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

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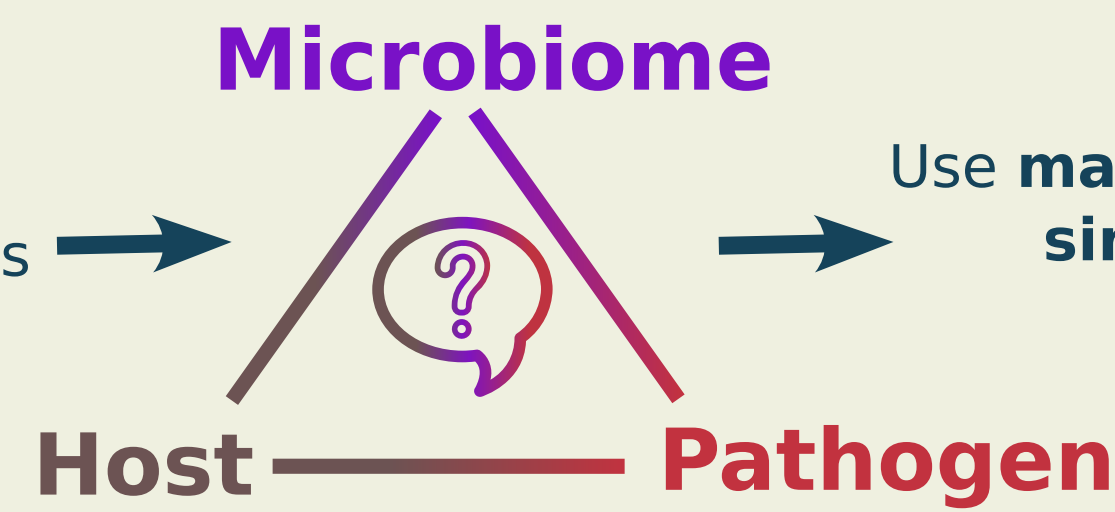
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Keywords: Constraint-based metabolic modelling -- host-microbiome-pathogen system -- Systems biology -- Gut microbiota -- *Salmonella enterica* Typhimurium -- ODE dynamic model



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**.



