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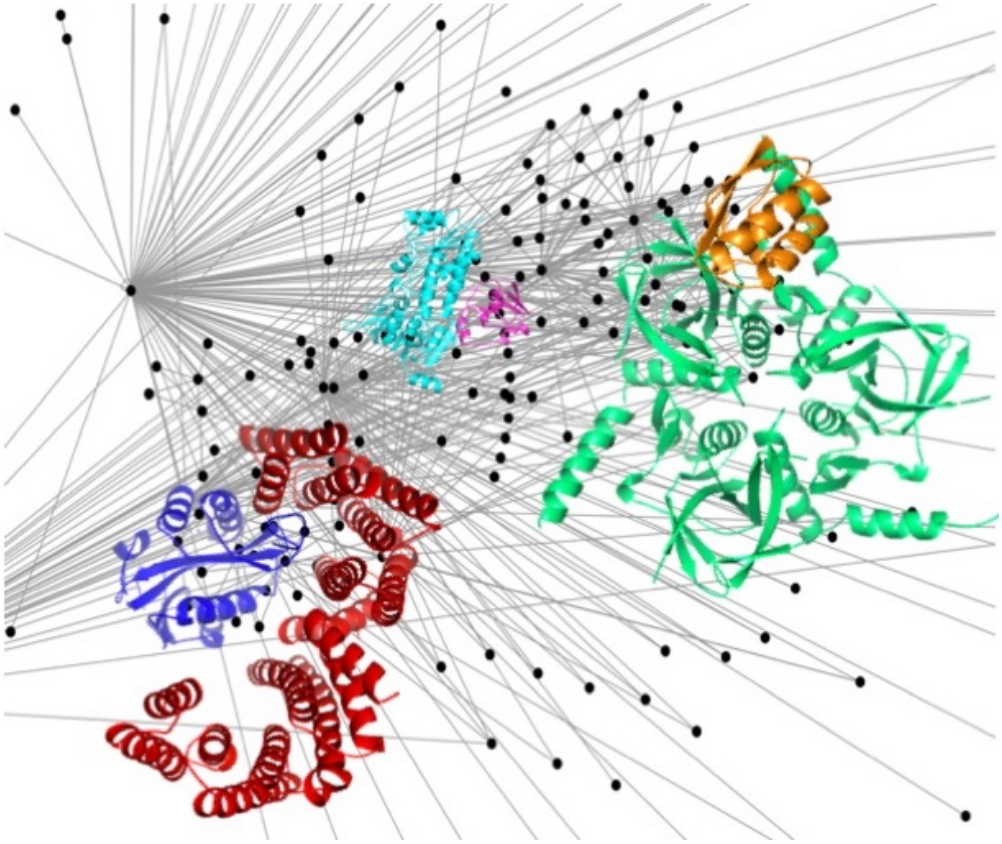

