

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

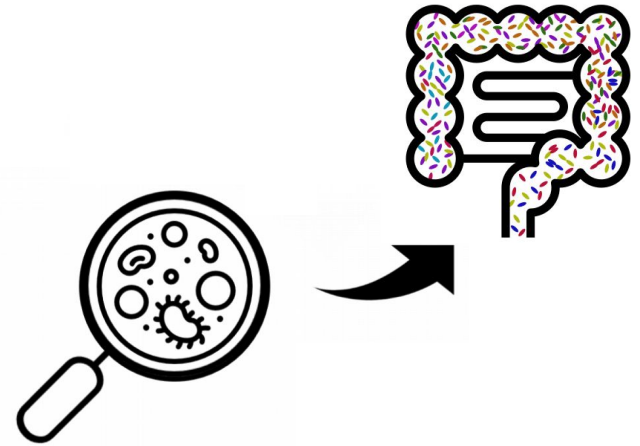
MULLER Coralie
UGALDE SALAS Pablo

7th International Symposium on Systems
Biology of Microbial Infection

September 21 – 22, 2023

Gut microbiota

- Gut microbiome is a complex community :
 - Thousands of interacting microbial species¹
 - Non-homogeneous spatial distribution²
 - Strong interaction with the host³
- The perturbations that it suffers may alter the stability of the community. e.g. pathogen invasion.



1 Arumugan et al. Nature (2011)

2 Labarthe et al. Journal of theoretical Biology (2019)

3 Levy et al, Nature Reviews Immunology (2017)

Case Study

- The case of *Salmonella enterica* Typhimurium infection in a human gut is a medical textbook example of an invader with huge societal costs. (88M € in Australia 2015)¹
- **Case study:** the pathogen turns around the immune system response to its advantage.²
- Experimental studies are costly:
Modelling to represent mechanistically the situation.
➡ Serve as a proxy for experimental design.³



Salmonella Typhimurium (red) invading cultured human cells. Credit: Rocky Mountain Laboratories, NIAID, NIH

¹Ford *et al* Journal of Food Protection, 2019.

²Rivera-Chávez and Baumlér Annual review of microbiology, 2015

³Kumar *et al*. Nature Microbiology, 2019

Modelling a Salmonella invasion

- The colonization of Salmonella in a healthy gut is a priori not ecologically possible.
- Salmonella thrives in aerobic environments, whereas the human gut is mostly anaerobic.

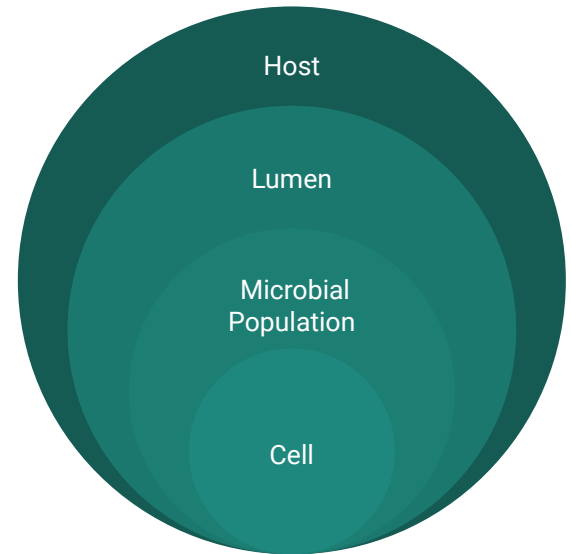
Rivera-Chávez and Baumber Annual review of microbiology, 2015

