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

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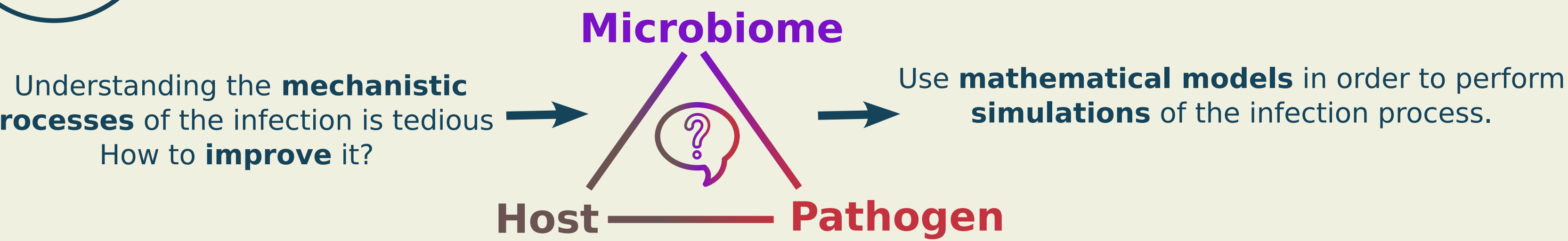
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Keywords: Constraint-based metabolic modelling -- host-microbiome-pathogen system -- Systems biology -- Gut microbiota -- *Salmonella enterica* Typhimurium -- ODE dynamic model



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**.



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.