PROGRAMME and ABSTRACTS

Programme

9h00-9h15	**Welcome and opening by the organizers**
Session 1: Genome Analysis	
9h15-10h10	**Keynote speaker**: **Eduardo Rocha**, *Institut Pasteur, Paris* Horizontal gene transfer: from gene acquisition to functional innovation
10h10-10h30	**Julie Lao**, *INRA* Toward an automatic annotation of Integrative Conjugative and Mobilizable Elements
10h30-10h50	*Coffee break*
10h50-11h05	**Sourav Ghosh**, *I2BC* Optimizing the mapping of Nanopore Direct-RNA reads for complex genomics applications
11h05-11h25	**Chris Papadopoulos**, *I2BC* Exploration of the potential of the non coding genome to give rise to novel genes through a structural approach
11h25-11h45	**Yunfeng Wang**, *I2BC* Cancer transcriptome at nucleotide resolution
11h45-12h05	**Javier Zea Diego**, *UPMC-LBCQ* ThorAxe: Transcript-aware orthology relationships among exons
12h05-12h25	**Haoliang Xue**, *I2BC* The Transipedia Project: representing and searching transcripts using k-mers
12h30-13h45	*Lunch Break*
Session 2: Structural Bioinformatics	
13h45-14h40	**Keynote speaker: Adrien Melquiond**, *Utrecht University, Netherlands* A tale with two tails! When integrated structural biology sometimes go wrong
14h40-15h00	**Coline Gianfrotta**, *LRI-UPSUD* A graph-based approach for classifying and predicting A-minor motifs in RNA structures
15h00-15h20	**Audrey Legendre**, *IBISC-UVSQ* Prédiction de structures secondaires de complexes d'ARN
15h20-15h40	**Jean-Charles Carvaillo**, *I2BC-UPSUD* Vers une meilleure compréhension des bases de l'auto-assemblage de la capside du norovirus.
15h40-16h00	*Coffee Break*
16h00-16h20	**Vaitea Opuu**, *Laboratoire de Biochimie-Polytechnique* Computational design of proteins and enzymes
16h20-16h40	**Charline Fagnen**, *LBPA-UPMC* Gating mechanism of a potassium channel, experimental and theoretical studies
Session 3: Integrative & Network Biology	
16h40-17h00	**Mélanie Fouesnard**, *INRA* A multi-omic approach reveals how microbiota-hypothalamus axis adapts to a Western-diet short-term exposure in rats.
17h00-17h20	**Jérémie Pardo**, *IBISC- Univ Paris-Saclay* Sequential reprogramming of biological network fate
17h20-17h30	**Concluding remarks**

Keynote Lecture

Horizontal gene transfer: from gene acquisition to functional innovation

Eduardo Rocha

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Evolutionary processes are typically described as the result of mutation, descent and selection. Many microbes lack sexual reproduction but have the ability to acquire genetic information from very distantly related organisms. Horizontal gene transfer allows the instantaneous acquisition of new complex adaptive traits and their transmission to subsequent generations. This speeds up evolutionary processes as exemplified by the acquisition of virulence traits in emerging infectious agents and by antibiotic resistance in many human bacterial pathogens. In this talk, I'll describe how bacteria control and organize the influx of novel genetic information, and how this results not only in the spread of adaptive functions, but also on radical functional innovation.

Toward an automatic annotation of Integrative Conjugative Elements and of Integrative Mobilizable Elements

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ICE (Integrative Conjugative Element) and IME (Integrative Mobilizable Element) are bacterial mobile elements that play a key role in horizontal transfers. They have the ability to integrate, excise and transfer themselves by conjugation from one bacteria to another. They also carry accessory genes that encode adaptation functions such as antibiotic resistance, heavy metal resistance or virulence factors. Though these elements are known to be highly prevalent in numerous bacteria, their automatic identification is challenging and they are currently not annotated in almost all public genomes.

So far two bioinformatics approaches allow to automatically detect and annotate ICEs and IMEs in bacterial genomes [1,2]. All of them first co-locate “signature proteins” (SPs) that are essential for a functional element. Search of element's boundaries is then carried out, either by using closely related genomes of the same species to delineate ICEs with surrounding core genes [1] or at the nucleotide level by searching DNA repeats at both ends of ICEs and IMEs [2].

However, none of these approaches can detect nested or tandem ICE/IME, which are frequently observed in bacterial genomes. Thus, we designed a 4 steps new approach, named ICEscreen than can detect both single ICE/IME and complex ICE/IME regions:

(i) Detection of SPs of ICE using a previously published approach and new SPs dedicated to IME detection.

(ii) Detection of ICEs by a recursive approach applied to co-localized SPs and dedicated rules and filters that allow to detect isolated, nested and tandem ICEs.

(iii) Detection of IMEs by co-localization of SP and dedicated rules that allow to detect isolated and tandem IMEs.

(iv) The search of ICEs that might host elements detected in steps (ii) or (iii).

We will present the ICEscreen approach and the first results obtained for the annotation of ICEs and IMEs in genomes of Firmicutes.

