



**HAL**  
open science

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

Coralie Muller, Pablo Ugalde Salas, Rafael Kaempfer, Arie Wortsman, Simon Labarthe, Clémence Frioux

► **To cite this version:**

Coralie Muller, Pablo Ugalde Salas, Rafael Kaempfer, Arie Wortsman, Simon Labarthe, et al.. Modelling the dynamics of Salmonella infection in the gut at the bacterial and host levels. SBMI 2023 - 7th International Symposium on Systems Biology of Microbial Infection, Sep 2023, Jena, Germany. . hal-04229130

**HAL Id: hal-04229130**

**<https://inria.hal.science/hal-04229130>**

Submitted on 5 Oct 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



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

Coralie MULLER<sup>1</sup>, Pablo UGALDE SALAS<sup>1</sup>, Rafael KAEMPFER<sup>1</sup>, Arie WORTSMAN<sup>1</sup>, Simon LABARTHE<sup>2,1</sup> and Clémence FRIOUX<sup>1</sup>

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

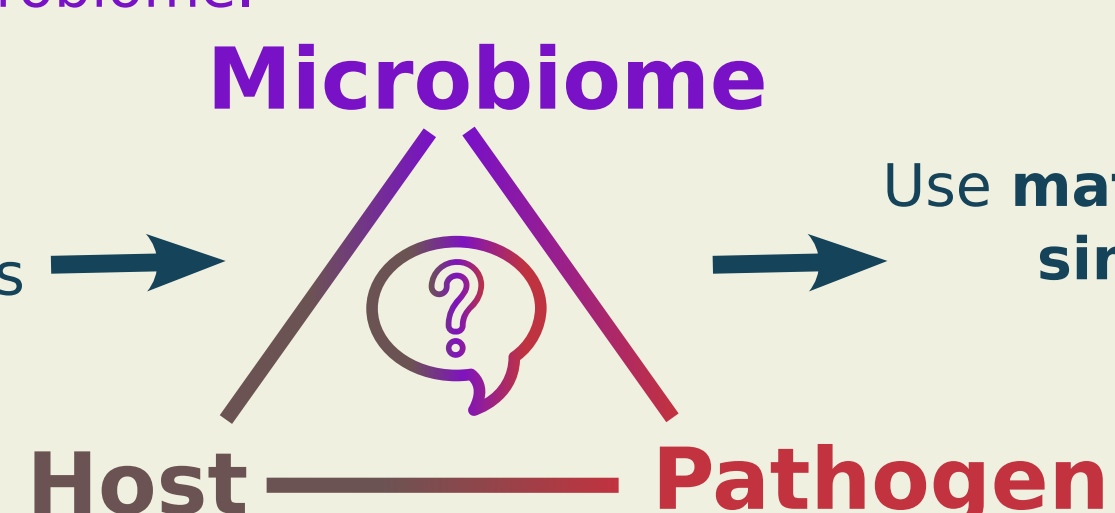
<sup>2</sup> INRAE, Univ. Bordeaux, BIOGECO, Pessac, France

**Keywords:** Constraint-based metabolic modelling -- host-microbiome-pathogen system -- Systems biology -- Gut microbiota -- *Salmonella enterica* Typhimurium -- ODE dynamic model



## A route to digital twins of microbiomes

The dynamics infection in the gut is the result of a **complex interaction** between the **pathogen**, the **host** and the **microbiome**.



Understanding the **mechanistic processes** of the infection is tedious  
How to **improve** it?

Use **mathematical models** in order to perform **simulations** of the infection process.

