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

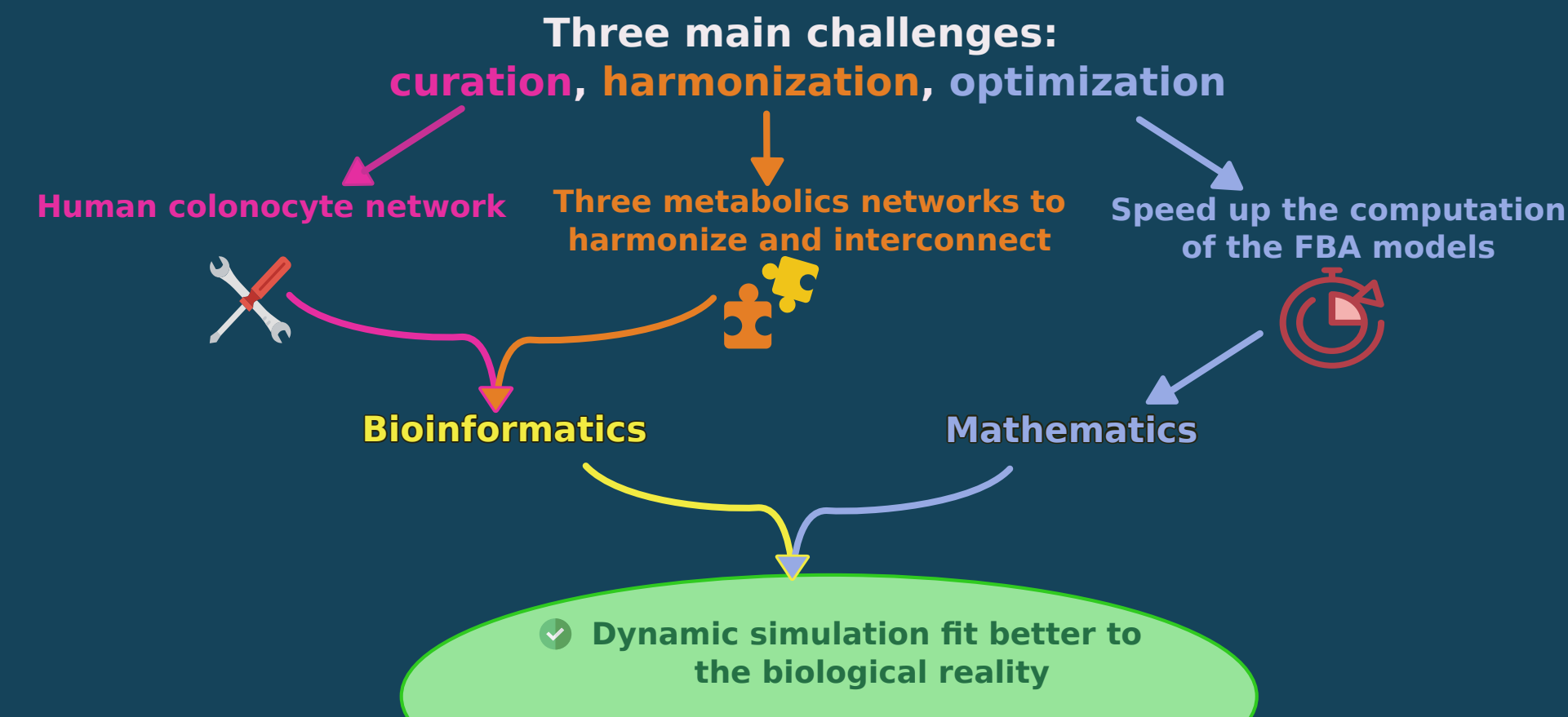
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Context : a multidisciplinary project

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]**.



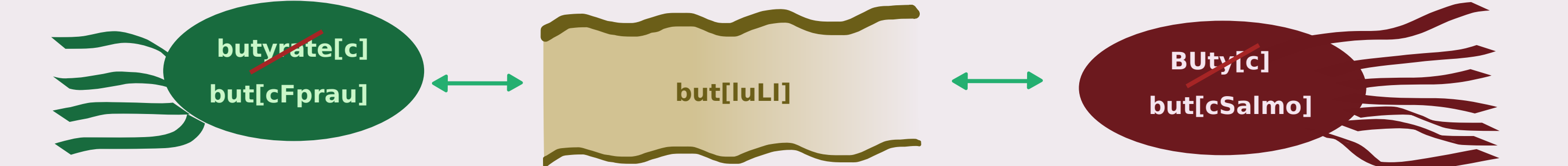
Harmonization

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 differentiate name for compartments between networks

