Robustness and plasticity of theoretical and biological networks

mardi 10 juin 2014 - jeudi 12 juin 2014

BioPark Archamps

Recueil des résumés

Overview

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Robustness and plasticity of theoretical and biological networks, 10 to the 12th of June 2014 at the BioPark, technopole drsquo;Archamps (Haute Savoie, France).

 The shape and the function of proteins are based on the interactions between atoms of the amino acids, the basic unit making proteins. Most of the amino acids of a protein resist mutation as their modification do not lead to functional and/or conformational changes. Nevertheless, few of them are vulnerable to modifications which yield severe changes associated to diseases, functional changes, or evolution (Dan Tawfik). In the recent years, proteins have been described as amino acid interaction networks with amino acids and interactions as nodes and links, respectively (Claire Lesieur). It is therefore possible to investigate how proteins combine robustness and plasticity towards local changes using theoretical approaches such as network/graph theories. Fortunately, the features and dynamics of theoretical, social and informatics networks are well studied by mathematics (Sylvain Seacute;neacute;), physics and computer science (Kave Salamatian). The goal of the meeting is to explore the robustness and the plasticity of non-biological networks to anticipate network measures most suitable to address structural, mechanical and functional changes in proteins. In a complementary way, the workshop will explore alternative approaches investigating the mechanisms that enable local information to spread globally and yield complex structures: Molecular dynamics combined to graph theory (David Wales), tiling/symmetry (Laurent Vuillon, Pierre Etienne Meunier), protein mechanical properties (Keqin Zhang) and protein pattern designs (Sylvie Ricard Blum).

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5

Networks and Protein assembly

Auteur: Claire Lesieur[1]

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Proteins are biological entities made of a chain of amino acids bound to one another in a specific sequence. Based on the sequence and the environment, the protein acquires a tridimensional shape called tertiary structure (3D-structure) suitable for its biological function. The vast majority of proteins are oligomers which assemble several copies of their chains in order to function. They either fold individual chains and subsequently associate them (lock and key mechanism) or fold and associate the chains concomitantly (fly-casting mechanism). The association of chains involves interactions between atoms of the amino acids of different chains to form a protein interface. Only some of the amino acids of the protein interface, so-called hot spots are regulating the association steps. In addition, there are some residues located outside the protein interface, often upstream, that regulate association [1, 2]. For example, a proline residue located upstream a protein interface domain changes the spatial position of the domain through a cis-trans isomerization and hence regulates the chain association [3]. The single modification of some of the amino acids of a protein is sufficient to (i) prevent assembly, (ii) modify assembly or (iii) change the route of assembly. At the same time, the mutation of most amino acids has no effect on the assembly. This implies that the protein combined fold/assembly robustness and fold/assembly plasticity through the regulation of local changes, namely single amino acid.
A network is a set of points (nodes) connected to one another by links. The strength of the network/graph theory is the capacity to yield information on the nodes, on the pairs of nodes (links) and on the dynamics of the network, ie the communication between nodes and more importantly beyond pairs of nodes.
We will discuss how such capacity is relevant to address protein fold robustness and plasticity [4, 5].

[1]. Csermely P. Creative elements: network-based predictions of active centres in proteins and cellular and social networks. Trends Biochem Sci. 2008 Dec;33(12):569-76. PubMed PMID: 18945619.
[2]. Zrimi J, Ng Ling A, Giri-Rachman Arifin E, Feverati G, Lesieur C. Cholera toxin B subunits assemble into pentamers - proposition of a fly-casting mechanism. PLoS One. 2010;5(12):e15347. PubMed PMID: 21203571.
[3]. Lesieur C, Cliff MJ, Carter R, James RF, Clarke AR, Hirst TR. A kinetic model of intermediate formation during assembly of cholera toxin B-subunit pentamers. J Biol Chem. 2002 May 10;277(19):16697-704. PubMed PMID: 11877421.
[4]. Feverati G, Achoch M, Vuillon L, Lesieur C. Intermolecular β-Strand Networks Avoid Hub Residues and Favor Low Interconnectedness: A Potential Protection Mechanism against Chain Dissociation upon Mutation. PloS one. 2014;9(4):e94745.
[5]. [4]. Lesieur C. The Assembly of Protein Oligomers: Old Stories and New Perspectives with Graph Theory. ISBN 980-953-307-1130-3. Book title: Oligomerization of Chemical and Biological Compounds, edited by Claire Lesieur, publised by INTECH; in press.