**Simulations** representing **metabolism** and its **interactions** are becoming increasingly **common** and very **useful**, but have their **limitations**:

- Dynamic simulation
- Lacks spatialization (different bacterial composition, ...)
- High computational cost (parameter inference, large microbial community)

Metamodels[1] and spatialization integration

- Dynamic simulation
- Reduced computational cost
- Add spatialization

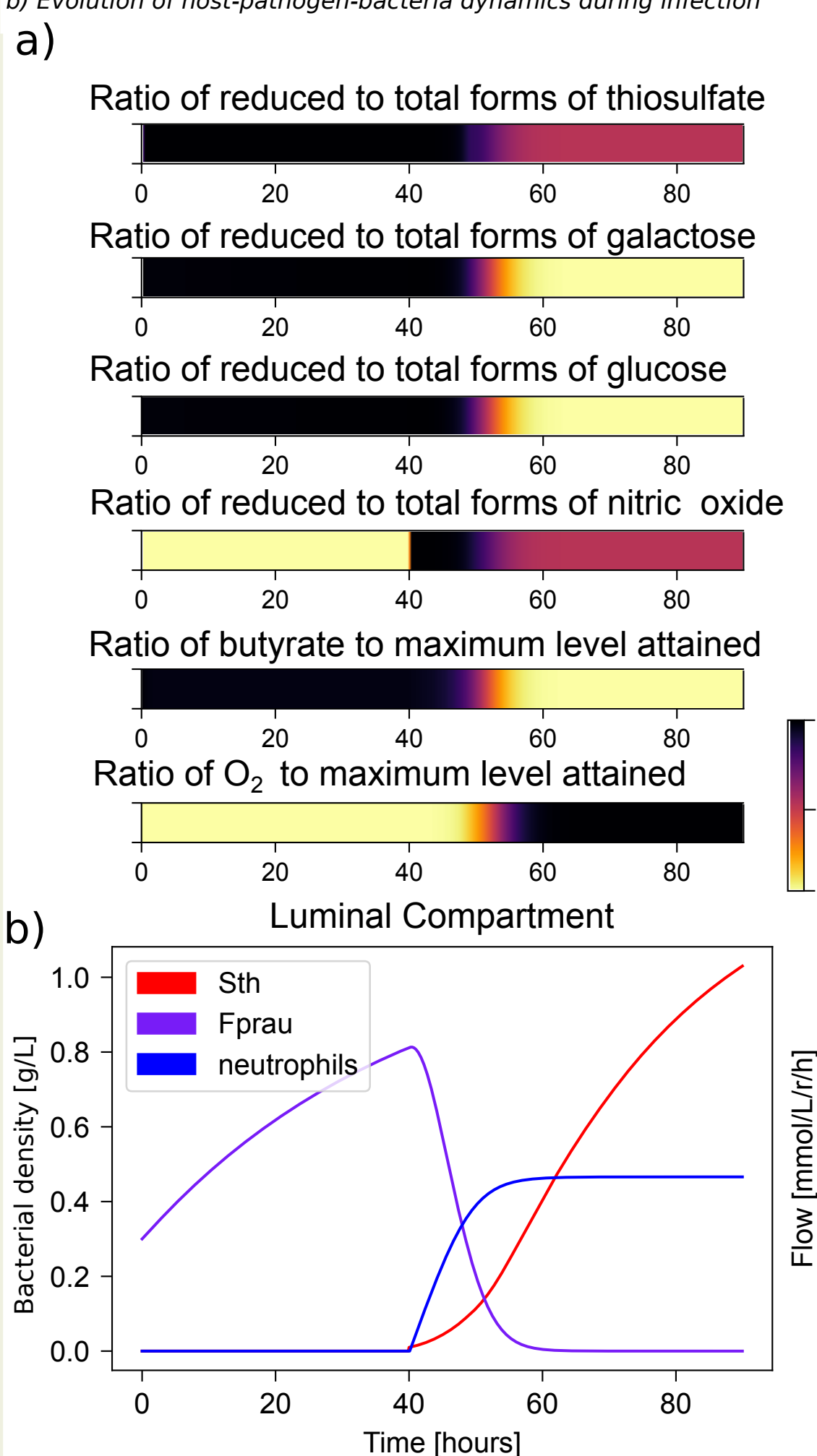
We model the metabolism of a **host-microbiota-pathogen system** to simulate *Salmonella Enterica* serova Typhimurium infection and use **statistical learning** to speed-up computation.



