XXIe congrès GGMM

Nice, 3-5 avril 2019

Conférences plénières

Nicolas Férey (LIMSI, Paris) : *Simulation interactive, réalité virtuelle et augmentée, interface tangible : usages et perspectives pour la biologie moléculaire*

Isabelle Callebaut (IMPMC, Paris) : *Utilisation de signatures structurales pour explorer le « dark proteome »*

Adèle Laurent (CEISAM, Nantes) : *Modélisation d'interaction protéine-protéine à l'aide d'approches de simulations multi-échelles*

Matthieu Chavent (IPBS, Toulouse) : *Comprendre l'action des lipides de Mycobacterium Tuberculosis sur la membrane des macrophages grâce à la modélisation moléculaire*

Olivier Taboureau (MTI, Paris) : *Big data : Les nouveaux défis de la chémoinformatique*

Sessions thématiques

Visualisation, Graphisme & nouvelles technologies
Simulations & expériences
Développements méthodologiques
Protéines membranaires
Chémoinformatique, Drug Design

Plus d'informations sur :
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Depuis 80 ans, nos connaissances bâtissent de nouveaux mondes
UNIVERSITÉ CÔTE D'AZUR

Table des matières

Mot de Bienvenue

Comme tous les deux ans, le congrès du Groupe de Graphisme et de Modélisation Moléculaire est l'occasion pour toute notre communauté d'échanger sur les dernières avancées dans le domaine de la modélisation moléculaire, mais c'est également le moment propice pour se rencontrer, pour discuter et mieux se connaître.

C'est dans cette double optique que nous avons le plaisir de vous accueillir à Nice pour cette XXIème édition durant laquelle, nous l'espérons, vous passerez d'excellents moments, tant scientifiques qu'amicaux.

Bienvenue !!!

Le comité d'organisation local.

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Programme

Mercredi 3 avril

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Conférences Plénières

Simulation interactive, réalité virtuelle et augmentée, interface tangible… : usages et perspectives pour la biologie moléculaire

Nicolas Férey

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Dès les prémices de la biologie structurale, les chercheurs ont très tôt construit des modèles physiques et tangibles pour se faire des représentations, adaptées à notre échelle, manipulables, accessibles à nos sens, pour mieux comprendre le fonctionnement et l'organisation des biomolécules. Ensuite, les progrès dans le domaine de l'informatique ont permis grâce à la visualisation moléculaire, de considérablement réduire le temps de construction de modèles 3D, numériques, avec le désavantage d'être moins tangibles. La difficulté d'interagir avec ces modèles 2D ou 3D numériques explique que des modèles physiques continuent d'être utilisés dans un cadre pédagogique ou pour illustrer élégamment les résultats de travaux en biologie structurale notamment grâce à l'impression 3D. Les progrès plus récents, en calcul intensif, en rendu graphique, en interaction humain machine, ont permis ensuite de coupler simulation et visualisation, offrant de nouveaux outils comme la modélisation permettant de construire interactivement des modèles complexe plus efficacement, et la simulation moléculaire interactive dans lequel l'utilisateur peut provoquer des évènements rares et tester in silico des hypothèses à valider expérimentalement. C'est dans ce contexte, que nous vous proposons de revenir sur les principales avancées méthodologiques en visualisation et en interaction humain machine qui ont accompagné la recherche en biologie moléculaire, puis de présenter quelques techniques contemporaines d'interactions hommes machines avancées et leurs résultats associées, pour enfin imaginer comment l'utilisation d'environnements de travail innovants incluant des techniques issues de réalité virtuelle, de la réalité mixte comme les interfaces tangibles, pourraient faire évoluer les usages dans le domaine de la biologie moléculaire.

Utilisation de signatures structurales pour explorer le « dark proteome »

Isabelle Callebaut

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La matière noire de l'univers des protéines est constituée de l'ensemble des régions pour lesquelles on ne dispose pas encore d'annotations, telles qu'elles peuvent être déduites des banques de domaines ou de structures. Cette matière noire constitue une part importante des protéomes, étant particulièrement présente chez les eucaryotes et les virus (e.g. 39 % de l'ensemble des acides aminés des protéines humaines sont non annotés vis à vis de la banque Pfam). Sa caractérisation fait l'objet d'intenses recherches, notamment par le biais du développement d'outils de détection d'homologues lointains ou de prédiction de désordre.

Nous avons développé des outils qui permettent de prédire, de façon exhaustive et à partir de l'information de la seule séquence, le répertoire des régions qui, au sein des protéines, sont susceptibles d'adopter une structure, soit en formant des domaines globulaires stables, soit en contactant un partenaire (repliement induit). Ainsi, on peut constater que les séquences non annotées reprennent une part importante de séquences repliables (35 % du protéome humain), incluant des domaines globulaires encore orphelins mais aussi des séquences subissant des transitions entre ordre et désordre.

Nous illustrerons ici ces approches et leur utilisation pour identifier de nouvelles familles de domaines et pour prédire des cas de désordre conditionnel, jouant un rôle clé dans la signalisation cellulaire et dans les transitions de phase à l'origine de condensats moléculaires.

Modélisation d'interactions macromoléculaires à l'aide d'approches de simulations multi-échelles.

Laurent Adèle D.

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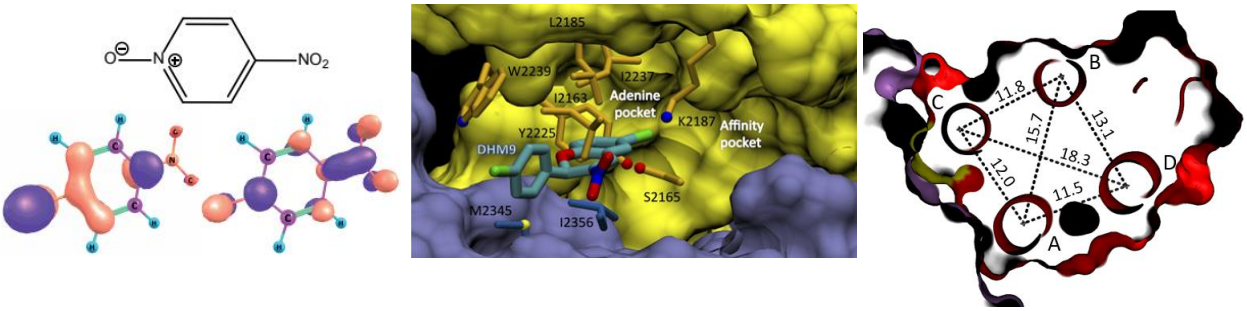
Différentes propriétés de composés organiques se trouvant dans des milieux complexes seront présentés en mettant en avant les approches hybrides alliant la mécanique moléculaire et la mécanique classique couplée à de la dynamique moléculaire. Ainsi, l'importance de la polarisation et de la dispersion sera discutée pour comprendre le phénomène de solvatochromisme de sondes moléculaires,[1] les propriétés électroniques d'inhibiteurs vis-à-vis de mTOR[2] ou encore la description d'interactions protéine-protéine visant la conception d'inhibiteurs.[3]



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Comprendre l'action des lipides de Mycobacterium Tuberculosis sur la membrane des macrophages grâce à la modélisation moléculaire.

Matthieu Chavent

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Mycobacterium tuberculosis (Mtb) is the main causative agent of the disease Tuberculosis. Among the various factors associated with the Mtb virulence, lipids constituting the bacterial cell wall have recently gained attention. These lipids can be used as virulence effectors acting at the macrophage membrane to damage it and modulate immune response. I will focus my talk around one particular mycobacterial lipid: the Phthiocerol dimycocerosate (DIM). I will show how using a multi-scale modeling approach helped to understand the structural and biophysical features of this lipid. Combining modeling with ssNMR, and cell biology experiments shed a new light on how this lipid may modulate macrophage biological function.

Big data : Les nouveaux défis de la chémoinformatique

Olivier Taboureau

Modélisation computationnelle des interactions Protéine-Ligand, Inserm U1133, CNRS UMR 8251, University of Paris Diderot.

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Depuis des décennies, la chémoinformatique a contribué à l'identification des relations entre des molécules chimiques et des propriétés physico-chimiques ou biologiques. L'accès à des données massives « omiques » provenant de nouvelles technologies à haut débit, telle que génomiques, protéomiques et métabolomiques suscite le développement de nouvelles méthodes en chémoinformatique. L'objectif étant de pouvoir traiter et analyser ces Big Data, notamment dans l'intégration et la fouille de données hétérogènes ainsi que la prédiction et la visualisation de ces données.

A travers plusieurs exemples, les nouveaux défis de la chemoinformatique dans la conception de nouveaux médicaments, dans l'aide à la décision sur le risque de toxicité de certaines molécules, et la médecine personnalisée seront discutés.

Structure and reactivity of complex DNA lesions: clustered abasic sites as a case study

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3 : laboratoire de chimie de l'ENS Lyon – CNRS : UMR5182 – Lyon, France

Although investigations on DNA damage and repair started several decades ago, the complexity and vastness of their chemical aspects are still matter of research as their molecular mechanisms remain ill-defined. The structural signature of DNA lesions is crucial for their repair, but only few structural data are available from X-Ray and NMR studies. In order to gain insights into their formation and structure, we investigated of a series of complex lesions within the double helix.

Abasic sites (Ap) are one of the systems we tackled. These lesions result from the cleavage of the nucleotide glycosidic bond, leaving only the deoxyribose moiety in the DNA strand. They can be generated by exposure to ionizing radiation or as the products of enzymes involved in DNA damage response. Ap can be highly genotoxic (mismatch during DNA replication) and cytotoxic (formation of interstrand crosslinks), hence their high biological relevance. We investigated the structural behavior of short oligonucleotides harboring clustered Ap, in order to rationalize experimental repair rate measurements [1]. We also studied their interaction with the human Ap endonuclease, APE1, responsible for their removal. Our approach, based on the use of classical MD simulations, provided insights into the structural signature of clustered Ap within DNA [2] and their processing by repair enzymes [3]. Our results allowed to improve the understanding of why clustered lesions are so challenging for DNA repair [1]. In line with those studies, we then started to work on the structural behavior of Ap within nucleosomal DNA, which constitute a more realistic yet computationally expensive model (manuscript in preparation).

Overall, this PhD thesis work shed new lights on damaged DNA reactivity, structure and repair, which provides perspectives for cell mechanisms understanding and biomedicine. E.B. is grateful to the French Minister of Higher Education and Research for PhD fellowship, and to the COST Action CM1201 and Labex PRIMES for fundings. The PSMN is acknowledged for computational resources.

1 Georgalikas, A. G.; Bennett, P. V.; Sutherland, B. M. NAR 2002. 2 Bignon, E.; Gattuso, H.; Morell, C.; Dehez, F.; Georgakilas, A. G.; Monari, A.; Dumont, E. NAR 2016. 3 Gattuso, H.; Durand, E.; Bignon, E.; Morell, C.; Georgakilas, A. G.; Dumont, E.; Chipot, C.; Dehez, F.; Monari, A. JPCL 2016.

Mots-Clés: Computational biochemistry, DNA lesions, all, atom molecular dynamics.

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Session 1 : Visualisation, Graphisme et nouvelles technologies

Session 1 : Visualisation, Graphisme et nouvelles technologies

Improved modelling of ECM proteins and structures

Camille Besançon[1], Hua Wong[1], Manuel Dauchez[1, 2], Jessica Prévoteau-Jonquet[1], Nicolas Belloy[1, 2], Stéphanie Baud[1, 2]

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The extracellular matrix (ECM) is a three-dimensional network of macromolecules that is the architectural support for cells and allows tissue cohesion. This dynamic structure regulates many biological functions such as adhesion, migration, proliferation, differentiation and cell survival. Four main families of macromolecules constitute this interstitial medium: collagens, structural glycoproteins, proteoglycans and elastins.

Molecular modelling (molecular dynamics (MD) simulations, ab initio calculations, molecular dockings ...) makes it possible to understand and decipher, at the atomic or coarse-grained levels, the behaviour of biological systems. In particular, it becomes an essential and powerful tool used to study the structure and structure/function/dynamics of biomolecules.

In the particular context of the structural and dynamic studies of the ECM, the usual molecular modelling methods allow scientists to obtain interesting and insightful results, but often limited in terms of complexity (molecules such as proteoglycans are not often taken into account or treated in modelling studies) or size (MD tools make it impractical to study the structure and dynamics of realistic matrix environment with a large number of biological actors) of the investigated systems.

We are developing approaches based on the Unity3D platform, in order to improve the modelling of ECM related systems. We illustrate two recent applications developed in our lab:

(i) the first application is related to the representation and analysis of N glycosylations during MD simulations. We aim at visualizing the impact of the sugar motions on the protein surface through the use of UnityMol. A dedicated methodology called the Umbrella Visualization allows to display the main positions adopted by the glycosylations chains on the protein surface and thus to discuss the protein/glycan interactions.

(ii) the second application is related to the modelling of the ECM at the mesoscopic level. Our rigid body dynamics developed with Unity3D and Physics engines, is combined with VR hardware in order to visualize/interact and model large biological molecules with preliminary results showing it is possible to characterize the self-assembling nature of the basement membranes' structure.

Session 1 : Visualisation, Graphisme et nouvelles technologies

Udock: a free interactive protein docking system

Benjamin Boyer[1],

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La prédiction de la géométrie des interactions protéine-protéine est un enjeu critique de la compréhension des mécanismes du vivant. Différentes méthodes ont été développées dans la littérature et permettent d'explorer de manière automatique différentes géométries d'interaction. Udock est un logiciel d'amarrage macromoléculaire (docking) protéine-protéine temps réel basé sur des techniques d'interaction et de manipulation issues du domaine du jeu vidéo. L'utilisateur explore par lui-même des solutions de docking, à l'aide de grappins qu'il place à la surface des protéines dont il veut explorer le(s) complexe(s). Les solutions proposées par l'utilisateur pourront être optimisées à la demande. Le score est calculé en temps réel et permet d'avoir un retour de la qualité de la géométrie proposée par l'utilisateur au cours de l'exploration. UDock a été développé de manière à optimiser l'usabilité et la capacité d'exploration pour l'utilisateur. Ainsi, différents modes de caméra sont disponibles (première personne, troisième personne, trackball, caméra libre) et les contrôles sont variés (clavier/souris; manette de jeu). UDock permet de traiter un très grand nombre de protéines en simultané, ce qui permet à l'utilisateur d'explorer de simples complexes binaires jusqu'à des macrocomplexes de grande taille.

Mots-Clés : docking ; multidocking ; protéine ; amarrage macromoleculaire ; Visualisation

Session 1 : Visualisation, Graphisme et nouvelles technologies

MS2MODELS: probing protein interaction networks by MS-based proteomics and structural data integration

Guillaume Postic [1,] Jessica Andreani [2,] Raphaël Guerois [2,] Julien Rey [1,] Christophe Bruley [3,] Virginie Brun [3,] Alexandre Burel [4,] Sarah Cianférani [4,] Yohann Couté [3,] Myriam Ferro [3,] Anne Gonzalez De Peredo [5,] Jérôme Gracy [6,] Agnès Hovasse [4,] Emmanuelle Mouton-Barbosa [5,] Jean-Luc Pons [6,] Yves Vandenbrouck [3,] Gilles Labesse [6,] Odile Burlet-Schiltz [5,] Pierre Tufféry [1,] *

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Mass spectrometry has become essential for characterizing molecular species and their interactions. Although requiring little material, this technique has gained an extreme precision, as well as a high-throughput rate. For numerous biological questions, proteomics and interactomics analyses are now key entry points. Nevertheless, such studies often stop at listing the interacting macromolecules (essentially proteins), without performing the analysis of the identified sequences. This is problematic when considering the fact that structural and evolutionary aspects provide a powerful analysis framework for biologists: e.g. for interpreting patients mutations that interfere with assemblies, setting up directed mutagenesis and functional dissection experiments, or virtual screening. The MS2MODELS project combines high-throughput bioinformatics tools for modeling protein 3D structures and their assemblies, in the aim of providing to researchers an easy-to-use interface for the post-processing of their screenings results (amplifying relevant information) and to perform the integrative modeling of their experimental data. The pipeline includes (i) the prediction of interacting proteins in multimeric complexes by the analysis of experimental structural data, and (ii) the template-based structural modeling of individual protein chains, the relative positioning of which being determined by protein-protein docking. Finally, this project will be beneficial to the whole community of biologists working on macromolecular interactions, with important applications such as the analysis of pathological dysfunctions related to altered interactions or isoforms.