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

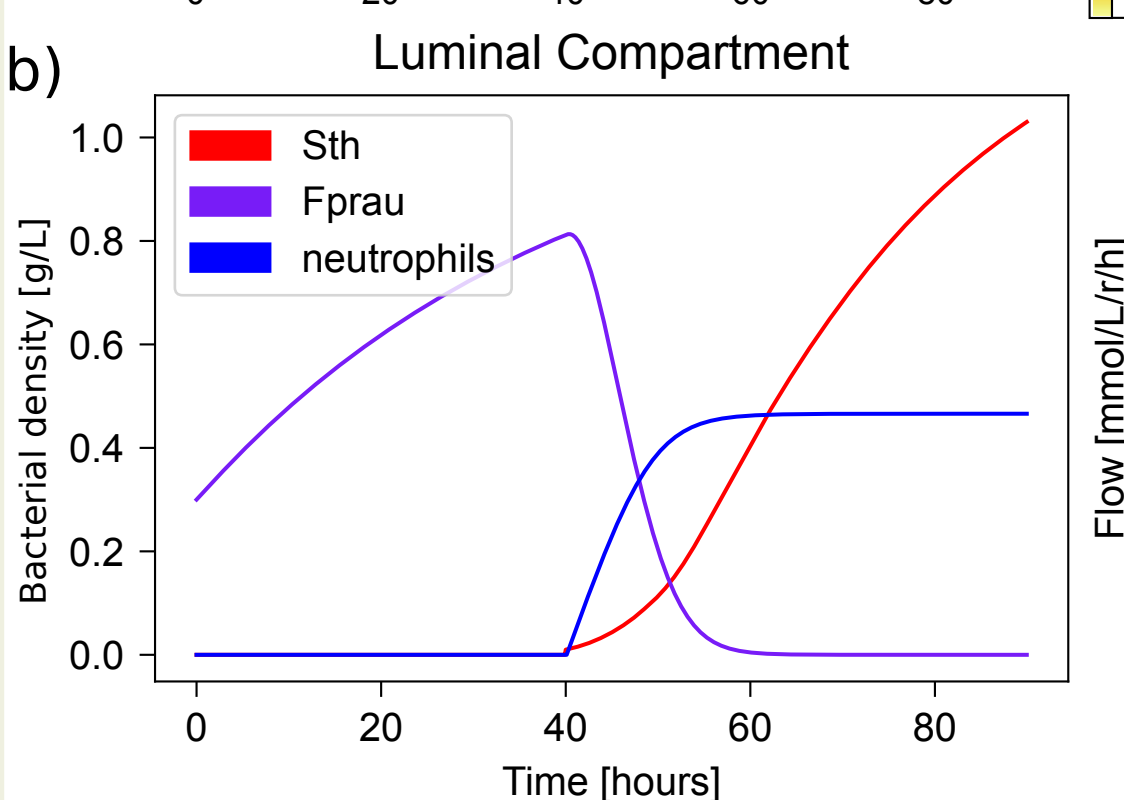
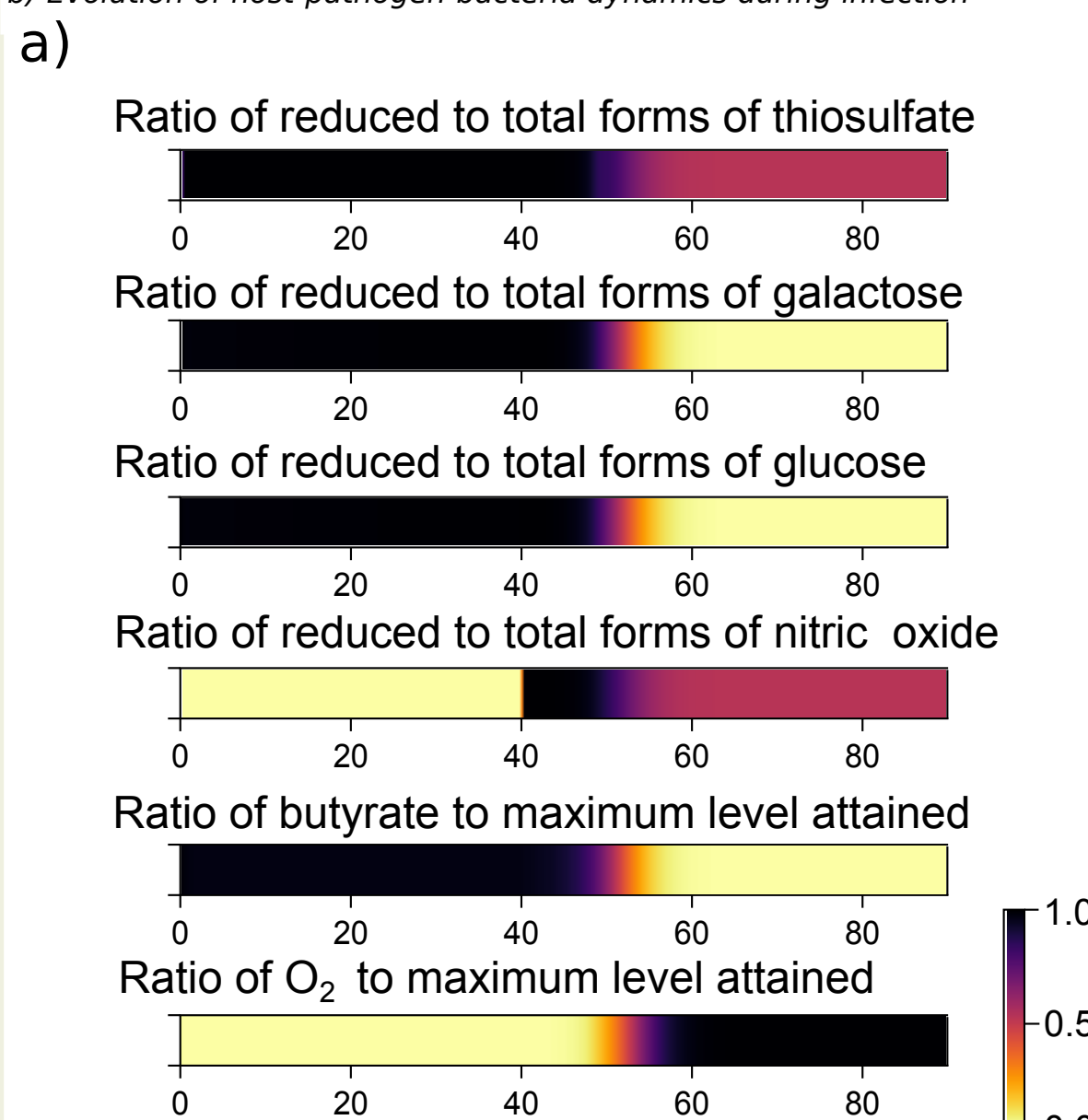
We model the metabolism of a **host-microbiota-pathogen system** to simulate *Salmonella Enterica* serova Typhimurium infection and use **statistical learning** to speed-up computation.