## Simulations

Our simulations represent correctly the infection process on two levels: the **lumen** of the intestine and the **enterocyte**.

Figure 4: Dynamics in lumen during infection to  
a) Proportion of metabolites in the lumen during infection  
b) Evolution of host-pathogen-bacteria dynamics during infection



### Dynamics in Lumen:

#### No infection(t0):

- No O<sub>2</sub> (Hypoxic)
- No oxidized elements
- No *Salmonella* presence
- Production of butyrate by Fprau
- No neutrophils recruitment
- Fprau growth (butyrate production, niche stability)

#### Infection(t40):

- Accumulation of O<sub>2</sub> (microaerobic)
- Production of **oxidized elements** (thiosulfate, NO<sub>3</sub>-, ...)
- Growth of *Salmonella*** and its oxidized niche (galactarate, glucarate, ...)
- Production of **virulence factors** by *Salmonella* triggering activation of neutrophils and the **inflammation**
- Neutrophils recruitment by virulence factors, target commensals
- Decline of Fprau** and its niche (glucose, galactose) and butyrate production

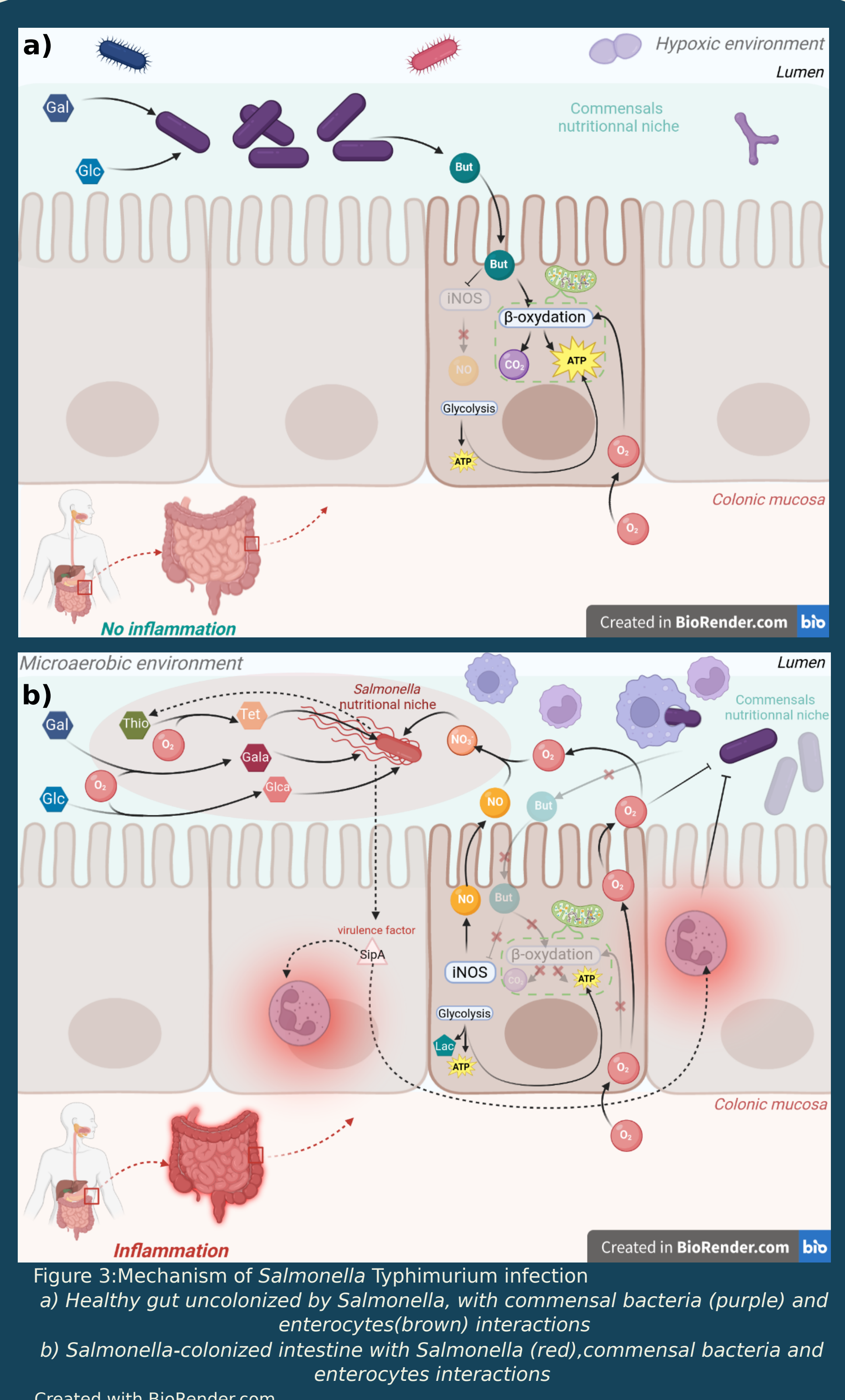


Figure 3: Mechanism of *Salmonella* Typhimurium infection  
a) Healthy gut uncolonized by *Salmonella*, with commensal bacteria (purple) and enterocytes (brown) interactions  
b) *Salmonella*-colonized intestine with *Salmonella* (red), commensal bacteria and enterocytes interactions

### Flow dynamics during infection:

- Decline of the butyrate flow causes by absence of production
- Overflow O<sub>2</sub> and NO in the lumen from enterocytes

## Model building

The **host-microbiota-pathogen system** uses **3 metabolic networks** one for each actor of the infection:

- A **commensal bacteria**: *Faecalibacterium prausnitzii* (Fprau: buyrate producer)[2]
- A **pathogen**: *Salmonella Enterica* serova Typhimurium[3]
- A **host cell**: human enterocytes[4]

## Mathematical models

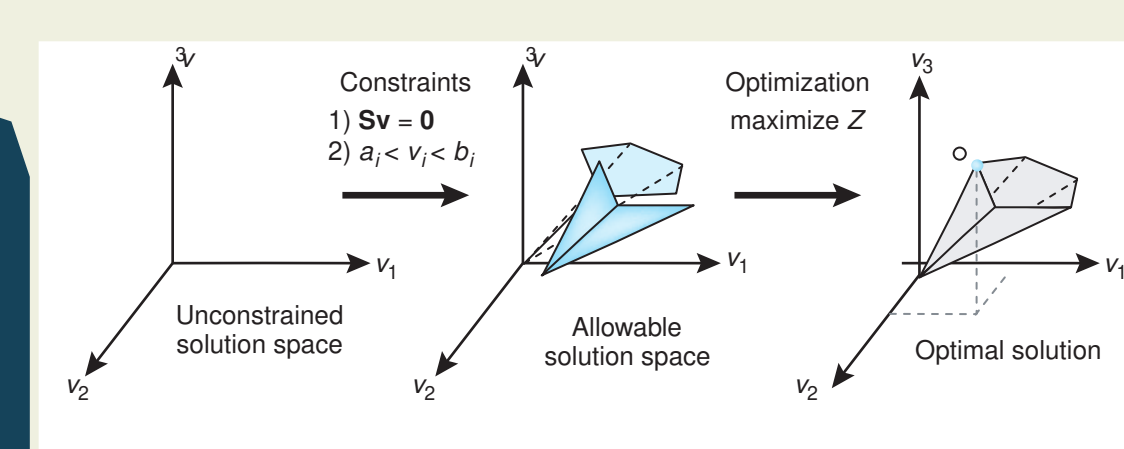


Figure 1: The conceptual basis of FBA  
Figure adapted from Jeffrey D Orth, & al. 2010

