predict ovarian cancer

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Thermal Liquid Biopsy (TLB) refers to the analysis of serum samples by differential scanning calorimetry, providing a a global picture of the serum proteins and their interactions. Our previous studies have contributed to the development of TLB. Our objective is to determine the ability of TLB to differentiate between controls (n=85) and ovarian cancer (n=17) in premenopausal state.

We applied a binomial generalized linear model with logistic regression to obtain a TLBscore (probability to be healthy or diseased subject). To improve the predictive capacity of the model, we used threshold according to Youden.

As results, we have obtained a model to predict ovarian cancer in premenopausal women with a sensitivity of 71% and a specificity of 76%, and an area under the ROC curve of 0.78, using a threshold of 0.18. We carried out a leave-one-out (LOO) study to validate the proposed TLBscore. There are not statistically significant differences between TLBscore prediction and its validation with LOO (Delong test: *p*-value=0.078; Pencina Net Reclassification Index = -12% (|Z|= 1.39).

Summarizing, TLB provides a minimally invasive, low-risk and low-cost clinical test that allows personalized follow-up of the patient for diagnostic evaluation of ovarian pathology and facilitates the decision-making process to the oncologist.

The Apoptosis Inducing Factor in cell death: past its key role in the assembly of the degradosome

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The Apoptosis Inducing Factor (AIF) is a moonlighting flavoprotein that contributes to the assembly of the mitochondrial respiratory complexes in healthy cells, but which is also able to trigger DNA cleavage and parthanatos. In response to apoptotic stimuli, AIF redistributes from the mitochondria to the cytosol, where upon association with endonuclease cyclophilin A (CypA) the optimal nuclear translocation of both proteins is favoured. In the nucleus, the AIF:CypA complex is proposed to recruit histone H2AX, leading to the formation of a ternary complex known as the “degradosome”. This complex has the capacity to bind DNA, inducing chromatin condensation and DNA degradation in a caspase–independent manner. Here, we provide evidence for the molecular assembly of such complex, as well as for the cooperative effects among its protein components to degrade genomic DNA into large fragments. Furthermore, we present binding studies showing that all DNA-degradosome components are able to produce binary and ternary interactions, envisaging binding cooperativity. Altogether these data evidence for the first time at the molecular level the simultaneous interplay of $AIF_{\Delta 101}$ with all components of the DNA-degradosome complex, as well as pointing to some features that potentially contribute to its assembly in the cell.

AIF's dimerization: deciphering its significance in AIF:CHCHD4 interaction and mitochondrial homeostasis

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The human apoptosis-inducing factor (AIF) is a flavoenzyme that exerts an important role in mitochondrial redox metabolism through its interaction with the chaperone CHCHD4 (coiled-coil-helix-coiled-coil-helix-domain containing 4)[1] in the mitochondrial intermembrane space (IMS). While CHCHD4 controls the importation and oxidative folding of subunits from respiratory complexes, AIF would act by regulating its proper localization [1,2]. AIF-CHCHD4 interaction has been described as NADH-dependent, being favored by reduced and presumably dimeric AIF [1]. In IMS, AIF exists in a monomer-dimer equilibrium shifted towards dimer by NADH oxidation, stabilization of a long-life $FADH^-/NAD^-$ charge transfer complex (CTC) and conformational reorganization [3].

We investigate the AIF's dimerization role in its physiological interaction with CHCHD4 and its contribution in mitochondrial AIF's NADH oxidase activity. For that, we performed the biophysical characterization of two mutants: the H454A variant, which affects the AIF's active site, leading to a dimer conformation in absence of NADH [4]; and the E413A/R422A/R430A variant - unable to stabilize the dimer in the presence of NADH [3]. To analyze the contribution of mutations in AIF:CHCHD4 interaction, we evaluated their effects in AIF redox activity, structural stability/conformation, CTC stabilization, and CHCHD4 interaction. These studies are key to understand the molecular basis of AIF redox activity in healthy cells.

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Variational Approximation for the Kinetics of Boolean Models. Application to simple gene regulatory networks.

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In this project we consider the application of a statistical physics method (the Cluster Variation Method) to the study of the kinetics of a class of boolean models for gene regulatory networks, namely activity flow gene networks that also behave as Markov processes. After studying the general approach, we apply it to the regulatory network of the cell cycle, aiming at reproducing computationally the evolution of its phases. We take a model from the GINsim repository, composed of the cyclin-dependent kinase complexes and other regulatory proteins such as p27, Cdc20, UbcH10, Cdh1, APC, E2F and Rb protein. We finally compare our results to simulations based on the well-established Gillespie algorithm (Kinetic Monte-Carlo).

Incorporating a New Summary Statistic into the Min–Max Approach: A Min-Max-Median, Min-Max-IQR Combination of Biomarkers for Maximising the Youden Index

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Linearly combining multiple biomarkers is a common practice that can provide better diagnostic performance. When the number of biomarkers is sufficiently high, a computational burden problem arises. Liu et al. proposed a distribution-free approach (min–max approach) that linearly combines the minimum and maximum values of the biomarkers, involving only a single coefficient search. However, the combination of minimum and maximum biomarkers alone may not be sufficient in terms of discrimination. In this sudy, we propose a new approach that extends that of Liu et al. by incorporating a new summary statistic, specifically, the median or interquartile range (min–max–median and min–max–IQR approaches) in order to find the optimal combination that maximises the Youden index. Although this approach is more computationally intensive than the one proposed by Liu et al, it includes more information and the number of parameters to be estimated remains reasonable. We compare the performance of the proposed approaches (min–max–median and min–max–IQR) with the min–max approach and logistic regression. For this purpose, a wide range of different simulated data scenarios were explored. We also apply the approaches to two real datasets (Duchenne Muscular Dystrophy and Small for Gestational Age).