References

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Optimizing the mapping of Nanopore Direct-RNA reads for complex genomics applications

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In multicellular organisms, chromosomes are folded into complex three-dimensional (3D) structures inside the nucleus, which are important to regulate gene expression. Changes in the 3D architecture of the genome can be directly observed in several complex disease conditions. Molecular biology-based Chromosome Conformation Capture (3C) techniques, particularly Hi-C, have revealed the function of 3D genome organization in a frame work of "Topologically Associated Domains (TADs)", which demarcate regions where promoters can interact with cis-regulatory elements. However, conventional 3C and Hi-C experiments give average population-wide descriptions from thousands of cells, thus lacking information on TAD structures and the detailed nature of chromatin interactions in single cells.

We have developed a new technology, 'Nano-C' that provides information on 3D genome organization for individual chromosomes. Nano-C uses long-read sequencing technology to identify multiple interacting fragments that are present within DNA molecules that constitute a 3C library. To do so, Nano-C combines 3C with in-vitro transcription of long fragments to amplify selected fragments with minimal size bias. The resulting RNA is subsequently characterized by direct RNA sequencing using the Oxford Nanopore Technologies MinION platform.

Because the resulting RNA reads can contain fragments from anywhere in the genome, combined with the relatively high error rate of direct RNA sequencing (~ 15%), no ready to use bioinformatics pipeline for analyzing the datasets was available. I have developed such an analysis pipeline to identify multiple interacting DNA fragments from the long 'Nano-C' RNA-sequencing reads. I have tested the currently available sequencing read mappers (MiniMap2 and BWA-MEM) and determined the optimal filtering parameters for mapping those complex RNA-reads. Using the current pipeline, I can identify up to 11 unique 'Nano-C' interactions for a defined viewpoint within a single cell. I will present the development of our bioinformatics pipeline to analyze 'Nano-C' datasets, covering challenges from genomic alignment to interaction identification and visualization in the UCSC genome browser.

Exploration of the potential of the non coding genome to give rise to novel genes through a structural approach

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Many studies in different organisms delineate examples of de novo genes emergence from non coding regions of the genome. Our analysis reveals an important number of InterGenic Open Reading Frames (IGORFs) in the genome of S.cerevisiae. Experimental data support the pervasive transcription of many of these IGORFs as well as their corresponding RNAs association with ribosomes, suggesting their in vivo translation. In addition, MSMS experiments have detected stable small peptides in native-like concentration that do not present any similarity with already known proteins.

All these show that the non coding regions of the genome host an important and underestimated number of IGORFs, potentially coding for more or less foldable peptides. The last, under specific conditions, could possibly be selected and established as de novo genes.

We used two physics-based molecular bioinformatics methods (HCA & IUPRED) to predict the foldability of these IGORF-translated potential peptides. Our results support that the IGORFs are enriched in (i) elementary secondary structures while present lower disorder probability compared to the proteins encoded by the coding genes of S.cerevisiae and (ii) hydrophobic amino-acids compared to coding sequences which seem to be enriched in charged and polar residues.

These results enable us to propose a new model of gene emergence, where the non coding genome contains already all the elementary foldable building blocks of the well established protein structures. The transition of these blocks towards functional proteins lies mostly at their evolutionary enrichment in charged residues (offering specificity) and in more disordered regions (offering flexibility). Both specificity and flexibility are necessary elements for proteins' functionality.

Cancer transcriptome at nucleotide resolution

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RNA-seq analysis performed at k-mer level using the DE-kupl software exhaustively captures all RNA variations including the genetic, transcriptional and post-transcriptional variations without using a reference. To address the replicability of DE-kupl discoveries, we compared differential events discovered by comparing tumor and normal tissues in two independent lung cancer cohorts. We identified a subset of stable events including splice variants, retained introns and lncRNAs. A subset of strictly tumor-specific events is particularly attractive as they may constitute recurrent neoantigens. The identified events can be further used as a predictive signatures to predict the tumor status of a sample, using a random forest model. The new k-mer-based predictor, although it contains only non-reference k-mers, reaches to a similar accuracy of more than 95% than a conventional gene-based predictor.