3

An introduction to self-assembly, theory and implementations

Auteur: Pierre-Etienne Meunier[1]

[1] *laboratoire d'informatique fondamentale de Marseille (LIF), UMR 7279, CNRS- Université Aix-Marseille, France*

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Self-assembly is the process by which unorganized atomic components coalesce into complex shapes and structures. Its study started at the end of the 90s, from the point of view of computer scientists. Since then, it has yielded both an accurate theory of how things form at the nanoscale, and an impressive number of practical implementations at the nanoscale, in particular using DNA: fractal structures, regular arrays, programmed nanoparticle placement, arbitrary 2D (connected) shapes ...

This is one of the fields of science in which theory and experiments are this close, as they are often done by the same persons. This proximity opens amazing horizons, from molecular programming inside living organisms, to testing new hypotheses on evolution and the origins of life.

In this talk, I will introduce the essential notions of the field at both levels, and present our next challenges.

6

Structure, plasticity and robustness of collagens at the molecular and supramolecular levels

Auteur: Sylvie Ricard-Blum[1]

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Twenty-eight collagen types have been identified so far in mammals and all of them contain a triple-helical domain, which is a characteristic feature of the collagen superfamily. The triple-helical domains of collagens are comprised of three polypeptide chains, called chains, which adopt a left-handed polyproline II helix conformation. These chains are predicted to be intrinsically disordered and the sequences folded into a polyproline II helix are the major sources of disorder (Peysselon et al., Mol Biosyst 2011 7:3353-65). The triple helix motif has an inherent plasticity in native, trimeric, collagen molecules. Indeed collagen triple helices tolerate significant local changes in helical twist to respond to sequence variability, imino acid content and Gly-X-Gly interruptions. These interruptions define regions of flexibility and molecular plasticity, which may result in kinks or bends visible in electron microscopy. A macroscopic model for this plasticity is a three-stranded rope that can be twisted or relaxed locally. This rope may react differently to torque forces along its length, with perhaps local "rigid"spots at which further twisting (or relaxing) may not be feasible (Bella et al., J. Mol. Biol. 2006 362:298-311).
Several collagen types form fibrils (15-500 nm in diameter), which show a banding pattern with a periodicity of 64-67 nm (Ricard-Blum, Cold Spring Harb Perspect Biol 2011 3:a004978). Collagen fibers are covalently cross-linked in vivo via the lysyl oxidase pathway (Eyre et al., Methods. 2008 45:65-74) and by glycation. Collagen cross-linking modulates the stiffness and mechanical properties (e.g. resistance to traction) of tissues.
Tensile overload causes discrete plasticity in collagen fibrils. With successive overload cycles, fibrils develop an increasing number of kinks along their length. These kinks-discrete zones of plastic deformation known to contain denatured collagen molecules-are accompanied by a progressive and eventual total loss of D-banding along the surface of fibrils, indicating a loss of native molecular packing and further molecular denaturation. The nanostructural motif characteristic of overloaded collagen fibrils is referred to as discrete plasticity (Veres et al., J Orthop Res 2013 31:731-7). Intrafibrillar plasticity through mineral/collagen sliding is the dominant mechanism for the extreme toughness of antler bone (Gupta et al., J Mech Behav Biomed Mater. 2013 28:366-82). Upon aging the increased stiffness of collagen affects the bone ability to plastically deform by fibrillar sliding, which then must be accommodated at higher structural levels, by increased microcracking (Zimmermann et al., Proc Natl Acad Sci USA 2011 108:14416-21). Fiber alignment and densification occur as a function of applied strain for both uncrosslinked and crosslinked collagenous networks. This alignment is irreversibly imprinted in uncross-linked collagen networks. Fibril-fibril junctions are likely to be where plastic deformation occurs, allowing fibrils to slide with respect to one another and thus inducing irreversible changes in the uncross-linked network topology (Vader et al., 2009 PLoS One 4:e5902). When adherent to damaged collagen fibrils, the cells clustered less, showed ruffled membranes, and frequently spread, increasing their contact area with the damaged substrate. There was clear structural evidence of pericellular enzymolysis of damaged collagen (Veres et al., J Biomed Mater Res A.

2014 Mar 10). Atomistic-based hierarchical multiscale modeling has been recently applied to investigate the source of visco-elasticity and deformation mechanisms of collagen at the nanoscale level (Vesentini et al., Muscles, Ligaments and Tendons Journal 2013 3: 23-34). The availability of a model may lead to the design of new biomaterials for regenerative medicine.

