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Abstracts

Vicente Acuña

Constraint-based methods for the study of genome scale metabolic models.

Vicente Acuña
Mathomics – CMM, Universidad de Chile

Constraint-based approaches brought new insight into our understanding of metabolism. By making very simple assumptions such as that the system is at steady-state and some reactions are irreversible, and without requiring kinetic parameters, general properties of the system can be derived. Simple questions as computing the biomass production of a bacteria, the set of metabolites needed to grow, or finding alternative pathways to produce a given metabolite can be modelled using modelling under constraints. Moreover, these techniques can be used also in the context of metabolic engineering to the design new thermodynamically feasible and kinetically efficient metabolic pathways. In these talk we give an overview of the different constraint-based models used to describe the space of metabolic fluxes and the algorithms to solve some of these problems.

Eduardo Agosín

Engineering microbial cell factories for the production of bioflavors

Department of Chemical and Bioprocess Engineering, School of Engineering, Pontificia Universidad Católica de Chile, Santiago, Chile. Email: agosin@ing.puc.cl.

Isoprenoids are the largest and most diverse group of natural compounds found in nature. They have attractive commercial applications as biofuels, therapeutic agents and flavors and fragrances. The latter have found place in perfumes, cosmetics, soaps, candles, and food amongst many common household products.

With their increasing global demand and difficulty in extraction from the natural source, alternative methods of their production are being sought. One sustainable method is to employ microorganisms for the production of these high value compounds. With the array of current tools for metabolic engineering, microorganisms can be modified to produce compounds such as esters, terpenoids, aldehydes, and methyl ketones.
In this presentation, I will review the major achievements and current challenges for the sustainable production of these bioactive compounds in microbial cell factories. Special emphasis will be given to the multifaceted family of apocarotenoids, which has been barely explored for biotechnological purposes, in spite of their high appreciation by the fragance and flavouring industry. Apocarotenoids, such as ✔- and 🚲-ionones, safranal or strigolactones, to name a few, are widespread in plants, especially in fruits and vegetables, and are also present in microorganisms and vertebrates. They are synthesized from carotenoids – carotenes and xanthophylls - by oxidative enzymes cleaving specific bonds of the polyene chain. They act as hormones, signaling compounds, chromophores, as well as scent/aroma constituents.
In particular, a series of metabolic engineering steps will be addressed, namely overexpression and fine-tuning of several enzymes of the biosynthetic pathway in the parental *S. cerevisiae* CEN.PK2 strain; protein engineering of key enzymes, such as Carotenoid Cleavage Dioxygenase (CCD1); genome-scale stoichiometric and kinetic modeling to reroute the carbon flux through the biosynthetic pathways, and unravel metabolic bottlenecks and shortage of key metabolites, respectively; and finally, the development of an improved fed-batch fermentation process for the reengineered strains, led to the production of >1 g/L product.

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Méziane Aïte

Tools for metabolic network comparison at genome-scale: application on algaes

One way to study different organism is to reconstruct their respective metabolic network and then analyze and compare them. For this purpose, it is necessary to take into account all possible biases that may lead to incorrect analysis and interpretation. Indeed, different quality of genome annotation or distinct workflow used for the reconstruction of the different metabolic networks will lead to manipulate networks of variable quality whose comparison will certainly highlight false positives. We propose a fully automated workflow of genome comparison based on metabolic network reconstruction, which minimizes bias related to the reconstruction process.
Starting from annotated genomes, we use this annotation data to create a first metabolic network for each organism of interest. The annotation data will enable to associate a gene with one or more enzymatic reactions. At this stage, the quality of the networks created depends entirely on the quality of the annotation. In fact, a genome rich in annotation will allow to obtain more genes - reactions association and thus a

more extensive network. To reduce this bias, we proceed to reciprocal blasts to search for orthologous genes between each genomes. Thereby even if a genome is better annotated than another, the search for orthologues will propagate this annotation quality. In other words, the annotation of a gene will spread to its orthologues.
To complete these first networks obtained we seek again for orthologous genes but this time with well curated models. Orthologous research supported by metabolic networks of quality will allow the recovery of gene - reaction associations that have been missed based on annotation only.
The metabolic networks obtained at the end of this workflow can then be compared and the differences highlighted will be more likely to true characteristics. All this process requires standard inputs such as Genbank file and is fully automatized. The final output is a complete report detailing the specificities and the differences between each organism on a functional level such as pathway completion rate and enzymatic reactions which can be handled.