### Dynamic FBA (dFBA)[5]:

- Enables metabolic simulations over time
- Integrates the fluxes calculated in FBA into a system of ordinary differential equations (ODEs)

### Flux Balance Analysis (FBA)[5]:

- Hypothesis of quasi-steady state
- Set of thermodynamical constraints
- Computes activity rates, or fluxes
- Used on unique species or community

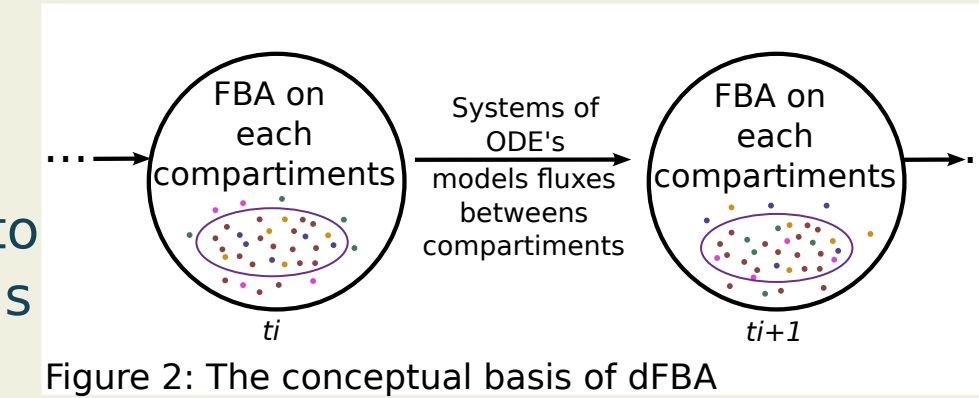


Figure 2: The conceptual basis of dFBA

### Main refinement steps

#### Host metabolism curation

- Butyrate metabolism
- Curation reactions related to feed the energy-related pathways

#### Objective functions

- Salmonella* Typhimurium → Biomass reaction
- Faecalibacterium prausnitzii* → Biomass reaction
- Human enterocytes → ATP synthase reaction (energy metabolism) [6]

