

Biophys 11

Biology and beyond

September 7 - 9, 2011 Arcidosso (GR), Italy

Scientific Program

Wednesday, September 7

15:00 Michele Caselle: "*Modeling the human regulatory network*"

16:00 Daniel Remondini: "*Exploring brain dynamics complexity by fNMRi*"

17:00 Coffee Break

17:30 Michele Caraglio: "*Confinement effects upon Thermodynamics and Kinetics of protein folding studied through a simple Ising-like model*"

18:00 Stefano Luccioli: "*Discrete breathers in a realistic coarse-grained model of proteins*"

Thursday, September 8

9:00 Franco Bagnoli: "*Chaos, Synchronization and Control in Cellular Automata*"

10:00 Gianluca Martelloni: "*A dynamical population modeling of invasive species with reference to the crayfish *Procambarus Clarkii**"

10:30 Coffee break

11:00 Benedetta Cerruti: "*Geometry, topology, and out-of-equilibrium dynamics in epithelial morphogenesis*"

11:30 Angelo di Garbo: "*Environmental enrichment impacts cortico-cortical coupling*"

12:00 Federica Piccirilli "*High pressure tuning of proteins structure, synchrotron infrared microscopy investigation of misfolded states*"

PAUSA PRANZO

15:00 Sebino Stramaglia: "*Redundancy and Granger causality*"

16:00 Coffee break

16:30 Antonino Natalello: "*Aggregation pathways of Ataxin-3: a polyglutamine disease protein*"

17:00 Velia Minicozzi: "*Proving metal involvement in beta-amyloid aggregation by ab-initio simulations and XAS measurements*"

17:30 Daniele Borin: "*High sensitivity MEMS for biomolecular detection*"

Friday, September 9

9:00 Armando Bazzani: "*Statistical laws for human mobility*"

10:00 Riccardo Gallotti: "*Human mobility predictability*"

10:30 Carlo Guardiani "*Computational exploration of the conformational landscape of a peptide with a potential for the diagnosis and treatment of Multiple Sclerosis*"

Exploring brain dynamics complexity by fNMRI

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We study fNMRI signals of spontaneous neural activity in human brain, with a time resolution of 1 sec and a spatial resolution corresponding to about 5000 voxels. Our aim is the characterization of the topological

architecture of the resting brain by the methods of complex networks, at different temporal and spatial scales. We characterize the time correlation structures at different time windows, showing a non trivial multi-scaling, and the resulting network obtained for different correlation thresholding values. Our results show a highly organized modular architecture and associated topological properties of the human brain even in the absence of specific stimuli or behaviors.

Confinement effects upon Thermodynamics and Kinetics of protein folding studied through a simple Ising-like model.

Michele Caraglio

In the past the majority of experiments on protein folding have been carried out in diluted solutions but in the last two decades it has become clear that these experiments do not take into account two issues which arise in vivo and whose relevance on thermal stability and equilibrium rates is not negligible. Namely, crowding and confinement [1, 2, 3, 4]. Crowding refers to the fact that about 30% of cells internal volume is occupied by macromolecules such as lipids, carbohydrates and proteins themselves [1]. This fraction could even reach 40% in *E. Coli* [5]. Confinement is merely a limitation in the volume available to the polypeptide chain as naturally occurs in the exit tunnel of ribosomes or in the chaperonin cavity. Experimentally, a procedure to mimic the effects of confinement is the encapsulation of proteins within pores of silica gels [6, 7] or glasses [8] or polyacrylamide gels [9]. These experiments reported, for most of the considered proteins, an increase in thermal stability when they are confined into nanopores. Melting temperature (T_f) shift is even dramatic in the cases of α -lactalbumin and RNase A, being as large as about 30 K [6, 8]. We have investigated the effects of confinement on protein thermal stability and folding kinetics using a generalized version of Wako-Saito-Mugnoz-Eaton model for protein folding [10, 11, 12, 13, 14, 15, 16]. which has been properly modified to include confinement of the polypeptide chain into a slit. To study thermal stability we have made use of the property of the model to be exactly solvable at equilibrium, while to study folding rates behavior we have resorted Monte Carlo simulations. Notwithstanding the simplicity of the model and its unidimensionality, we obtained results which follow the general trend of previous experimental studies [7, 8, 9] and simulations [17, 18, 19]: provided the native state is compact, decreasing the size of confining cage will increase both unfolding temperature T_f and folding rate k_f until a certain size which depends on the protein. If the confining cage size is further decreased unfolding temperatures and folding rates decrease. According to theoretical considerations [20, 18], enhancement of folding temperatures and rates depends on the confinement size R by the scaling law $\Delta T_f \sim \Delta \ln k_f \sim R^{-\gamma}$. We found that among the various theoretical values of γ exponent reported in the literature, our results are best fitted by $\gamma = 5/3$ which is the value expected for an excluded volume chain confined into a slit or a cylinder.