Mots-Clés : Proteomics ; Structural modeling ; Protein ; protein docking ; Network biology

Session 1 : Visualisation, Graphisme et nouvelles technologies

NAfragDB: a multi-purpose structural database of nucleic-acid – protein complexes for advanced users

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2 : Molecules Thérapeutiques in-Silico (MTi) - INSERM, Universite Paris Diderot, Université Denis Diderot 35 rue Hélène Brion, case 7113, 75205 Paris Cedex 13 - France

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Many structural bioinformatics databases support automated searches via a limited number of pre-defined criteria and their combinations. Here, we present NAFragDB, a structural database of nucleic-acid (NA) - protein complexes that supports arbitrarily advanced queries and any combination thereof via python-written requests directly on the raw data.

We have extended our earlier pipeline for automated creation of NA fragment libraries to include many "low level" combinable information units. To build a database, we retrieve all protein-NA structures from the PDB, extract relevant data (resolution, NA type, etc), clean each structure (add missing atoms, list incomplete nucleotides, etc), and characterize the interface (sugar/phosphate/base - protein distances, water contacts, etc). We then use the 3DNA program [1] for NA structure description that gives exhaustive data in easily parsable Json format. Finally, we rearrange the data per nucleotide (eg. “nucleotides 5 to 15 make a stem-loop” → “nucleotide 5 is at position 1 in an 11-nucleotides stem-loop”).

We provide a description at both the structural and nucleotide levels of the full set of protein-bound NAs from the PDB in a single Json file, and a tool to build customised queries. This allows the user to:

* create specific benchmarks for targeted purpose (ex. Retrieve all complexes with a stretch of 7 consecutive single-stranded nucleotides, of which at least 5 are within 4 Angstrom of the protein).

* compute various statistics (ex. Do single-stranded RNA establish H-bonds more preferentially via the base/sugar than via phosphates compared to double-stranded RNA?).

* build targeted fragment libraries

We will provide a live demo of building a database, applying search queries, and computing statistics. The source code to create, update, and search a database is available at **https://github.com/isaureCdB/NAfragDB.git**. We hope to encourage the sharing of such database capabilities to increase interoperability and ease complex use-cases by advanced users.

[1] X-J Lu & WK Olson. 3DNA: a software package for the analysis, rebuilding and visualization of three-dimensional nucleic acid structures. Nucleic Acids Research (2003) 31(17), 5108-21.

Mots-Clés : protein ; nucleic acid complexes ; nucleic acids structure ; structural database

Rescoring of Docking Poses under Occam's Razor – Are there Simpler Solutions?

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Affinity prediction by docking relies on highly empirical and diverse protocols, which often involve the re-scoring of poses generated by a Force Field (FF) based Hamiltonian to provide either estimated binding affinities. Re-scoring is performed by so-called scoring functions - typically, a reweighted sum of FF terms augmented by additional terms (e.g., desolvation/entropic penalty, hydrophobicity, etc.). Sometimes, the scoring function actually drives ligand positioning, but often it only operates on the best scoring poses ranked top by the initial ligand positioning tool. In either of these scenarios, scoring functions are docking-specific models, and most require machine-learning-based calibration. Therefore, docking makes less physical sense than simulations in which the FF Hamiltonian defines the energy, and affinity emerges as an ensemble average property over pools of representative conformers.

Paraphrasing on Occam's Razor principle, additional model complexity is only acceptable if demonstrated to bring a significant improvement of prediction quality. In this work we therefore examined whether the complexity inherent to scoring functions is indeed justified. For this purpose we compared S4MPLE (Sampler for Multiple Protein-Ligand Entities), a general purpose conformation sampler based on the AMBER/GAFF FF, complemented with continuum solvation terms with several state of the art docking tools that rely on calibrated scoring functions (Glide, Gold, Autodock-Vina) in terms of its ability to top-rank the actives from large and diverse ligand series associated with various proteins. There is no clear winner of this study, where each program performed well on most of the targets, but also failed with respect to at least one of them. Therefore, a well-parameterized force field with a simple, energy-based ligand ranking protocol appears to be as effective docking protocol as intricate rescoring strategies based on scoring functions. Such a tool that can sample the conformational space of the free ligand, the bound ligand and the protein binding site using the same force field can alleviate many of the approximations common to contemporary docking protocols and allow e.g., for docking into highly flexible active sites when current scoring functions are not well suited to estimate receptor strain energies.

Mots-Clés : docking ; scoring ; force fields

Session 2 : Simulations et expériences

Session 2 : Simulations et expériences

Structural characterization of the intrinsically disordered N-WASP domain V and its conformational selection by actin

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Intrinsically disordered proteins (IDP) are characterized by one or several regions which lack stable secondary and tertiary structure in their unbound state under physiological conditions. They frequently play crucial roles in the regulation of many biological processes and, to exert their functions, interact with several molecular partners. Formation of IDP-protein complexes can follow two extreme mechanisms: the ''coupled folding and binding'', in which the disordered region binds to the protein partner and folded into an ordered structure on its surface, and the ''conformational selection'', in which the folded structure preexists in the IDP unbound state and is recognized by the protein partner. To gain insight into the structure and recognition mechanism of IDP-protein complexes, it is thus worthwhile to preliminary explore the conformational ensemble of IDP.

However, due to their large conformational heterogeneity, the structural characterization of IDPs is very challenging using classical X-ray crystallography or NMR NOE analysis. Nevertheless, secondary chemical shifts and residual dipolar couplings from NMR experiments can provide local information about the propensity of each residue to form transient secondary structures. On the other hand, small-angle X-ray scattering (SAXS) can deliver global information about IDP structures in terms of average size and shape. But, in order to infer a detailed conformational ensemble from NMR and SAXS data, it is most often necessary to use complementary *in silico* approaches to generate atomic scale structures, such as statistical coil generator or molecular dynamics (MD) simulations [Rauscher *et al.*, *Biochem. Cell Biol.* ***2010***, 88: 269–290; Ball *et al.*, *J. Phys. Chem. B* ***2014***, 118: 6405–6416; Bonomi *et al.*, *Curr. Opin. Struct. Biol.* ***2017***, 42: 106–116].

In the present study, we combined NMR, SAXS and *in silico* techniques to characterize the conformational ensemble of the totally disordered verprolin homology domain (V) of the Neural Wiskott-Aldrick Syndrome Protein (N-WASP), a pivotal protein in the regulation of the actin cytoskeleton dynamics and organization. Then, we used representative structure of the most populated clusters of its conformational ensemble to model the quaternary structure of N-WASP domain V in complex with actin.

Mots-Clés : Intrinsically disordered protein ; Multiple molecular dynamics Simulation ; Combining MD with NMR/SAXS data ; IDP ; protein interaction ; Protein docking

Session 2 : Simulations et expériences

Coarse-grain simulations on NMR conformational ensembles highlight non catalytic functional residues in proteins

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Dynamics are a key feature of protein function, and this is especially true of gating residues, which occupy cavity or tunnel lining positions in the protein structure, and will reversibly switch between open and closed conformations in order to control the diffusion of small molecules within a protein's internal matrix. Earlier work on globins and hydrogenases have shown that these gating residues can be detected using a multiscale scheme combining all atom classic molecular dynamics simulations and coarse grain calculations of the resulting conformational ensemble mechanical properties. Here we show that the structural variations observed in the conformational ensembles produced by NMR spectroscopy experiments are sufficient to induce noticeable mechanical changes in a protein, which in turn can be used to identify residues important for function and forming a mechanical nucleus in the protein core. This new approach, which combines experimental data and rapid coarse-grain calculations and no longer needs to resort to time-consuming all-atom simulations, was successfully applied to five different protein families.

Mots-Clés : NMR conformational ensembles ; proteins mechanics ; coarse ; grain simulations ; elastic network model

At the Limit of Additive Molecular Dynamics: Quantum Effects in Calcium-dependent Lectin/Carbohydrate Complex

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The developments of additive carbohydrate force fields[1] increased the reliability of molecular dynamics simulations (MD) of protein-carbohydrate complexes. The presence of bridging Ca2+ ions can, however, pose problems for structural and energetic description due to quantum effects, such as charge transfer.[2],[3],[4] To overcome this limitation, we had developed Ca2+ parameters with effective electronic polarisation for use with additive force fields4 and applied them to a calcium-dependent lectin/carbohydrate complex. Such a treatment improved the structural description of the binding site (Ca2+...Ca2+ distance) but failed to reproduce the pattern of protein/carbohydrate interactions and the location of specific bridging water molecules. Quantum mechanical/molecular mechanical (QM/MM) calculations helped us identify other polarization phenomena extending beyond the first coordination shell of the Ca2+ ions, which limit the reliability of plain classical MD. Utilizing the crystallographic structural information, we have simulated the binding process using “targeted MD” and evaluated the bridging solvent thermodynamics by use of the GIST tool. In summary, we have utilized advanced computational techniques and parameters to gain atomistic understanding of a rare ligand conformation in a challenging Ca2+-dependent lectin/carbohydrate complex.

[1] Fadda E and Woods RJ Drug Discovery Today 2010, 15, 596-609.

[2] Mitchell EP et al. Proteins: Struct Funct Bioinf 2005, 58, 735–746.

[3] Lepsik M and Field MJ J. Phys. Chem. B 2007, 111, 10012-10022.

[4] Kohagen et al. J. Phys. Chem. Lett. 2014, 5, 3964−3969.

Mots-Clés : dynamique moléculaire ; calcium ; lectin ; oligosaccharide

Session 2 : Simulations et expériences

Structuration du domaine C-terminal de la protéine Core du virus de l'hépatite B

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La protéine Core du virus de l'hépatite B (VHB – 183 aa) est composée d'un domaine d'assemblage structuré N-terminal (NTD, résidus 1-149) suivi d'un domaine désordonné d'interaction avec les acides nucléiques C-terminal (CTD, résidus 150-183). Le CTD est directement impliqué dans nombre d'étapes du cycle viral, comme l'encapsidation de l'ARN pré-génomique lors de l'assemblage de la capside immature ou la transcription inverse qui suit, mais aussi le trafic de la nucléocapside mature vers le noyau. Dans ces processus, l'activité du CTD est régulée par des phosphorylations spécifiques. Des structures cristallographiques du NTD sous forme assemblée en capside vide montrent qu'en l'absence d'acide nucléique les résidus 1-140 sont organisés en un domaine composé d'hélices. Ainsi Core s'associe en dimères en formant une spicule composée d'un faisceau de quatre hélices, tandis que des contacts latéraux entre les autres hélices et boucles de la structure produisent les interactions entre dimères.

A partir des structures atomiques de NTD disponibles à la PDB et avons modélisé des dimères de Core complets (2x183 résidus comprenant les parties CTD), non phosphorylés ou triplement phosphorylés pour les sérines S155, S162 et S170. Nous avons alors produit des simulations de dynamique moléculaire de ces dimères de Core. Elles montrent que les CTD, riches en résidus arginine, tendent à s'organiser en réalisant des contacts avec les régions électronégatives des NTD. La cartographie de ces interactions préférentielles montre que ces régions se situent : (**i**) autour et/ou en dessous des hélices et boucles capable de former des contacts entre dimères (résidus 30-50 et résidus 100-120) et (**ii**) sur la partie supérieure de la spicule (résidus 75-90). Nos résultats démontrent que le CTD peut transitoirement se structurer ce qui permet de proposer une interprétation à l'échelle atomique de données disponibles de microscopie électronique de nucléocapside immature (Wang *et al*, 2014) et recombinante (Wang *et al*, 2012) (Yu *et al*, 2013).

Mots-Clés : Simulations de Dynamique Moléculaire ; MD ; HBV ; Core

Session 2 : Simulations et expériences

Enhancing biosurfactant activities of surfactin, a cyclic bacterial lipopeptide : a structural study.

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Surfactin is a small cyclic lipopeptide surfactant synthesized by a non-ribosomal synthetase in Bacillus Subtilis. It is composed of seven L or D-amino acids (GLU – LEU – DLEU – VAL – ASP – DLEU – LEU) forming a cycle linked to a fatty acyl chain of varying length (from 12 to 16 carbons usually). Surfactin possesses a wide range of interesting biological activities such as antimicrobial, antifungal and hemolytic properties. Those activities are mostly related to its amphipathic and cyclic features. It can be used for different applications such as detergent, wetting agent, foaming agent or dispersant.

Regarding surfactin, it is still unclear what are the main structural features that make it one of the most powerful biosurfactants to date. In the context of bioremediation, we aim at developing new surfactants with higher efficiency and lower ecotoxicity, based on surfactin features. Understanding the molecular and structural features that give a high efficiency to surfactin is hence a priority. This report will present results of molecular dynamic simulations on surfactin and its variants (biologically active and inactive forms) to extrapolate structure-activity relationships, taking into account experimental data on surfactant activities and ecotoxicity. This should help design more efficient molecules and drive experimental investigation.

Mots-Clés : Molecular dynamic simulations ; surfactin ; surfactant ; cyclic lipopeptide ; bioremediation

Session 3 : Développements méthodologiques

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In silico prediction of residence time for protein kinase inhibitors

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In the early stage of the drug discovery process, the selection of ligand is mainly based on experimental values that reflect the compound affinity (IC50, Kd, ...). Compound prioritization is often performed on structure-activity relationships (SAR) that consider the potency of a drug on its target. However, the in vivoefficacy of a ligand is not always adequately described by the SAR because it could also depend on the lifetime of in vivointeractions between the ligand and its receptor. Today, structure-kinetic relationships (SKRs) are of major interest for the discovery of new drugs, particularly in the early stage of optimization of molecules in order to better evaluate their safety and efficacy. Among the kinetic measurements, the evaluation of the residence time (RT) of a compound inside its target is postulated as a good indicator of the in vivocompound efficacy.

In the search of relevant in silicotools for drug design, a research axis of the SB&C (Structural Bioinformatics and Cheminformatics) team at ICOA is dedicated to the development of new methodologies to understand the unbinding mechanism of a ligand from its biological target and to predict its RT value.

Two protocols, based on biased molecular dynamics simulations, have been developed to carry out the unbinding process of protein kinase inhibitors and to predict the associated residence time from these simulated pathways. Each protocol uses a different methodology and shows different speed and accuracy performances depending of the required precision on RT value. Further analysis of the energy profiles calculated from trajectories may also provide insights on the structural determinants responsible for the energetic barriers detected during the simulations. Such information can then be used by the chemists to optimize compound efficacy.

Mots-Clés : binding kinetics ; residence time prediction ; biased molecular dynamics simulations

Session 3 : Développements méthodologiques

"Infostery", a method to describe proteins mutational landscape.

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The question of how amino acid sequence variations (re-)shape the conformational landscape of proteins and impact their function is one of outstanding importance in biology. Many disease-associated mutations do not seem to produce any effect on the global shape nor motions of the protein. Consequently, these effects are difficult to probe directly and unambiguously. Computational techniques such as molecular dynamics (MD) simulations provide mechanistic details and can help predict/describe the impact of mutations on protein structural stability and internal dynamics.

We have previously developed a method called COMmunication MApping (COMMA), to describe the dynamical architecture of proteins and protein complexes. COMMA extracts dynamic features and integrates them into a graph theoretical framework. This method permits to compare in a direct way the dynamical behavior either of proteins with different characteristics or of the same protein in different conditions. [Karami *et al.*, BMC Bioinformatics, 2016]

Here, we show how COMMA can be used to identify residues highly sensitive to mutations, without expert knowledge of the studied system. We propose an original approach for predicting proteins mutational effects at large scale using MD simulations and introduce the new concept of ”infostery”, that is information contained in the arrangement of residues in 3D space. We performed relatively short all-atom simulations of the wild type and 175 mutants of PSD95's third PDZ domain in complex with its cognate ligand. Infostery analysis enabled us to predict the severity of those mutants. Moreover, we showed that by exploiting simulations of the wild type, one can detect 80% of the positions highly sensitive to mutations with a precision of 89%. Importantly, we showed that even in the absence of mutation-induced conformational changes, meaningful information is contained in and can be retrieved from the arrangement of residues in space and their atomic fluctuations. Our approach is implemented as a fully automated tool, COMMA2 (http://www.lcqb.upmc.fr/COMMA2), that can be used to guide medicinal research by selecting important positions/mutations. [Karami *et al.*, Sci. Rep, 2018] Further investigations are needed to evaluate the possibility of exploiting more coarse-grained methods rather than all-atom simulations.

Mots-Clés : mutation ; protein structure ; molecular dynamics ; communication ; PDZ

Session 3 : Développements méthodologiques

Pushing the computational frontiers of Multistate Protein Design

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Structure-based computational protein design (CPD) plays a critical role in advancing the field of protein engineering and accelerating the delivery of fine-tuned proteins displaying high specificity, efficiency and stability. Using an energy function and a reliable search method, CPD tries to identify amino acid sequences that fold into a target structure and ultimately perform a desired function.