Modelling a Salmonella invasion

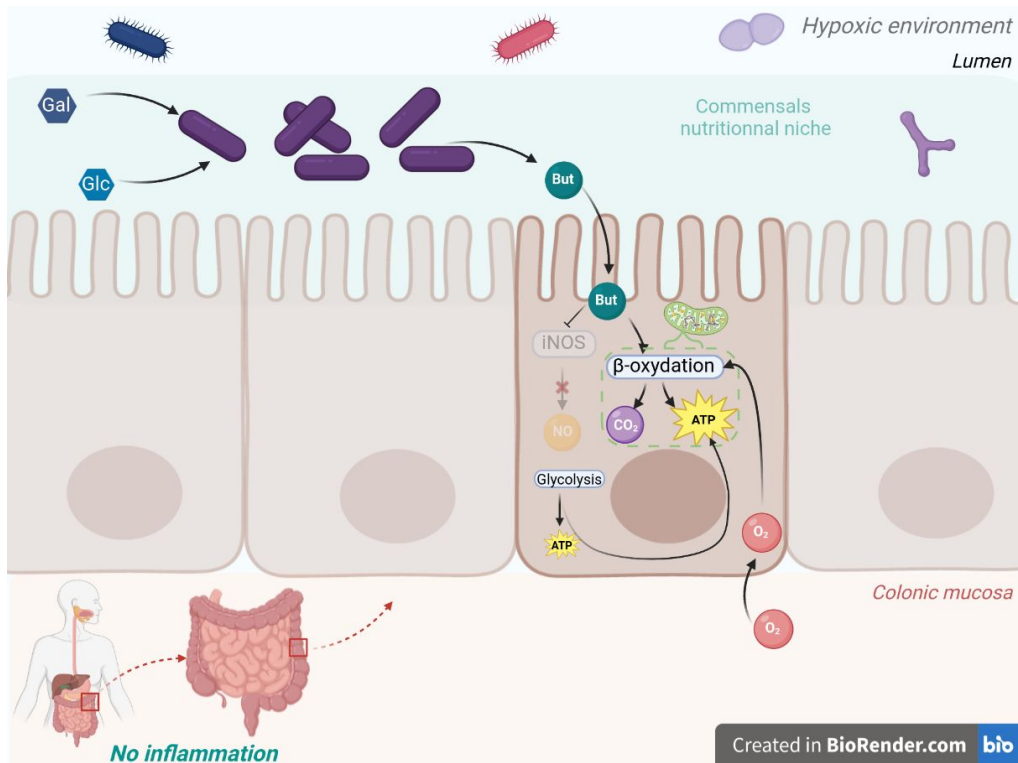
- The colonization of Salmonella in a healthy gut is a priori not ecologically possible.
- Salmonella thrives in aerobic environments, whereas the human gut is mostly anaerobic.
- Modelling:
 - Take into account nutrient variability and metabolic activity of the agents involved.
 - The host immune system response and the passage from an anaerobic to aerobic environment.

Objectives

1. Model the ecological process taking into account the role of species and host metabolism as well as its immune system response.
2. Propose a framework to overcome the difficulty of scale integration.
 - a. Metabolic models
 - b. Dynamic model
 - c. Surrogate model



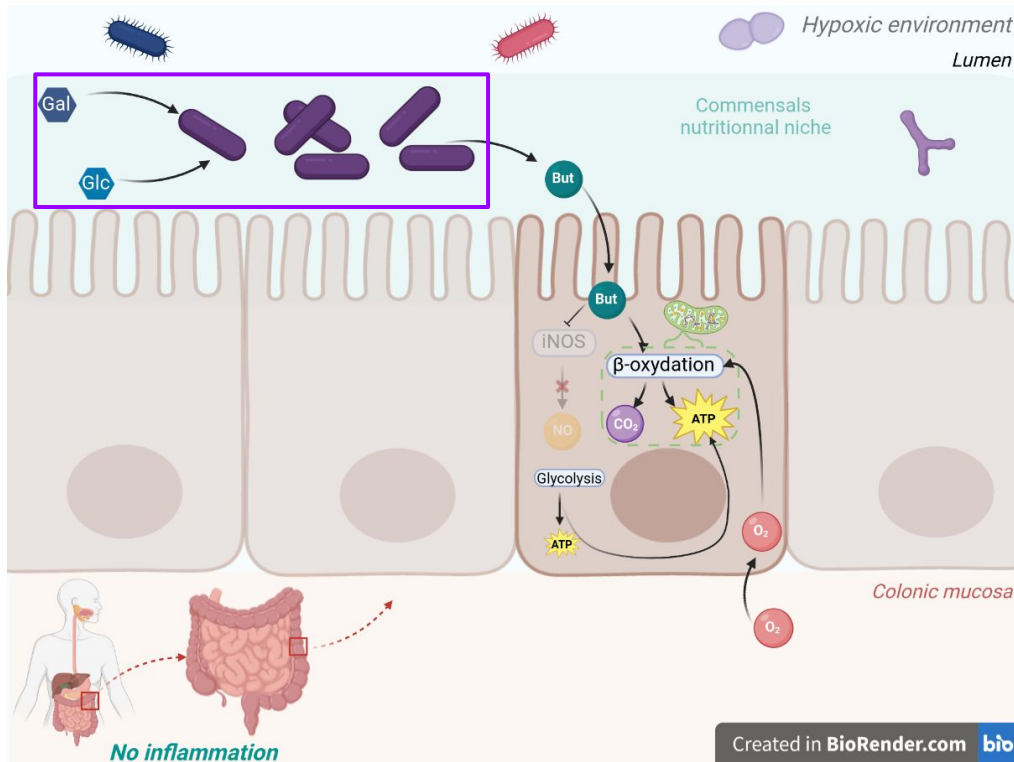
Biological setting: Healthy gut



Fabian Rivera-Chávez and Andreas J. Bäumler. *Annual Review of Microbiology* (2015)

