PhD offer

Towards a digital twin of the gut microbiota: a multidisciplinary approach for an in-depth understanding of composition, function and interaction with the host.

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To apply send an email with CV and transcripts with subject 'APPLICATION FOR PhD'.

Thematic keywords

Biomathematical models in microbial ecology, modeling, numerical analysis, dynamic systems, data analysis.

Scientific background

Microbial communities in the human body, including bacteria, phages, viruses, and fungi, form the human microbiota. These microorganisms are present in organs and tissues, creating various ecosystems, such as digestive, cutaneous, pulmonary, and vaginal microbiota. As a result, the human body is an ecological unit consisting of different ecosystems of microorganisms and human cells [3]. Human health and physiology rely on the constant and mutual interactions between the host cells and microbiota. For instance, digestion and protection against pathogens are carried out by both human cells, such as epithelial and immune cells, and the intestinal microbiota. The gut microbiota, mainly consisting of more than 500 different bacterial species, live in a community whose relative abundance can change constantly due to diet. The intestinal mucosa, composed of immune and epithelial cells, is the first layer of cells that separate the microbiota from the inner environment. Mucus, a gel-like substance composed of complex glycoproteins, lines the epithelium, preventing direct contact between cells and bacteria [2]. Dysbiosis, a state of imbalance between human cells and microbiota, is linked to pathologies such as inflammatory diseases. Understanding host-microbiota interactions, including the composition, diversity, and metabolic activity of the microbiota and the physiology of the host, is crucial for human and animal health, in order to design effective treatment for these diseases.

For several years, *in silico* models of the dynamics of the intestinal microbiota and the digestive physiology of the host have been developed, integrating the knowledge available in the literature and data. Some of these models propose large-scale modeling of the microbiota within the colon including a more or less detailed description of the host, while others propose microscale modeling of the dialogue between epithelial cells and bacterial metabolites. Very macroscopic models at the host scale have also been published.

The thesis project aims to interface several models and lay the foundations of a computational framework, also known as **digital twin** to describe the host-microbiota interaction at different scales. We recall that a digital twin can be broadly defined as a combination of data and a digital model designed to reflect, as closely as possible, a real object - or system - (state, characteristics, behaviour), in order to help decision-making about it. For host-microbiota interaction, the general principle is presented in Fig. 1. At the microscopic scale, these new developments will involve coupling a distributed spatial fluid mechanics model of the colon with a crypt model, simulating the interactions between the host and the microbiota. In this way, the effects generated at the microscopic scale will influence the behavior of the host's digestive and cardiovascular systems at the macroscopic scale. The modeling of these macroscopic systems is crucial in order to be able to integrate individual-specific data (personalized models) such as inputs describing the diet or treatments (prebiotics, probiotics, drugs) or biological measurements - analysis of blood samples - which will be compared with the model simulation results.