Anaïs Baudot

Mining networks to study rare and common human diseases.

Networks are scaling-up the analysis of gene and protein functions, hence offering new avenues to study the diseases in which these macromolecules are involved. In this context, we develop algorithms to explore interactome networks containing thousands of physical and functional interactions. We have in particular extended community detection and random walk approaches to multiplex networks, i.e., networks composed of different layers of interaction, such as protein-protein interaction or gene co-expression. I will show how we use these approaches to study rare and common diseases, and more particularly premature aging diseases and diseases-disease comorbidity relationships.

Marko Budinich:

The role of energy in Metabolic Modelling

Flux Balance Analysis (FBA) methods for metabolic modeling relays in the steady-state assumption of the stoichiometric matrix to explore phenotypic capabilities of microorganisms. In practice, this translates into the use of mass conservation equations to adequately describe the feasible flux space and in optimality growth assumptions to explore it. However, while these approaches have been successfully applied to single organisms, is not clear that they suffice in microbial community modeling.
In the following presentation, we propose the use of thermodynamic criteria based in Maximal Entropy Production (MEP) Principle, which is based in entropy balance equations, to complement the FBA-like approaches and review its applicability in a case of study.

Verónica Cambiazo

Insights into the virulence and genome diversity of Piscirickettsia salmonis isolates

Verónica Cambiazo1,2, Pamela Aravena1,2, Javiera Ortiz1,3, Dante Travisany4, Alejandro Maass2,4 and Francisco Chávez3.
1Bioinformatics and Genetic Expression Laboratory, INTA-University of Chile, 2FONDAP Center for Genome Regulation, 3Systems Microbiology Laboratory, Faculty of Science, Universidad de Chile, 4Mathomics, Center for Mathematical Modeling, Universidad de Chile

Piscirickettsia salmonis, a facultative intracellular bacterium, is the causative agent of Salmonid Rickettsial Septicaemia (SRS), the disease with major economic impact for the Chilean salmon aquaculture industry. One relevant aspect of *P. salmonis* virulence is the ability to survive and replicate in macrophages, however the strategies employed by *P. salmonis* to avoid eradication by macrophages have been poorly described. Our result on the transcriptomic response of intracellular *P. salmonis* revealed that this bacterium makes metabolic adjustments to adapt to changes in nutrient availability, shutting-down the expression of genes implicated in protein translation and energy metabolism. Adaptation to the harsh intracellular conditions also implied the up-regulation of genes involved in the stringent response mediated by ppGpp. Direct implications of this alarmone in the virulence, pathogenesis and survival of microorganisms inside the host have been found in several intracellular pathogens.
Interestingly, field isolates of *P. salmonis* have shown variable levels of virulence that have been linked to genetic diversity among isolates. To gain insights into the genetic complexity of *P. salmonis*, we combined next-generation sequencing technologies to compare de novo, single-contig genome assemblies from eight *P. salmonis* isolates collected from sub-acute or chronic outbreaks of SRS. Our results support the existence of two clusters among *P. salmonis* isolates that have been often named after the reference strains as, LF-89-like or EM-90-like. Using both pulsed-field gel electrophoresis (PFGE) and whole-genome sequence alignment, several insertions, deletions, and inversions were seen in all genomes of the isolates relative to the reference strain LF-89, although a more extensive genomic variation exists among isolates belonging to the EM-90 clade. Ten distinct genome rearrangement were experimentally validated, all of which were distinct from the genome structure of the reference strain. These rearrangements appear to be mediated by mobile genetic elements such as insertion sequence (IS) elements. Genomic findings were validated in virulence assays demonstrating a distinct pathogenic potential among *P. salmonis* isolates. Our study identified several genetic marks, some of which may be associated with bacteria virulence. These markers are valuable in the development of a robust typing system critical for diagnostic, and epidemiological studies.

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María Paz Cortés

Multiobjective metabolic modeling applied to a biomining bacterial community

María Paz Cortés
Mathomics – CMM, Universidad de Chile

Many biotechnological processes involve complex tasks that cannot be fully met by isolated strains and require the concert action of microbial communities to be successfully accomplished. Understanding and modeling how microorganisms interact and what is their role in these communities is of special interest to improve the effective design of microbial consortia with particular biotechnological goals.
In this work we study potential metabolic trade-offs between members of a bioleaching consortia through a multi-objective constraint-based approach. As a case of study we consider a simple community made of two acidophilic bacterial species: Acidithiobacillus ferrooxidans and Sulfobacillus thermosulfidooxidans. We first describe this community by calculating the Pareto front between the growth-rate of both bacteria. Moreover, owing to the fact that growth is not the only biological function that must be met, we apply a methodology that allows us to use our model to characterize the space of possible states of the community in terms of other relevant biological goals. Through this process we show that the community phenotypic space is shaped by these additional requirements and that more realistic growth points can be identified by mapping them in the space delimited by the growth rate Pareto front.