Because of the vastness of the search space and the intractable combination of many degrees of freedom , the most usual CPD approaches consider a single rigid protein backbone, and usually ignore protein flexibility. This traditional Single State Protein Design (SSD) contrasts with the increasing evidence that proteins do not remain fixed in a unique conformational state but rather sample conformational ensembles. Large-scale protein motions ranging from local flexibility to large conformational rearrangements may play key roles on protein properties and functions. By exploiting and extending our efficient AI-based CPD methods [1-4], we developed innovative MultiState Design (MSD) methods aiming to alleviate SSD limitation by considering several conformational states simultaneously [5]. These methods seek to identify a sequence that optimizes a function of its optimal energies on the different considered states. We introduce efficient reductions of positive MSD problems to Cost Function Networks with two different fitness definitions and implement them in the POMPd (Positive Multistate Protein design) software. POMPd is able to identify guaranteed optimal sequences of positive multistate full protein redesign problems and exhaustively enumerate sub-optimal sequences close to the MSD optimum which is convenient for sequence library design. On various positive MSD problems we show that it is possible to identify an optimal MSD sequence and observe that the average energy fitness provides the best sequence recovery. Our method outperforms state-of-the-art guaranteed computational design approaches by several orders of magnitudes and can solve MSD problems with sizes previously unreachable with guaranteed algorithms.

[1-4] Viricel et al. 2018 Bioinformatics ; Traoré et al. 2016 J Comput Chem. ; Simoncini, et al. 2015 J Chem Theory Comput. ; Traore et al. 2013 Bioinformatics.
[5] Vucinic et al. Bioinformatics, submitted

Mots-Clés : Computational Protein Design ; Artificial Intelligence ; Protein flexibility ; Combinatorial optimization exact algorithms ; Multistate Protein Design

Session 3 : Développements méthodologiques

Extraction of Eu3+ with BTP toward Ionic Liquids: A Molecular Dynamics study

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In the context of nuclear fuel retreatment process, the separation of Actinides (An3+) from Lanthanides(Ln3+) remain a key problem. Soft (S, N) donor ligands, such as bis-triazinyl pyridine (R-BTP), have been designed to selectively complex An3+ions during the extraction processes.

Bhattacharyya et al.[1] proposed to use Ionic Liquids (ILs) as extractant phase as an alternative to more classical organic solvents to enhance extraction and improve the radiation resistance of R-BTP extraction system [2]. The experimental results show an impressive improvement of the extraction and separation with ILs and especially with [BMI][Tf2N] and [OMI][Tf2N]. The extraction mechanism and the specific role of ILs remain however unclear.

We propose to use Molecular Dynamic (MD) simulations on Eu(NO3)3salt with Me-BTP at a [BMI][Tf2N]/water interface to get insights from the Eu3+extraction systems. We report here the first results were we particularly focus on the (i) representation of the extracted complexes (ii) stoichiometry of the complexes (iii) role and nature of the IL phase during the phase separation and the extraction process (iv) influence of acidity.

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2. Yuan, W.; Ao, Y.; Zhao, L.; Zhai, M.; Peng, J.; Li, J.; Wei, Y., Influence of radiation effect on extractability of an isobutyl-BTP/ionic liquid system: quantitative analysis and identification of radiolytic products, RSC Adv. **2014,**4 (93), 51330-51333.

Mots-Clés : Liquides Ioniques ; Extraction ; Interface liquide ; liquide ; Dynamique moléculaire ; Europium

Session 3 : Développements méthodologiques

Predicting protein-ligand interactions with Convex-PL potential

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Binding of small molecules to proteins is driven by thermodynamic laws and can be described using the notion of free energy, whose minimum should correspond to the system's most stable conformation. However, its rigorous computation is very computationally challenging. This has lead the community to an extensive development of new approximate methods. Our approach, called Convex-PL [1], is a knowledge-based scoring function based on the idea that the information about protein-ligand interactions can be extracted from the geometry of known complexes in form of pairwise inter-atomic potentials. We let these potentials to be of a free shape, accepting that they can be decomposed into a polynomial basis with unknown expansion coefficients, which are then deduced from structural data by solving an optimization problem.

However, such approaches are unable to fully estimate the binding free energy due to the lack of the information about the environment and unknown entropic contributions. Due to these reasons, knowledge-based scoring functions, which perform quite good at finding near-native poses [2], are less reliable at binding affinities estimations. To overcome this problem, we created an implicit solvent model to take into account the voluminous contribution of displaced solvent and trained a linear ridge regression model to predict binding constants from a set of descriptors consisting of the original Convex-PL score, a ligand flexibility measure, atomic solvent-accessible surface area, and radial distribution functions of the ‘‘solvent'' probe atoms. Finally, we assessed Convex-PL using the CASF 2013 and CASF 2016 Benchmarks [3]. Convex-PL outperformed other scoring functions in the pose prediction and virtual screening exercises. Using Convex-PL as a scoring function, we have also achieved poses with overall mean RMSD lower than 1A in the pose prediction stage of the recent D3R Grand Challenge 4 docking challenge.

This study was partially supported by the the Ministry of Education and Science of the Russian Federation (grant no. 6.3157.2017/PP).

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[2] Kadukova, Grudinin, J. Comput. Aided Mol. Des., 2018, doi: 10.1007/s10822-017-0062-1
[3] Su et al, J. Chem. Inf. Model., 2018, doi:10.1021/acs.jcim.8b00545

Mots-Clés : protein ligand ; scoring function ; solvation ; knowledge based ; machine learning ; entropy

Session 4 : Protéines membranaires

Session 4 : Protéines membranaires

Etude de la déformation et de la fission de membranes contenant des phospholipides avec différentes chaînes aliphatiques.

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Le bon fonctionnement des organismes eucaryotes réside dans la capacité des membranes à former une barrière de protection tout en étant suffisamment malléable pour se déformer. Les phospholipides, principaux composants des membranes, diffèrent par la nature de leur tête polaire et par la longueur et le niveau d'insaturation de leurs chaînes aliphatiques (sn1 et sn2). La plupart des membranes cellulaires contiennent des phospholipides aux chaînes aliphatiques saturées et monoinsaturées. Cependant, les phospholipides polyinsaturés, appelés oméga 3 et oméga 6, sont extrêmement abondants dans certaines membranes spécifiques comme les vésicules synaptiques. Au cours des dernières années, plusieurs études ont montré que la présence d'oméga 3 et 6 augmentait la plasticité des membranes (Pinot et al., 2014; Rawicz et al., 2000). Notre équipe a récemment publié une étude complète expliquant la dynamique des chaines aliphatiques selon divers profils et leur impact sur les déformations membranaires (Manni et al., 2018). Cette étude alliant expérimentations et simulations de dynamique moléculaire a permis de mettre en évidence que (i) les phospholipides à deux acides gras polyinsaturés, peu fréquents naturellement, favorisent fortement la vésiculation mais en contre parti ces membranes sont très perméables ; (ii) les phospholipides polyinsaturés asymétriques (sn1-saturés-sn2-polyinsaturés) offrent un compromis entre une vésiculation efficace et une faible perméabilité des membranes ; (iii) une fois intégrés aux phospholipides, les acides docosahexanoïques (DHA ; omega-3) sont plus faciles à déformer que les acides arachidoniques (omega-6). Cette étude a été réalisé sans tenir compte de la composition asymétrique au niveau des feuillets membranaires. En effet les deux feuillets d'une bicouche membranaire ont naturellement une composition en phospholipides différente. Combinant des approches de Dynamique Moléculaire All-atoms (AA) et Coarse-grained (CG), nos premiers résultats montrent que la capacité de déformation de la membrane est différente selon la position des phospholipides polyinsaturés dans les feuillets membranaires.

Mots-Clés : membranes ; dynamique moléculaire ; lipides polyinsaturés

Session 4 : Protéines membranaires

Unravelling features of drug-membrane crossing events by MD simulations

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Membrane crossing by xenobiotics is a **key pharmacological step**. Xenobiotics can insert and partition in lipid bilayer membrane. According to their chemical structure, they interact with and anchor to the **polar head group region** of the bilayers. According to the depth of penetration they can either directly achieve their biological activity (*e.g.*, antioxidant action), or be taken over by membrane metabolizing enzyme (*e.g.*, CYP450).

Again, according to their chemical structure, xenobiotics can cross membranes. Although passive permeation can be relatively slow, or virtually impossible for certain derivatives, they can alternatively be taken over by **membrane transporters**, *e.g.*, solute carrier or ATP-binding transporters (**SLC**or **ABC**, respectively). Based on molecular modeling simulations, agreeing with and supporting experimental data, we will provide an overview of xenobiotic compound / membrane interactions, partitioning and crossing.

Special attention will be paid to the transport of xenobiotics systems through ABC transporters, which requires **large conformational changes** from Inward-Facing (IF) to Outward-Facing (OF) conformers. This pumping motion is far beyond the reach of classical molecular dynamics (MD) simulations and to be explored, and it requires the use of biased MD simulations. Using metadynamics parameterized with a series of collective variables, we have studied the energetic landscape of the large conformational changes associated with the **transport of xenobiotics** through a prototypical ABC transporter surrounding by a lipid bilayer. Several intermediate conformers were identified, allowing construction of the preferred path from the IF to OF conformers. The IF-occluded conformers, where all domains are in close contact, was thoroughly analyzed to understand how this triggers domain swapping responsible for the transport.

Also, we constructed a molecular human ABCC4/MRP4 structure. With these molecular models and their dynamics in hands, **docking of various xenobiotics compound s**can be accurately carried out to establish **structure activity relationship** enabling better understanding of the transport of xenobiotics through membranes.

Mots-Clés : biased molecular dynamics ; in silico pharmacology ; drug ; membrane crossing events

Molecular dynamics studies predict the alternative mechanism of glucose transfer by GluT1

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Glucose is an essential source of energy for the mammalian cells. Its transport to erythrocytes and endothelial cells of the blood-brain barrier occurs as the result of the facilitative diffusion governed by the human glucose transporter type 1 (GluT1). GluT1 belongs to the Major Facilitator Superfamily (MFS) of membrane transporters and shares common MFS protein fold. It consists of 12 transmembrane helices organized in two distinct domains forming a large hydrophilic cavity at the center of the protein. According to the generally accepted hypothesis on the alternating access mechanism, glucose transport by GluT1 appears through a cycle of major conformational changes: the protein must adopt outward facing (open to the extracellular medium) conformation for the ligand uptake, and then switch to the inward facing (open to cytoplasm) state for the ligand release. All the resolved GluT1 structures are obtained for the inward facing state in the presence of detergent. We have used the 4PYP X-ray structure to model GluT1 conformational behavior in membrane environment with help of molecular dynamics simulations. We observed the protein transition and stabilization in the outward-facing state. Using this conformation as an initial state, for the first time we have obtained a complete unbiased trajectory of the glucose transport through GluT1. Interestingly, glucose transfer can occur without any prominent transition of the overall GluT1 conformation. It is actually driven by the side chain translocation and minor rearrangement of helical segments. We identify the main binding sites occupied by glucose molecule during its diffusion through the protein cavity. Besides energetic aspects, we also explore kinetic properties of transfer by examining glucose residence time in binding sites and the transition probability between them. This study clearly revisits the alternating access mechanism and brings new clues to better understand how GluT1 accompanies glucose transit.

Mots-Clés : molecular dynamics ; alternating access mechanism ; glucose transporter ; membrane protein

Session 4 : Protéines membranaires

Coarse-grained simulations to predict the dynamical interactions of GPCRs with their partners

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Despite an apparent low level of structural complexity, G-protein Coupled Receptors (GPCRs) are highly dynamical proteins, their conformational plasticity being directly involved in their ligand binding, activation or coupling to intra-cellular partners. The prediction of protein-protein or peptide-protein interaction constitutes one of the most interesting modelling challenge as it requires a proper exploration of all conformations, not only of the isolated partners but also of the resulting complex(es). In a pioneer work, Dror et al. demonstrated that Molecular Dynamics (MD) simulations performed with classical « all-atoms » force fields could achieve such a goal and predict at the molecular scale the binding of a drug to its receptor [1]. Unfortunately, the size of these systems and the time-scale (>> µs) required to observe such a binding strongly limit the use of this approach to laboratories having access to huge computational facilities dedicated to MD.

These last years we have tested and validated a new unbiased method that combines the MARTINI coarse-grained model [2] and Replica-Exchange MD (REMD) simulations to predict the binding of peptides to proteins. The main advantage of this approach is to be much less computationally expensive and can be employed at a medium throughput scale.

During my presentation, I will briefly describe how we validated our protocol on the two Neurotensin and CXCR4 receptors, predicting the binding modes of their cognate peptides in close agreement with experimentally-resolved structures [3].

In a second step, I will describe how we obtained a model of the ghrelin peptide bound to its receptor, helped by a cross validation with NMR experiments. We were able to propose a dynamical view of the conformation ensemble of ghrelin in the context of the receptor. We also shown that the method was able to qualitatively reproduce the binding propensity of both acylated and unacelytaed ghrelin, which are shown experimentally to possess different binding affinity to the ghrelin's receptor.

To conclude, and as perpective, I will present the possible extension of our protocol to the prediction of protein:protein interactions.

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Mots-Clés : GPCR ; Coarse grain force field ; protein:peptide binding

Session 4 : Protéines membranaires

Mechanism of GPCR activation triggered by ligands, mutations and protonation

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G protein-coupled receptors (GPCRs) are the targets of more than 40% of marketed drugs. Atomistic-level description of their activation mechanism is highly pursued for structure-based drug design. Over the last few years, we have implemented an effective enhanced-sampling molecular dynamics simulation protocol, which enabled monitoring in detail the complex GPCR activation mechanism, such as in the three cases below.

(1) The neurotensin receptor type 1 (NTSR1)–a class A GPCR and the receptor of neurotensin, a peptide that acts as a neurotransmitter and hormone in the central nervous system and in the gut. We found that the neurotensin peptide frequently changed its conformation at the entrance of the receptor orthosteric pocket. This oscillated the pocket and activated, in a long range, the conserved "connector" residues at the receptor core. The connectors drove the receptor activation at the intracellular end in a loosely coupled manner. We also showed how point mutations diminished or enhanced this activation process.

(2) The C-X-C chemokine receptor type 4 (CXCR4)–a class A GPCR that controls cell migration involved in cardiovascular organogenesis, hematopoiesis, immune response, and cancer metastasis. We focused on the allosteric modulation mechanism by the conserved Na+-binding site at the receptor core. We found that two constitutively active mutations at the allosteric site promoted activation by i) diminishing Na+ binding into the allosteric site and ii) facilitating activation of the connector residues. Protonation of the conserved Na+-anchoring residue, D2.50, was found to favor activation via an alternative pathway.

(3) The metabotropic glutamate receptor 5 (mGluR5)–a class C GPCR and receptor of the neurotransmitter, glutamate. We studied the truncated transmembrane domain (TMD) of mGluR5, which had been shown to behave like class A GPCRs. Our simulations revealed how a positive allosteric modulator (PAM) activated the mGluR5 TMD, whereas a negative allosteric modulator (NAM) and a point mutation inhibited the activation.

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Mots-Clés : GPCR ; molecular dynamics ; replica exchange ; allosteric modulation

Session 5 : Chémoinformatique, Drug Design

Accélérer la Découverte de Composés Actifs grâce à l'Utilisation de Techniques de Modélisation Avancées et d'Apprentissage Profond

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L'obtention d'une très forte affinité tout en maintenant les propriétés du ligand requises pour assurer la sécurité et l'efficacité biologique, est un objectif primordial de la découverte de nouvelles molécules biologiquement actives. Nous présenterons comment des modèles d'apprentissage générés automatiquement peuvent être utilisés pour accélérer rapidement l'identification de propriétés satisfaisantes dans des conditions réalistes de projet de découverte de médicaments. Nous nous intéresserons plus particulièrement à l'application de méthodes d'apprentissage profond en combinaison avec des méthodes de modélisation moléculaire afin de gérer des molécules synthétisables et ayant des propriétés d'intérêt. Nous discuterons également de l'application de l'apprentissage profond et des réseaux neuronaux convolutifs à la modélisation QSAR. Enfin, nous discuterons de l'état des nouvelles architectures de réseaux neuronaux profonds afin de récapituler des calculs de mécanique quantique et de l'impact potentiel de ces nouvelles méthodes dans la recherche de composés actifs.

Mots-Clés : Deep Learning ; Drug Design ; FEP ; Enumeration ; QSAR ; Machine Learning

Session 5 : Chémoinformatique, Drug Design

Modèle numérique des relations structure-saveur

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La compréhension des mécanismes moléculaires de la perception des saveurs est fondamentale pour concevoir de façon rationnelle de nouveaux modulateurs du goût. L'identification de nouveaux composés sapides est un enjeu central pour l'industrie agro-alimentaire et intéresse également l'industrie pharmaceutique, notamment pour masquer l'amertume de nombreux médicaments. Automatiser l'identification de nouveaux composés sapides revient à répondre à la question suivante : un ordinateur peut-il apprendre à goûter ?