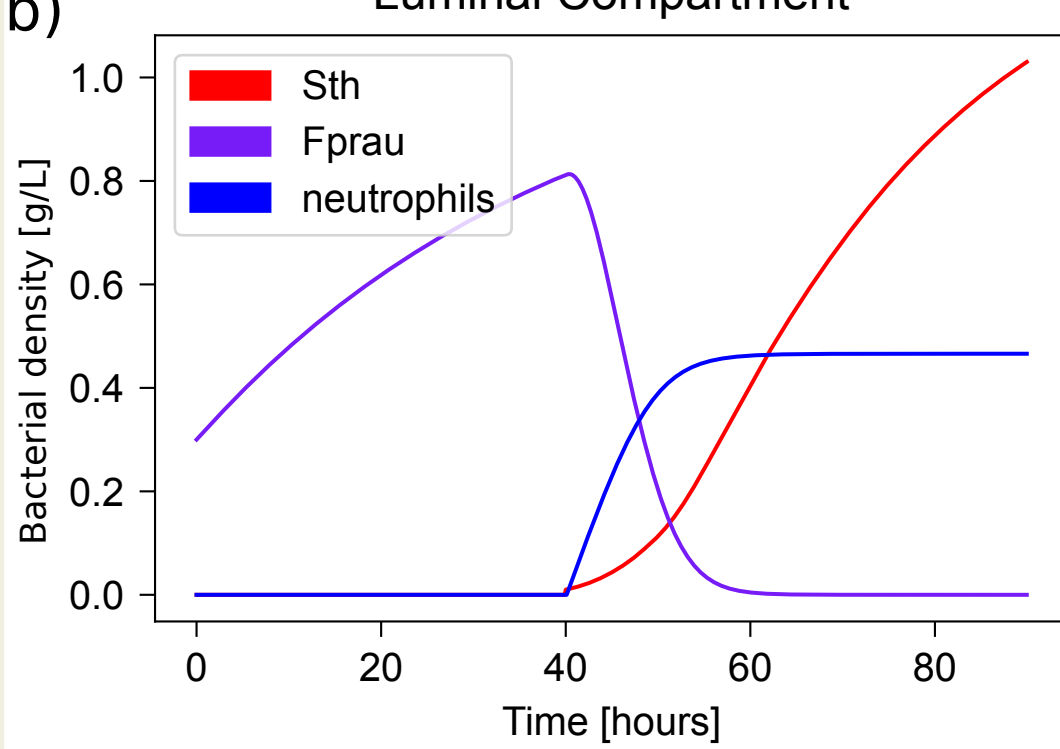
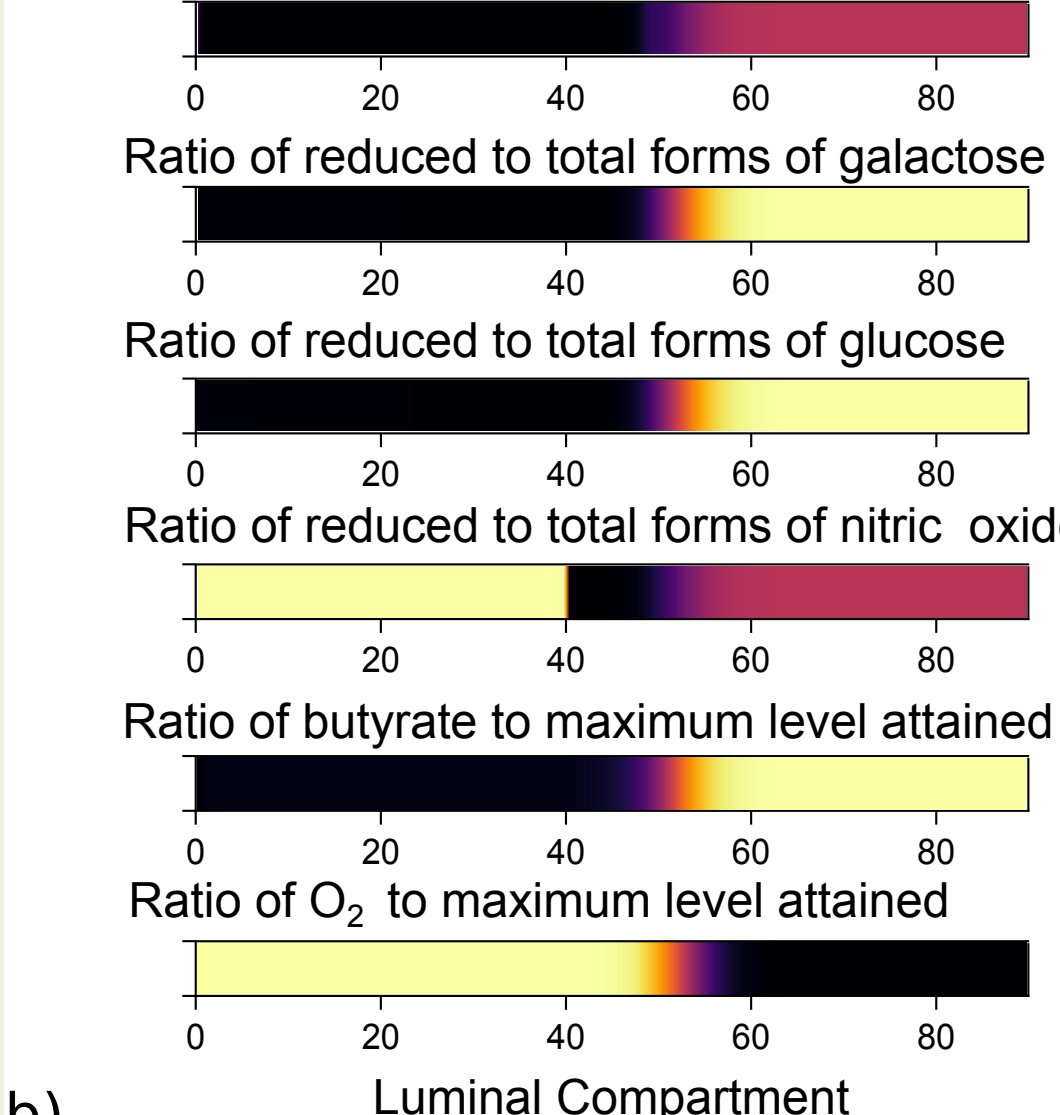
Simulations