Clémence Frioux

Scalable and exhaustive screening of metabolic functions in microbiotes.

The selection of species exhibiting metabolic behaviors of interest is a challenging step when switching from the investigation of a large microbiota to the study of functions effectiveness in small communities. Approaches based on a compartmentalized framework are not scalable. The output of scalable approaches based on a non-compartmentalized modeling may be so large that it has neither been explored nor handled so far. We propose a tool to facilitate the selection of a community optimizing a desired function in a microbiome by reporting several possibilities, which can be then sorted according to biological criteria and expert knowledge. Communities are exhaustively identified using logic programming and by combining the non-compartmentalized and the compartmentalized frameworks. Metabolic functions are screened and their dependencies towards symbionts are identified. We illustrate our methodology using the gut microbiota data and we apply it to marine biology with a community selection for the brown alga *Ectocarpus siliculosus*.

Mauricio González

Taxonomic response of soil microbiome to native plants species: analysis of microorganism interaction patterns in an extreme environment.

Dinka Mandakovic, Jonathan Maldonado, Mauricio Latorre, Dante Travisany, Claudia Rojas, Rodrigo Gutiérrez, Sergio Navarrete, Damien Eveillard, Alejandro Maass, Verónica Cambiazo, **Mauricio González.**

Considering that changes of the nutritional soil matrix, due to plant presence, bring on restrictions and opportunities that may promote, under similar abiotic conditions, modifications in the bacterial community, we are studying the impact of native plants (n=33 species) presence on soil microbiome composition, including their interactions with available soil nutrients. We analyzed the soil bacterial communities from two different compartments defined according to their distance to the plant roots: the non-rhizosphere surrounding root soil (bacteria loosely attached to the roots, NRSRS) representing the soil included into the plant´s fine fibrous root system and the bulk soil (BS), that represent soil samples obtained from bare soil located one meter away from the plant. Our hypotheses are: (I) plants positively impact on NRSRS microbiome by promoting the growth of NRSRS specific bacteria; (II) in the transition from BS to NRSRS microbiome, noncore NRSRS OTUs changes the taxonomy, functional structure and the patterns of association of the NRSRS microbiome. The results obtained by using high-throughput sequencing of the 16S rRNA gene indicated that BS and NRSRS exhibited 1,864 and 2,632 exclusive OTUs, respectively (noncore OTUs), and 10,089 shared OTUs (core OTUs). Thus, despite the fact that vegetation coverage represents only a 1% of TLT surface, the NRSRS compartment contributes with a 17% of the soil OTUs, suggesting that TLT plant community contributes to increase the heterogeneity of the environment and the richness of soil bacterial community. In this Workshop on Systems Biology Chile-France 2019, we will present our results in two research areas: 1) Co-occurrence patterns in microbial communities under acute environmental stress, and 2) Bacterial communities associated to Chilean altiplanic native plants from the TLT.

Mauricio Latorre

Transcriptional and metabolic regulatory network in *Enterococcus faecalis*

Mauricio Latorre Mora[1-4]

[1] Instituto de Ciencias de la Ingeniería, Universidad de O'Higgins, Av. Del Libertador Bernardo O'Higgins 611, Rancagua, Chile.
[2] Mathomics, Center for Mathematical Modeling, Universidad de Chile, Beauchef 851, 7mo piso, Santiago, Chile.
[3] Center for Genome Regulation (Fondap 15090007), Universidad de Chile, Blanco Encalada 2085, Santiago, Chile.
[4] Laboratorio de Bioinformática y Expresión Génica, INTA, Universidad de Chile, El Líbano 5524, Macul, Santiago, Chile.
mauricio.latorre@uoh.cl