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 O₂ (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 O₂ (microaerobic)
- Production of **oxidized elements** (thiosulfate, NO₃-, ...)
- 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

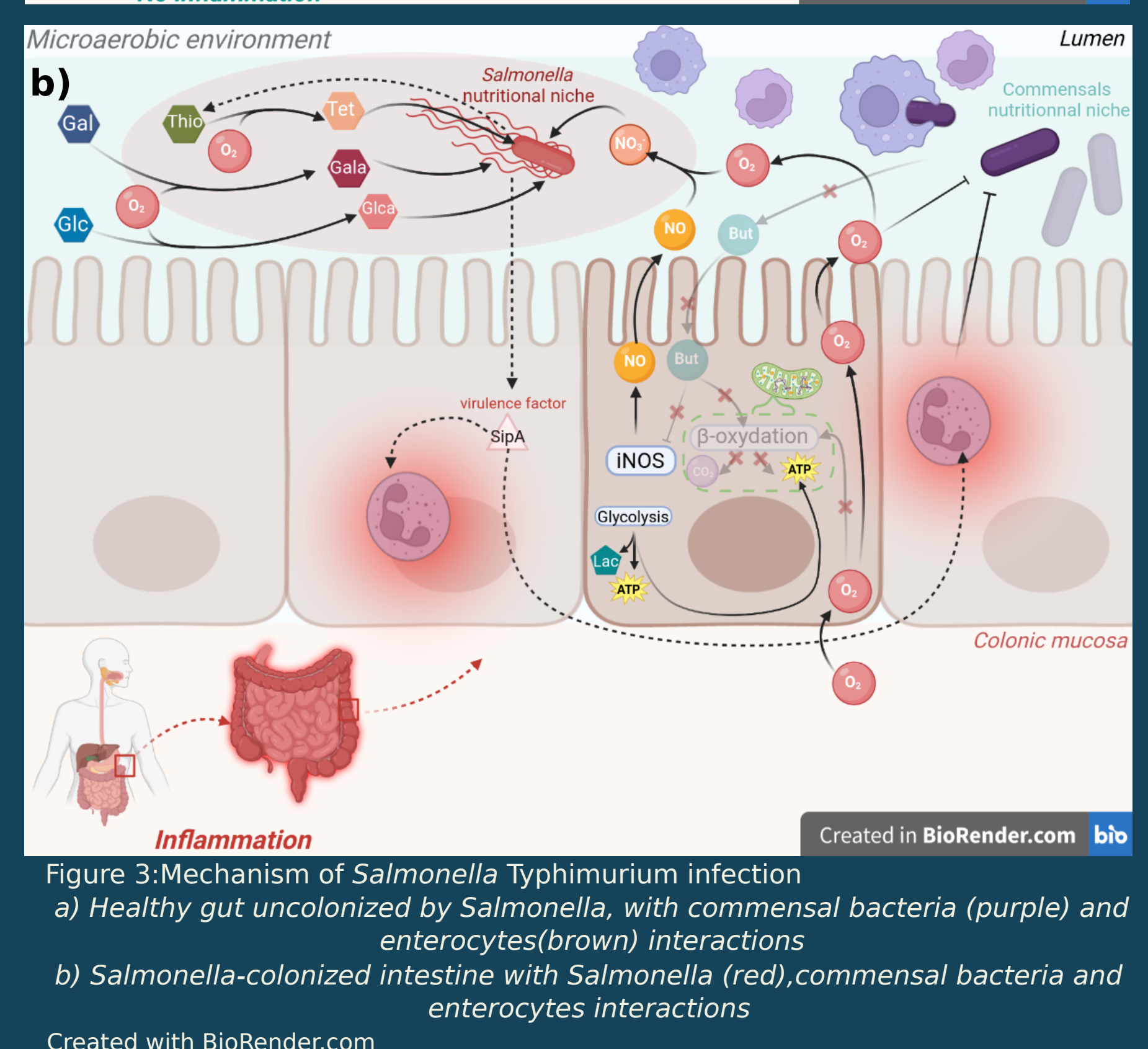
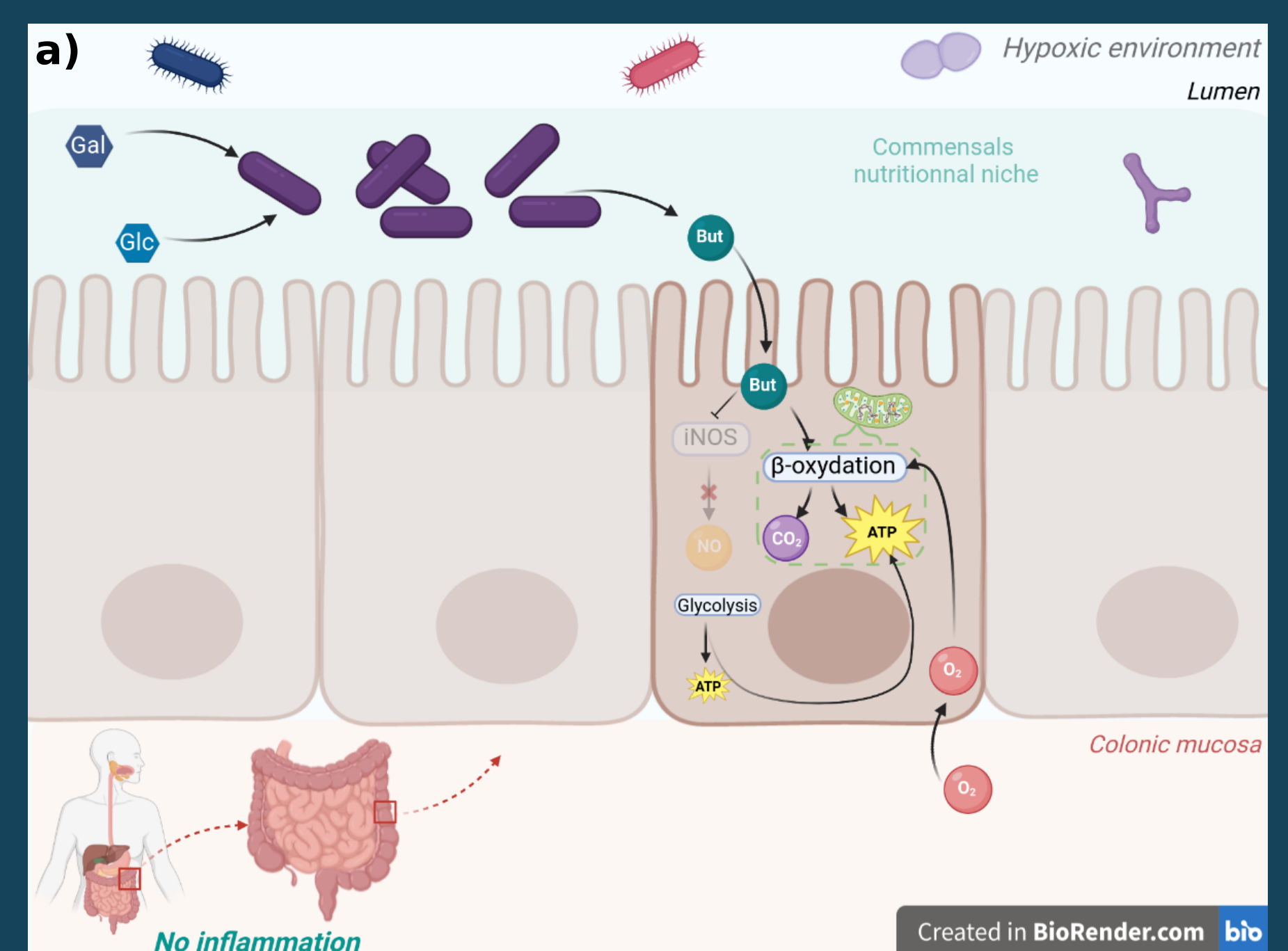


