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

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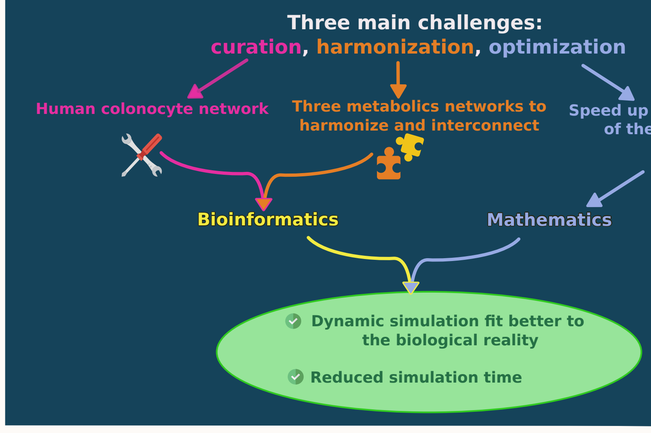
Context : a multidisciplinary project

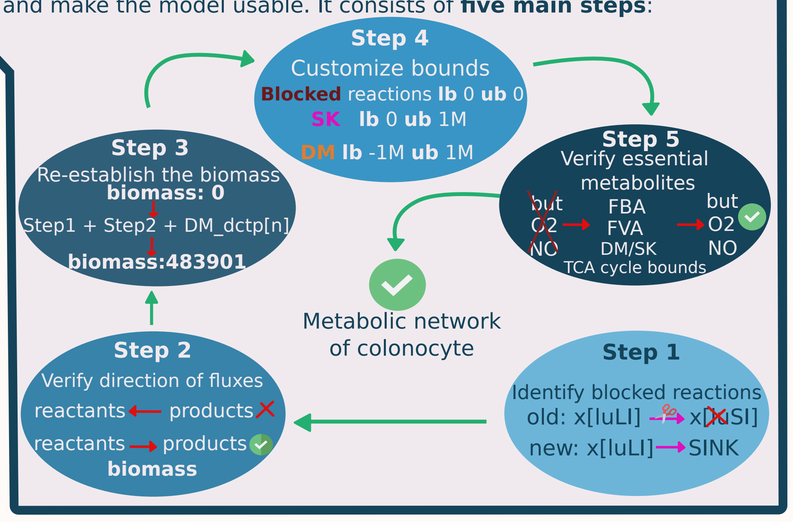
▶We want to model the dynamics of a host-microbiota-pathogen system through the dFBA method. **Dynamic FBA** (dFBA) integrates the fluxes calculated in FBA into a system of **ordinary differential equations (ODEs)**, enabling us to model the temporal dimension of metabolic simulations. In order to speed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

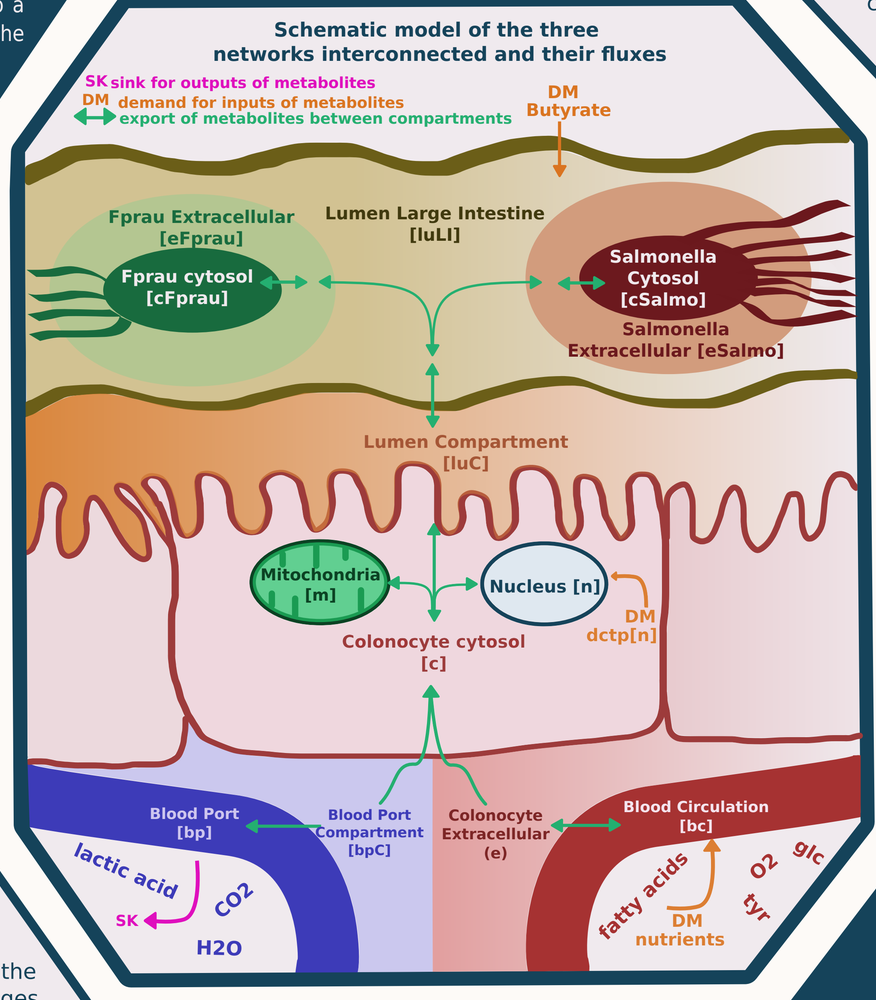


Colonocyte metabolic network curation

▶ We **extracted** and **cleaned** reactions occurring in colonocytes (epithelial cell) from a metabolic network of the whole human body [2].