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Discrete breathers in a realistic coarse-grained model of proteins

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We report the results of molecular dynamics simulations of an off-lattice protein model featuring a physical force-field and amino-acid sequence. We show that localized modes of nonlinear origin, discrete breathers (DB), emerge naturally as continuations of a subset of high-frequency normal modes residing at specific sites dictated by the native fold. In the case of the small beta-barrel structure that we consider, DB-mediated localization occurs on the turns connecting the strands. At high energies, discrete breathers stabilise the structure by concentrating energy on few sites, while their collapse marks the onset of large-amplitude fluctuations of the protein. Furthermore, we show how breathers develop as energy-accumulating centres following perturbations even at distant locations, thus mediating efficient and irreversible energy transfers. Remarkably, due to the presence of angular potentials, the breather induces a local static distortion of the native fold. Altogether, the combination of this two nonlinear effects may provide a ready means for remotely controlling local conformational changes in proteins.

Ref. S. Luccioli, A. Imperato, S. Lepri, F. Piazza and A. Torcini, *Phys. Biol.* 8 (2011) 046008

Chaos, Synchronization and Control in Cellular Automata

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Control theory is a set of techniques for making a dynamical system behave in a desired way by exerting an external effort. In the case of a minimum effort one speaks of optimal control. It is obviously hard to reach the optimum limit, but many investigations are devoted to minimize the control for a desired behavior. In general, the problem of control of a dynamical system may be split into two parts: the driving a system to a target area in phase space, and the stabilization of a trajectory originating from this area.

Chaotic systems are ideal targets for control: their sensitivity to

small changes may be exploited to drive them to the target area [1], after which chaos may be suppressed in order to make them follow, for instance, a desired periodic orbit [2]. The problem of driving a chaotic system may be seen as the problem of synchronizing a replica with a “drive” system that happen to pass through the desired area. This type of synchronization, can be called master-slave, identical or replica synchronization [3]. While in the usual studies about synchronization one exerts little attention to the optimization of coupling, when formulated as a control problem this becomes a crucial issue.

CA are widely used to model many systems in various fields, from computer science to earth sciences, biology, physics, sociology, etc. They are usually defined on a graph or a regular lattice, but may easily be extended

to include mobile agents. The modeling of a system using cellular automata is conceptually much simpler than those using partial derivatives, and the evolution of such a system is easily performed by a digital computer, with- out rounding errors. However, for such systems continuity and smoothness (differentiability) do not apply. It is therefore hard to extend the usual techniques used in control theory [5] and to define quantities like Lyapunov exponents and chaotic trajectories. It is however still possible to define the derivatives of discrete systems [6], which prove useful in synchronization

investigations [7]. In the case of replica synchronization, the “minimal strength” needed

to synchronize a system is related to its chaoticity, defined by the largest Lyapunov exponent in low-dimensional systems. For extended systems, the correspondence between the minimal strength and Lyapunov exponents may

break down [4]. In synchronization experiments, the “force” is generally applied blindly,

without any relation with the dynamics. The corresponding synchronization effect is analogous to a directed percolation phase transition. The two systems synchronize when their difference goes to zero. Their difference grows due to their “chaotic”

dynamics, along the directions identified by the Jacobian matrix of the evolution rule. The synchronization “pressure” reduces the paths along which a difference can propagate. When this reduction overcomes the chaotic growth, the system synchronizes. In

control problems, one wants to exploit the knowledge about a system. It is therefore analogous to a synchronization problem of two different systems with a “targeted” force, that tries to “kill” the growing directions of the difference as soon as possible. We

show how the concept of Boolean derivative and that of Boolean Jacobian matrix can be used to achieve this goal. The result is however rather surprising: the control efforts should concentrate on the regions exhibiting less distance among replicas, while

chaos can be exploited to “self-synchronize” the systems.