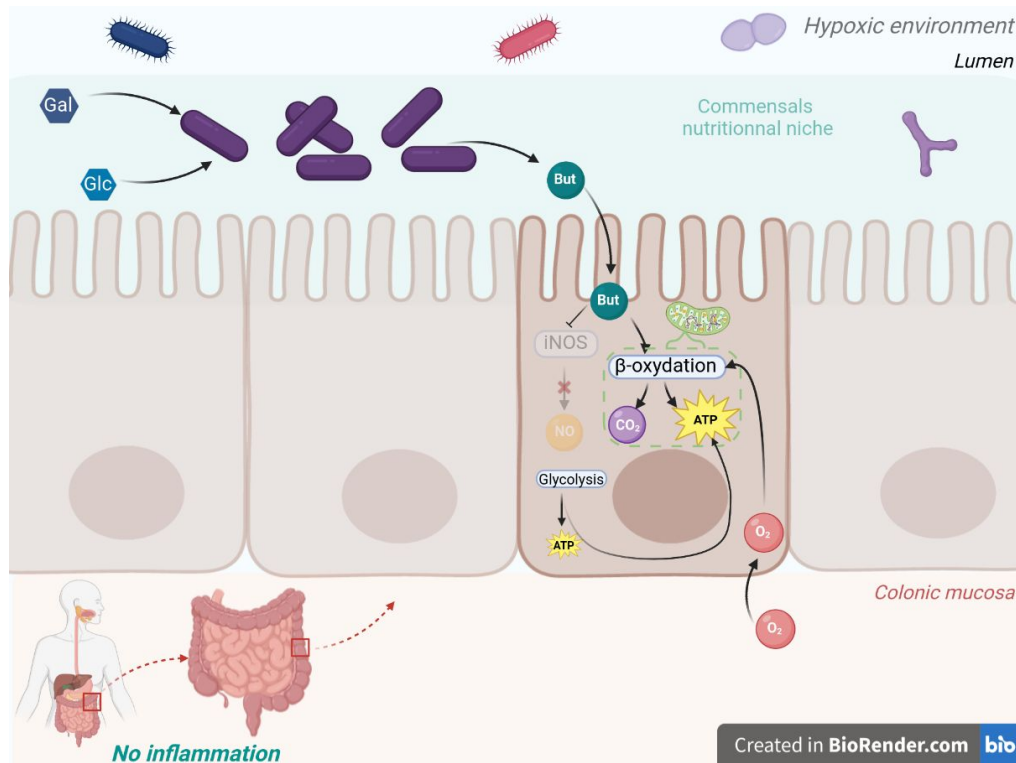
Biological setting: Healthy gut

-Growth of commensal bacteria



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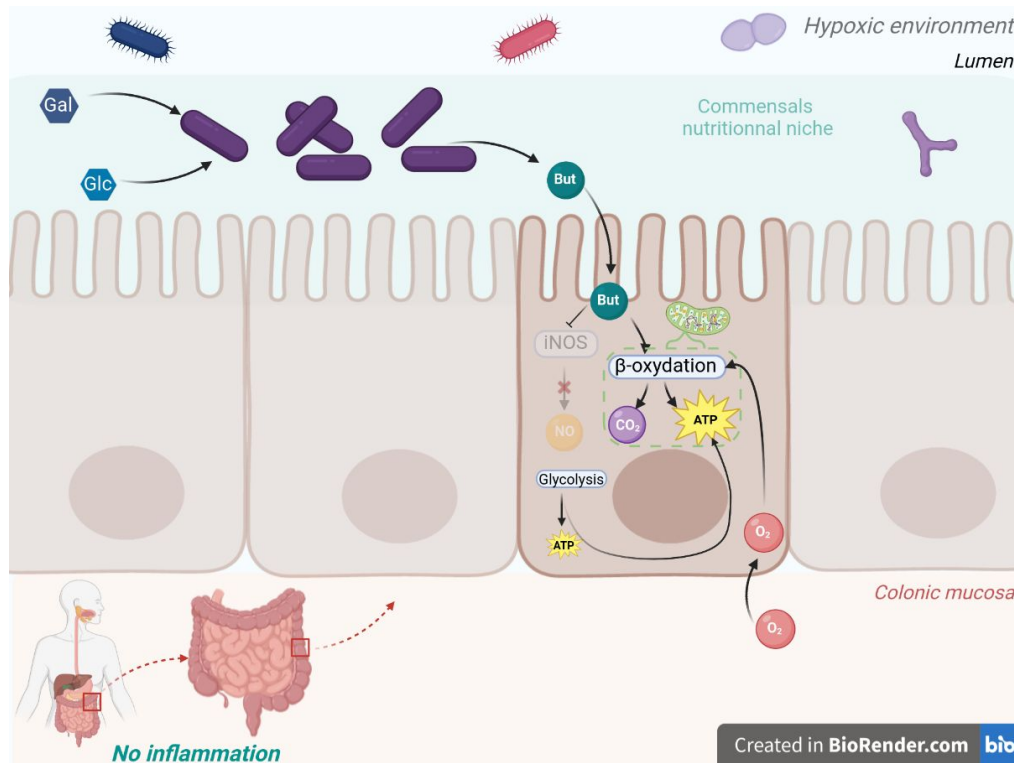


-Growth of commensal bacteria

-Commensal niche