Les goûts sucré, umami, et amer sont détectés par les récepteurs gustatifs (TASR) appartenant à la famille des récepteurs couplés aux protéines G (RCPG). À ce jour, de nombreuses structures tridimensionnelles de RCPG ont été résolues expérimentalement, mais aucune d'entre elles ne fait partie des récepteurs chimiosensoriels. Sans cette information, prédire l'activité et le mécanisme d'action d'une molécule sapide vis à vis d'un récepteur gustatif reste un défi. Le génome humain compte une trentaine de gènes fonctionnels codant pour un récepteur de la famille des TASR. Le code combinatoire à la base de la perception des saveurs explique pourquoi un nombre limité de récepteurs gustatifs permet d'identifier un très grand nombre de composés sapides chimiquement et structurellement distincts. Cette complexité spectaculaire justifie l'utilisation de modèles in silico élaborés, basés sur la modélisation des récepteurs et/ou l'intelligence artificielle.

Nous présenterons les derniers modèles de relations structure-saveur mis au point en combinant tests fonctionnels in vitro, expériences de mutagénèse dirigée, machine-learning et modélisation moléculaire des TASR dans un environnement physiologiquement inspiré.

Mots-Clés : saveur ; goût ; modélisation moléculaire ; TASR ; RCPG ; machine learning

Session 5 : Chémoinformatique, Drug Design

Improving ligand screening by exploiting structure ensembles and machine learning

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Nuclear receptors (NRs) are DNA-binding transcription factors and one of the most important cellular mediators for sensing (hormones, drugs, xenobiotics) and signal transduction. Therefore, their dysfunction and the subsequent aberrant signaling is associated with many diseases concerning cancer or reproduction and metabolism disorders. Due to their ligand binding ability they are of interest for a broad scientific field, in particular for the pharmaceutical industry as potential pharmaceutical targets and for drug development and in toxicology and environmental science for risk assessment. In particular the Estrogen Receptor alpha (ERα) is an important target for medical treatment and among the most studied NRs.

Predicting the interactions between small molecules and receptors plays a critical role in drug discovery and development.

During our study, **exhaustive docking** for all known ERα ligands present in BindingDB was achieved using parallel docking on conformational ensembles, which also result in more precise pose predictions. This result enables us to employ a **random forest** (RF) **machine learning** algorithm on a large high quality data set in order to predict precise **binding affinities**. Here, the “sampling problem” is tackled by using structure ensembles, while taking advantage of numerous scoring schemes for virtual screening to better evaluate ligand conformation and protein-ligand interactions.

These results pave the way for a web server dedicated to rapid and high-accuracy docking into the estrogen receptors (EDMON: http://atome4.cbs.cnrs.fr/ATOME_V3/SERVER/EDMon_v3.html).

Mots-Clés : machine learning ; random forest ; affinity prediction ; nuclear receptor

Session 5 : Chémoinformatique, Drug Design

Combiphore (Target-based and Ligand-based) approach to design novel allosteric CD73 inhibitors as cancer chemotherapeutic agents and their biological evaluation

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Despite the great advances in the development of monoclonal antibodies in cancer immunotherapy, their promise has not been translated into clinical successes in large part due to tumor-associated immune suppression. The only remarkable success was obtained by using checkpoint inhibitors such as anti-PD-1 or PD-L1 (programmed death-ligand 1) antibodies. Multiple immunosuppressive mechanisms impede anti-tumor response. Among them, the accumulation of extracellular adenosine (ADO) which is a potent immunosuppressive agent. Decreasing ADO levels represents a promising strategy in the treatment of cancer alone or in combination with anti-PD-L1 based therapy.

CD73, known as ecto-5'-nucleotidase is *overexpressed on cancer* and immune cells. This membrane-bound enzyme attached to the extracellular cell-surface catalyzes the hydrolysis of adenosine monophosphate (AMP) into ADO and inorganic phosphate and therefore participates actively in the accumulation of high level of ADO in the tumor microenvironment. CD73-generated ADO has been shown to promote cancer progression and metastasis in breast, ovarian, bladder and gastric cancers. By using silencing methods blocking CD73 expression, mice models could become resistant to carcinogenesis.

In this context, we develop new CD73 allosteric inhibitors using a combined approach: first, a Target-based design was used to identify CD73 inhibitors. For this purpose, an allosteric site identified in the dimeric enzyme was used for virtual screening using a set of protein conformations sampled by Targeted Molecular Dynamics (TMD). This screening allowed identifying hit compounds against CD73. Kinetic studies were performed to determine the inhibition mechanism of these molecules. Among this series, several molecules exhibited a non-competitive inhibition mode compatible with allosteric inhibitors.

Second, a Ligand-based design was used to improve the activity of theses allosteric hits by generating a 3D pharmacophore specific to the allosteric cavity. Then, it was used, in combination with the Target-based approach, to identify new analogs of the more potent hits. This original strategy allowed us to improve the understanding of the binding mode and to establish a thorough structure/activity relationships study, which in fine led to optimized leads.

Mots-Clés : Drug design ; Allosteric inhibitor ; Docking ; Pharmacophore ; Cancer chemotherapy

Session 5 : Chémoinformatique, Drug Design

Structure-Based Drug Design of Dual Mcl-1/Bcl-xL Inhibitors

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Protein-protein interactions (PPIs) control many important physiological processes within human cells.

A hallmark of cancers is the evasion of apoptosis, which is often associated with the upregulation of the anti-apoptotic members of the Bcl-2 family of proteins. These proteins comprise pro-survival (Bcl-2, Bcl-xL, Mcl-1) and pro-apoptotic members. In many cancers, the balance between the pro- and anti-apoptotic Bcl-2 family members is tipped towards survival. Drugs inhibiting the pro-survival activity of Bcl-2 proteins to restore cell death may therefore be valuable as cancer therapeutics.

Even though potent and selective inhibitors of Bcl-2 and Bcl-xL have been developed, it is not enough to re-establish the apoptosis. Mcl-1 protein has been shown to cause resistance to chemotherapeutics; consequently, the inhibition of this protein is required to maintain activity. Our laboratory has synthesized a selective inhibitor of Mcl-1 protein, pyridoclax.a,b However, the discovery of dual Mcl-1 and Bcl-xL inhibitors would be an important advance in cancer treatment.

Starting from the structure of our lead compound, pyridoclax, fragments have been designed with the objective to retain an activity against Mcl-1 and concomitantly target Bcl-xL. For that, the proteins have been analyzed and compared to find the common features. The design, synthesis and the first biological results of these compounds will be presented in this poster.

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Mots-Clés : Mcl1 ; dual inhibitor ; design ; structure ; based

Posters

Poster 1 _____

Degradation of High Energy Molecules using Biological Reduction : a Rationnal Way to Reach Bioremediation

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High Energy Molecules (HEMs) are molecules or substances, which when subjected to heat, pressure, detonation or catalysis, undergo a very rapid decomposition accompanied with the production of a large amount of energy. In other words, HEMs is a generic term used for the materials known as explosives.

Toxicological tests have been performed on such molecules and have demonstrated their potential toxicity for health and environment. The manufacturing, testing, using and destruction of HEMs, and more generally their extensive use during the past century for military purposes, have led to large contamination of soil and groundwater.

Physicochemical treatments of contaminated sites exist, but they are costly, damaging for the environment and in most cases, unfeasible. Bioremediation has emerged recently as an alternative way to detoxify soil from HEMs. By using bacteria or plants, it offers a more environmentally friendly approach to solve contamination issues. However, some metabolic pathways remain unclear and the rate of detoxification is variable from one HEMs to another.

To address this, we propose a rational design strategy for the modelisation of a nitroreductase able to specifically reduce the nitro group of the HEM HMX (High Melting eXplosive). We based our study on *E Cloacae* nitroreductase NTR (PDB structure 5J8G). It has been shown that NTR reduces a broad range of nitroaromatic compounds such as HEM TNT (TriNitroToluene). We used the Rosetta modelling Suite, and specifically the Coupled Moves algorithm, to redesign the active site of the nitroreductase around the new substrate HMX.

Poster 2 _____

Simulations of protein/surface adsorption processes for the conception of antimicrobial coating for new medical devices.

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Hospital-acquired infections, also known as nosocomial diseases, are a major public health care problem. Half of the infections is imputable to the use of invasive medical devices such as catheters, stents or cardiac valves which allows the growth of bacterial biofilm on the surface responsible for the infection.

The purpose of our project is to create a surface coating able to specifically block the Staphylococcus Aureus bacteria. To do this task, a designed protein is grafted on an inorganic surface. The protein sequence can be divided into three parts: a bioinspired anchorage part, a cleavable part specific to Staphylococcus Aureus and an antimicrobial peptide. This way, at the device vicinity, the bacteria cleave the protein and deliver its own poison. Our system works well in solution but its antimicrobial property is annihilated when the protein is grafted on the surface (quartz or gold) indicating that surface/protein specific interactions prevent the biological activity. Therefore, we need to understand at the molecular level the surface/protein adsorption processes in order to propose alternatives able to restore the biological activity of our device.

Our investigations started with gold and quartz surfaces force-field parameterizations through QM computations. Adsorption processes were investigated for two peptides oxidation states through original molecular dynamics protocols and analyses. Free energies of adsorption were determined with umbrella sampling techniques and confirm the experimental results. Our results were able to understand why the bacteria were not able to cleave when the protein is grafted on the surface. Finally, our molecular modeling investigations were able to propose a new coating of materials able to restore the biological activity.

Poster 3 _____

NEW COMPUTATIONAL METHODS & TOOLS FOR STRUCTURE-BASED PROTEIN DESIGN

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Structure-based Computational Protein Design (CPD) has become an increasingly valuable tool for engineering of proteins with desired properties and for investigating sequence-structure relations in ways that were not previously possible. CPD seeks to identify amino acid sequences that will fold into a given 3D-scaffold and possess the targeted property. The application of CPD is broad, ranging from medicine, biotechnology, and synthetic biology to nanotechnologies.

Herein, we present our most recent methodological advances in the CPD field that enabled overcoming technological bottlenecks and hence propose innovative computational methods and tools to explore large sequence-conformation spaces while providing more accuracy and robustness than classical approaches. In particular, relying on our previous Artificial Intelligence-based protein design methods [1-5], we developed EasyE and JayZ, two methods for predicting changes in protein-protein binding free energy upon mutations that either ignore or include conformational entropic contributions [6]. Assessed on a large benchmark of binding affinity experimental measures, both methods outperform existing established approaches.

We also introduce our recent Shades tool, a fully automated data-driven CPD method that exploits local structural environments in known protein structures together with energy to guide sequence design, while sampling side-chain and backbone conformations to accommodate mutations [7]. Shades is based on customized libraries of non-contiguous in-contact amino acid residue motifs. On a benchmark of 40 proteins selected from different protein families, Shades was able to effectively reconstruct sequences by assembling non-contiguous residue sequences coming from similar in-contact residue tertiary motifs in unrelated proteins. Moreover, Shades outperforms a flexible backbone design application, from the Rosetta software, at rebuilding target sequences.

[1-5] Traoré et al. 2017 *Methods Mol Biol. 107-123* – Traoré et al. 2016 *J Comput Chem. 1048-58* – Simoncini et al. 2015 *J Chem Theory Comput. 5980-9* – Allouche et al. 2014 *Artif. Intell. 59-79* – Traore et al. 2013 *Bioinformatics. 2129-2136*.
[6] Viricel et al. 2018 *Bioinformatics. 2581-258.* [7] Simoncini et al. 2018 *Bioinformatics, in press.*

Poster 4 _____

Modeling protein loops with multiple stable conformations: a challenge for sampling and scoring methods

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Protein loops are involved in a variety of biological processes, and in many cases, their flexibility is strongly related to their function. Therefore, a global understanding of their structural and dynamic properties is crucial in determining their role and mechanisms. Despite this, current loop modeling methods mostly focus on finding a unique stable conformation. While these have shown interesting results for many systems, they still struggle with modeling flexible loops, in particular those known to adopt several stable conformations [1].

This work focuses on reconstructing the energy landscapes of such flexible loops. In particular, we studied nine loops for which several high-resolution structures have been experimentally determined. MoMA-LS [2] was first employed to generate ensembles of conformations for these loops. This method is a recent contribution in the field of loop sampling which performs global explorations of a loop's conformational space. Although it focuses on exhaustive sampling rather than single state prediction, it is capable of sampling conformations very close to experimental structures in all the studied cases. Four different loop scoring methods were then applied to the generated ensembles and the resulting energy landscapes reconstructed. The consistency of these landscapes is assessed, along with the ability of these methods to identify the known energy basins.

Results show that fast statistical loop scoring methods can perform better than traditional force fields and show very promising results. However, in many cases, the scaffold used proved to be decisive for conformational sampling. Indeed, structural changes outside the loop can cause collisions with otherwise stable loop conformations, preventing their sampling from other protein states. Therefore, in addition to efficient sampling methods and accurate scoring functions, the ability to consider some flexibility in the rest of the protein backbone seems to be an important requirement for more general and reliable loop modeling methods.

[1] Marks C, Shi J, Deane CM, Valencia A. Predicting loop conformational ensembles. Bioinformatics. 2018 Mar 15;34(6):949–56.
[2] Barozet A, Molloy K, Vaisset M, Siméon T, Cortés J. A reinforcement learning approach to enhance exhaustive protein loop sampling. 2019. Manuscript in preparation.

Poster 5 _____

Dynamique moléculaire gros-grain du transport ionique à travers un nanopore protéique

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La méthode de spectroscopie des nanopores (Nanopore Force Spectroscopy) consiste à appliquer une différence de potentiel à travers un nanopore artificiel ou protéique, inséré dans une membrane solide ou lipidique, en présence d'une solution saline, afin de guider un polymère chargé. La molécule qui passe dans le pore le bloque partiellement et induit un changement du courant ionique caractéristique de la molécule et du pore. L'alpha-hémolysine est une toxine couramment utilisée comme nanopore protéique pour les expériences de NFS. Afin d'interpréter au niveau microscopique les processus physiques impliqués dans ces expériences, des simulations de dynamique moléculaire sont grandement utiles.

Nous utilisons le champ de force de MARTINI afin de tester l'efficacité des modèles gros-grains pour simuler le transport ionique à travers les nanopores protéiques. Nous avons d'abord calculé la conductivité des ions gros-grains en solution, avec le modèle d'eau polarisable PW de MARTINI, et nous l'avons comparée avec les résultats expérimentaux. Ensuite, nous avons étudié les propriétés électrostatiques d'une bicouche lipidique de DPPC entourée d'ions et de solvant polarisable, en présence d'un champ électrique extérieur. Nous avons montré que cette approche reproduisait bien les conditions expérimentales d'une différence de potentiel appliquée de part et d'autre de la membrane. Enfin, nous avons effectué des simulations de dynamique moléculaire gros-grains du transport ionique à travers l'alpha-hémolysine insérée dans une bicouche lipidique, en présence de différents champs électriques extérieurs, pour des durées de 2 à 3 microsecondes. La courbe I-V (courant/différence de potentiel appliquée) issue de nos simulations est cohérente avec la courbe expérimentale, même si les courants mesurés sont plus faibles. En particulier, l'asymétrie de courant entre potentiels positifs et négatifs est bien reproduite. De plus, nous avons mis en évidence l'importance de prendre en compte la flexibilité du pore dans les simulations.

Poster 6 _____

Dynamic Atomic Models of Full Hepatitis B Vaccine Particles During Structuration and Maturation

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From “simple” proteins to full live-attenuated pathogens, vaccines are complex bio-systems. This complexity results in numerous sources of heterogeneity, and traditional bio-immuno-chemistry analytic tools are often limited in their ability to fully describe the molecular surface organization of antigens (Ag). The gap between functional Ag characterization and epitopic surface description can be reduced when Ag atomic 3D models are available. For the Hepatitis B vaccine particle (HBsAg), no atomic data are available yet, but the main know elements of HBsAg structure were used to reconstitute and model the Ag particle's confection (synthesis and maturation) at a molecular level. For the first time, full HBsAg particle Dynamic Atomic Models (DAMs) were built based on partial data and amino acid sequence analyses. A dedicated computational workflow was used to correlate structural/antigenic knowledge with the HBsAg particles' DAMs. The quality of the *ab initio* HBsAg model was checked for its accuracy and compared with other not fully characterised experimental data.