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A dynamical population modeling of invasive species with reference to the crayfish *Procambarus Clarkii*

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In this work we present a discrete dynamical population modeling of invasive species, with reference to the swamp crayfish *Procambarus Clarkii*. As this species can cause environmental damage of various kinds, it is necessary to evaluate the impact of this crayfish in areas not infested: a structured model is built, taking into account all biological information available to us, including the environmental variability through stochastic parameters (coefficients of fertility, death, etc.). This model is based on a structure with 7 age classes (Anastacio et al., 1999), i.e. a Leslie mathematical population modeling type. The last one is calibrated with laboratory data provided by Department of Animal Biology and Genetic of Florence (see reference). The model presents many interesting aspects: with the calibration the population has a high initial growth, then it stabilizes like the logistic growth, but with a oscillation (a double limit cycle in the phase plane). The analysis of sensitivity shows a good resilience of the model and for low values of reproductive female fraction the fluctuations may lead to the extinction of the species or not: this can be a controlling factor for growth of the species. Moreover the probability of extinction is valuated with Inverse Gaussian (*Cox and Miller, 1965); in 20 years this probability is 0.115% and the last one is confirmed by experimental data and field observation: this species is diffused in Italy from 1989 and it has shown a natural tendency to the growth. Finally the spatial mobility is introduced in the model, simulating the movement of the crayfishes in a virtual lake of elliptical form by means of simple rules encouraging the movement towards the banks of the catchment (as it happens in reality) and a random walk is imposed in the banks. According to the diffusive modeling the peak of density in the banks is 15 individual/m², result in agreement with the literature.

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Geometry, topology, and out-of-equilibrium dynamics in epithelial morphogenesis

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Epithelial tissue morphodynamics is a crucial aspect in metazoan development that lends itself to be studied by means of in vitro representative models. Cysts serve as a paradigm for the formation of hollow spherical structures in vivo. The orderly development of cell aggregates into spheroidal monolayers delimiting a single lumen is a process subject to mechanical constraints and depends on the establishment and maintenance of cellular apico-basal polarity. In order to characterize in detail the geometry and topology of growing cysts, we reconstructed their three-dimensional structure by means of computer-assisted segmentation. We show that cell-cell contact statistics bears a clear signature of the out-of-equilibrium character of cyst morphogenesis. Out-of-equilibrium dynamics drives the appearance of aberrant multiluminal phenotypes, unless strict control of cell division geometry is enforced. Theoretical modeling and numerical simulations allow for a quantitative comparison with experimental results and unveil the presence of multiple local equilibria associated with geometrically frustrated configurations. The single-lumen phenotype is rescued and the quasi-equilibrium topology is attained upon inducing tissue fluidization through the inhibition of ROCK activity.

Environmental enrichment impacts cortico-cortical coupling

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Environmental enrichment (EE) is an experimental protocol based on a complex sensorimotor stimulation that dramatically affects brain development. While it is widely believed that the effects of EE result from the unique combination of different sensory and motor stimuli, it is not known whether and how cortico-cortical interactions are shaped by EE. Since the primary visual cortex (V1) is one of the best characterized targets of EE, we looked for direct cortico-cortical projections impinging on V1, and we identified a direct monosynaptic connection between motor

cortex and V1 in the mouse brain. To measure the interactions between these areas under standard and EE rearing conditions, we used simultaneous recordings of local field potentials (LFPs) in awake, freely moving animals. LFP signals were analyzed by using different methods of linear and nonlinear analysis of time series (cross-correlation, mutual information, phase synchronization). We found that EE decreases the level of coupling between the electrical activities of the two cortical regions with respect to the control group. From a functional point of view, our results indicate, for the first time, that an enhanced sensorimotor experience impacts on the brain by affecting the functional crosstalk between different cortical areas.

High pressure tuning of proteins structure, synchrotron infrared microscopy investigation of misfolded states

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Protein aggregation is an important phenomenon that alternatively is part of the normal functioning of nature or has negative consequences via its hypothesized central role in neurodegenerative diseases. The role of misfolded species, the amyloid fibrils, in the development of many diseases, like Parkinson or Alzheimer disease, is not yet clearly understood and fibrils structure has remained elusive because of the difficulty of growing well diffracting crystals. The mid infrared absorption spectrum of a protein is very sensitive to its secondary structure and can be easily used for studying the aggregation properties of beta amyloid peptides and the effects of environmental variables (solvent, pH, ions, pressure and temperature) on aggregation[1]. Recent decades have witnessed a growing interest on the use of high pressure (HP) as a variable acting on proteins structure. Since HP affects only the volume contribution to the Gibbs free energy, it is able to perturb the structure of proteins in a reversible way. The principle governing pressure effects is that it tends to shift a system towards the state that occupies the smallest volume, it causes the electrostriction of charged and polar groups, the elimination of packing defects, and the solvation of hydrophobic groups[2]. Cavities and packing defects are expected to be major contributors to volume changes and their presence will make the system more susceptible to pressure unfolding/dissociation. We focused our attention on the study of bovine Insulin, a small protein widely used as model for the description of ordered aggregates because of its tendency to form fibrils if subjected to unfolding conditions. We observed that increasing pressure it is possible not only to perturb the state of insulin amyloids leading to the

partial rupture of fibrils but also to create favorable conditions for the crystallization of the protein in a state that seems to be intermediate between the native and the fibrillar one. We obtained small crystals with a diameter of about 10µm at a pressure of about 5kbar with a secondary structure composition very similar to the protein in its fibrillar state. It has been possible to characterize the crystals we obtained through the use of synchrotron Infrared Microspectroscopy, working with a spot size of 10X10µm. It could be useful to take advantage of the very unusual phenomenon we observed optimizing the high pressure growth of these species for X-ray single crystal measurements.