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, gluconate, ...)
- 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

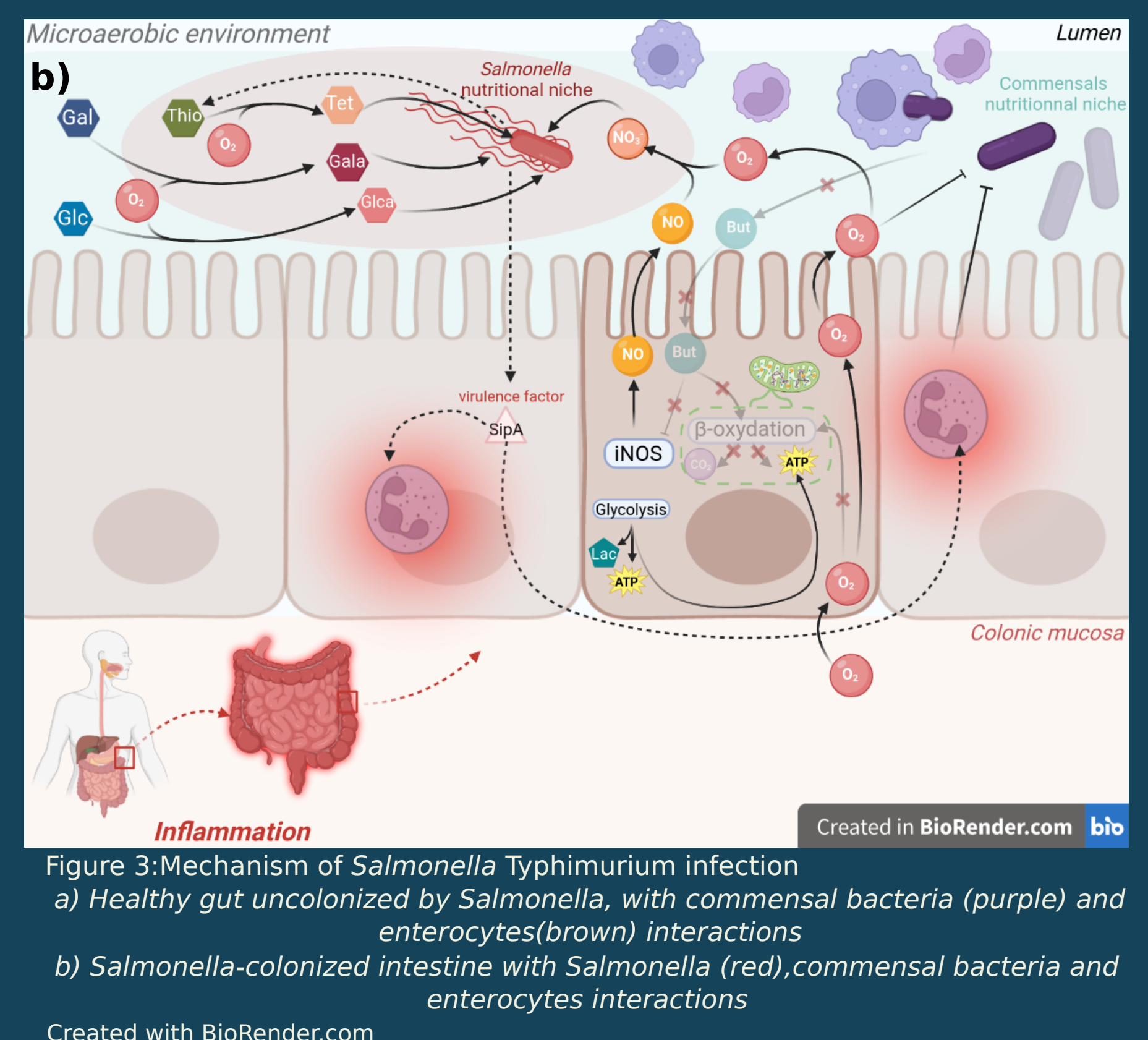
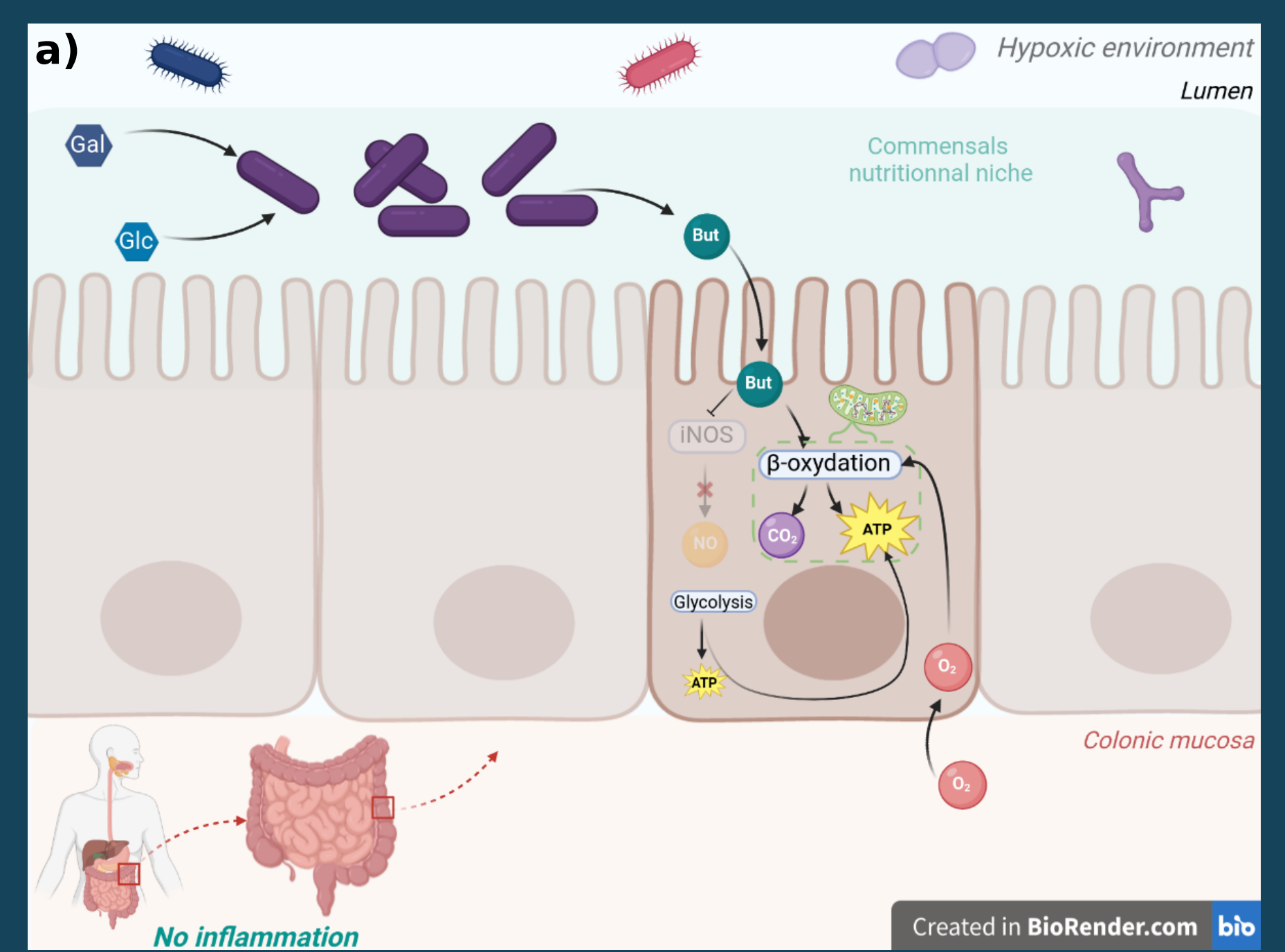