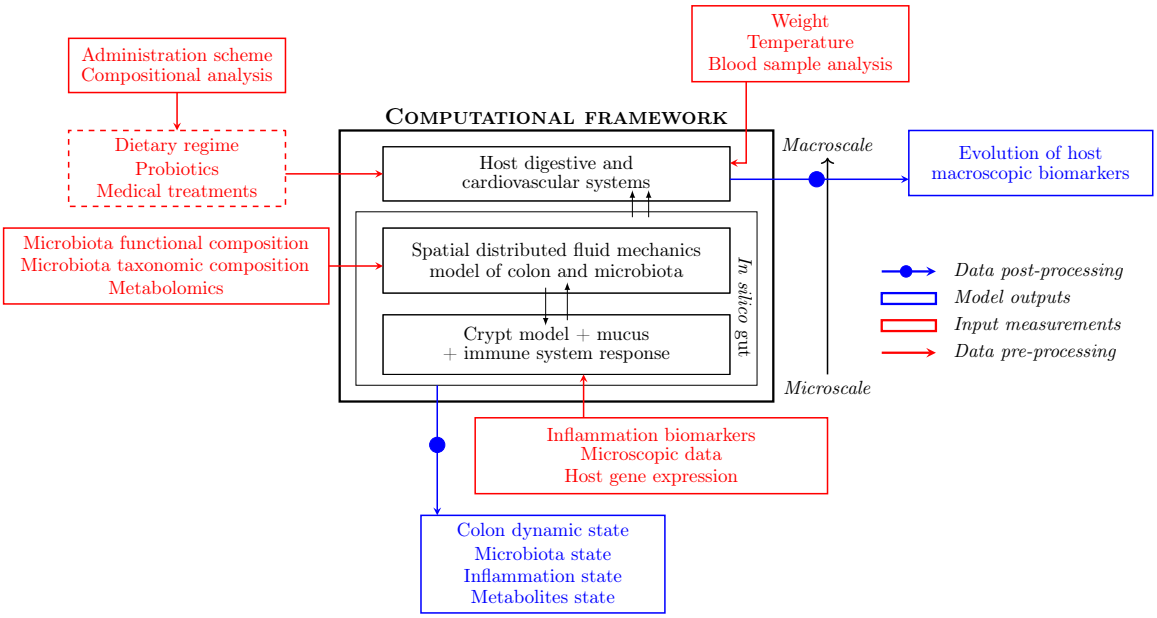

Figure 1: Host-microbiota interaction across scales.

Objective

The aim of this thesis is to establish the groundwork for a *digital twin* by designing a unique modeling and computational structure capable of combining biological data and simulating the progression of host-microbiota symbiosis. To achieve this, the structure must be modular, allowing for flexibility in the calculation process, which means only relevant physiological mechanisms determined by biologists' expertise are activated.

This modular aspect presents new methodological challenges. Firstly, innovative numerical approaches are required to simulate the multiscale system entirely, enabling the prediction of the evolution of significant macroscopic biomarkers. Secondly, advanced model order reduction techniques such as POD or meta-modeling approaches must be developed to minimize computational costs and make tasks like sensitivity analysis and model parameter estimation feasible.
Specifically we identify four research directions:

- coupling between the microscale crypt model developed in [1] and the colon macroscale model presented in [4];
- modeling the host digestive vascular system, then to be integrated at a microscale with the crypt model [1], in particular for the absorption processes;
- integrate the data within the computational framework, in particular microscopic data and inflammation biomarkers for the crypt model [1], and microbiota function and taxonomic composition data for the colon model [4];
- apply advanced method for order model reduction in order to allow the employment of parameter estimation method and perform a sensitivity analysis study.

Context and collaborations

The project will take place in the MaIAGE unit (Béatrice Laroche and Lorenzo Sala). The work of these will be done in collaboration with several INRAE teams with which solid exchanges have already been established: the Metagenopolis unit, MICALIS institute (FINE, Probihôte, MIHA and CPE teams), which will contribute their expertise on (i) the microbiota and the holobiont, (ii) data sets and (iii) will help define the needs in terms of simulation outputs: biomarker monitoring, visualization. Finally, it will be interesting to contact other scientific partners such as the M2ISH unit, and the PNCA and STLO units to complete the knowledge on existing models for inflammation and pathogens, food and host physiology, the Université de Technologie de Compiègne (UTC) for their expertise in model order reduction, the Université d'Orléans for their expertise in

numerical analysis and modeling for life science and INRIA Saclay teams MUSCA and SIMBIOTX for their expertise on the numerical methodology for similar computational models and the human vascular transport modeling.

Candidate background and skills

The candidate should have a Master's degree in Applied Mathematics or equivalent.
A strong background in modeling, numerical analysis and deterministic (ODE/PDE) dynamical systems is required. As well, proficiency in scientific programming (*e.g.* Matlab, R, Python or C++) is recommended. Previous experiences with data analysis, especially at the interface with biology, are very welcome.

References

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[2] M. E. Johansson, J. K. Gustafsson, J. Holmén-Larsson, K. S. Jabbar, L. Xia, H. Xu, F. K. Ghishan, F. A. Carvalho, A. T. Gewirtz, H. Sjövall, et al. Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis. *Gut*, 63(2):281–291, 2014.

[3] G. E. Kaiko and T. S. Stappenbeck. Host–microbe interactions shaping the gastrointestinal environment. *Trends in immunology*, 35(11):538–548, 2014.

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