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# Modelling the dynamics of *Salmonella* infection in the gut at the bacterial and host levels

Coralie MULLER<sup>1</sup>, Arie WORTSMAN<sup>1</sup>, Pablo Andres UGALDES SALAS, Clémence FRIOUX<sup>1</sup>, and Simon LABARTHE<sup>2,1</sup>

<sup>1</sup>Inria, Univ. Bordeaux, INRAE, F-33400 Talence, France

<sup>2</sup>INRAE, Univ. Bordeaux, BIOGECO, Pessac, France

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## Context : a multidisciplinary project

We want to model the dynamics of a host-microbiota-pathogen system using the Dynamic Flux Balance Analysis method. dFBA integrates the fluxes calculated in FBA into a system of ordinary differential equations (ODEs), enabling us to model the temporal dimension of metabolic simulations. In order to speed up the computation of the FBA models needed for a thorough numerical exploration, the metabolic models will be approximated by a **metamodel method** [1].

Three main challenges:

curation, harmonization, optimization

Speed up the computation of the FBA models

Three metabolics networks to harmonize and interconnect

Human colonocyte network

Bioinformatics

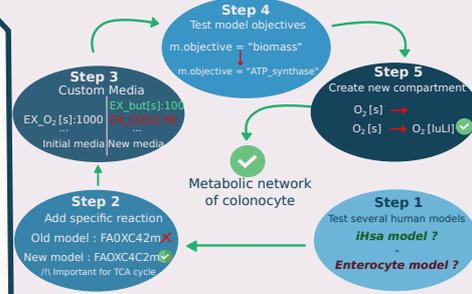
Mathematics

Dynamic simulation fit better to the biological reality

Reduced simulation time

## Colonocyte metabolic network curation

A manual curation process was performed in order to clean up and make the model usable. It consists of **five main steps**:

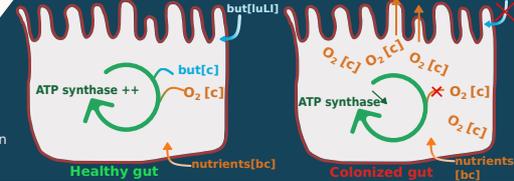


## Colonocyte model validation

We want to simulate two main cases to validate our model

**Colonized gut:**

- NO production of but by commensal bacteria
- Accumulation of O<sub>2</sub> and transfer to [luLI]
- Decreased of production of energy



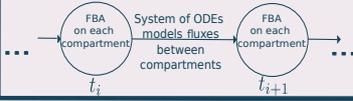
- Healthy gut:**
- Production of butyrate by commensal bacteria
  - Consumption of but and O<sub>2</sub> in TCA cycle
  - Good production of energy

## Simulation: FBA - dFBA

For the simulation, we consider that the system works by maximizing biomass production. Also, we assume that the system is in a stationary state. This way, can model the system by solving the linear optimization problem

$$\min_{\nu \in \mathbb{R}^{N_r}} \nu_{\text{biomass}} \quad A \cdot \nu = 0 \quad c_{\min} \leq \nu \leq c_{\max}$$

Our model assumes that FBA holds for each instant [2]. Then, for simulating it for a period of time, it is necessary to solve FBA on each compartment. After this timestep, an ODE system models the fluxes between different compartments, until the next step...



What does ODE system look like?

$$\dot{s} = \frac{Q_{in} s_m - Q_{out} s}{V} + \text{biological and chemical reactions} + \text{transport to other compartments}$$

## Harmonization of the models

We model the host-microbiota-pathogen system by gathering three metabolic models: *Faecalibacterium prausnitzii* [3] as a representative butyrate producing commensal bacterium, *Salmonella Enterica serovar* Thompsonium [4] for the enteric pathogen, these models previously used in CEMRACS[1] project, and a host genome scale metabolic network of human [5] called iHsa, to simulate the epithelial cell.

In order to make the simulation with the 3 models, we have harmonized the networks between them on two points:

Different IDs for the same metabolite and differentiate name for compartments between networks

Fix fluxes for essential reactions in the right compartments for the exchanges

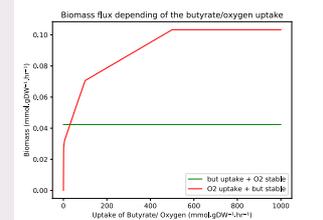


## Simulation of growth in the human

We performed simulations with a custom medium to observe biomass growth as a function of O<sub>2</sub> and butyrate uptake.

We observed a dependence of biomass growth on O<sub>2</sub> uptake but not on butyrate uptake.

These results are not surprising because biomass includes many are not directed related to the energy metabolism and therefore do not depend on butyrate.

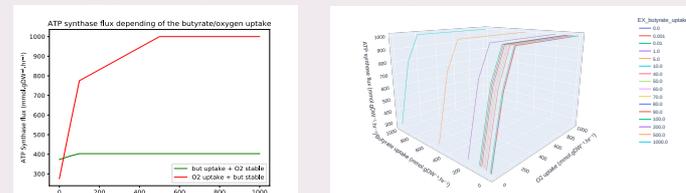


## Effect of but and O<sub>2</sub> on energy production

The electron transport chain (ETC) is the source of energy production of the cell, it is located in the mitochondria and allows to produce at the end of the chain ATP. To function, ETC needs in part O<sub>2</sub> and FADH<sub>2</sub> to enable electron transport. FADH<sub>2</sub> is a product of the Krebs cycle reactions (TCA) whose main reactant is butyrate in enterocytes. Butyrate is produced by the beta oxydation of fatty acids in the cell.



The ATP synthase is the main energy production reaction of the mitochondria and reflects the energy production [6] of the cell. With this activity, we want to monitor the *Salmonella* infection.



The butyrate/O<sub>2</sub> uptake has an impact on the ATP synthase activity, when the other uptake is stable.

The effect of O<sub>2</sub> uptake has a greater impact on ATP synthase activity than butyrate uptake.

## Next steps

Each time iteration of the model implies an optimization step in a high dimensional space, which means that the simulation has a very high computational cost.

Are there ways to solve this?



Is there a big trade-off between computation cost and precision?

Simulations involving the uptake of O<sub>2</sub> and butyrate on ATP synthase activity are encouraging. The next steps of the project will be:

- 1 Simulate with dFBA to validate that the reduced of butyrate uptake lead to O<sub>2</sub> accumulation in the lumen [luLI].
- 2 Learn the behaviour of the system and build a metamodel able to efficiently approximate the dynamics.
- 3 Generalize the approach to other ecosystems which functions are important for dynamics of the community.

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