Figure 3: Mechanism of *Salmonella* Typhimurium infection

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

Created with BioRender.com

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

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

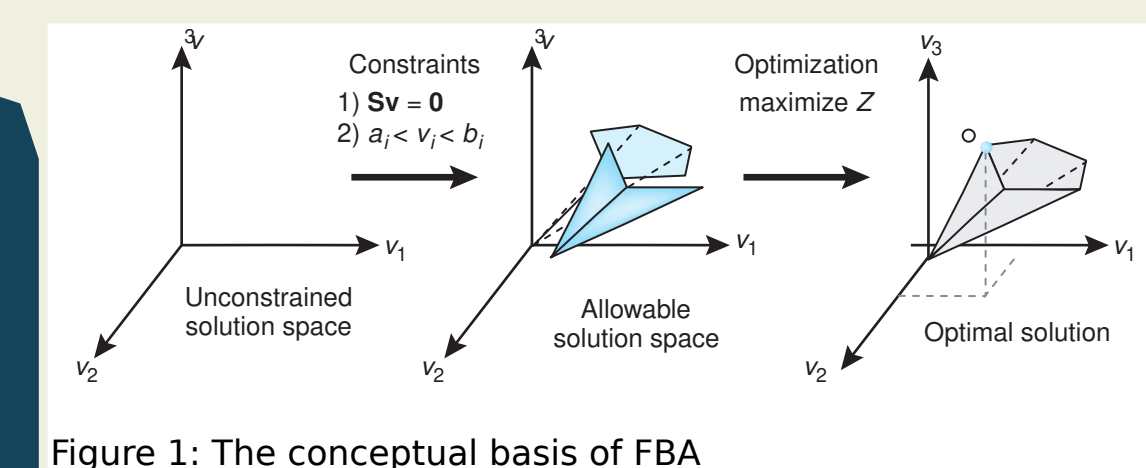


Figure 1: The conceptual basis of FBA

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

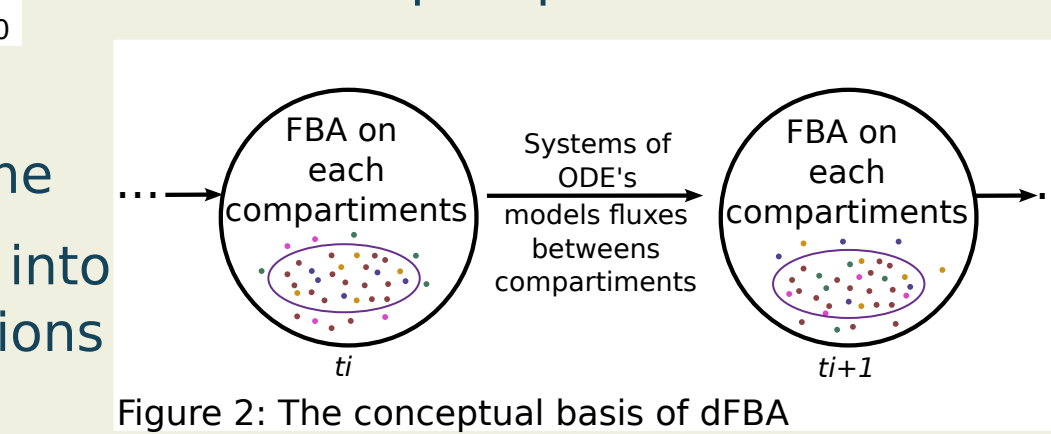


Figure 2: The conceptual basis of dFBA

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 O₂ in TCA cycle and electron
- Production of energy (ATP) from butyrate

Infection(t40):