2

Why the asian camel has two humps or a peripatetic journey on the basis of redundancy and resilience

Auteur: Kave Salamatian[1]

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A major characteristic in biology is resilience. We witness in permanence resilience in form of redundancy in biological systems, the human has two kidneys, for example. At the same time biological system are very efficient and do not waste resources. The aim of this talk will be investigate resilience from a system theory and information theory view point and to introduce concepts of fragility and anti-Fragility. Indeed the topic is gigantic and has been investigated thoroughly in the past decades; however the topic is coming back as a hot topic specially with the emergence of network as a major explicative factor of resilience. We will try to describe last developments.

1

Interaction networks and their environment

Auteur: Sylvain Séné[1]

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In this talk will be presented fundamental results which show formally that the environment of interaction networks plays a central role on their dynamical behaviours. Although an application to a biological network will be discussed, the focus will notably put on probabilistic cellular automata.

9

The robustness and innovability of protein folds

Auteur: Dan S. Tawfik[1]

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Over 60% of the known folds carry out one or two enzymatic functions, while few folds, e.g. the TIM-barrel and Rossmann folds, exhibit hundreds. Are there structural features that make a fold amenable to functional innovation (innovability)? Do these features relate to robustness –the ability to readily accumulate sequence changes? I will discuss several hypotheses regarding the relationship between the architecture of a protein and its evolutionary potential. I will describe how, in

a seemingly paradoxical manner, opposite properties such as high stability and rigidity vs. conformational plasticity, and respectively, structural order vs. disorder, promote robustness and/or innovability. Indeed, polarity –differentiation and low connectivity between a protein's scaffold and its active-site, is a key prerequisite for innovability.

4

From tilings to fibers: bio-mathematical aspects of fold plasticity

Auteur: Laurent Vuillon[1]

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Protein oligomers are made by the association of protein chains via intermolecular amino acid interactions (interaction between subunits) forming so called protein interfaces. This talk proposes mathematical concepts to investigate the shape constraints on the protein interfaces in order to promote oligomerization. First, we focus on tiling the plane (2 dimensions) by translation with abstract shapes. Using the fundamental Theorem of Beauquier-Nivat, we show that the shapes of the tiles must be either like a square or like a hexagon to tile the whole plane. Second, we look in more details at the tiling of a cylinder and discuss its relevancy in constructing protein fibers. The universality of such "building"properties are investigated through biological examples.

8

Exploring and Analysing Energy Landscapes for Proteins

Auteur: David J. Wales[1]

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Coarse-graining the potential energy surface into the basins of attraction of local minima provides a computational framework for investigating structure, dynamics and thermodynamics in molecular science. Steps between local minima form the basis for global optimisation via basin-hopping and for calculating thermodynamic properties using the superposition approach and basin-sampling. To treat global dynamics we must include transition states of the potential energy surface, which link local minima via steepest-descent paths. We may then apply the discrete path sampling method, which provides access to rate constants for rare events. In large systems the paths between minima with unrelated structures may involve hundreds of stationary points of the potential energy surface. New algorithms have been developed for both geometry optimisation and finding connections between distant local minima, which allow us to treat such systems. A graph transformation approach enables rate constants and committor probabilities to be extracted from kinetic transition networks containing over a million states. Applications will be presented for a range of different protein examples, ranging from atomistic to coarse-grained models.

Selected Publications:

D.J. Wales, Curr. Op. Struct. Biol., 20, 3-10 (2010)
D.J. Wales, J. Chem. Phys., 130, 204111 (2009)
B. Strodel and D.J. Wales, Chem. Phys. Lett., 466, 105-115 (2008)
D.J. Wales and T.V. Bogdan, J. Phys. Chem. B, 110, 20765-20776 (2006)
D.J. Wales, Int. Rev. Phys. Chem., 25, 237-282 (2006)
D.J. Wales, "Energy Landscapes", Cambridge University Press, Cambridge, 2003

7

Silk Fibers: the interplay of their sequence / structure with mechanical properties

Auteur: Ke-Qin Zhang[1]

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Nature produced a wide variety of materials with an extensive array of interesting structures which have been explored and adapted for human use. One of the best natural materials is silk, which has been used since ancient times. As a functional fiber, silk features exceptional mechanical properties such as high tensile strength and great extensibility, making it one of the toughest materials known. Hence, it has drawn the great attentions of scientists to explore the structure of this biologic protein fiber. We present here the current understanding of molecular composition, secondary structures in spider dragline silk and Bombyx mori silk. How the structure of the natural silks relates to the remarkable mechanical properties are also discussed. Clearly, these fundamental achievements have the potential to contribute to the development of abilities for biomimetic polymers and a wide range of enhanced applications.

10

Besides Science

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Besides Science: there is rock climbing