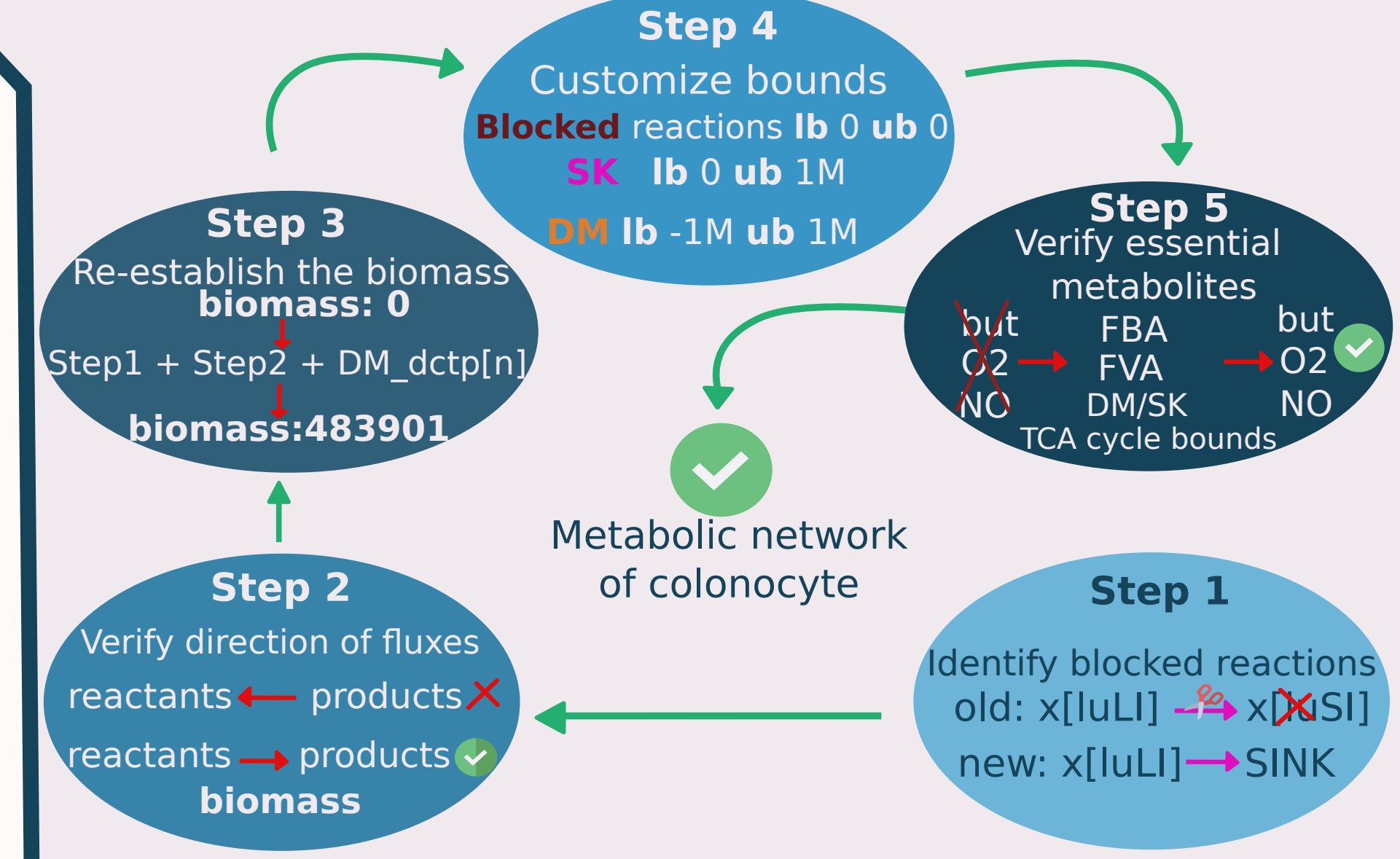
Fix fluxes for essential reactions in the right compartments for the exchanges



Colonocyte metabolic network curation

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

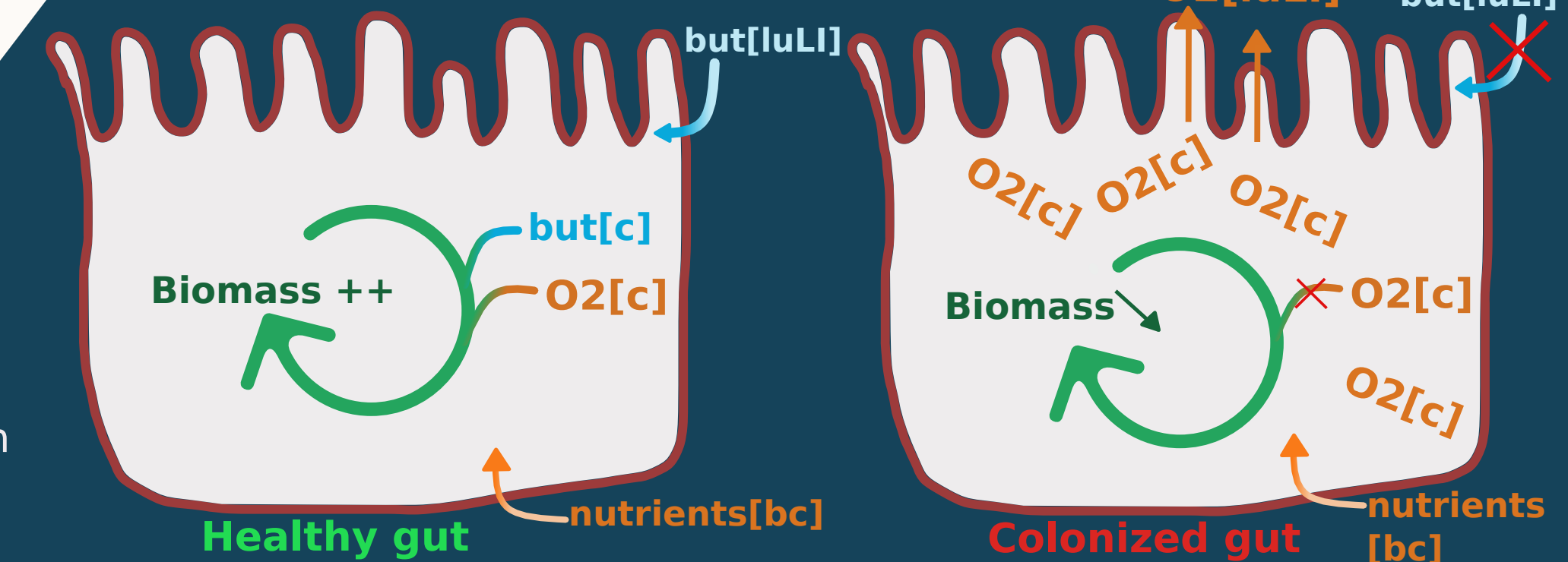
A long **manual curation** process was performed in order to clean up and make the model usable. It consists of **five main steps**:



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 transfer 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**:

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

$$A \cdot \nu = 0$$

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

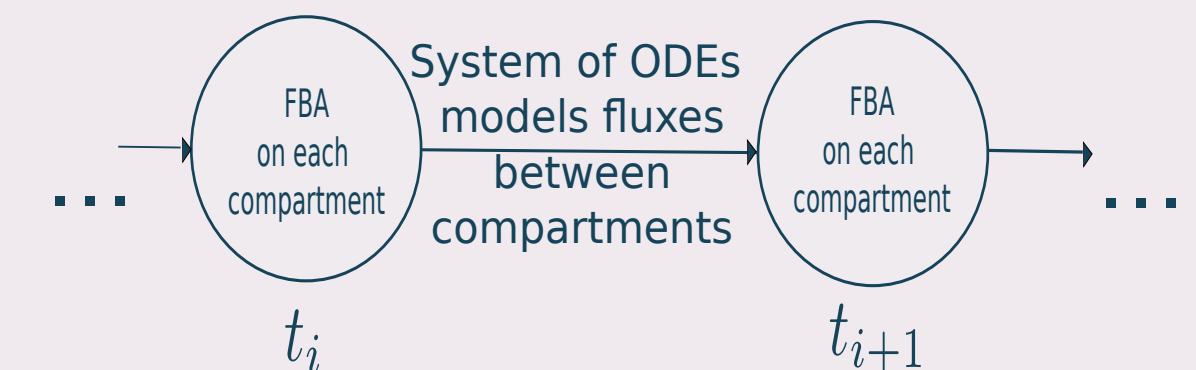
We assume all three of the system's compartment's follow the FBA assumptions. We also define the function that maps constraints to the optimal flux according to FBA [5] by:

$$\mathcal{F} : \mathbb{R}^{N_{up}} \rightarrow \mathbb{R}^{N_r}$$

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

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: $\partial_t S_{th} = (\mathcal{F}_{S_{th},1}(m_l, S_{th}, F_{prau}) - \rho_{m_l} - D_{S_{th}}) S_{th}$

$$\partial_t F_{prau} = (\mathcal{F}_{F_{prau},1}(m_l, S_{th}, F_{prau}) - \rho_{m_l} - \alpha \frac{O_{2l}}{K_{O_2} + O_{2l}} - D_{F_{prau}}) F_{prau}$$

$$\partial_t n_l = \gamma_n (n_e - n_l) - d_n n_l - D_{n_l}$$

$$\partial_t m_l = D(m_e - m_l) + \mathcal{F}_{S_{th},m_l}(m_l, S_{th}, F_{prau}) S_{th} + \mathcal{F}_{F_{prau},m_l}(m_l, S_{th}, F_{prau}) F_{prau} + \beta m_l O_{2l} + \text{diag}(\gamma) T_r(m_e, m_l)$$

Epithelial compartment:

$$\partial_t n_e = C_{but,n} n_e \left(n_e - L_n \frac{but_e}{K_{but} + but_e} \right) (L_n - n_e) - d_n n_e + \gamma_n (n_m - n_e) + VF(S_{th})$$

$$\partial_t NO_e = \gamma_{NO}(NO_e - NO_e) + VF(S_{th})$$

$$\partial_t O_{2e} = \mathcal{F}_{ent,O_2}(NO_e,)_{2e}, but_e) - d_{O_2} O_{2e} + L_{O_2} + \gamma(O_{2l} - O_{2e})$$

$$\partial_t but_e = \mathcal{F}_{ent,but}(NO_e,)_{2e}, but_e) + \gamma_{but}(but_m - but_e)$$

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 not 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.

References:

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