ThorAxe: Transcript-aware orthology relationships among exons

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Detecting orthology relationships between exons is crucial for estimating rates of exon creation/loss (1) and the dN/dS ratios of exons (2). Moreover, in the context of alternative splicing (AS), identifying orthologous exons is necessary to infer evolutionary scenarios explaining the observed transcripts (3).
Orthologous exons are exons in different species derived from a single gene present in the last common ancestor through speciation events. Orthology detection is challenging because duplication events can create highly similar sequences, paralogs, that confound the orthology signal. Previous efforts have been engaged to match exons between species, by using pairwise alignments of genomic sequences (1,2) or multiple sequence alignments (MSAs) of concatenated translated exons (3). However, there exists no automated and/or general method to detect orthologous exons while accounting for transcript diversity. ThorAxe combines pairwise alignment-based exon clustering with MSAs of concatenated exonic regions to identify orthologous exonic regions (s-exons). The clustering step aims at grouping exons sharing some similarity to decrease alignment errors.
In this work, we present ThorAxe, a practical method to infer orthology relationships between exonic regions in the context of AS. ThorAxe, is easy-to-use and robust Python 3 package that can be used as a starting point for further investigations. We also introduce the concept of s-exon, orthologous exonic regions that can be viewed as a high-resolution building block for proteins. S-exons accounts for the variability observed between transcripts of the same species and between different species.

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The Transipedia Project: representing and searching transcripts using k-mers

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Most bioinformatics software for omics analysis apply a data-driven methodology – they traverse the entire content of each available sample for analysis. This approach was successful in a context of scarce sequencing data and limited gene annotation in the early-stage omics. If we look around the bioinformatics world today, however, the situation has changed. Firstly, sequencing is no longer a costly experiment, and the rate of sequence data generation has far surpassed the development of computer technologies such as hard drives and processors. This distance will keep growing in the coming era of personal genomes and transcriptomes. Secondly, although the catalogue of reference genes in human is now relatively stable (80,000 genes, 200,000 transcripts), the actual gene set in any individual genome or transcriptome is infinite, due to genetic and regulatory variations.

The Transipedia project aims to develop a new data model and a query system to deal with transcript datasets in the personal transcriptome era. In this model, instead of quantifying all transcripts in a moderate number (about 100) of samples, we quantify only a given list of transcripts but in large-scale samples (over 10 000). To allow searching and quantifying an arbitrary transcript in today's vast amount of RNA sequencing data, the system uses a k-mer representation that reduces both search time and database size. I will present computational challenges encountered in making sure this system returns a reliable estimation of transcripts.

Keynote Lecture

A tale with two tails! When integrated structural biology sometimes go wrong

Adrien Melquiond

Utrecht University, Netherlands

Advances in biophysics and biochemistry have pushed back the limits for the structural characterization of biomolecular assemblies. Large efforts have been devoted to increase both resolution and accuracy of the methods, probe into the smallest biomolecules as well as the largest macromolecular machineries, unveil transient complexes along with dynamic interaction processes, and, lately, even dissect whole organism interactomes using high-throughput strategies. However, the atomic description of such interactions, rarely reached by large-scale projects in structural biology, remains indispensable to fully understand the subtleties of the recognition process, measure the impact of a mutation or predict the effect of a drug binding to a complex. Mixing even a limited amount of experimental and/or bioinformatic data with modelling methods, such as macromolecular docking, presents a valuable strategy to predict the three-dimensional structures of complexes. This hybrid approach combines powerful algorithms with experimental data from various sources to generate high-resolution models of protein complexes. With an unprecedented wealth of data, time has come to combine and conquer, keeping in mind that data do not always speak the truth!