Poster 7 _____

Modeling of the CPIII:C1C2:BMP-1 complex

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Procollagen C-proteinase enhancer-1 (PCPE-1) is a secreted protein that specifically accelerates proteolytic release of the C-propeptides from fibrillar procollagens, a crucial step in fibril assembly. As such, it is a potential therapeutic target to improve tissue repair and prevent fibrosis, a major cause of mortality worldwide. Here we present a model of the crystal structure of the active CUB1CUB2 (C1C2) fragment of PCPE-1 bound to the C-propeptide trimer of procollagen III (CPIII) and complexed with a specific proteinase, the bone morphogenetic protein-1 (BMP-1). This shows that the two CUB domains bind to two different chains of CPIII and that the N-terminal region of one CPIII chain, close to the proteolytic cleavage site, lies in the cleft between CUB1 and CUB2. This suggests that enhancing activity involves unraveling of this chain from the rest of the trimer, thus facilitating the action of the proteinase involved.

Poster 8 _____

Importance des modifications post-transrationnelles pour les interactions entre les protéines et les surfaces minérales

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Les nanoparticules sont abondamment utilisées par les industries alimentaire, cosmétique et pharmaceutique et leur présence dans notre corps n'est pas un mystère. Une fois au contact d'un milieu biologique, la nanoparticule ne reste pas nue mais interagit immédiatement avec les protéines présentes dans son environnement proche pour former la corona. La compréhension des mécanismes impliqués dans l'interaction des protéines avec les surfaces inorganiques est d'un intérêt majeur à la fois pour la recherche fondamentale mais également ses applications dans l'industrie. Nous nous intéressons depuis plusieurs années aux nanoparticules de silice (E551) utilisées fréquemment comme additif alimentaire [1-4].

Par spectroscopie de masse, nous avons pu déterminer que les protéines cellulaires ayant la plus grande affinité pour les nanoparticules de silice comportaient des motifs arginine-glycine-glycine (RGG) [5]. Des expériences biochimiques complémentaires ont confirmé que les motifs RGG interagissaient fortement avec les surfaces de silice. De plus, l'affinité de ces motifs est encore augmentée lorsque le résidu R est asymétriquement diméthylé alors que ce n'est pas le cas quand il est symétriquement diméthylé. Les simulations de dynamique moléculaire montrent que la diméthylation asymétrique génère une asymétrie électrostatique le groupe guanidinium du résidu R, en l'orientant et en le stabilisant la surface de silice. Les motifs RGG (méthylés ou non) ciblent systématiquement les groupes siloxyde à la surface de la silice par une interaction ionique, immédiatement renforcée par des liaisons hydrogène avec des groupes silanol et siloxane proximaux. Étant donné que, *in vivo*, les motifs RGG sont souvent diméthylés de manière asymétrique par des méthylases cellulaires spécifiques, nos données confortent l'idée selon laquelle ce type de méthylation est un mécanisme essentiel permettant aux cellules de réguler l'interaction des protéines RGG avec leurs partenaires cellulaires.

Poster 9 _____

Modélisation de l'orientation d'enzymes sur la surface d'électrodes pour la production d'énergie verte

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Les enzymes sont des biocatalyseurs pouvant réaliser de multiples réactions dans diverses conditions physiques. Une fois immobilisées sur des supports conducteurs, les enzymes redox peuvent avantageusement remplacer les catalyseurs au platine (rares, chers et difficilement recyclables) dans des dispositifs tels que les biopiles. Grâce aux recherches sur la production de H2 basée sur des ressources renouvelables, les biopiles à H2/O2 peuvent être considérées comme un dispositif de production d'énergie "propre".

Le projet ANR ENZYMOR vise à déterminer les paramètres moléculaires optimisant l'efficacité des enzymes adsorbées afin de maximiser la durabilité et les performances des biopiles. Ce projet implique les équipes BIP (Bioénergétique et Ingénierie des Protéines, UMR 7281, Marseille), CBMN (Chimie Biologie des Membranes et Nanoobjets, UMR 5248, Bordeaux), et LBT (Laboratoire de Biochimie Théorique, UPR 9080, Paris).

Les performances des prototypes de biopiles conçus par l'équipe BIP sont bien en deçà de celles attendues. Des résultats expérimentaux suggèrent que les enzymes sont fonctionnelles, mais mal orientées vis à vis de la surface de l'électrode. Cette mauvaise orientation entraînerait un transfert électronique médié, tandis qu'une orientation optimale rapprocherait suffisamment le relais d'électrons à la surface de la protéine de la surface de l'électrode pour permettre un transfert électronique direct enzyme/électrode.

Nous souhaitons ici étudier par dynamique moléculaire l'adsorption de protéines d'intérêt (telles que la bilirubine oxydase de *Myrothecium verrucaria* ou la laccase de *Thermus thermophilus*) sur une surface d'électrode métallique fonctionnalisée grâce à l'ajout de monocouche auto-assemblée (self-assembled monolayer, ou SAM). Ces simulations, réalisées au LBT, ont pour but de déterminer des orientations préférentielles de l'enzyme par rapport à la surface de l'électrode et de décrire leurs variations si les propriétés physico-chimiques de l'électrode sont modifiées. Ces informations nous permettrons de déduire les modifications à apporter à l'électrode pour obtenir une de biopile fonctionnelle, et seront validées par l'étude expérimentale du système menée par le CBMN.

Poster 10 _____

Allosteric inhibitors targeting 5'-nucleotidases to restore the antitumor therapy efficacy

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Human 5'-nucleotidases represent an important class of enzymes in charge of the regulation of the intracellular nucleotide pool as well as the extracellular circulating adenosine. High level of expression has been described for two of these enzymes on cancer or immune cells leading to dramatic consequences in cancer therapy. Indeed, the cytosolic nucleotidase II (cN-II) affects the pharmacological activity of intracellular anticancer drugs and secondly, the membrane-bound extracellular ecto-5'-nucleotidase (CD73) was reported to promote tumor growth, cancer cell invasion and metastasis through the blockade of antitumor immune response. In this respect, we applied an innovative bioinformatics approach including virtual screening and molecular dynamics simulations in order to design new and selective inhibitors against these enzymes. The first approach consisted in screening small fragments able to bind cN-II in order to propose later new potent inhibitors (by linking three fragments together). Starting from an experimental screening by NMR and targeting cN-II, fragment hits have been identified and assembled using molecular docking tools. After chemical synthesis of these innovative compounds, inhibition kinetics assays showed a non-competitive inhibition mode for most of the compounds. These results were expected for allosteric inhibitors and the mode of action was confirmed by solving the crystal structure of the complex. The second strategy applied to CD73 includes two major criteria in the screening, the functional dynamics of the enzyme and the selection of an allosteric binding site. For the second targeted enzyme (CD73), the large domain motions of the enzyme were reproduced by targeted molecular dynamics simulations. 1,000 conformers issued from these simulations were selected to reflect the enzyme conformational changes and used for the search of druggable cavities that do not overlap with the substrate binding site. Hits identified by virtual screening could be evaluated for their inhibition potential either with the purified recombinant enzyme or directly on CD73 expressing breast cancer cells. Promising hit compounds are currently investigated for structural optimization in order to improve their efficiency by means of pharmacophore or combiphore models (*see abstract Braka A. et al.*).

Poster 11 _____

Modélisation tout-atome du complexe d'attaque membranaire.

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Le complexe d'attaque membranaire (MAC) est un des moyens de défense du système immunitaire inné contre les hôtes pathogènes. L'assemblage du MAC est contrôlé par le système du complément, et conduit à la formation d'un complexe multi-protéique. Ce complexe s'assemble à la surface de la membrane de l'hôte pathogène, et forme un pore transmembranaire (diamètre interne de ~10 nm) entraînant la lyse de la cellule cible.

À partir de données structurales éparses, nous avons construit un modèle tout-atome du MAC dans sa forme active (ancrée dans la membrane), en faisant notamment appel à la modélisation par homologie. Une optimisation de ce système par dynamique moléculaire et l'analyse des interfaces entre les sous-unités a permis de proposer une stratégie pour le développement d'inhibiteurs d'interaction protéine-protéine ciblant l'assemblage du MAC. Pour ce faire, nous avons filtré une chimiothèque d'environ 100 000 composés afin d'extraire ceux ayant un profil semblable à celui de la classe des inhibiteurs d'interaction protéine-protéine. Puis, nous avons réalisé un criblage virtuel par docking (SBVS) qui a permis l'identification de plusieurs molécules capables de bloquer l'assemblage du MAC.

La structure tout-atome du MAC a ensuite été utilisée pour en construire un modèle gros-grain basé sur le champs de force Martini, afin de réaliser une longue trajectoire de dynamique moléculaire du MAC ancré dans une bichouche lipidique et un solvant explicite (eau) entourant le système. La trajectoire, d'une durée de 8 microsecondes, a permis de caractériser l'ancrage et d'observer le mécanisme de rupture de la membrane par le MAC.

Poster 12 _____

Interactions structurales entre l'enzyme VKORC1 et les vitamines K1 (phylloquinone), K2 (ménaquinones) et K3 (ménadione)

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La vitamine K hydroquinone constitue le cofacteur exclusif de la gamma-glutamyl carboxylase (GGCX), enzyme indispensable à l'activation de facteurs de coagulation (dans le foie), à la prévention des calcifications artérielles et au métabolisme énergétique (dans les tissus extrahépatiques). Une fois la GGCX activée, la vitamine K est retrouvée à l'état époxyde (biologiquement inactif), puis est réduite en vitamine K quinone et hydroquinone par la vitamine K épxoyde réductase (VKORC1). Cette enzyme membranaire du réticulum endoplasmique assure le recyclage de la vitamine K et donc l'activité physiologique de la GGCX.

Cependant, plusieurs molécules composent la famille des vitamines K : la phylloquinone (vitamine K1), les ménaquinones (vitamines K2) et la ménadione (vitamine K3). Peu d'informations sont disponibles concernant la distribution tissulaire des vitamines K et leur prise en charge respective par l'enzyme VKORC1.

L'objectif de nos travaux était donc l'analyse des interactions structurales entre les vitamines K et VKORC1, afin de définir la capacité de VKORC1 à réduire spécifiquement ou non certaines vitamines K. Une étude par modélisation moléculaire a ainsi été menée, impliquant des simulations de dynamique moléculaire et des calculs d'énergie libre de liaison sur différents complexes vitamine K - VKORC1. Les vitamines K1, K3 et deux formes de vitamine K2 (MK4 et MK7) ont été considérées à l'état époxyde, quinone et hydroquinone. La structure 3D de VKORC1 restant non résolue expérimentalement, un modèle structural construit par homologie avec une VKOR bactérienne a été utilisé. Les résultats générés *in silico* ont été confrontés à des tests d'activité enzymatique *in vitro*, permettant de valider les observations structurales obtenues par modélisation.

Nous avons ainsi démontré la capacité de VKORC1 à recycler les vitamines K1 et MK4 (réduction de la forme époxyde en quinone puis hydroquinone), mais pas les vitamines MK7 et K3. Les caractéristiques structurales responsables de l'activité de VKORC1 vis-à-vis des différentes vitamines K ont été identifiées, notamment les acides aminés participant à la fixation des vitamines K. Un effet membrane vis-à-vis de la chaîne hydrophobe des vitamines K a également été mis en évidence.

Poster 13 _____

EROS-DOCK: Pairwise and Multi-Body Protein Docking using Branch-and-Bound Rotational Search

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Protein-protein docking aims to predict the 3D structure of a binary complex using the structures of the individual proteins. This typically involves searching and scoring in a six-dimensional space. Many docking algorithms use FFT techniques to exhaustively cover the search space and to accelerate the scoring calculation. However, the results often depend on the initial protein orientations with respect to the Fourier sampling grid. Furthermore, Fourier-transforming a physics-base force field can involve a serious loss of precision.

Here, we present a novel docking algorithm, EROS-DOCK (Exhaustive Rotational Search based Docking), to rigidly dock two proteins using a series of exhaustive 3D rotational searches, in which non-clashing orientations are scored using ATTRACT coarse-grained (CG) force field. Eros-DOCK retains the exhaustive nature of FFT-based search algorithms while using a sensitive physics-based scoring function. Rather than calculating an O(N∗M) interaction energy explicitly at every grid point, we use a quaternion "π-ball" to represent the space of all possible 3D Euler angle rotations, and we recursively sub-divide the π-ball in order to cover the rotational space in a systematic way. We apply a "branch-and-bound" approach for the efficient pruning of rotations that will give steric clashes. This is the first time that a branch-and-bound rotational search has been applied to the rigid-body protein docking problem.

EROS-DOCK was tested on a benchmark of 173 complexes. Compared to ATTRACT, our algorithm was able to find local minima that were missed by the ATTRACT gradient-driven atom-based search. After refinement by a short CG minimisation, the EROS-DOCK results were significantly superior to ATTRACT's results according to the standard CAPRI criteria.

Given this first success of EROS-DOCK, we are now applying it to multi-body combinatorial docking. The EROS-DOCK program is available at http://erosdock.loria.fr.

Poster 14 _____

Analyse d'une base de données répertoriant les sites prédits de liaison des gaz nobles dans les protéines et comparaison avec les sites cristallographiques

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Les sites d'interaction des gaz nobles (xénon, krypton, argon, néon et hélium) ont été modélisés dans un grand nombre de protéines de la PDB par un algorithme de docking sur une grille (1). La base de données résultante répertorie la position des sites de liaison des gaz et leur énergie d'interaction (http://group18.csiro.au). La comparaison de cette base de données avec les sites de liaison cristallographiques du xénon et du krypton a montré que cette méthode prédisait correctement les sites de liaison expérimentaux (1).

Toutefois, pour une protéine donnée, il n'est pas facile de discriminer entre un site prédit qui correspond à un site cristallographique et les nombreux autres sites prédits qui peuvent donc être des artefacts, l'analyse de l'énergie de liaison ne permettant pas de faire le tri entre les sites.

Nous avons montré qu'en analysant une famille de protéines structuralement alignée, les sites de liaison prédits dans toute la famille correspondaient le plus souvent à un site cristallographique, et qu'un site de liaison qui n'était prédit que dans un membre de la famille avait plus de chances d'être un artefact.

Cette analyse par famille permettra d'analyser des familles de protéines potentiellement intéressantes où les sites de liaisons des gaz n'ont pas été déterminés expérimentalement.

(1) Winkler DA, Katz I, Farjot G, Warden AC, Thornton AW (2018) ChemMedChem 13:1931-1938 ‘Decoding the rich biological properties of nobles gases: how well can we predict noble gas binding to diverse proteins?

Poster 15 _____

Analyse fine de la dynamique des protéines : rigidité, flexibilité, déformabilité ou désordre ?

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Les structures protéiques sont des macromolécules hautement dynamiques. Nous avons exploré la simulation à grande échelle avec 169 protéines, pour observer la dynamique des conformations locales des protéines avec différents points de vues. La question de la flexibilité protéique est abordée en utilisant des approches classiques telles que le RMSf, ou l'accessibilité au solvant, mais aussi entropiquement.

Dans un premier temps, nous avons analysé de manière spécifique comment les trois types d'hélices peuvent s'interchangés, amenant des résultats surprenant (Narwani, Craveur, Shinada *et al*, 2018). Dans un second temps, nous avons analysé les feuillets, ainsi que les coudes β maintenus ou non par des liaisons hydrogènes (*turns* et *bends*). Ces deux derniers sont le plus souvent considérés comme appartenant à la même catégorie, mais en fait leur dynamique est très différente. Les coudes changent vers les *bends* préférentiellement alors que les *bends* iront vers l'état boucle. Pour décrire plus finement, un alphabet structural a été utilisé. Il est capable d'approximer chaque partie des conformations des structures protéiques, et se nomme Blocs Protéines (BPs). Nous avons analysé (i) la manière dont chaque conformation locale initiale de protéines, évolue au cours de la dynamique, à l'aide du logiciel PBxplore (Barnoud *et al*, 2017) et (ii) si certains échanges peuvent exister entre les BPs. Les résultats sont beaucoup plus complexes que de simples échanges entre structures répétitives et boucles, permettant une catégorisation de rigidité / déformation locale suivant la conformation initiale (Narwani, Craveur, Shinada *et al*, en préparation).

Dans un troisième temps, cette analyse nous a amenés à caractériser la notion de désordre à l'aide du même critère entropique. Nous avons déjà vu qu'elle permettait de trouver des régions rigides au sein de zone très flexible (Goguet *et al*, 2017). Utilisant une banque de données de protéines désordonnées, nous avons pu voir qu'elle permettait de clairement caractériser la notion de rigidité, de flexibilité et de désordre suivant sa valeur, amenant aussi la question de la notion de déformabilité (résultats non publiés).