Figure 3: Mechanism of *Salmonella* Typhimurium infection
a) Healthy gut uncolonized by *Salmonella*, with commensal bacteria (purple) and enterocytes (brown) interactions
b) *Salmonella*-colonized intestine with *Salmonella* (red), commensal bacteria and enterocytes interactions

Flow dynamics during infection:

- Decline of the butyrate flow causes by absence of production
- Overflow O₂ and NO in the lumen from enterocytes

Model building



Metabolic networks

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

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

Mathematical models

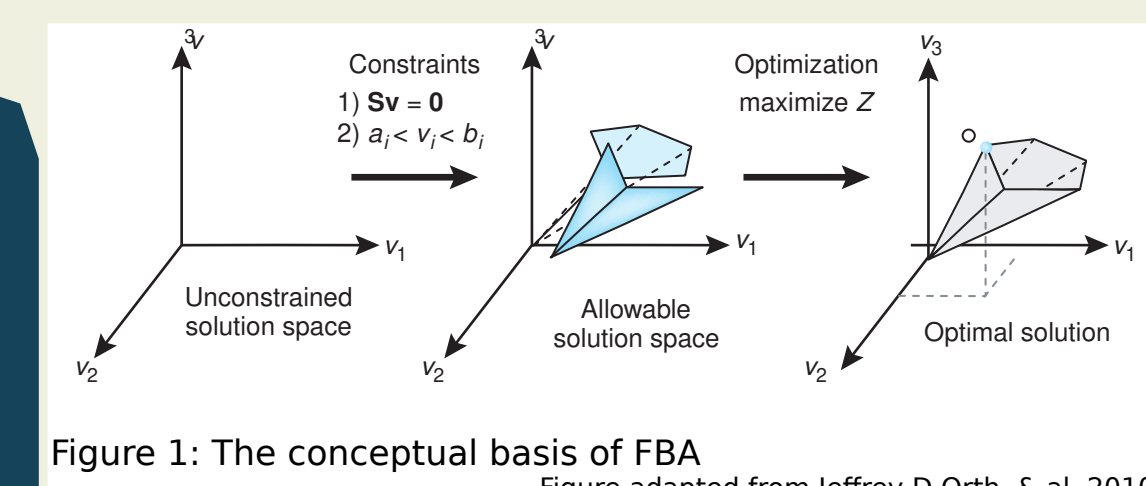


Figure 1: The conceptual basis of FBA
Figure adapted from Jeffrey D Orth, & al. 2010

