Modelling the dynamics of Salmonella infection in the gut at the bacterial and the host level

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

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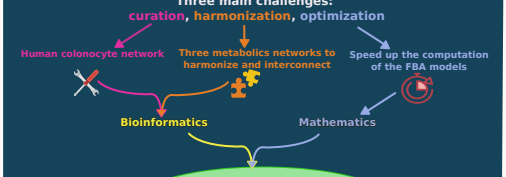
Keywords: ***Gut microbiota - Metabolic network - Biological system - System of ODE - Metamodelling - Numerical metabolic modelling***

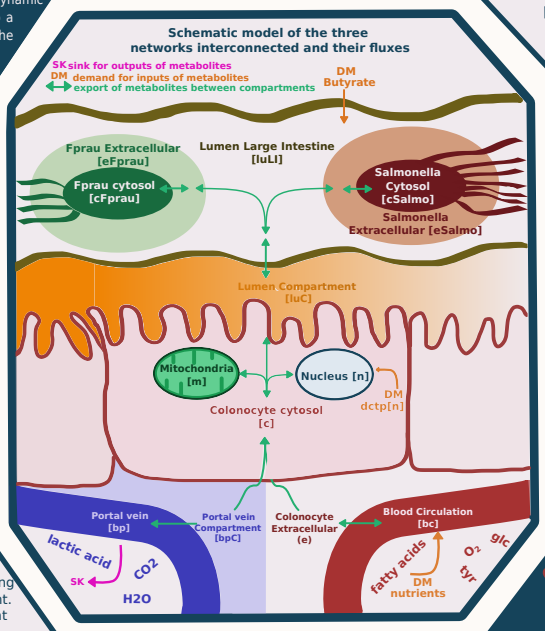
Context : a multidisciplinary project

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

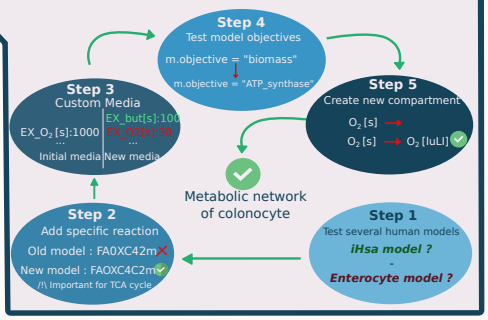


Schematic model of the three networks interconnected and their fluxes



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**:

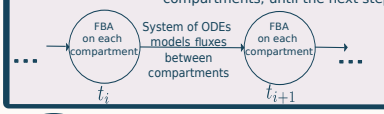


Simulation: FBA - dFBA

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?

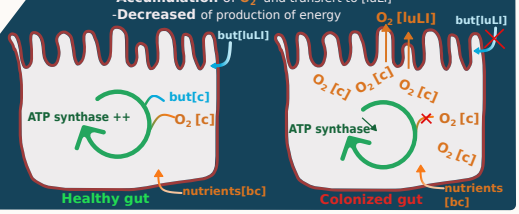
$$\partial_t s = \frac{Q_{in} s_{in} - Q_{out} s}{V} + \text{biological and chemical reactions} + \text{transport to other compartment}$$

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_2 and transfert to [luLI]
-**Decreased** of production of energy

Healthy gut:
-**Production** of butyrate by commensal bacteria
-**Consumption** of **but** and O_2 in TCA cycle
-**Good** production of energy



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 Thiphimurium [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 differenciate name for compartments between networks

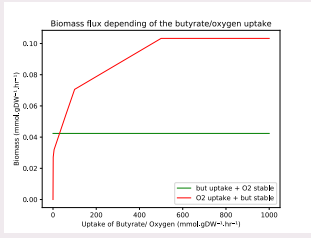
Fix fluxes for essential reactions in the right compartments for the exchanges

Simulation of growth in the human

We performed simulations with a custom medium to observe **biomass growth** as a function of O_2 and butyrate uptake.

We observed a **dependence of biomass growth on O_2 uptake** but **not** on **butyrate uptake.**

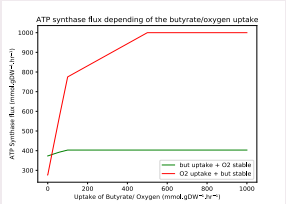
These results are not surprinsing because biomass includes many ***are not directed related to the energy metabolism*** *and therefore do* ***not depend on butyrate.***



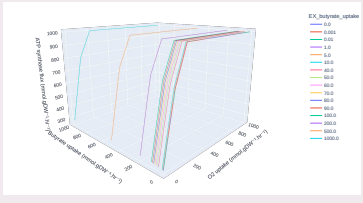
Effect of but and O_2 on energy production

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_2*** and ***FADH2*** to enable electron transport. ***FADH2*** 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_2 uptake has an impact on the ATP synthase activity, when the other uptake is stable.



The effect of O_2 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_2 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 O2 accumulation in the lumen [luLI].
2. Learn the **behaviour** of the system and **build a metamode**l 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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