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Aggregation pathways of Ataxin-3: a polyglutamine disease protein

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Ataxin-3 (AT3) is a poly-glutamine protein involved in the amyloid disease spinocerebellar ataxia type 3, when the polyglutamine stretch is expanded beyond a critical threshold of about 50 glutamines. A characterization of the structural changes occurring during aggregation of AT3 and of its variants has been performed by complementary biochemical and biophysical approaches, including Fourier transform infrared (FTIR) spectroscopy and atomic force microscopy (AFM).

Under physiological conditions (incubation at 37°C), we observed an irreversible aggregation only for the pathological expanded form (containing 55 glutamines) characterized by a network of hydrogen bonds involving the glutamine side-chains, as demonstrated by H/D exchange FTIR experiments. These interactions are responsible of the SDS-insolubility of the amyloid fibrils of the expanded polyQ protein. AT3 thermal aggregation was also investigated. We found that the non pathological AT3 variant undergoes an aggregation pathway similar to that observed at 37°C, with SDS-soluble aggregates as end products. Instead, the expanded pathological form leads to amorphous thermal aggregates, which are different from the SDS-insoluble fibrils obtained after incubation at 37°C.

Proving metal involvement in beta-amyloid aggregation by ab-initio simulations and XAS measurements

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Many experimental and numerical studies have been (and still are) devoted to elucidate the role played by metal ions in particular Zn(II) and Cu(II) in the formation of beta-amyloid fibrils in the brain of Alzheimer's patients. In this work we concentrate on Zn(II) and we show that Zn(II) is capable of promoting inter-peptide aggregation. This conclusion is reached by demonstrating, by means of ab-initio molecular dynamics, the stability of the inter-peptide binding suggested by the available XAS experiments [1] in which four imidazole rings are stably bound to a Zn ion.

High sensitivity MEMS for biomolecular detection

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Proteomic analysis is playing a growing role in diagnostic, because protein expression and protein-protein interactions give important information about physiological processes and hence about patient's health [Hanash, S.M. et al., Nat.Rev.Clin.Oncol., 2011]. For this reason, monitoring the expression level of protein, especially those that have been recognized as diagnostically relevant, and their temporal evolution with a fast detection, represents a milestone in the diagnostics of the near future.

Nanotechnology offers the possibility for the development of highly sensitive, highly throughput and, possibly, low cost tools for analysis of protein and other kind of biomolecules. In our team, we focused on nanoelectromechanical systems (NEMS) to develop a diagnostic technique based on a micromechanical transduction of biomolecular adsorption, with the same principle of the quartz microbalance or resonating cantilevers [Fritz, J. et al., Science, 2000]. In contrast to the existing methods of oscillating cantilevers, our geometry is that of vertical pillars with the sensing

surface located at the top end and size that is at least two orders of magnitude smaller [Melli, M. et al., *Microel. Eng.*, 2010]. Locating the sensitive area of the oscillator at the top allows for a more

precise frequency-change vs. mass calibration, because it avoids the modification of the elastic constant of the resonator due to molecular adsorption on the lateral walls, as instead happens in common cantilever technology. Furthermore, for diluted samples the adsorption (diffusion limited) on a small area implies diffusion from a spherical volume all around the sensing area. In

contrast to this, the adsorption on a macroscopic surface (infinite on the diffusion length scale of the molecules in solution) occurs from a much larger linear volume directly above the adsorbing surface and, as a consequence, is slower by up to almost three orders of magnitude.

With this device we've already measured the kinetics of absorption of DNA oligos, to form a self-

assembled-monolayer (SAM) on the top of the pillar, and of hybridization with cDNA, demonstrating the higher speed and efficiency compared to most common technologies (i.e., cantilever resonator, SPR, ...) [Melli, M. et al., submitted to *ACS nano*, 2011]. We're currently measuring the ultimate performance of our sensor in protein recognition: preliminary results show that a pillar sensor would be able to detect protein at the picomolar concentration after less than 1 minute of incubation. This performance is comparable or better than the present state-of-the-art [Arlett, J.L. et al., *Nat. Nanotech.*, 2011]. For example, the standard ELISA test requires

longer analysis time, almost 1 hr, for the same concentration (1 pM).