System biology has emerged as a powerful descriptive, predictive and integrative discipline that allows for the study of complex systems to investigate biological phenomena. For the last ten years, we have been working with the pathogenic bacteria ***Enterococcus faecalis*** and its relationship with metals using a systems-biology approach. Using several systems-biology strategies we generated the first **global transcriptional and metabolic regulatory network (GRN)** in this bacterium, composed of genes, reactions (pathways) and their corresponding transcriptional factors. Integration of global expression data into the GRN showed that the bacterium was able to activate different **functional units of regulation** in order to maintain homeostasis and viability during copper (Cu), iron (Fe) and zinc (Zn) fluctuations, a strategy that had not been previously presented in an experimental and systematic manner. These functional units are mainly composed of: i) operons and regulons involved in metal homeostasis, each isolated from the rest of the network and controlled by local regulators, ii) functional modules containing a high number of genes encoding for proteins involved in several functions, which are highly interconnected inside the network and controlled by global regulators. The GRN in its current state represents the 60% of the global transcriptional response of *E. faecalis* activated under different metal conditions, supporting the fact that, besides the participation of transcriptional factors controlling gene expression, there should exist other regulatory elements influencing the transcription and/or stability of the mRNA.

Marine Louarn

Integration of omics data for the specification of regulation networks in health; identification of regulatory mechanisms

Marine Louarn, INSERM and INRIA

Differentiation of B lymphocytes is one of the key feature of the immune response. Naive B cells (NBC) can differentiate either in Immunoglobulin M or G memory B cells (MBC), or in plasmablasts (PB). MBC can also differentiate into PB, but through distinct mechanisms.
To better understand these processes, we identify the genetic and epigenetic regulators of this differentiation.
Using omics data and Semantic web technologies to create a pipeline to extract the regulatory network of specific genes sets of given expression pattern. We use Answer Set Programming to find minimal sets of transcription factors regulating genes sets.

Vinicius Maracaja-Coutinho

Integrative Bioinformatics and Systems Biology of Non-Coding RNAs

Advanced Center for Chronic Diseases – ACCDiS, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile

Non-coding RNA (ncRNA) research is already routine in every genomics or transcriptomics project, with their predictions and functional annotations part of most of the bioinformatic pipelines. These molecules are components of important cellular machineries, recognized as essential players in different biological processes in organisms from the three domains of life. Moreover, ncRNAs are associated to different human diseases and being applied as biomarkers for diagnosis and/or prognosis. However, the large-scale prediction and functional assignation of ncRNAs require multiple tools along the process, imposing a great obstacle for researchers with lesser computational or bioinformatics background. Furthermore, it is worrisome the fact that most of the non-coding transcriptome of archaeal or eukaryotic organisms belongs to transcripts without any functional annotation. In this process, systems biology emerges as an important approach for the functional assignation of ncRNAs through co-expression networks analyses. Here, we describe the development and application of a series of strategies, databases and tools developed in order to facilitate the identification and functional assignation of non-coding RNAs in organisms from different biological kingdom and human diseases.

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Pablo Marquet

The central role of metabolism in ecology and evolution

Metabolism, or the sum of all biochemical reaction that sustain the persistence of life as we know it, has emerged as a first principle to understand the functioning of ecological systems and their evolution. In this talk I will introduce the basic concepts underlying this metabolic view with special attention to the Metabolic Theory of Ecology. I will emphasize the central role of metabolisms in accounting for the abundance of micro and macro organisms in ecological communities, the controlling role of temperature in modulating metabolism and diversity and the ramifications of individual level metabolic processes in accounting for ecosystem functioning. I will end by pointing out what metabolic theory can tell us about the human phenomenon and the ensuing global change.

Martín Montecino

Epigenetic controlling of the genome: Applications in precision medicine

Martín Montecino, Institute of Biomedical Sciences and FONDAP Center for Genome Regulation, Faculty of Medicine, Universidad Andres Bello, Santiago, Chile.

Epigenetic mechanisms have arisen in the last few years as major regulatory components during control of the expression of the human genome. These mechanisms include processes like DNA methylation, post-translational modifications in proteins associated with genomic DNA, and the activity of long and short non-coding RNAs, among others. In this presentation, the growing knowledge about the regulatory components of these epigenetic mechanisms will be discussed in relationship with their potential role during development of new personalized medicine-oriented strategies that effectively face relevant pathologies affecting the human population in the planet.

Elisabeth Remy

Qualitative mathematical modeling of regulatory networks to decipher the functioning of biological processes

The mathematical modeling of biological interaction networks and their analysis provide a better understanding of biological processes and shed some interesting lights on their properties.