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

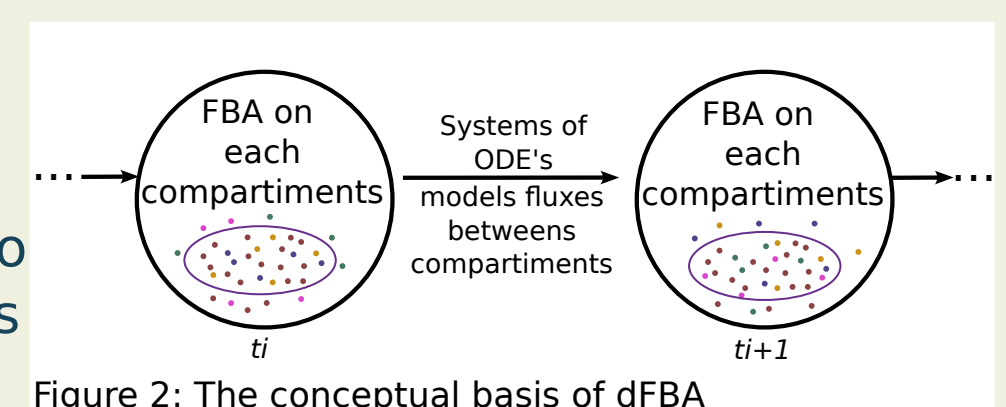


Figure 2: The conceptual basis of dFBA

Main refinement steps

Host metabolism curation

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

Objective functions

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

Dynamics in Enterocyte:

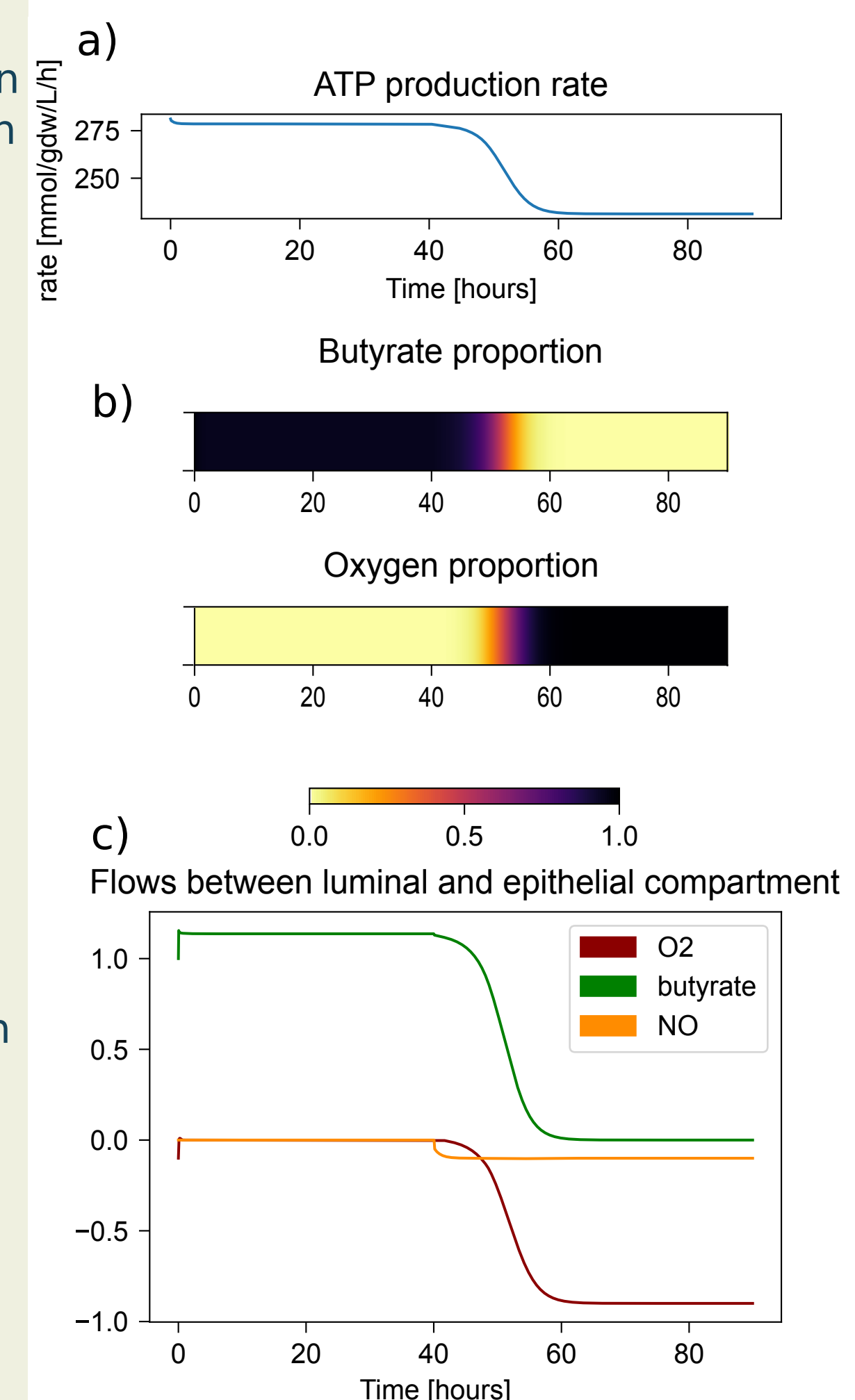
No infection(t0):