Fabian Rivera-Chávez and Andreas J. Bäumler. *Annual Review of Microbiology* (2015)

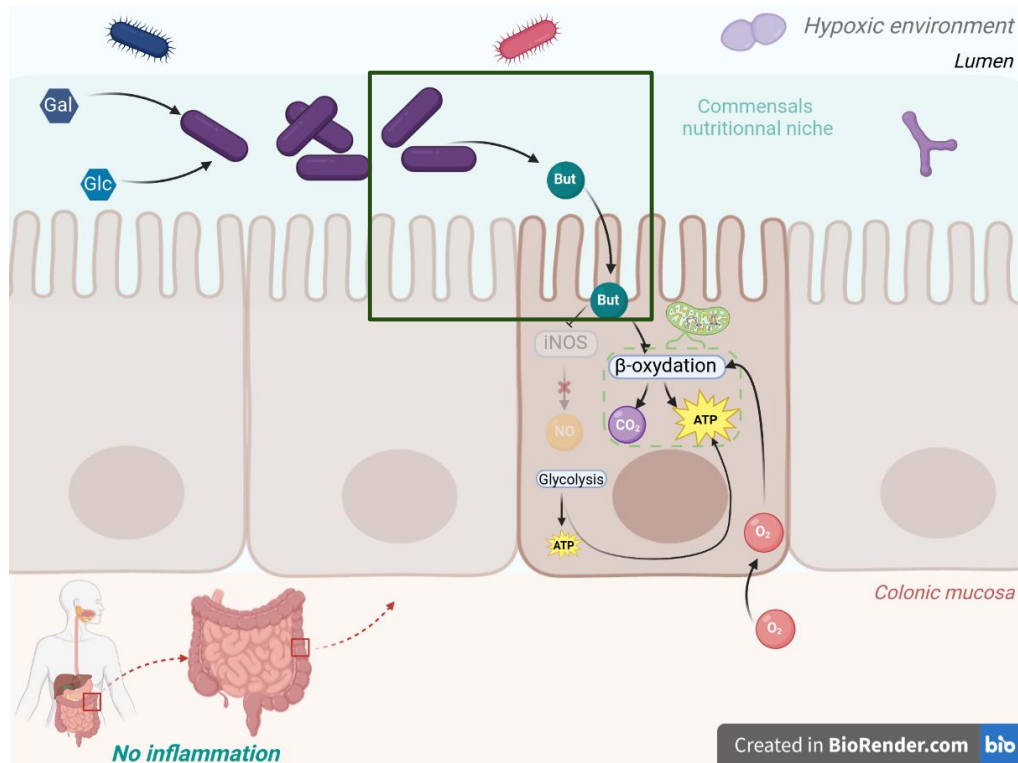
Biological setting: Healthy gut



- Growth of commensal bacteria
- Commensal niche
- Lumen is hypoxic

Fabian Rivera-Chávez and Andreas J. Bäumler. *Annual Review of Microbiology* (2015)