This presentation will focus more particularly on a qualitative formalism, the logical modeling. After a description of the characteristics and potential of this method, we

will discuss associated methodological challenges. Finally, we will see through biological applications how this method performs and enables hypothesis and prediction to be validated by biologists.

Claudia Rojas

Getting deep into soils: how can we use biological networks to better understand microbiome's contribution to key ecosystem services?

Claudia Rojas, PhD. in Soil Science and Biogeochemistry
Assistant Professor, Institute of Agricultural and Veterinary Sciences, Universidad de O'Higgins

Ecosystem services are the benefits society directly or indirectly obtain from ecosystems. Soils play a central role in these services, therefore, any alteration to their normal functioning will compromise the benefits they can provide to society and their natural resiliency to further disturbances. Soil microbiomes play key roles in a vast number of soil benefits, as they are essential to maintain the capacity of soils to function as part of the environment and support aboveground life. In the last decade, analysis of microbial co-occurrence networks has allowed to extend the fundamental knowledge on how microbial communities interact and adapt to diverse environmental settings. Such studies have evidenced dramatic impacts of environmental disturbances on microbial network structure. Thus, these analyses can contribute to better understand the ecological significance of soil microorganisms on proper soil ecosystem functioning. Considering the previous background, the present study proposes to use such ecological molecular analyses to study dynamics of soil microbiomes under natural and disturbed soil environments, and thus to better elucidate their role in key soil ecosystem services.

Pedro Saa

Kinetic models of metabolism: a natural framework for integrating multi-omics datasets for metabolic engineering

Pedro A. Saa
Department of Chemical and Bioprocess Engineering, Pontificia Universidad Católica de Chile, Santiago, Chile.

During the past decade, genome-scale stoichiometric models have enabled exploration and calculation of metabolic phenotypes using constraint-based modelling methods. Such methods have proved to be extremely useful in characterizing metabolic behaviours under different environmental conditions as well as predicting the result of particular genetic modifications. Although stoichiometric models enable a diversity of analysis, their predictions are limited by lack of enzyme kinetics. As

opposed to stoichiometric models, kinetic models are described by highly heterogenous nonlinear expressions, which are difficult to formulate and fit. Recent modelling frameworks promise new ways to overcome these obstacles while paying special attention to thermodynamic consistency. During this talk, I will give an overview of the relevant mathematical frameworks for kinetic formulation, construction and analysis used for metabolic modelling. I will also present relevant examples of the application of kinetic models for multi-omics data integration, metabolic engineering and pathway prediction.

Anne Siegel

AskOmics: heterogeneous data integration with semantic web technologies

Olivier Filangi, Xavier Garnier, Anthony Bretaudeau, Fabrice Legeai, Anne Siegel, Olivier Dameron

More than 1500 databases co-exist in life science, each able to answer important questions in a particular domain. It is crucial to combine these knowledge to answer question that span domain boundaries. Classical data management technologies used by the life science community range from data storage in the form of multiple tabulated files analyzed with spreadsheets or silo models in complex database management systems with a predetermined scheme of federated data. These solutions answer to immediate integration needs but they are poorly compatible with scalable and flexible integration. We will introduce AskOmics, a solution to facilitate the efficient use of raw data by non-expert users using Semantic Web technologies. By converting and creating queries "on the fly" based on the graph of relations between the data. The AskOmics software aims, AskOmics therefore answers to three difficulties: automatic creation of data relations schemes, assistance to the iterative construction of semantic queries, use of Linked Open Data knowledge sources by facilitating the interoperability of databases.

Anne Siegel

Learning Boolean regulations of a metabolic network: a case-study.*

***A. Cornet (Irisa, Univ Rennes), C. Barouck (Inra, Toulouse), A. Bockmayr (Frei Berlin Univ), L. Cottret (Inra, Toulouse), L. Paulevé (LRI, Univ Paris Sud), A. Siegel (Irisa, Univ Rennes)*

Several technologies (CellNopt, Caspo, Trempi) have been developed to infer Boolean regulations from a prior knowledge network and experimental data such as phosphoproteomics data describing the response of a biological network to several combinations of perturbations of stimuli and inhibitors. An important feature for the application of these methods is to be able to clamp the values of the stimuli and inhibitors to a fixed value (activated or inactivated) during the total duration of the

considered experiment. This is a main limitation for the application of such technics to learn Boolean rules which control the adaptation of metabolic networks to external stimuli, such as observed in a diauxic shift.