### Dynamics in Enterocyte:

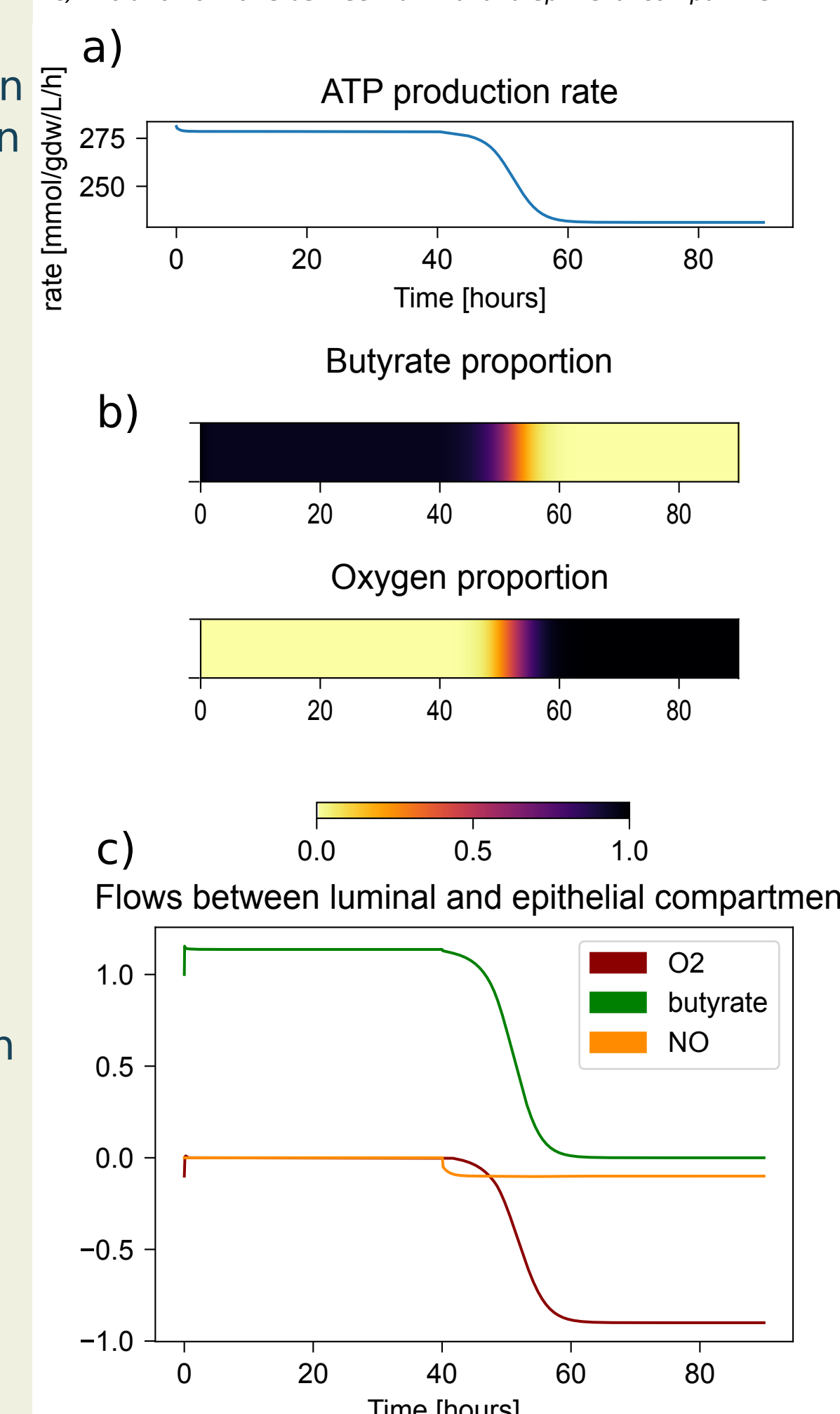
#### No infection(t0):

- Production of **NO inhibited by butyrate** from Fprau
- Consumption of butyrate** and O<sub>2</sub> in TCA cycle and electron
- Production of energy (ATP)** from butyrate

#### Infection(t40):

- Production of NO** without its inhibition by butyrate
- No consumption** of butyrate and O<sub>2</sub> in TCA cycle
- O<sub>2</sub> **leakage** to lumen
- Reduction in energy production (ATP)**

Figure 5: Dynamics in enterocyte during infection  
a) Evolution of the ATP production during infection  
b) Proportion of O<sub>2</sub> and butyrate in the enterocyte during infection  
c) Evolution of flows between luminal and epithelial compartment



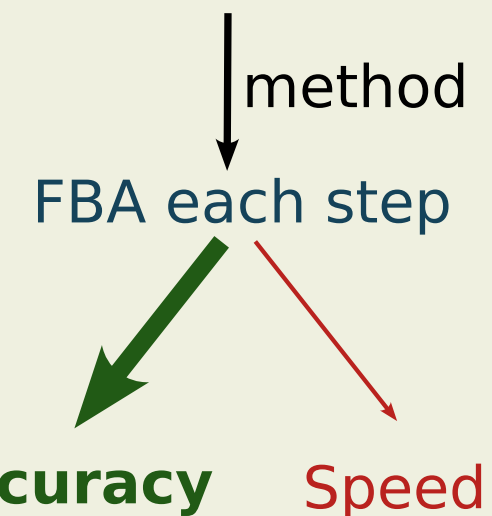
## A surrogate to speed up simulations

dFBA simulations can represent a **high computational cost**, therefore, we want to provide an **efficiently computed surrogate of the dFBA model**.