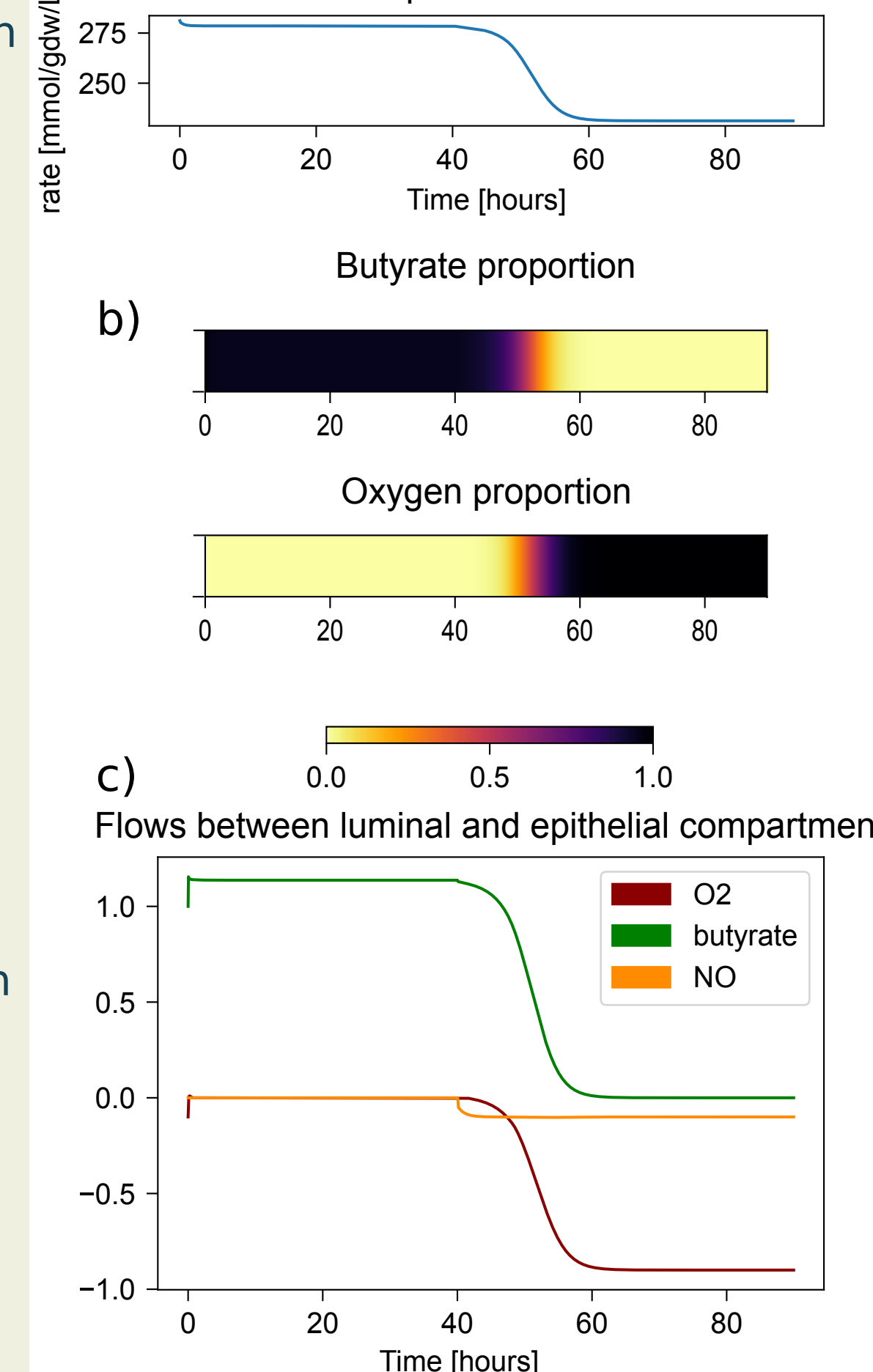
- Production of NO without its inhibition by butyrate
- No consumption of butyrate and O₂ in TCA cycle
- O₂ leakage to lumen
- Reduction in energy production (ATP)