In this work, we will introduce a prototype of pipeline which could lead to the inference of such Boolean rules from experimental data describing the quantities of metabolites and fluxes in a metabolic network in response to different external metabolic stimuli.

By focusing on a very simplified case-study of the diauxic shift model, we show that the regulatory control of the metabolic system can be accurately recovered by combining the resolution of a combinatorial optimization problem and the filtering of candidate solutions with dynamic FBA-based approaches [6]. Compared to the case of signaling networks identified from phosphoproteomics data by minimizing a MSE metric between data and predictions, the study of regulations of metabolic networks requires to reformulate the optimization problem by replacing the MSE metric by a metric taking into account the quantitative disruptions of the metabolic compounds measurements.

We will present the scheme of a generic pipeline allowing to solve this issue by combining and adapting the Caspo time-series software (initially developed for the learning of Boolean rules of signaling networks) [2] and the FlexFlux software (developed for the dynamic-FBA based simulation of regulated metabolic network).

Mario Tello

Dysbiosis Induced by the Antibiotics modifies Parameters of Innate Immune Response in Atlantic Salmon

Joselin Rojas[1,2,3], Natalia Valdez[1,2,3], Jonathan Morales[2,3], Alex González [4], Rodrigo Vargas 1, Diego Paine[1,3], Mario Tello[1,2,3].
[1]Laboratorio de Metagenómica Bacteriana; [2]Facultad de Química y Biología, Universidad de Santiago de Chile;
[3]Centro de Biotecnología Acuícola (CBA).
4 Laboratorio de Extremófilos, Universidad de Los Lagos

The Chilean salmon industry uses large quantities of antibiotics, which leads to changes in the composition of the *Salmo salar* microbiota. It is unknown whether these changes in the composition of the microbiota (dysbiosis) resulting from the administration of antibiotics affect the physiology of fish. **Methods**: To study the effect of the microbiota on the physiology of salmonids, dysbiosis was induced by administration antibiotics (Forfenicol or bacitracin / neomycin) to pre-smolt specimens for two weeks. The total bacterial load in stool and intestine was evaluated by qPCR, quantifying copies of the 16S ribosomal gene (16S rDNA). The richness of the community was evaluated through the amplification of a variable V3 region of the 16S

rDNA gene, and Metagenomic analysis. The effect on the immune system was assessed by a) quantification of leukocyte populations in immunological organs by flow cytometry; and b) quantification of the expression of cytokines such as IL1β, TNFα and TGFβ by RT-qPCR. The **results** show that the administration of antibiotics leads to a reduction of the bacterial load, reduces the richness of the microbial communities of the feces and the intestine, reduces the populations of leukocytes in the kidney of the head and increases the expression of IL1β and TNFα. These effects were not reversed after the elimination of antibiotics. **Conclusions:** The administration of antibiotics causes dysbiosis in *Salmo salar* and generates an inflammatory state reducing the cellular immune response. The results suggest that the normal microbiota of fish regulates their immune response, stimulating lymphocyte populations and an anti-inflammatory state.

Dante Travisany

Generation and Robustness of Boolean Networks to model *Clostridium difficile* Infection

Dante Travisany
Mathomics – CMM, Universidad de Chile

The most commonly reported pathogen in healthcare-associated infections is the bacterium *Clostridium difficile* which alters the composition of the gut flora generating Chronic diarrhea. The most successful therapy against this pathogen is the fecal microbial transplant (FMT). The microorganisms of the FMT their interactions and inner dynamics reshapes the gut microbiome to a healthy state displacing the *C. difficile* and contributes to the gut microbiome resilience and stability preventing further episodes of chronic diarrhea. Nevertheless, little is known about these interactions and properties. To explore the aforementioned interactions, we propose the construction of a neutral space conformed by a set of models that differ in their interactions, but share the final community states of the gut microbiome under antibiotic perturbation and *C. difficile* infection (CDI). Starting with a previously described Boolean network model for CDI, we proceed to analyze all the possible subnetworks using the nodes determined as external parameters to identify the core microorganisms in the CDI Boolean model. This is represented as a threshold Boolean network. Using evolutionary computation, we generate a set of alternative threshold Boolean models and organize them into clusters that share similar dynamic behavior. For each cluster, the respectively neutral graph is constructed and the most relevant interactions are identified. Finally, we discuss how these interactions can either affect or prevent CDI. This work illustrate how neutral networks can be used to explore the dynamics and the robustness of the gut microbiome.