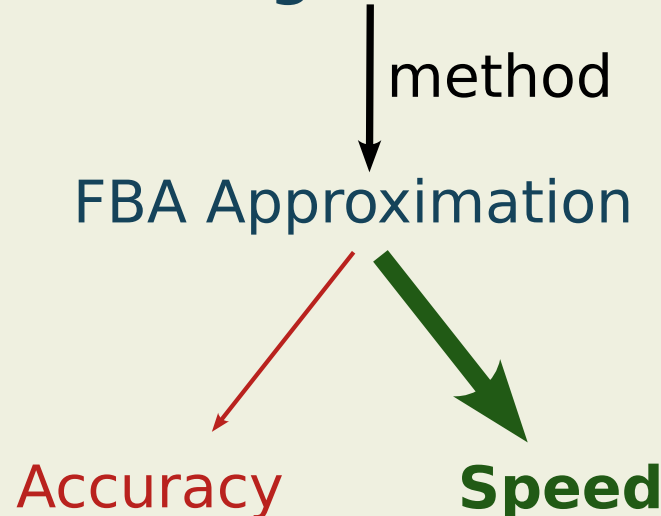
The **metamodel approximates the FBA** by using **ANOVA-Reproducing Kernel Hilbert Space (RKHS)**[7].

The FBA approximation **replaces the FBA** in each time

### dFBA model



### Surrogate Model

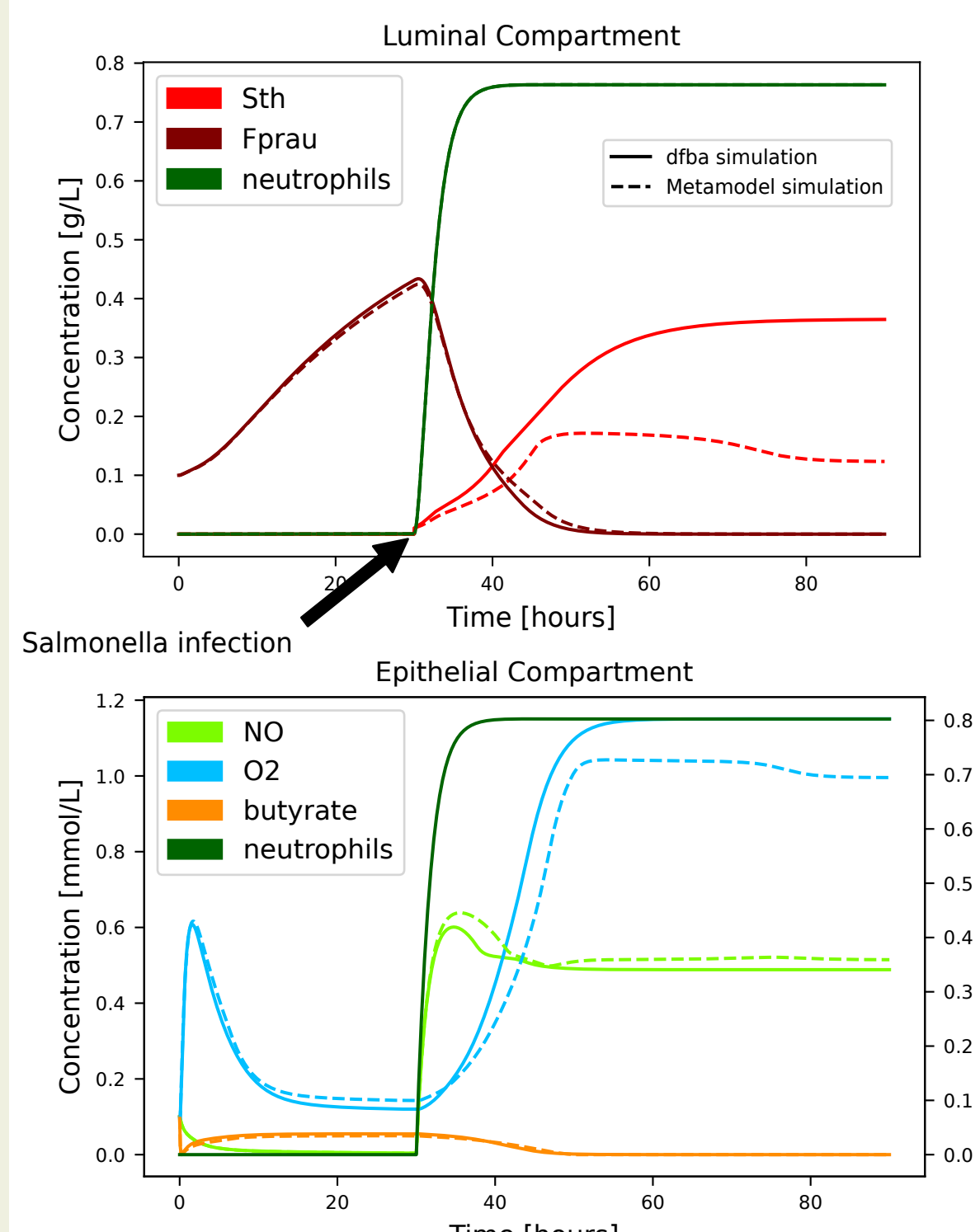


### Our Results:

- The comparison between the two methods shows a small difference in **precision (<5% error)**
- Dynamic simulations are **speed-up by factor x45**

**Improvements:** the precision could be improved and other techniques are being studied to improve speed-up.

Figure 6: The ecological dynamics of both dFBA and the accelerated model



## Towards spatialization ...

### Take-Home Message

- Success at efficiently **capturing** and **predicting** the metabolic roles of each partner in the infection at the **cost of limited loss** in accuracy
- A **mechanistic** and **accurate metabolic model** of a complex system involving a human metabolic network
- Our model paves the way to a more **systematic use of metabolic models** as descriptors of **microbe-microbe** and **host-microbe** interactions during infections

### Improvements:

- Optimize** the speed-up and the accuracy
- Add** spatialization to our model
- Generalize** the approach to other ecosystems which functions are important for dynamics of the community