Poster 16 _____

Effet des charges de l'alpha-hémolysine sur le courant ionique étudié par dynamique moléculaire gros-grain

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Les nanopores sont des trous de l'ordre du nanomètre qui permettent le passage de molécules à travers une membrane. Ils ont diverses applications telles que la détection de molécules biologique, le séquençage des acides nucléiques (ADN et ARN) et l'étude de la structure et de la séquence des protéines. Certains de ces pores consistent en des molécules biologiques qui s'insèrent dans des bicouches lipidiques et permettent, par exemple, le transport de molécules entre les différents compartiments cellulaires. Parmi ces nanopores biologiques, l'alpha-hémolysine est très étudiée car elle forme un pore stable dans une large gamme de pH et de température et pour son implication dans la pathogénicité des bactéries *S. aureus*.

La dynamique moléculaire est une approche qui permet de déterminer les processus physiques impliqués lors du transport des molécules à travers les nanopores. De plus, l'utilisation de modèles gros-grains, qui représentent plusieurs atomes par un seul site, permet d'atteindre des durées de simulation plus longues que les modèles tout-atomes et ainsi de se rapprocher des conditions expérimentales. Nous avons donc réalisé des simulations par dynamique moléculaire gros-grains, avec le champ de force MARTINI, d'un système composé d'une alpha-hémolysine insérée dans une bicouche lipidique dans une solution de 1 M de KCl en présence d'un champ électrique. Nous avons ainsi pu atteindre des durées de plusieurs microsecondes, et après avoir étudié le passage des ions à travers le pore, nous avons obtenu des courants ioniques en accord avec ceux mesurés expérimentalement. Nous avons également étudié l'influence de la charge de certains acides aminés situés à des positions clefs de l'alpha-hémolysine sur l'asymétrie du courant et la sélectivité pour les anions qui sont caractéristiques de ce nanopore. Nous nous sommes plus particulièrement intéressés aux Asp127, Asp128, Lys131 en bas du pore et aux Glu111 et Lys147 localisés au niveau de la constriction du canal.

Poster 17 _____

Etude de la protéine transmembranaire TSPO par simulations de dynamique moléculaire

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TranSlocator PrOtein (TSPO) est une protéine transmembranaire suspectée d'être impliquée dans de nombreux processus biologiques, tels que l'érythropoïèse et le transport de cholestérol. Elle est également suspectée d'être impliquée de près ou de loin dans d'autres processus dans divers organismes (régulation de la photosynthèse bactérienne, apoptose, métabolisme de la porphyrine, etc...). De par ses différents rôles, elle peut être considérée comme une cible intéressante dans de nombreux cas de maladie, comme les cancers ou les maladies neurodégénératives comme la maladie d'Alzheimer. Récemment, des études par RMN et cristallographie par rayons X ont permis la résolution des structures de TSPO pour la souris et deux bactéries (*R. Sphaeroides* et *B. Cereus*) (Jaremko et al., Science, 2014 ; Liu et al., Science, 2015). La dynamique jouant apparemment un rôle essentiel dans les fonctions de transport de cette protéine, nous nous sommes intéressés à l'étude par simulations de dynamique moléculaire de ce système. Nous avons étudié l'impact de la liaison d'un ligand de diagnostic (PK-11195) sur la dynamique de la protéine, en résolution tout-atome, ainsi que le phénomène de dimérisation de TSPO par des approches de type gros-grains. Nos résultats proposent une description des phénomènes dynamiques de TSPO en présence d'un ligand, qui stabilise la structure secondaire de la protéine, comparé à sa forme apo, et modifie la dynamique du motif de liaison du cholesterol de l'hélice transmembranaire 5. Enfin, sans être hautement spécifique, les interfaces mises en jeu dans le processus de dimérisation impliquent fréquemment les couples d'hélices 3 et 4. Ceci souligne aussi la capacité de TSPO d'interagir avec d'autres partenaires. Cette étude fournit ainsi des informations précieuses sur la nature de résidus impliqués dans le processus d'oligomérisation proposé par les études expérimentales mais aussi sur les mécanismes dynamiques conduisant à ce phénomène.

Poster 18 _____

On recent methods for incorporating receptor flexibility in molecular docking

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A detailed understanding of the interactions between drug candidates (ligands) and target proteins (receptors), through molecular docking is the computational basis of Rational Drug Design. Given a target protein receptor, molecular docking samples hundreds of thousands of orientations and conformations of a ligand inside the protein binding site and evaluates the binding free energy (or a certain approximation to it). While the majority of molecular docking algorithms addresses ligand flexibility, receptor flexibility remains a computational and algorithmic challenge due to the numerous degrees of freedom involved. However, proteins are inherently flexible systems and their flexibility is frequently essential to determine their functions. Therefore, realistic docking simulations need to take into account the molecular flexibility, for both the receptor and the ligand molecules. Indeed, in many cases the lock-and-key binding model does not work well and ligand–protein interactions resemble more the hand-in-glove association model, where both partners are flexible and adjust to complement each other.

Here, we review some recent approaches that handle receptor flexibility in molecular docking. The vast majority of methods considers a single rigid protein structure and only allows some side chains of the receptor in the binding site to be flexible. The choice of the flexible side chains can be often done manually. However, these can also be selected algorithmically. An alternative approach to incorporate the receptor flexibility consists in considering an ensemble of protein structures as the receptor partner. These structures can be obtained experimentally (using several X-ray structures, or multiple NMR solutions), or generated through molecular dynamics simulations or the normal mode analysis. Then, the set of structures can be projected on the same rigid grid for the subsequent docking simulations. Otherwise, a series of individual docking simulations can be performed using one receptor conformation at a time. State of art of sequential and ensemble docking approaches have been presenting better results when compared with rigid receptor docking. In addiction, different scoring functions have been developed that take into account the putative flexibility of receptor side chains and/or backbone atoms.

Poster 19 _____

Development of an in silico protocol to initiate novel substrate promiscuity

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Biocatalysis is increasingly applied across various industries as a means to achieve more sustainable chemical processes. In nature, enzymes have been shaped by up to billions of years of evolution to specifically catalyze one reaction on a narrow substrate scope. An optimization step is thus usually needed to transform a naturally occurring enzyme into an industrial useful biocatalyst. Directed evolution (DE), a process which mimics Darwinian evolution by applying iterative rounds of mutagenesis and selection, has become a powerful tool for engineering novel enzymes.

DE original philosophy and strength involves the generation of random genetic diversity without the need for structural knowledge of the protein. However when such information is available it can be used to create “smarter” libraries and enable time-, labor- and cost-effective procedures. More specifically one critical checkpoint in directed evolution is the selection of an appropriate starting point. It has been highlighted that starting with an enzyme with promiscuous activity on the target substrate increases the chance of success.

Here we describe an *in silico* protocol to identify a set of minimal mutations to expand the substrate promiscuity. The protocol uses a biased MM/GBSA Monte Carlo approach to perform an affinity-based sampling. Molecular dynamics are then performed on the highest ranked variants in order to filter out unstable variants. A tyrosine ammonia-lyase (TAL) was used as a case study with the aim of extending the substrate scope from its original ligand (tyrosine) to other amino acids with different chemistries. Since TAL contains an unusual 3,5-dihydro-5-methylidene-4H-imidazol-4-one (MIO) cofactor in its active site, the first part of the work involves a parameterization step; generalized Born (GB) parameters are optimized to reproduce solvation free energy values obtained with explicit solvation. A set of mutants have emerged from the protocol and should be tested experimentally.

Poster 20 _____

Etude structurale de cystéines dans le protéome entier de l'algue Chlamydomonas reinhardtii subissant des modifications post-traductionnelles rédox

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La cystéine joue un rôle structural et de régulation dans les protéines, contribuant à maintenir l'homéostasie et à réguler la signalisation dans et entre les cellules. La fraction thiol de la cystéine peut évoluer vers des modifications post-traductionnelles rédox réversibles (PTM). Les plus étudiés sont la formation de liaisons disulfure (SS), la glutathionylation (SSG) et la nitrosylation (SNO). Notre objectif est de comprendre les mécanismes moléculaires sous-jacents et les déterminants structuraux permettant de prédire la réactivité de la cystéine.

Nous utilisons des données protéomiques caractérisant des PTM de 1417 protéines de la microalgue verte *Chlamydomonas reinhardtii* pour étudier les paramètres physicochimiques régissant la sélectivité de ces trois modifications des cystéines. Sur des modèles 3D de ces protéines, différents critères sont explorés comme les résidus voisins de la cystéine, le pKa, la surface accessible au solvant... afin de rationaliser le lien entre environnement structural de la cystéine et la/les PTM.

Quelques caractéristiques ont été mises en évidences, notamment le fait que de nombreuses cystéines modifiées se trouvent enfouies. Une majorité de ces cystéines enfouies se situent sur des structures quartenaires de type sandwich ou pli Rossmann [1]. Des études approfondies par des simulations de modes normaux ou en visualisant les modèles protéiques, montrent parfois l'apparition d'un canal, rendant ces cystéines accessibles à de petites molécules comme le NO, ou bien à des ligands plus imposants comme le tripeptide GSH ou GSNO.

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Poster 21 _____

Getting divalent ion–biomolecule interactions right in Molecular Dynamics simulations

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Ion-biomolecule interactions are ubiquitous and play a central role in a number of fundamental biological processes, from calcium signaling to the formation of DNA–protein complexes. Molecular level understanding of these key biological processes first requires to characterize the interaction between biomolecules (proteins and nucleic acids) and divalent cations, which is both an experimental and computational challenge. Indeed, standard biomolecular simulations using non-polarizable force fields suffer from severe overbinding artefacts—especially with divalent cations like Ca2+ and Mg2+—that prevent them to properly capture ion-biomolecule interactions.

We aim to improve the description of divalent cations in simulations and use it to tackle biologically relevant problems. Our strategy is to start with small model systems, where simulation results can be directly compared both to experimental data (e.g. neutron scattering, capillary electrophoresis, etc.) and to reference high-level ab initio simulations in order to systematically assess the validity of our descriptions. These results are used to develop a scaled charge description of the ions and charged biomolecular groups (starting with proteins and lipids), which takes into account electronic polarization in a mean field way [1-3]. Such a description has been shown to successfully improve ion-binding properties in different biosystems.[3,4]

This new original method opens the way to large-scale, accurate, and computationally cheap simulations of divalent cation containing biosystems. Future plans are to use it to improve our molecular understanding of the impact of ions on nucleic acid structure and reactivity.

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Poster 22 _____

Mutations on β-lactamases evaluated using free energy calculations

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Antibiotic resistance is a worldwide public health issue whose exponential increase is threatening the quality and the security of medical care. This resistance is mainly due to β-lactamases, which are enzymes able to cancel the antibiotic effect of β-lactam compounds by hydrolyzing them. This phenomenon is especially worrying with the emergence of new bacteria producing β-lactamases active on all classes of β-lactams (even the carbapenems that are only used as last resort treatment in intensive care units) and leading to therapeutic failure. Some of these were classified in a global priority pathogens list [1].

We are currently interested in the study of interactions between β-lactamases and β-lactam antibiotics to better understand their hydrolytic behaviour. Given that outcomes of docking calculations could be greatly influenced by significant differences in binding sites, molecular dynamics (MD) simulations are required to consider the flexibility of these enzymes.

In this work, we focused on the analysis of oxacillinases (usually named OXA), enzymes belonging to serine-β-lactamase family. To this end, the PMX protocol, initially developed by de Groot team [2] and based on alchemical free energy calculations, was adapted to scan the active site of OXA proteins in order to determine the contribution of each amino acid to the β-lactam hydrolysis. In this work, we show that PMX is a powerful tool providing an automated framework for the introduction of mutations in proteins through the creation of hybrid structures and topologies.

MD-based free energy calculations using OXA enzymes in the presence or absence of ligands provided accurate and reproducible results, that may be further used to predict *in silico*the evolution of β-lactamase-mediated antibiotic resistance. Future investigations will be carried out on other β-lactamase classes and all this information could be a valuable asset for the design of efficient β-lactamase inhibitors.

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Poster 23 _____

MOLECULAR DYNAMICS SIMULATION OF THE ALLOSTERIC MODULATION OF A GPCR BY A MINI-G PROTEIN

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Through their coupling to G-proteins, G-Protein Coupled Receptors (GPCRs) trigger cellular responses to various signals. Some recent experiments have interestingly demonstrated that the G-protein can also act on the receptor by favoring a closed conformation of its orthosteric site, even in the absence of a bound agonist. In this work, we explored such an allosteric modulation by performing extensive molecular dynamics simulations on the adenosine A2 receptor (A2AR) coupled to the Mini-Gs protein. In the presence of the Mini-Gs, we confirmed a restriction of the receptor's agonist binding site that can be explained by a modulation of the intrinsic network of contacts of the receptor. Of interest, we observed similar effects with the C-terminal helix of the Mini-Gs, showing that the observed effect on the binding pocket results from direct local contacts with the bound protein partner that cause a rewiring of the whole receptor's interaction network.

Poster 24 _____

Prédiction d'affinité de complexes PDZ-peptide de structures connues

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Les domaines PDZ sont une famille de domaines protéiques pouvant se lier aux acides aminés C-terminaux de leur protéine partenaire, par une extension de leur feuillet bêta. Ils sont présents dans environ 250 protéines chez l'humain. Leur omniprésence et leur implication dans de nombreux processus biologiques font d'eux des cibles thérapeutiques intéressantes. La conception de peptides inhibiteurs de l'interaction entre un PDZ et sa protéine partenaire peut être aidée par une fonction de score capable de prédire les affinités PDZ-peptide. Dans ce travail, nous avons comparé la fonction de score empirique de Rosetta et différentes variantes de l'approche MMPBSA. Les affinités PDZ-peptide ont été calculées pour un ensemble de complexes de structures connues et comparées aux données expérimentales.

Poster 25 _____

Combining free and local comparative modeling: a new divide an conquer strategy for protein structure prediction

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Despite recent progress, protein structure prediction from sequence remains one of the major challenges in biology. The two main methods used are comparative modeling, that performs well but requires an homologous protein as structural template and free modeling that gives a model of lower accuracy and can treat only proteins of moderate size but does not require a template.

We present a new strategy of the protein structure prediction based on the Protein Units (PUs). PUs describe a new level of the protein 3D structure organization: these are compact structural units, smaller than domains, present in all folds. Starting from a non-redundant set of protein structures, we have identified PUs and clustered them according to their structural similarity. Thus, PUs were classified in families that cover nearly 75% of all fold positions with high accuracy.

We have developed a protein structure prediction strategy using a combination of free modeling and comparative modeling. First, we identify the protein regions corresponding to PUs using a new version of the fold recognition method previously developed by our group (ORION). These regions have then a template structure to perform a local comparative modeling. The remaining not resolved regions are then the subject of free modeling by Rosetta molecular modeling suite. Hence, the degrees of freedom of the system decrease leading to better performance.

This new strategy has been benchmarked, and showed convincing results compared to those obtained by Rosetta alone. Moreover, our method decreases drastically the computation cost.

The method has been used in the last edition of CASP competition (CASP13) in the server category where we have obtained good results on some targets (1st place on five targets).

Poster 26 _____

Structural design and analysis of the rhoA-arhGEF1 binding mode, challenges and applications for protein-protein interface predictions

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The interaction between two proteins may involve local movements such as small side-chains repositioning or more global allosteric movements such as domain rearrangement. We studied how one can build a precise and detailed protein-protein interface using existing protein-protein docking methods, and how it can be possible to enhance the initial structures using molecular dynamics simulations and information-based human inspection. We shall present how this strategy was applied to the modeling of rhoA-arhGEF1 where similar complexes of the GEF family were bound to rhoA and thus could be used for comparative assessment. In parallel, a more crude approach based on structural superimposition and molecular replacement was also assessed. Both models were then successfully refined using molecular dynamics simulations leading to protein structures where the major data from scientific literature could be recovered. We expect that the detailed strategy used in this work will prove useful for other protein-protein interface design.

Poster 27 _____

Dynamique structurale du complexe de récepteurs nucléaires PPARg-RXRa

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Les récepteurs nucléaires constituent une large famille de protéines impliquées dans la transcription des gènes. Leur dysfonctionnement est associé à de nombreuses maladies (cancer, inflammation, diabètes...) ce qui fait de ces protéines des cibles thérapeutiques importantes mais avec des effets secondaires souvent indésirables. Un précédent traitement du diabète à base de thiazolidinedione ciblant le récepteur PPARg a été retiré du marché car certainement impliqué dans l'accroissement du taux de tumeurs. De même, de récentes études ont montré que certaines mutations de ce récepteur ou de son partenaire RXRa sont associées à une augmentation de la transcription des gènes en l'absence de ligands activateur des récepteurs, et présentes dans certains cas de cancers de la vessie.