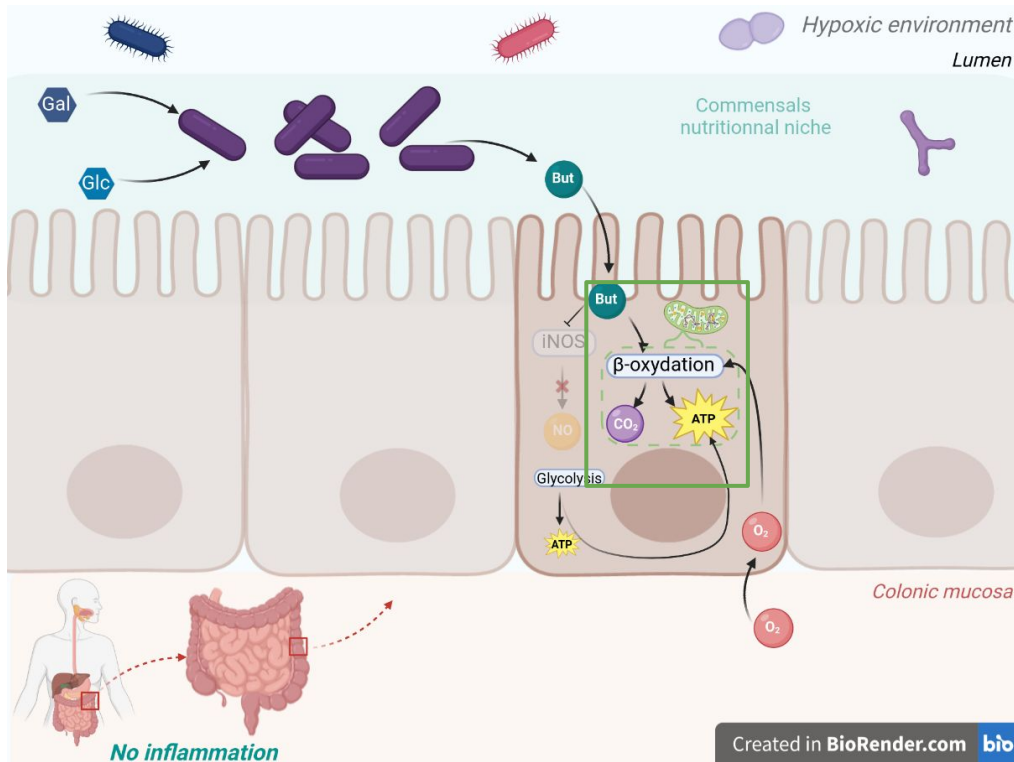
Biological setting: Healthy gut



- Growth of commensal bacteria
- Commensal niche
- Lumen is hypoxic
- Butyrate production ensured by commensal bacteria

Fabian Rivera-Chávez and Andreas J. Bäuml. *Annual Review of Microbiology* (2015)