- Production of **NO** inhibited by butyrate from Fprau
- Consumption of butyrate and O₂ 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 O₂ in TCA cycle
- O₂ 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 O2 and butyrate in the enterocyte during infection
c) Evolution of flows between luminal and epithelial compartment



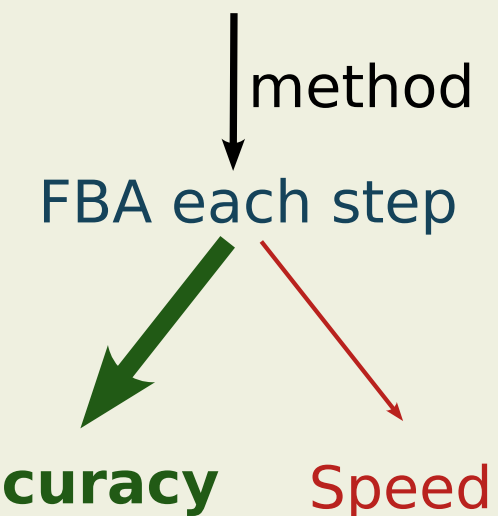
A surrogate to speed up simulations

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

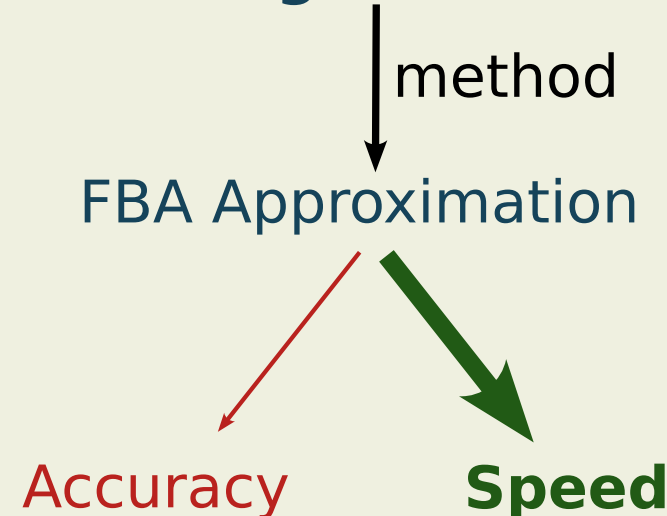
The **metamodel approximates the FBA** by using **ANOVA-Reproducing Kernel Hilbert Space (RKHS)**[7].