L'activité des récepteurs membranaires reposent sur un mécanisme allostérique permettant la communication entre leurs différents domaine (celui lié à l'ADN, au ligand, aux protéines co-activatrices). Les méthodes de dynamique moléculaire sont idéales pour décrire ces mécanismes et mieux comprendre le fonctionnement du complexe hétérodimère PPARg-RXRa avec ou sans ligand, sauvage ou muté. Toutefois, la structure complète de ce complexe n'est pas totalement établie: il existe une structure cristallographique, incomplète, et incompatible avec les données en solution (SAXS en particuliers). Nous présentons ici nos premiers résultats de dynamique moléculaire de ce complexe, tentant de comparer les différentes possibilités structurales.

Poster 28 _____

3D models of Tau aggregates related to Alzheimer's disease

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Alzheimer's disease is a slow neuronal degeneration characterized by short-term memory troubles, executive performance disruptions and time and space orientation function disturbance. Brain study of patients with Alzheimer's disease has shown two types of damages which decisively identify the diagnosis: amyloid plaques and neurofibrillary tangles. Each of those two types of lesions is associated to one protein compound: beta-amyloid peptide (Aβ) for senile (amyloid) plaques and hyperphosphorylated tau protein for neurofibrillary tangles. For both of these proteins, key-peptide sequences were identified as responsible for early oligomerization initiating the whole amyloidogenic process(a,b). In this process, these peptides shape in a beta sheet structuration. We are aiming to design and synthetize small peptidomimetic molecules as protein-protein interaction disruptors in order to prevent oligomerization responsible for the disease.

The present study was initiated by a conformational analysis of the Tau key peptide sequences implied in aggregation. The various aggregates were built and their stabilities were assessed through MD (Molecular Dynamic) simulations. Then the analyses of intra- and intermolecular interaction in various aggregate cores were carried out and they will be presented.

Furthermore, MD simulations of Tau aggregates with palmatine, a Tau aggregation disruptor(c), were launched and mechanisms of aggregation disruption will be proposed.

From the unit expertise in rational design of abiotic foldamers, molecular aromatic scaffolds that could disturb the interactions will then be designed, synthesized and biologically tested.

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Poster 29 _____

Three Weaknesses for Three Perturbations: Comparing Protein Unfolding Under Shear, Force, and Thermal Stresses

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Can proteins unfold in shearing fluid flows, and to what extent? How do the tensile forces exerted by the solvent affect the protein compared to other types of external perturbations such as thermal denaturation, or directional pulling forces used in optic/magnetic tweezers or atomic force microscopy (AFM) experiments? Conventional all-atom molecular dynamics simulations often require too much computational effort, hence, we have developed an original methodology using Lattice Boltzmann Molecular Dynamics (LBMD) and the Optimized Potential for Efficient peptide folding Prediction (OPEP) coarse-grained model to inquire the unfolding features of a small Cold Shock Protein subjected to three different perturbations: shear flow, heat shock and pulling force. Since the implicit-solvent OPEP model inherently lacks hydrodynamics, the Lattice Boltzmann framework allowed us to realistically simulate the flow interaction with the protein, while retaining good computational efficiency with respect to explicit-solvent approaches. The direct comparison of the unfolding mechanisms evidenced that the three perturbations act on different weaknesses of the protein, and thus lead on average to very different unfolding pathways. Funny enough, for this small globular protein shear flow acts more similarly to thermal excitation then a direct mechanical force. Our results suggest that the interpretation of experimental studies that rely on force-spectroscopy techniques to investigate natural shear-activated systems, such as the von Willebrand factor or the bacterial adhesin FimH, is not straightforward.

Poster 30 _____

Design of cyclic peptides targeting pockets of protein complexes

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Cyclic peptides are well suited to target protein-protein interactions. Here we present our preliminary results of the *de novo* design of cyclic peptides binding in large surface pockets of protein complexes.

The *in-silico* design protocol aims to optimize the binding affinity by searching for the best complementarity between the peptide and the pocket and by selecting the peptides with the highest conformational stability to reduce the loss of conformational entropy upon binding.

We use Rosetta and its PeptiDerive protocol [1] to help us in the design phase. To evaluate the conformational stability of the top ranking designs, we perform Replica-Exchange Molecular Dynamics (REMD) simulations and our EGSCyP method using robotics algorithms [2].

In addition, docking methods are applied for the analysis of interactions between target protein and peptides.

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[1] Sedan Y., Marcu O., Lyskov S., Schueler-Furman O. (2016) "Peptiderive server: derive peptide inhibitors from protein–protein interactions", NAR V 44(Web Server issue), pp W536–W541.

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http://dx.doi.org/10.1021/acs.jcim.8b00375

Poster 31 _____

TransINT: An interface-based prediction of membrane protein-protein interactions

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Membrane proteins account for about one-third of the proteomes of organisms and include structural proteins, channels, and receptors. The mutual interactions they establish (membrane protein-protein interactions or MPPI) play crucial roles in organisms, as they are behind many processes such as cell signaling and protein function. These proteins and their molecular complexes present potential pharmacological targets par excellence for a variety of diseases, with very important implications for the design and discovery of new drugs. Yet, structural data coming from experiments is very scarce for this family of proteins.

To overcome this problem, we propose a computational approach for the prediction of transmembrane multimeric protein higher-order structures at the plasma membrane of eukaryote cells through data mining, sequence analysis, motif search, extraction, identification and characterization of the amino acid residues at the interface of the complexes. This leads us to the formulation of binding sites used to scan protein sequence datasets for generating new potential interacting protein couples. Our template motif-based approach using experimental MPPI recognition sites leads us to predict new binding sites and to thousands of new binary complexes between membrane proteins when allowing for amino acid mutations to take place.

From our results we generate a database of the interactions we predict. Because of their number and diversity, these complexes and their interfaces represent potential pharmacological targets for the discovery of drugs or peptides modulating or inhibiting the interaction.

Poster 32 _____

UnityMol, une plate-forme made in France de visualisation moléculaire multifonction et évolutive

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Modéliser et visualiser sont des fonctionnalités indispensables en biologie moléculaire pour construire et développer des modèles de systèmes biologiques de plus en plus complexes et réalistes, émettre de nouvelles hypothèses, analyser et explorer des données de plus en plus massives. Dans ce but, la plate-forme *UnityMol* [1] vise à intégrer un ensemble d'outils de visualisation performants en se basant sur le moteur de jeu Unity3D et de proposer un cadre logiciel pour faciliter l'ajout de briques de visualisations (exemple [2]).

Une refonte complète de l'outil et de récents développements ont permis d'élargir le catalogue de fonctionnalités (une console python, un langage de sélection, un mode multi-utilisateur), tout en profitant des nombreuses avancées technologiques du domaine.

Ces fonctionnalités se combinent toujours avec la lecture de trajectoires tout-atome ou gros-grains (Martini, OPEP, HireRNA) personnalisables, tout en offrant la possibilité d'effectuer des simulations interactives, dans un contexte de réalité virtuelle ou sur un ordinateur classique.

Un mode docking protéine-protéine interactif, avec un aperçu visuel de l'énergie potentielle du système, développé en collaboration avec le laboratoire du Dr. M. Levitt à Stanford est également disponible pour explorer un complexe multi-domaine. Ce mode est parfaitement approprié comme première étape de modélisation interactive controlée pour préparer une seconde étape de docking de raffinement plus classique, tout en bénéficiant de la richesse d'interaction du dispositif, des connaissances et de l'intuition de l'expert.

UnityMol propose des modes de visualisation originaux, une interaction potentiellement immersive dans vos données moléculaires en tirant profit de dispositifs de visualisation avancés comme un mur d'image pour un travail collaboratif ainsi que les casques de réalité virtuelle pour bénéficier d'une perception 3D immersive. L'intégration de recherches issues de l'interaction homme-machine reste donc centrale dans ces problématiques.

[1] Lv et al., Game on, Science - how video game technology may help biologists tackle visualization challenges (2013)

[2] Besancon et al., New visualization of dynamical flexibility of N-Glycans: Umbrella Visualization in UnityMol. (2018)

Poster 33 _____

Exploring the flexibility of Pin1 peptidyl-prolyl isomerase using molecular dynamics simulations

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Pin1 is a peptidyl-proplyl isomerase (PPiase) that catalyses the cis/trans isomerization of the phosphorylated Serine/Threonine-Proline *(pS/T-P)* motifs [1]. Pin1 is involved in many biological processes and the perturbation of its expression level has been implicated in several diseases and different types of cancer. In this manner, Pin1 appears as a therapeutic target in cancer treatment. The main features of Pin1 consist of two distinct domains, the N-terminal WW domain and C-terminal PPiase domain. Both domains are known to bind the pS/T-P motifs but only the PPiase domain acts as a catalytic binder. The WW and PPiase domains are connected by a flexible linker.

Several studies promoted the understanding of how Pin1 exerts its catalytic activity [2-3]. Here we present a computational study to evaluate the dynamics of Pin1 structural features, taking into account the solvent environment and the conformational changes of the cis/trans proline residue.

There is evidence suggesting some form of interdomain communication, however the linker between the WW and PPIase domains has never been crystallized due to its high flexibility. In our present work, we carried out homology modeling to complete the linker followed by molecular dynamics simulations in the apo form and in the presence of known inhibitors.

Furthermore, by combining the data from solution-phase NMR and computational ensembles we aim to better understand the dynamic side of crucial interactions within the two domains. Explicit comparison with experimental data will thus provide a more complete atomistic picture of the whole Pin1 leading to the optimization of known inhibitors and the design of new inhibitors.

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Poster 34 _____

PatchSearch: a tool for off-target protein identification

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During the drug discovery process, binding sites comparison can assist in the identification of interactions of drugs with undesired targets (off-targets) and the understanding of adverse effects. Binding site comparison is also helpful drug repositioning and ligand selectivity optimization.

PatchSearch program was specifically designed to search for similar binding sites in the PDB in order to identify off-target proteins. PatchSearch is based upon a clique search in correspondence graph to compare a query binding site to an entire protein surface.

Currently, we aim to improve PatchSearch effectiveness by the use of an energetically scoring function to estimate the affinity between the ligand and the binding site on the probable off-target proteins. Thus, based on the atoms alignment proposed by PatchSearch, the ligand is positioned in the potential similar site and a local optimization is carried out by the Smina program in order to evaluate accurately a binding affinity. Patchsearch

Poster 35 _____

Phylogénie structurale des récepteurs couplés aux protéines G. Focus sur les récepteurs aux odorants

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L'Homme possède environ 400 types de récepteurs olfactifs (ROs). Leur activation combinatoire nous donne la capacité de discriminer un espace spectaculaire de composés chimiques. Ce code combinatoire reste cependant majoritairement inconnu, ce qui rend pratiquement impossible la prédiction de l'odeur d'une molécule en se basant sur sa structure chimique.

La classification actuelle des ROs est basée sur l'homologie de séquence. Ce classement n'est malheureusement pas corrélé aux espaces chimiques associés à ces récepteurs. Afin de relier l'espace récepteur à l'espace chimique, nous proposons de classer l'ensemble des ROs selon les caractéristiques physico-chimiques de leur cavités orthostériques. Cette approche permet d'identifier des néo-orthologues, qui bien que possédant des séquences très variables, partagent des cavités similaires. Cette approche ouvre la voie à la déorphanisation computationnelle de la plus grande famille multigénique du génome humain.

Poster 36 _____

Improving the accuracy of MM/PBSA binding free energy calculations by including the conformational entropy loss of the ligand

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In recent years, computational methodologies have become fundamental in drug discovery campaigns [1]. The molecular mechanics, Poisson-Boltzmann surface area (MM/PBSA) method is one among the most popular computational approaches to predict relative binding free energies [2]. In this strategy, the ΔG of binding is evaluated from configurational sampling of the protein, the ligand and the protein-ligand complex by Molecular Dynamics and includes three components: a potential energy term in vacuum, a solvation free energy term, and an entropic contribution typically accessed by normal-mode analysis [3]. For reasons of efficiency, relative binding free energies via MMGBSA are often accessed via configurational sampling of the protein-ligand complex only (i.e. 1-average approach) and the entropy contribution is neglected [4]. Here, we intend to show that the configurational sampling of the ligand in the unbound state and its entropy loss upon binding are important and may be used to improve the correlation with experiments. For this purpose, we selected ten protein-ligand complexes from the Greenidge dataset [5] and compared predictions obtained with and without entropy correction. The results show that the correlation between calculated and experimental ΔG, which was initially poor (R2 = 0.32), increases by 20% upon introduction of this entropy correction yielding R2 = 0.51. Moreover, the correction is found to be ligand dependent, moderately correlating with the number of rotatable and molecular size. These results suggest that accounting for the conformational entropy loss of the ligand may be useful to reduce the systematic dependence on ligand size and improve the accuracy of MM/GBSA binding free energy calculations.

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Poster 37 _____

Alternative splicing events impact on human protein structure

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In Eukaryotes, alternative splicing (AS) is considered as the major source of the proteome diversity and therefore has a crucial impact on protein function. In order to decipher how structural alteration could affect functional diversity, as proteins structure are the molecular support of function, we investigated some structural properties of human exons through the exon skipping events. Exons of medium length have been systematically characterized in an extensive way both in terms of amino-acids and structural properties. Our results show that alternative splicing events tend to target not well-structured regions at the protein surface, thus preserving the global protein architecture. We also investigated AS impact on enzymes' active sites, showing that they tend to be spared during alternative splicing events. All these results highlight that the functional diversity induced by AS result mainly in the conservation of proteins' core structure and alteration of peripheral regions to create or modulate protein functions or interactions. Finally, considering these results and literature, the mechanisms used by AS to increase functional diversity seem to depend on the exons' length.

Poster 38 _____

NR-DBIND : A database dedicated to nuclear receptor binding data including negative data and pharmacological profile.

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Nuclear receptors (NRs) are transcription factors capable of regulating gene expression in various key physiological processes through their interaction with small hydrophobic molecules. They constitute an important class of targets for drugs and endocrine disruptors and they are widely studied for both human health and environmental risks. Today, the NR family is among the most studied protein families, and the quantity of experimental binding and activity data published in the literature should be valuably used to boost NRs compounds profiling, ligand-based and structure-based drug design, and SAR studies. Accordingly, we gathered diverse NR experimental data that have been published in the literature in a database named Nuclear Receptors DataBase Including Negative Data (NR-DBIND) to help extracting qualitative information for chemists, biologists and toxiciologists. Since the integration of negative data can be critical for accurate modeling of ligand activity profiles, we manually collected and annotated affinity data for molecules experimentally tested against NRs, including both positive and negative results. The NR-DBIND contains the most extensive information about interaction data on NRs, with 15 116 positive and negative interactions data provided for 28 NRs together with 593 PDB structures. The entire database is freely available at http://www.nr-dbind.drug-design.fr and propose multiple datasets.

In the future, the NR-DBIND and all the knowledge it brings to the scientific community should facilitate rational drug discovery for documented NRs and help predicting the NR-related risk of endocrine disruption.

Poster 39 _____

Characterizing the structural variability of HIV-2 protease upon the binding of diverse ligands by mining PR2 crystallographic structures

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HIV-2 demonstrated reduced susceptibility to protease inhibitors (PIs), one major class of antiretroviral drugs [Desbois et al., **2008;** Raugi et al., **2013 ;** Visseaux et al., **2016**]. To better understand this resistance, it is important to characterize PR2 structural changes induced by ligand binding.

In this study, we explored the structural backbone variability of PR2. We compared local conformations of the 18 available crystallographic structures of PR2 in complex with various using SA-conf tool (Regad et al., **2017**), a new tool based on the structural alphabet HMM-SA (Camproux et al., **2004**). We located PR2 structurally conserved positions -- i.e., positions with the same backbone conformations in all PR2 structures -- and structurally variable positions, i.e., positions exhibiting different backbone conformations in all PR2 structures. The analysis of the flexibility of the structural variable positions, measured by B-factor values, allowed to identify positions with structurally variability resulting from PR2 intrinsic flexibility. We then analyzed structural variability of the PR2 binding pocket. We located structurally conserved residues of the pocket important for ligand binding and catalytic function, pocket residues important for ligand recognition that adjust their backbone in response to ligand binding and regions important for the pocket opening and closing that have large intrinsic flexibility. We also showed that induced structural changes in the binding site are accompanied by other induced structural rearrangements located all along the structure revealing cooperative moves in response to ligand binding. The comparison of local conformations of PR2 pockets complexed with two drugs with totally different effectiveness against PR2 suggests that the binding of these drugs causes different backbone deformations that could lead to modifications of interaction networks that could partially explained the differences in drug effectiveness.