## References

- Clémence Frioux et al. Accelerating metabolic models evaluation with statistical metamodels: application to *Salmonella* infection models. working paper or preprint, April 2022.
- El-Semman et al. "Genome-scale metabolic reconstructions of *Bifidobacterium adolescentis* L2-32 and *Faecalibacterium prausnitzii* A2-165 and their interaction." *BMC systems biology* 8.1 (2014): 1-11
- Raghuathan et al. Constraint-based analysis of metabolic capacity of *Salmonella typhimurium* during host-pathogen interaction. *BMC Syst Biol* 3, 38 (2009). <https://doi.org/10.1186/1752-0509-3-38>
- Kocabaş, K., Arif, A., Uddin, R., & Çakir, T. (2022). Dual transcriptome based reconstruction of salmonella human integrated metabolic network to screen potential drug targets. *PLOS ONE*, 17, e0268889 <https://doi.org/10.1371/JOURNAL.PONE.0268889>
- Ove Öyås and Jörg Satellin. Genome-scale metabolic networks in time and space. *Current Opinion in Systems Biology*, 8:51-8, 2018.
- Schuetz, R., Kuepfer, L., & Sauer, U. (2007). Systematic evaluation of objective functions for predicting intracellular fluxes in *Escherichia coli*. *Molecular Systems Biology*, 3, 119. <https://doi.org/10.1038/MSB4100162>
- Sylvie Huet and Marie-Luce Taupin. Metamodel construction for sensitivity analysis. *ESAIM: Proceedings and Surveys*, 60:27-69, 2017.