Human mobility predictability

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Thanks to the wide spreading of the new information-communication technologies, there are now many massive data-sources regarding human mobility. In particular, these data permit us to track the movements of different individuals over long distance and for long periods. Alongside all these informations, comes then the possibility of an individual mobility modeling, which aims to predict the future whereabouts of the tracked people. The potential maximum predictability of such models is related to the entropy of each individual's trajectory. Besides, a minimum predictability can be estimated evaluating the goodness of some simple models based on the regularities of the trajectories. In our work, we have analyzed three different forecast approaches, focusing on the dependence of the predictability limits over the length of the shortest time interval considered. Confirming precedent studies, our results show a remarkable high value for the predictability. The human behavior appears enchainned to habits and time schedules constraints. Naturally, there is also a random mobility, which emerges if we focus on short activities. From the study of the individual mobility predictability comes out that it is possible to foresee a good part of the movements of the people. In future, the development of individual mobility forecast models might lead to novel applications to the analysis of epidemic spreading, urban planning or traffic forecast.

Collective chaos and chimera states in pulse-coupled neural networks

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Understanding the collective motion of networks of oscillators is crucial in many contexts, starting from neuronal circuits [1]. So far, most of the efforts have been devoted to the characterization of strong forms of synchronization. However, more subtle phenomena, like the onset of coherent oscillations in an ensemble of neurons can also play a relevant role for information coding. A peculiar coherent state, termed *Chimera*, appears in two symmetrically coupled populations of oscillators, where a population fully synchronizes while the other exhibit an asynchronous dynamics [2]. This can represent an idealized mathematical representation of the so-called unihemispheric sleep. Many creatures sleep with only half their brain at a time [3]. Such phenomenon was first reported in dolphins and other sea mammals and, recently, in birds; when brain waves are recorded, the awake side of the brain shows desynchronized electrical activity, corresponding to millions of neurons oscillating out of phase, whereas the sleeping side is highly synchronized.

In our study we have investigated the dynamics of two symmetrically coupled populations of identical leaky integrate-and-fire neurons characterized by excitatory coupling [4]. Upon varying the coupling strengths between and within the two populations, we found symmetry-breaking transitions that lead to the onset of various chimera states. To be more specific, in the observed chimera states one population is fully synchronized, while the other one is in the so-called Partially Synchronous (PS) regime. This regime is characterized by a coherent periodic activity at a collective level (somehow corresponding to the Local Field Potential), while the single neurons behaves quasi-periodically [5]. To our knowledge this represents the first evidence of chimera states in pulse-coupled neural networks.

Furthermore a new regime, where the two populations are both PS but with a different degree of synchronization have been also observed. Even more interesting is the identification of a regions of parameters where the coherent activity of the network, characterized by collective variables, becomes chaotic. Collective chaos, meant as irregular dynamics of coarse-grained observables, has been found in ensembles of fully coupled one-dimensional maps as well as in two-dimensional continuous-time oscillators. In both classes of models, the single dynamical unit can behave chaotically under the action of a periodic forcing. Only a few examples of low-dimensional chaotic collective motion have been found in ensembles of phase oscillators because in this setup there is little space for a high-dimensional dynamics [6].

The computation of the the finite-amplitude Lyapunov exponent allows us to firmly establish the chaoticity of the (collective) dynamics in a finite region of the phase plane. The further numerical study of the standard Lyapunov spectrum reveals the presence of several positive exponents, indicating that the microscopic dynamics is high-dimensional.

References

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Computational exploration of the conformational landscape of a peptide with a potential for the diagnosis and treatment of Multiple Sclerosis.

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Multiple Sclerosis (MS) is a high-disabling auto-immune disease for whose treatment early diagnosis is essential. The synthetic glyco-peptide CSF114(Glc) proved to be able to specifically recognize pathogenic auto-antibodies in the sera of MS patients.

In this work we performed Hamiltonian Replica Exchange Molecular Dynamics simulations on a CSF114(Glc)-derived heptapeptide in water and in a water/hexafluoroacetone mixture. The fraction of bioactive hairpin-like conformations was comparable in both solvents suggesting a potential use of this peptides not just for diagnosis but also for the treatment of the disease. Moreover, the excellent agreement between the distributions of many structural parameters of the glucosylated and un-glucosylated forms suggests that the conformation of the peptide is only marginally affected by the presence of the sugar. This provides further support to the notion of a direct interaction between the minimal Asn-Glc epitope and the MS antibodies.