A graph-based approach for classifying and predicting A-minor motifs in RNA structures

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Functions of RNA are numerous and many of them are essential to a living organism, from expression of genetic information to catalysis of chemical reactions. These functions rely on a good folding of the molecule, through the formation of bonds between non-consecutive nucleotides. Consequently, it is necessary to predict the three-dimensional structure of an RNA to determine its function. Nowadays, effective algorithms based on dynamic programming are able to predict a first level of folding, called secondary structure, composed of canonical interactions. However, more complex interactions exist, and some of them stay currently unpredictable. This is due to several reasons, such as the absence of experimental information about these interactions. A-minor like motifs fall into this category. These motifs are the most frequent interactions binding distant regions of the molecule.

The final goal of our work is so to be able to predict these interactions. For this purpose, we are studying real occurrences stored in the PDB. In particular, we are interested in the structural context of the interaction, e.g. the set of bonds around the motif, to find common characteristics in occurrences. Our purpose is to use these characteristics to establish an exhaustive classification of the different forms of the motif and use them also as prediction criteria. We model these structural contexts by graphs, and then develop graph comparison and clustering algorithms in order to cluster these graphs in classes of similar motifs. We are looking for groups of contexts that share specific maximum subgraphs, that could be a first form of criteria for classification and/or prediction. In this talk, I will present this work and show some preliminary results.

Prédiction de structures secondaires de complexes d'ARN

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Les ARN peuvent interagir et former des complexes ayant des rôles variés dans la cellule, comme le ribosome ou le splicéosome. La prédiction de la structure secondaire de ces complexes est une première étape afin d'identifier leur fonction, leur structure 3D, etc.
Nous proposons ici une approche interactive tirant parti des nombreux outils disponibles pour prédire les structures secondaires d'ARN et d'interactions ARN-ARN pour prédire des structures de complexes composés de plus de deux ARN.
Nous avons formulé le problème de prédiction comme la détermination des meilleures combinaisons de structures secondaires d'ARN et d'interactions ARN-ARN. Ce problème nous a permis de développer un premier outil mono-objectif, appelé RCPred (RNA Complex Prediction), trouvant les combinaisons de plus basses énergies.
Notre méthode est basée sur un problème d'optimisation combinatoire, et plus particulièrement sur un problème de graphe visant à trouver la clique pondérée maximum. Ce problème est connu comme étant NP-difficile à résoudre (Bomze et al., 1999) et difficile à approximer (Hastad, 1997). Nous avons alors basé notre méthode sur une heuristique de recherche locale appelée Breakout Local Search (Benlic et Hao, 2013).
Nous avons ensuite développé une seconde version de cet outil, appelé C-RCPred (Constrained-RNA Complex Prediction), qui est multi-objectif.
Dans cette version, les meilleures combinaisons répondent à plusieurs critères, assimilés à des fonctions objectif : tout d'abord l'énergie libre, mais aussi l'accord avec des données structurales (telles que des données SHAPE) et le respect de contraintes utilisateurs.
Les meilleures combinaisons correspondent aux solutions de l'ensemble de Pareto, or, il n'existe pas de méthode permettant de générer un ensemble de Pareto du problème de la clique maximum en temps polynomial. Nous proposons donc une heuristique permettant de trouver un ensemble de Pareto approché de ce problème.
L'outil RCPred est disponible en tant que webserver sur la plateforme EvryRNA et l'outil C-RCPred le sera très prochainement.

Vers une meilleure compréhension des bases de l'auto-assemblage de la capside du norovirus.

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Les norovirus sont la cause principale de gastroentérites virales aigues chez les humains et les animaux. Leur protéine majeure de capside VP1 (530 résidus) s'auto-assemble spontanément en une capside icosaédrique de 90 dimères. La structure cristallographique de cette particule pseudo-virale (VLP) pour le génotype humain GI.1 (Prasad et al., Science. 1999) a révélé la structure atomique de VP1. Prasad et al. ont proposé qu'un premier intermédiaire d'assemblage serait un pentamère de dimères (POD) de VP1. Ils ont naturellement supposé que ce premier noyau croîtrait de façon isotrope vers la capside/VLP. Expérimentalement, nous avons montré par diffusion centrale des rayons X résolue en temps sur une VP1 du génotype bovin GIII.2 que (i) le seul intermédiaire de longue durée de vie détectable lors de l'assemblage de la VLP est de stoechiométrie 10-11 dimères (ii) la forme de cet intermédiaire est incompatible avec un chemin d'assemblage passant par la croissance isotrope d'un POD (iii) l'intermédiaire, très allongé et présentant une courbure voisine de celle de la VLP, est bien interprétable comme un morceau de capside, qui aurait des dimensions et une forme voisines de deux POD reliés par un dimère interstitiel (Tresset et al., J. Am. Chem. Soc. 2013).