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

method

FBA each step

Accuracy Speed

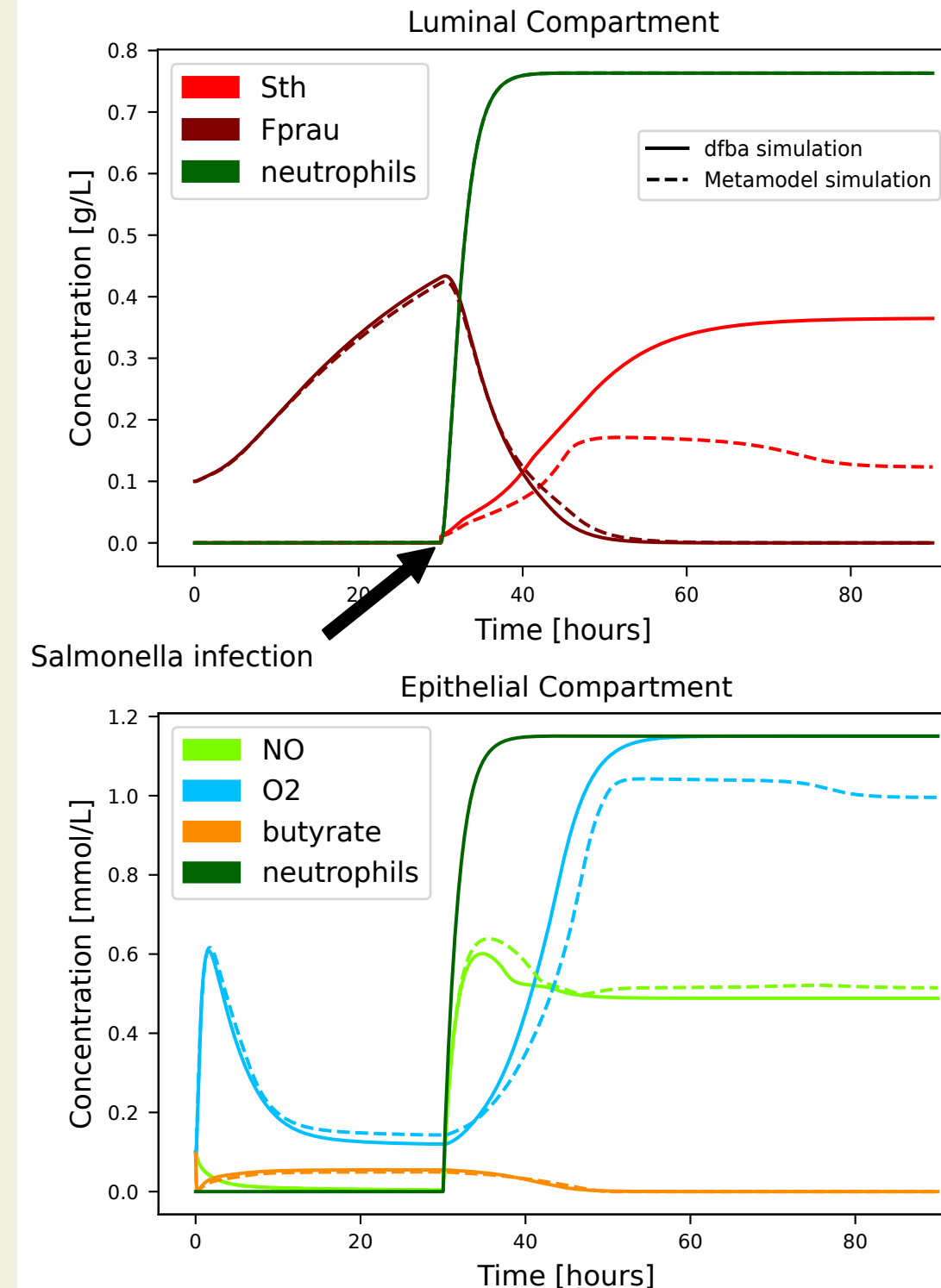
Surrogate Model

method

FBA Approximation

Accuracy Speed

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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