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

dFBA model



Surrogate Model

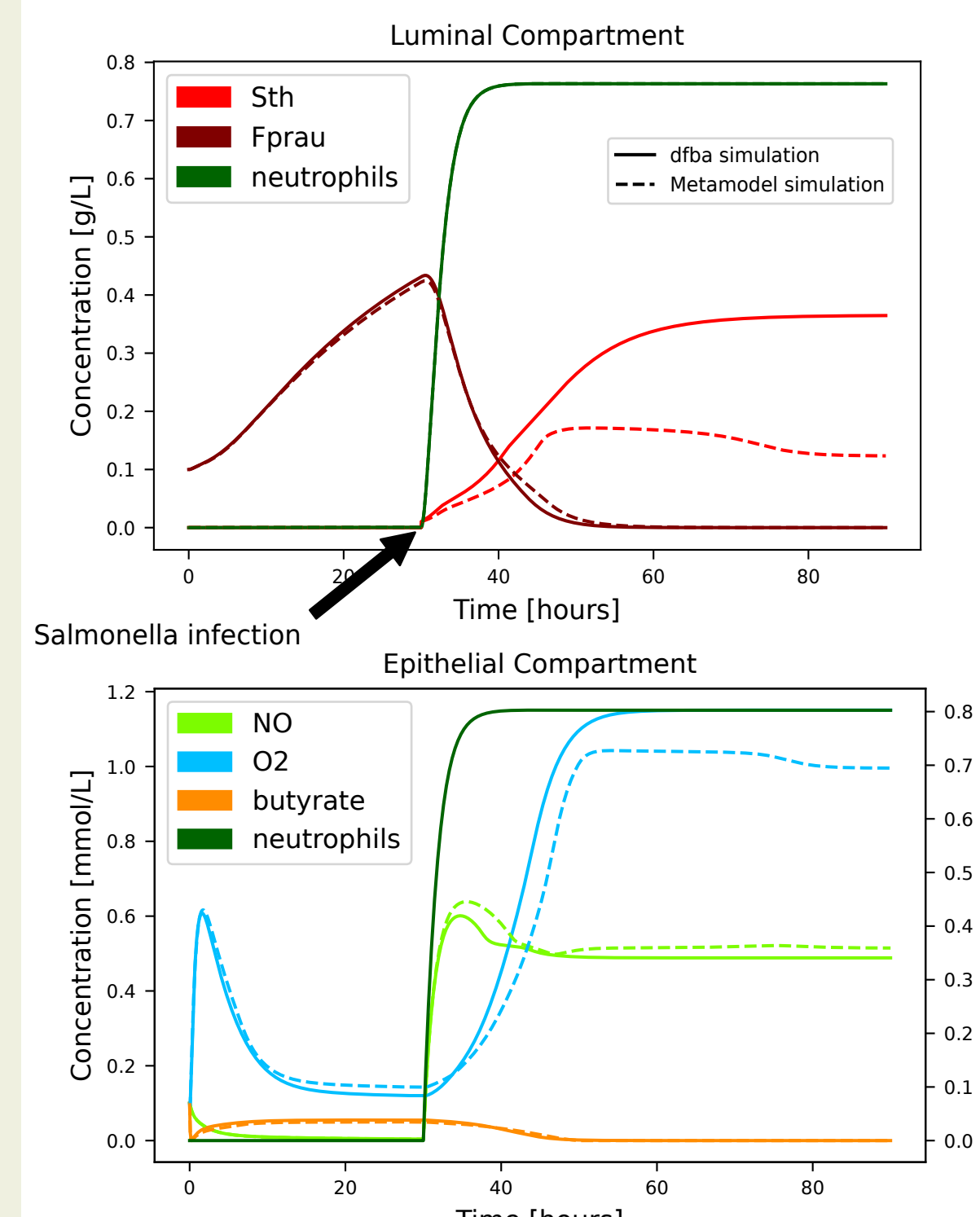


Our Results:

- The comparison between the two methodes 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

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