En combinant différentes approches computationnelles, nous cherchons à déterminer les bases moléculaires de l'assemblage de la capside des norovirus. Nos résultats sur des assemblages de plus en plus importants révèlent une rupture de symétrie dès l'étape POD. Ainsi la fixation du premier dimère au POD favoriserait les positions adjacentes pour la fixation du second dimère entraînant une croissance dans la direction de fixation initiale. Nos résultats montrent que pour une protéine de capside comme VP1, la conformation des assemblages intermédiaires peut différer considérablement de celle qu'ils auront dans l'assemblage final et conduire à un chemin d'assemblage différent de celui qui serait supposé sur la seule base de celui-ci. Ils contribuent aussi à expliquer pourquoi la croissance à partir du POD se fait rapidement et anisotropiquement, conduisant à l'intermédiaire allongé observé par TR-SAXS par Tresset et al. en 2013, mais qui ne serait pas le 11-mère de dimères proposé alors.

Computational design of proteins and enzymes

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Structure-based computational protein design (CPD) addresses the inverse folding problem, exploring a large space of amino acid sequences and selecting ones predicted to adopt a chosen fold. We recently showed that a PDZ domain can be entirely redesigned using CPD with a "physics-based" energy function that combines molecular mechanics with a continuum electrostatic solvent model. Many thousands of sequences were generated by Monte Carlo simulation, using our Proteus software. Among the lowest-energy sequences, three were tested experimentally and all shown to fold into the correct, PDZ structure, despite having 50 of 83 amino acids mutated. This represents a striking validation of our "physics-based" CPD approach. Next, we applied CPD to enzyme design. A designed enzyme should satisfy multiple criteria: stability, substrate binding, transition state binding. Such multi-objective design is computationally challenging. We recently proposed a new method based on adaptive importance sampling. By first flattening the energy landscape of the apo protein, we obtained positive design for the bound state and negative design for the unbound. We have now extended the method so as to design an enzyme for its specific transition state binding, ie, its catalytic power. We considered methionyl-tRNA synthetase (MetRS), which attaches methionine (Met) to its cognate tRNA, establishing codon identity. We redesigned MetRS computationally to bind several ligands: the Met analog azidonorleucine, the natural ligand methionyl-adenylate (MetAMP), and the activated ligands that form the transition state for MetAMP production. Enzyme mutants known to have azidonorleucine activity were recovered, and 17 mutants predicted to bind MetAMP were characterized experimentally and all found to be active. Mutants predicted to have low activation free energies for MetAMP production were found to be active and the predicted reaction rates agreed well with the experimental values. We expect that in the future, the present method will become the paradigm for computational enzyme design.

Gating mechanism of a potassium channel, experimental and theoretical studies

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Inwardly-rectifying potassium (Kir) channels are transmembrane proteins responsible for the membrane electrical excitability and K+ transport; it controls the membrane resting potential by opening and closing the channel. Some mutations blocks this gating causing channelopathies including Andersen's syndrome, a rare disease currently without treatment, causing periodic paralysis or serious heart problems. This investigation is divided in two parts: the first is led to understand the dynamics of the gating of the KirBac3.1 channel (a homologous of Kir2.1) and the second to resolve the structure of Kir2.1 WT.