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





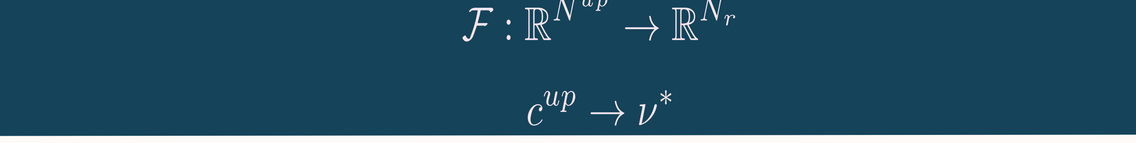
Harmonization

▶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 metabolic model of colonocyte as human [2] **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

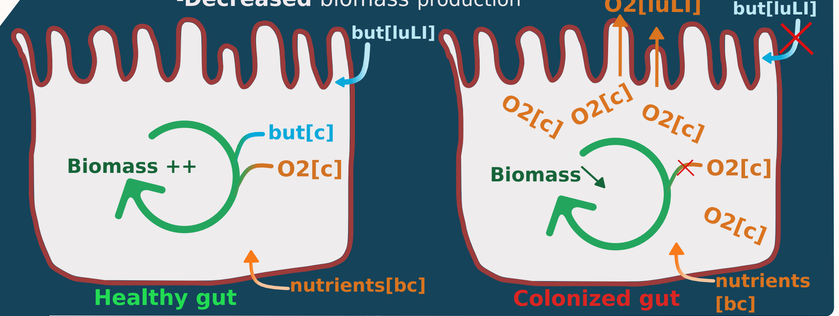
Fix fluxes for essential reactions in the right compartments for the exchanges



Validation colonocyte model

▶ We want to simulate two main cases to **validate** our model

Colonized gut:
-**NO** production of **but** by commensal bacteria
-**Accumulation** of **O2** and transfert to [luLI]
-**Decreased** biomass production



Healthy gut:
-**Production** of butyrate by commensal bacteria
-**Consumption** of **but** and **O2** in TCA cycle
-**Good** production of **biomass**

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

Simulation: FBA

▶ 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**:

$$\min_{\nu \in \mathbb{R}^{N_r}} \quad \nu_{\text{biomass}}$$

$$A \cdot \nu = 0$$

$$c_{\min} \leq \nu \leq c_{\max}$$

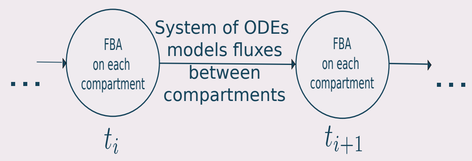
▶ We assume all three of the system's compartment's follow the FBA assumptions. We also define the function that maps constraints to the optimal flux according to FBA [5] by:

$$\mathcal{F} : \mathbb{R}^{N^{up}} \to \mathbb{R}^{N_r}$$

$$c^{up} \to \nu^*$$

Simulation : dFBA

▶ Our model assumes that FBA holds for each instant [5]. 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. . .



▶ How does the equations of the **ODE system look like?**. For the concentration of a component, we have the following form :

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

Mathematical model of the system

▶ Luminal compartment:

$$\begin{aligned}
\partial_t S_{th} &= (\mathcal{F}_{S_{th},1}(m_l, S_{th}, F_{\text{prau}}) - \rho n_l - D_{S_{th}}) S_{th} \\
\partial_t F_{\text{prau}} &= (\mathcal{F}_{F_{\text{prau}},1}(m_l, S_{th}, F_{\text{prau}}) - \rho n_l - \alpha \frac{O_{2_l}}{K_{O_2} + O_{2_l}} - D_{F_{\text{prau}}}) F_{\text{prau}} \\
\partial_t n_l &= \gamma_n (n_e - n_l) - d_n n_l - D_{n_l} \\
\partial m_l &= D(m_i n - m_l) + \mathcal{F}_{S_{th},m_l}(m_l, S_{th}, F_{prau}) S_{th} + \mathcal{F}_{F_{prau},m_l}(m_l, S_{th}, F_{prau}) F_{prau} \\
&\quad + \beta m_l O_{2_l} + \text{diag}(\gamma) T_r(m_e, m_l)
\end{aligned}$$

▶ Epithelial compartment:

$$\begin{aligned}
\partial_t n_e &= C_{but,n} n_e \left(n_e - L_n \frac{but_e}{K_b ut + but_e} \right) (L_n - n_e) - d_n n_e + \gamma_n (n_m - n_e) + VF(S_{th}) \\
\partial_t NO_e &= \gamma_{NO} (NO_e - NO_e) + VF(S_{th}) \\
\partial_t O_{2_e} &= \mathcal{F}_{ent,O_2}(NO_e,)_{2_e}, but_e) - d_{O_2} O_{2_e} + L_{O_2} + \gamma (O_{2_l} - O_{2_e}) \\
\partial_t but_e &= \mathcal{F}_{ent,but}(NO_e,)_{2_e}, but_e) + \gamma_b ut (but_m - but_e)
\end{aligned}$$

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?

▶ There are still reactions in the colonocyte network that do no behave as expected. Mainly, the consumption of butyrate in the network has some problems we've been looking at.
Solving this is a work in progress.

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