Understanding the specificity of bitopic drugs to the Dopamine 3 Receptor

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Aminergic receptors (ARs) comprise dopamine, serotonin, histamine, acetylcholine, adrenaline and trace amine receptors. ARs are G-Protein Coupled Receptors and are the target for 25% of current drugs (e.g. antipsychotics, Parkinson's treatment, anti-histamines...). However, most of these drugs present side effects mainly due to their promiscuous binding to other ARs as they share high sequence similarity in the ligand binding site. Bitopic compounds are novel drugs that combine two pharmacophores: one binds to the conserved orthosteric site and other binds to a secondary pocket which is less conserved, conferring greater specificity. Here, we describe the structural basis for binding specificity of a bitopic compound 50 times more selective for D_3R than D_2R (one of the most difficult cases is to distinguish pharmacologically receptors with near identity in the binding pocket). We determined the structure of the D_3R:Gαβγ complex bound to the bitopic ligand by cryo-electron microscopy (3.16 Å) and used cellular functional assays and molecular dynamic simulations to discover the formation of a new secondary binding pocket within the receptor that has the potential to host specific ligands for other ARs. These results will aid in the development of improved drugs for a variety of disease where ARs are involved.

Minimum lockdown to avoid sanitary collapse under limited resources

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The epidemiological literature has extensively addressed the characterization of the epidemic threshold, where the transition between the non-epidemic and active phases intervenes. In addition, in recent months, numerous investigations have addressed the issue of detection strategies, triggered by the global pandemic that has occurred. However, little has been said about screening strategies with limited resources, which could lead to the collapse of the health system. Here, we show analytically how limited containment strategies can bring about additional transition within the active phase of the epidemic. In addition, we show numerically how this transition may be of the first order, so that in the event of a collapse, the control measures taken could have been in vain. To end up we determine the minimum fraction of population under lockdown necessary to avoid sanitary collapse given the available resources and the epidemic basic reproduction number.

Design of a Rapid Test for Phenylalanine Detection in *PKU* Patients

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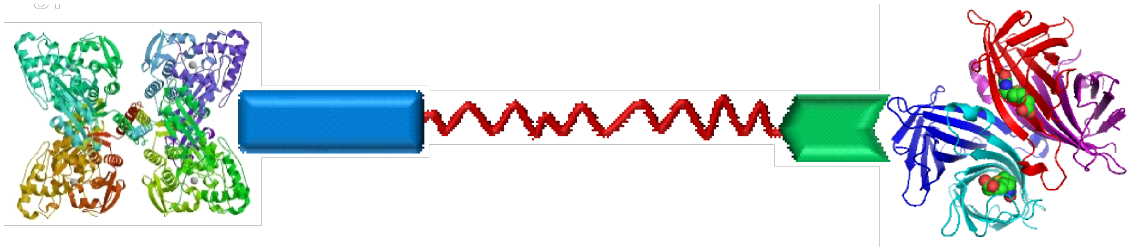
The *phenylketonuria* (PKU) is a rare metabolic disease caused by mutations in the encoding gene for the human enzyme phenylalanine hydroxylase (PAH) that bring about decreased enzymatic activity in liver [1,2]. PAH catalyzes the L-phenylalanine (Phe) hydroxylation to L-tyrosine, whereby an enzymatic malfunction increases Phe blood levels, which is toxic to the brain and it is called hyperphenylalaninemia. The normal range of Phe blood concentration is 50-110 µM. Over this levels, the condition can be classified as moderate hyperphenylalaninemia (120-600 µM), moderate PKU (600-1200 µM) and classical PKU (>1200 µM). Early diagnosis of the disease and a low protein diet therapy are essential to avoid the serious physiological problems due to the increased Phe blood levels. In this work, we present the design of a rapid test for the control of Phe levels in PKU patients at home derived from the competition between Phe and pharmacological chaperones by binding to the enzyme active site. With this aim, we carried out the synthesis of a bifunctional molecule based on a chaperone and a tag binding by a flexible linker. These bifunctional molecules can interact at the same time with PAH and a tag-binding protein facilitating the monitoring of Phe blood concentrations.



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Bacterial NrdI protein: bioinformatics analysis and optimization of expression and purification of the protein from *Brucella ovis*.

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Brucella ovis is a gram-negative bacterium that causes a reproductive disease that affects all breeds of sheep. Ribonucleotide reductases (RNRs) are essential proteins involved in the biosynthesis of nucleic acids and might be potential targets in the development of antimicrobials. Among *B. ovis* RNRs, the flavoprotein NrdI component has been identified as a potential virulence factor. The FMN cofactor of NrdI has been reported to be involved in both one and two electron transfer processes, acting particularly as two-electron reductant in the regeneration of the dimanganese(III) cofactor in the β subunit (NrdF) of class Ib RNRs. Moreover, *B. ovis* has a bacterial type ferredoxin-$NADP^+$ reductase (BoFPR) for which electron acceptor has not been identified yet, being NrdI a potential candidate. The present study examines the sequence and structural homology of NrdIs from different species, some of which already characterized biochemically and structurally. We also report on the initial steps of setting up a protocol for BoNrdI overexpression in several strains of *E. coli*, cultured under different conditions, and its purification.