COLLEGE ED MATHEMATIQUES
DOCTORAL STIC
PAYS DE LA LOIRE

THÈSE DE DOCTORAT DE

NANTES UNIVERSITÉ

ÉCOLE DOCTORALE N° 641
Mathématiques et Sciences et Technologies du numérique
de l'Information et de la Communication
Spécialité : Informatique

Par

Anna Lambert

Metabolic modeling of the small intestine - microbiota ecosystem

En vue de la soutenance de Thèse à Nantes, le 16 janvier 2023
Unité de recherche : UMR 6004 - LS2N and UMR 1235 - TENS

Rapporteurs avant soutenance :

Almut HEINKEN	Professor	Inserm U1256 NGERE, Université de Lorraine
Sara VIEIRA-SILVA	Associate professor	University Medical Center, Johannes Gutenberg University, Mainz, Germany

Composition du Jury :

Président :	Hervé BLOTTIERE	Fonction	établissement d'exercice
Examinateurs :	Almut HEINKEN	Professor	Inserm U1256 NGERE, Université de Lorraine
	Sara VIEIRA-SILVA	Associate professor	Johannes Gutenberg University, Mainz, Germany
Dir. de thèse :	Damien EVEILLARD	Professor	Nantes Université, Nantes, France
Co-enc. de thèse :	Samuel CHAFFRON	Researcher	CNRS, LS2N UMR6004, Combi Nantes, France
Co-enc. de thèse :	Maxime MAHE	Researcher	INSERM, TENS UMR1235, Nantes, France

COLLEGE ED MATHEMATIQUES
DOCTORAL STIC
PAYS DE LA LOIRE

Titre : titre FR

Mot clés :

Résumé :

Title: Metabolic modeling of the microbiota - small intestine ecosystem

Keywords:

Abstract: The gut microbiota is a complex ecosystem whose composition varies within each individual depending on genetics, age, and diet. Uncovering how microorganisms impact our health became central to the progress of human medicine. Among other techniques, experimental protocols co-culturing bacteria and organoïds, human stem cells grown in vitro into human intestinal epithelium-like cultures, offer valuable insights. However, their culture remains technically complex, costly, and time-consuming, limiting its application to bacteria selected beforehand with less restrictive methods. Complementary, high-throughput sequencing has allowed us to identify microorganisms associated with health conditions, but it fails to elucidate the underlying mechanisms of action.

In this thesis, we leverage Genome-Scale Metabolic models (GEMs) to simulate and explore the complexity of metabolic interactions taking place in the small intestine between enterocytes and gut microbes. The f rst chapter introduces a metabolic computational framework to infer interaction scores between microorganisms and the host. Applied to up to f ve organisms, these scores highlight the positive impact of gut microbes on the maintenance of enterocytes. In a second chapter, this thesis screens for bacteria of interest to supplement food products. For this purpose, we inferred the interaction score of 879 automatically reconstructed strains with the enterocyte and selected high-scoring bacteria. We observed a strain specif city of score variations, demonstrating the ability of GEMs to produce insightful strain-level predictions. In a last chapter, for linking our modeling framework with in vitro experiments, nutritional constraints were tailored and curated to design an experimental growth medium. We predicted that, in these particular conditions, the maintenance of the enterocyte would be favored by supplementation of choline. Overall, this thesis advances our ability to explore the complexity of metabolic interplay within microbial ecosystems and to predict putative host-microbiomes interaction mechanisms.