To conclude, this study is the first characterization of the PR2 structural variability considering ligand diversity. It provides information about the recognition of PR2 to various ligands and its mechanisms to adapt its local conformations to bound ligands. This work was published in Triki et al. JBSD. 2018.

Poster 40 _____

Fungal membrane lipids interactions study by means of Molecular Dynamics simulations

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In agriculture, the intensive use of chemical pesticides is environmentally-unfriendly and potentially harmful to our health. Therefore, the development of new approaches with less environmental and health impacts is quite a critical challenge. Because some amphiphilic molecules produced by certain microorganisms have antibacterial and / or antifungal properties, while remaining harmless for humans, they can be considered as a reasonable alternative to agrochemicals. Based on direct interactions with the lipids from the target cell membrane, the mode of action of these molecules is rarely known in details.

This PhD project is focused on a family of amphiphiles already used in agrochemistry. These molecules, which are called rhamnolipids, have already been characterized in our laboratory by solid-state NMR experiments. In this context, Molecular Dynamics (MD) simulations are used as an interesting and complementary approach for obtaining a complete description of the interactions of the amphiphilic molecules with fungal membranes.

Slipids ("Stockholm lipids"), an all-atom force field (FF), seems to be the most suitable for our purposes since it explicitly considers atom interactions between heterogeneous biomembrane lipids. However, neither the ergosterol, which is a fungal-specific membrane sterol, nor sitosterol or stigmasterol, which are specific of plants, were described in this FF. Our approach was to use the cholesterol as a reference molecule since it has been considerably more studied and it is very similar to these sterols. Therefore, several simulations of very simple models studied in the litterature have been carried out in order to validate this approach. Using membranes made of 70% phospholipid (DMPC, DOPC or DPPC) and 30% sterol, we were able to validate our sterol topologies by comparing order parameters from MD simulations and NMR experiments.

We have also performed a temperature study of pure DPPC systems from 0°C to 60°C. The phase transition from the gel phase to the liquid phase is well achieved. Currently, we work on more complex models with 53% POPC, 23% POPG and 25% sterol and the interaction with rhamnolipids. This will allow us to study the effect of sterol nature on lipid dynamics and compare with previous experimental results from our lab.

Poster 41 _____

Exploration de la répartition des repliements de protéines au sein d'une phylogénie d'espèces.

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Les protéines se replient par un arrangement de structures secondaires dans l'espace : les folds.

Seulement 1200 folds environ sont répertoriés dans les bases de données comme SCOPe(Fox et al, 2014) ou CATH(Dawson et al, 2017). Ce nombre reste stable depuis 2013. Cependant la diversité en séquences continue de croître dans les bases de données. Peu d'études ont été menées à ce jour pour faire le lien entre les folds et l'évolution des espèces. Dans ce cadre, nous proposons d'étudier les points suivants :

- Comment les folds apparaissent-ils et se conservent-ils dans l'arbre du vivant ?
- Les folds sont-ils un bon signal phylogénétique ?

Dans cette étude, nous avons échantillonné l'arbre du vivant tel qu'il est défini dans la « Classification phylogénétique du vivant » de G. Lecointre et H. Le Guyader. Les 108 espèces sélectionnées ont toutes un génome complet qui a été annoté structurellement et échantillonne les différentes profondeurs de l'arbre. La présence ou l'absence de chaque fold est reportée dans chaque espèce à l'aide du serveur Superfamily (Gough et al, 2001), qui associe un profil HMM à chaque superfamille de SCOPe. Ces données sont ensuite analysées par l'utilisation de méthodes classiques d'exploration des données(ACP, clustering ascendant hiérarchique, heatmap).

L'étude préliminaire de ces données montre que la répartition des folds permet de séparer les trois super-règnes du vivant de façon pertinente. La heatmap corrobore ces résultats en mettant en évidence une répartition spécifique des folds dans les trois super-règnes du vivant Elle permet aussi de mettre en évidence des folds ayant une répartition particulière pouvant être due à des événements évolutifs tels que de la convergence ou des transferts horizontaux.

Poster 42 _____

Binding affinity prediction of protein-peptide complexes with bias-exchange metadynamics

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The prediction of the binding affinity of protein-protein and protein-peptide complexes is still very difficult, even if the 3D structure of the complex is already known. Several algorithms attempt to predict it, however, to obtain an accurate prediction it is necessary to take into account several contributions, like solvation, hydrophobic and polar contacts and most difficult : the entropy.

We propose here a new approach using a bias-exchange metadynamics protocol [1] with four collective variables (distance between the protein and its ligand, hydrophobic or polar contacts and solvatation) to obtain reliable values of the binding affinity. We will present some examples, notably cyclic peptides binding protein interfaces and pockets.

In a first step to reduce the conformational entropy upon binding of flexible peptides, we evaluate their conformational stability in free form by temperature replica-exchange molecular dynamics simulations (REMD) in implicit solvent [2]. In an second step, for the most stable peptides, we use bias-exchange metadynamics simulations to evaluate their binding affinity for their target in explicit solvent. By this way, we can select the best candidats for an *in-vitro* test.

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Poster 43 _____

Fitness landscape analysis to improve computational protein design

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Computational Protein Design (CPD) seeks to engineer proteins with a desired structure or function, and have many practical applications in Biotechnology and Synthetic Biology. CPD methods aim at finding a protein amino acid sequence which minimizes an energy function typically calibrated to maximize the stability of the protein. Search space sampling algorithms such as Simulated Annealing are suitable methods for this task, given the size of the search space and the NP-hardness of the problem. However, we have shown in a previous study that sampling methods fail to get close to the global optimum for some CPD problems and need improvement [1]. Fitness landscapes, which can be seen as a spatial representation of the search space where each solution has a height corresponding to its fitness, can provide useful information on the search space and help to devise efficient optimization strategies. The geometry and properties of the fitness landscapes of CPD are not well understood, due to the difficulty for sampling methods to access the multiple optima and explore their neighborhoods. Using some powerful exact optimization method, we exhaustively enumerate all protein sequences in the vicinity of the global optimum of CPD problems. We provide various features, such as multimodality and local optima networks, in order to characterize the fitness landscapes. By comparing the features of two instances of CPD, we identify some crucial differences in the fitness landscapes and explain the failure of Rosetta, a well-known molecular modeling software, on one of the instances. The structure of the landscape, with the presence of several sub-optimal clusters of local optima disconnected from the basin of attraction of the global minimum, is the main reason for the failure of the simulated annealing algorithm implemented in Rosetta [2]. Our analysis suggests that methods able to periodically perturb the solutions and escape local minima would be more suitable for CPD problems.

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Poster 44 _____

On the export mechanism by RND proteins: AcrB's structure-based study

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RND family proteins are transmembrane proteins identified as large spectrum drug transporters [1]. The paradigm model of those proteins is AcrB, a protein found in bacteria. It was identified as responsible for antibiotic resistance in selected gram negative bacteria, but the drug efflux mechanism is still under debate.

AcrB forms an homotrimer, and the available structures are either symmetric ones (all subunits in the same state), or asymmetric ones (subunits are in three different states, ABE). In its asymmetric state, the protein extrudes a drug molecule against proton uptake. Unfortunately, the size of the system (1049 amino-acid per monomer and membrane) is such that dynamic simulations failed to unveil the detailed mechanism [2].

This study [3] makes a stride towards a finer understanding of the export mechanism, exploiting the known crystal structures (35) as well as novel modeling tools.

- First, we show that all asymmetric trimers occupy the ABE state.
- Second, we exhibit states for domains of AcrB, and ascribe these to states of whole subunits.
- Third, we characterize the conformational changes undergone by the domains of a given subunit, which is key to correctly classify monomers and trimers.
- Fourth, we delineate the evolution of contacts between subunits and the drug during the export mechanism.

Finally we confront the obtained results to the rest of RND's available structures.

Altogether, these insights pave the way to performing dynamic simulations of AcrB, by focusing on those degree of freedom which are key during the export mechanism. In turn, these findings may foster the design of molecules blocking the efflux.

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Poster 45 _____

Identification and characterization of exploitable pockets for the allosteric modulation of the Glycine receptor function

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Pentameric ligand-gated ion channels (pLGICs) are neurotransmitter receptors that mediate the intercellular communication in the brain and the nervous system by converting a chemical signal into an ion current at chemical synapses [1]. Among them, glycine receptors (GlyR) play a critical role in motor coordination and essential sensory functions including vision and audition, and have been since long recognized as pharmacological targets for chronic pain, autism and the startle disease [2]. At the structural level, GlyR is by far the best-characterized pLGIC. Several high-resolution structures with modulatory ligands have been recently deposited [3] [4] [5] [6], and recent simulation work by us [7] has contributed to the establishment of an atomistic model of the physiologically active state. Here, we continue the exploration of the structure-function assignment in GlyR by Molecular Dynamics in the resting and the desensitized states. Starting with the high-resolution structures of GlyR α1 in complex with the antagonist strychnine [3] and GlyR in complex with ivermectin and the positive allosteric modulator AM3607 [4], we collected sub-µs trajectories of the channel in the native lipid membrane environment. The simulations provide a detailed description of the conformational dynamics of the modulatory sites and highlight changes in volume and shape promoted by the functional isomerizations. This analysis is relevant for the rational design of positive and negative allosteric modulators of GlyR.

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Poster 46 _____

Structure-guided design of Mcl-1 inhibitors, application to the ovarian cancers treatment.

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Protein-protein interactions are attractive targets because they control numerous cellular processes. In oncology, apoptosis regulating Bcl-2 family proteins are of particular interest. Bcl-2 proteins are crucial regulators of the intrinsic mitochondrial pathway of apoptosis and comprise both pro-apoptotic and anti-apoptotic proteins.1 Apoptotic cell death is controlled *via* PPIs between the anti-apoptotic proteins hydrophobic groove and the pro-apoptotic proteins BH3 domain. Mcl-1 (an anti-apoptotic Bcl-2 member) is a key regulator of cancer cell survival and a known resistance factor to Bcl-2/Bcl-xL pharmacological inhibitors making it an attractive therapeutic target. As interaction among Bcl-2 family proteins occurs through α-helices, our laboratory has developed a new family of compounds able to mimic α-helix side chain distribution (abiotic foldamers) using as structural chemical units pyridine and/or phenyl2. The designed and synthesized oligopyridines were evaluated by their capacity to inhibit Mcl-1 in live cells and to sensitize ovarian carcinoma cells to Bcl-xL-targeting strategies and Pyridoclax was emerged a lead.3,4 Here, using a structure-guided design from the Pyridoclax, we identified a novel selective Noxa-like Mcl-1 inhibitor, MR31367 that selectively binds to Mcl-1 hydrophobic groove and releases Bak and Bim from Mcl-1.5

Poster 47 _____

RESPIRE: Repository of Enhanced Structures of Proteins Involved in the Red blood cell Environment

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The RESPIRE database [1] assembles external data and original protein structure annotations about Red Blood Cells (RBC) useful to a wide audience of biologists, clinicians and structural biologists. RBC are metabolically-driven cells vital for processes such a gas transport and homeostasis undergoing a controlled cell differentiation leading to the removal of most of the transcription and translation machineries. To provide a more compendious view of the protein content of erythrocytes, we have assembled data linking sequence, structure, and function of erythrocyte proteins, including antigenic annotations important for transfusion. Since a lot of proteins entries lack an experimental 3D structure, we modelled proteins structures using state-of-the art methods for comparative, threading or ab initio molecular modelling methods, with a special attention paid to membrane proteins. We shall discuss during the GGMM congress our results, the challenges and the limitations of bioinformatics data assembly and what can what is nowadays accessible for advanced protein structure prediction.

Database URL: http://www.dsimb.inserm.fr/respire

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Poster 48 _____

GENERATION AND INVESTIGATION OF PROTEIN-BASED CAVITY PHARMACOPHORES

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Identifying the very first ligands of pharmacologically important targets in a fast and cost-efficient manner is an important issue in drug discovery. In the absence of structural information on either endogenous or synthetic ligands, computational chemists have not many possible choices other than docking compound libraries to a binding site of interest, with well-known biases arising from the usage of scoring functions. Recent international docking challenges agree to conclude that the success in ranking ligands by a structure-based approach is strongly related to the level of available knowledge of both the target and its existing ligands, thereby promoting the development of knowledge-based strategies in prioritizing docking poses. For ligand-orphan targets, such approaches are no more possible and novel algorithms need to be developed to find putative ligands from the simple knowledge of a protein structure. We herewith propose a novel approach consisting in the generation of simple cavity-based pharmacophores to which potential ligands could be aligned by the use of a smooth Gaussian function. The method, embedded in the IChem toolkit, automatically detects ligand-binding cavities, then predicts their structural druggability, and creates a structure-based pharmacophore for predicted druggable binding sites. A companion tool (Shaper2) was designed to align ligands to cavity-derived pharmacophoric features. The proposed method is as efficient as state-of-the-art virtual screening methods (ROCS, Surflex-Dock) in both posing and virtual screening challenges. Interestingly, IChem-Shaper2 is clearly orthogonal to these latter methods in retrieving unique chemotypes from high-throughput virtual screening data.

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Le GDR 3003 Bioinformatique Moléculaire (BIM) est un GDR d'animation de l'INS2I (CNRS). Son champ scientifique couvre l'ensemble des approches informatiques et mathématiques pour le traitement de l'information liée aux molécules biologiques. Il regroupe 1200 chercheurs au niveau national, issus des différentes disciplines constitutives de la bioinformatique: biologie, informatique, mathématiques, physique,…

Le Réseau Français de Chimie Théorique est une institution reconnue et financée par le ministère de l'Enseignement Supérieur et de la Recherche, via le CNRS. Il affiche cinq objectifs :
(1) animer la recherche en Chimie Théorique ;
(2) appuyer les collaborations au niveau national et international ;
(3) relier les mondes académiques et industriels ;
(4) soutenir la formation des futurs diplômés ;
(5) créer et maintenir un outil de communication au sein de la communauté.

La Société Française de Biophysique a pour objectifs de :
- promouvoir le développement et d'assurer la diffusion de la Biophysique en tant que discipline scientifique.
- fédérer la communauté des biophysiciens et la représenter à l'échelon national et international.

La SFCi a été créée en 2007 suite à deux manifestations organisées par nos collègues strasbourgeois. Le but de cette société est de fédérer les chemoinformaticiens francophones, qu'ils soient industriels ou académiques. Actuellement la SFCi fédère plus de 100 scientifiques français (60% académique, 40% industriels) issus de 35 laboratoires académiques (dont 4 à l'étranger) et de 27 sociétés privées.

Le Centre national de la recherche scientifique est un organisme public de recherche (Établissement public à caractère scientifique et technologique, placé sous la tutelle du Ministère de l'Éducation nationale, de l'Enseignement supérieur et de la Recherche). Il produit du savoir et met ce savoir au service de la société.

Université Côte d'Azur est un regroupement d'établissements d'enseignement supérieur qui rassemble les principaux acteurs de l'enseignement supérieur et de la recherche sur la Côte d'Azur. Université Côte d'Azur vise à développer le modèle du XXIe siècle pour les universités françaises, basé sur de nouvelles interactions entre disciplines, un modèle expérimental de coordination entre recherche, enseignement et innovation et de solides partenariats avec le secteur privé et les collectivités locales. Cette dynamique est fondée des valeurs d'excellence et d'intégrité scientifique de la recherche. Elle est appuyée par la responsabilité sociétale universitaire d'UCA qui met en œuvre l'égalité femme-homme, la lutte contre les discriminations et pour la diversité et enfin le développement d'une science écoresponsable sur des campus écoresponsables. En janvier 2016, l'Université Côte d'Azur a remporté le prestigieux prix «IDEX» du gouvernement français pour son projet UCA-JEDI, qui l'a placée parmi les 10 meilleures universités françaises de classe mondiale.

PROGRAMME

	Mercredi 3 Avril	Jeudi 4 Avril	Vendredi 5 Avril
8:45		Plénière 3	Plénière 5
9:00		Flash Poster 3	Session 5
10:00		Session 2	
11:00		Pause café	Pause café
		Flash Poster 4	**Prix GGMM**
12:00		Session 3	**Prix Poster**
			Assemblée Générale GGMM
13:00	Accueil	Déjeuner	Déjeuner + Départ
14:00			
	Bienvenue	Plénière 4	**LEGENDE**
15:00	Plénière 1	Flash Poster 5	Plénières
	Flash Poster 1	Session 4	Posters
16:00	Pause café		Sessions orales
	Session 1		Repas
17:00		Session Poster + Pause café	
	Flash Poster 2		
18:00	Session Poster		
19:00	Plénière 2	*Réorganisation des salles*	
20:00	Dîner	Dîner de Gala	
21:00			