The dynamic study was achieved on the wild-type protein KirBac3.1. To study the behavior of this system, Molecular Dynamics using excited Normal Modes (MDeNM) method was used. The Molecular Dynamics (MD) allows us to observe particularly fast and small amplitude movements such as side-chain movements or loops, while the normal modes describes slow and collective movements of large amplitude. This mixed approach gives access to a wider exploration of the conformational space than MD alone, and allows moreover to determine the conformational populations of the different states (open and closed).

The simulations carried out with MDeNM provided us the intermediate structures between the closed and open ones. They allowed us to determine the key motions in the gating like the involvement of the cytoplasmic domain and slide-helix as well as of the transmembrane helices during the opening of the channel. These observations were confronted to HDX-MS Spectrometry and electrophysiological experiments for validation. Our investigation is continued with some mutations of the channel: KirBac3.1 W46R known to be very stable and opens the channel more often than the KirBac3.1 WT.

To determine the structure of Kir2.1 WT, our laboratory obtained cryogenic electron microscopy images of Kir2.1 from which the determination of its 3D structure is presently being conducted.

A multi-omic approach reveals how microbiota-hypothalamus axis adapts to a Western-diet short-term exposure in rats

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Each individual can be considered as a holobiont, whereby host organs and its cohabiting microorganisms interact to maintain homeostasis. However, understanding the adaptative relationship between the microbiota and physiological functions remains challenging. The hypothalamus is the major brain structure that regulates energy homeostasis. It integrates peripheral signals, indicators of the energy status, but also microbial signals, such as metabolites that can impact energy homeostasis. The gut microbiota is highly responsive to dietary changes, but it is not known how the hypothalamus integrates these new signals. We used an integrative multi-omic approach to study the early adaptation of the microbiota-hypothalamus axis during a severe dietary switch from standard diet to Western diet (WD).

30 rats were euthanized before (T0) and after 2 hrs (T2H), 1 (TD1), 2 (TD2) and 4 (TD4) days after a switch from standard to WD. Caecal microbiota composition was determined by 16S rDNA V3-V4 region sequencing (Illumina). Metabolomic analysis were performed on hypothalamus (UHPLC/MS/MS) and caecal content (GC-HRMS coupled to QToF). Data integration between microbiota and caecal and hypothalamic metabolomes was performed using R (WGCNA and mixOmics packages).

Multivariate analysis revealed that the evolution of the three datasets followed different kinetics. One day of WD consumption is sufficient to increase *Proteobacteria* relative abundance, generally associated with gut inflammatory condition, as well as oxidative stress in the hypothalamus (increase in pro-oxidant metabolites). Data integration revealed a positive correlation between these pro-oxidant metabolites and set of caecal bacteria, not identified by the temporal analysis, *via* unknown caecal metabolites.

We provided a broad view of intestinal ecosystem and hypothalamic metabolic adaptations to short-term WD, emphasizing inflammation and oxidative stress. The data integration approach revealed potential microbiota-mediated relationships between WD switch and hypothalamic oxidative stress. Further investigations are needed to study how and when this altered symbiosis is propelled beyond resilience limits leading to a "pre-disease" state that may ultimately lead to chronic disease.

Sequential reprogramming of biological network fate

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Cell reprogramming consists in modifying gene expression to induce a particular cell behavior naturally or artificially. A number of potential beneficial outcomes in the field of medicine such as cancerous targeted therapy, regenerative or precision medicine could come from such reprogramming. The action of targeted therapies can be interpreted as network rewiring. The effect of mutations and drugs can be described as elementary topological actions on the network, assimilated to a control. The main issue is to infer the control inputs (i.e. topological actions) redirecting the biological system dynamics to an expected fate. Two computational approaches of controls can be studied: single control or sequential control of the interaction network. In this talk, we will present a framework investigating the sequential control of Boolean controlled networks. Control sequence Inference is a decision problem which is PSPACE-hard. Thus, in the aim to find a minimal parsimonious control sequence, we propose a heuristic method focused on the partitioning of the states dependent on observed variables and an abductive-based inference.