Biological setting: Healthy gut



-Growth of commensal bacteria

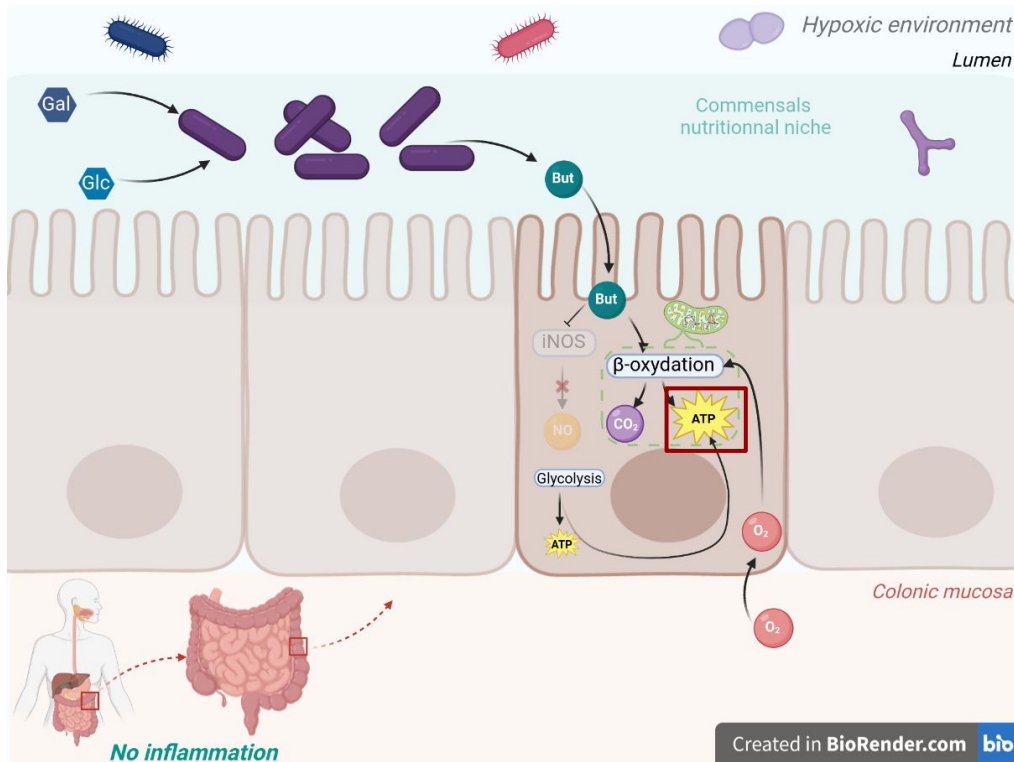
-Commensal niche

-Lumen is hypoxic

-Butyrate production ensured by commensal bacteria

-Butyrate is a crucial precursor for β -oxidation, essential for the Krebs Cycle (TCA)

Biological setting: Healthy gut



-Growth of commensal bacteria

-Commensal niche

-Lumen is hypoxic

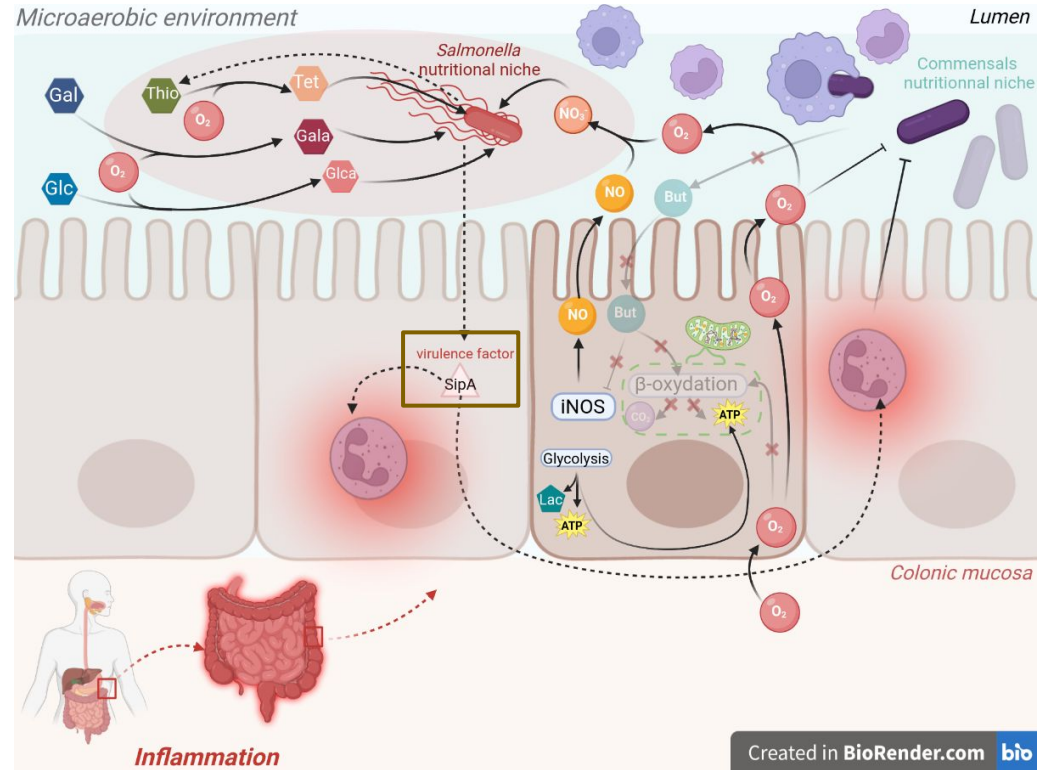
-Butyrate production ensured by commensal bacteria

-Butyrate is a crucial precursor for β -oxidation, essential for the Krebs Cycle (TCA)

-ATP production via the electron transport chain (ETC)

Biological setting: Colonized gut

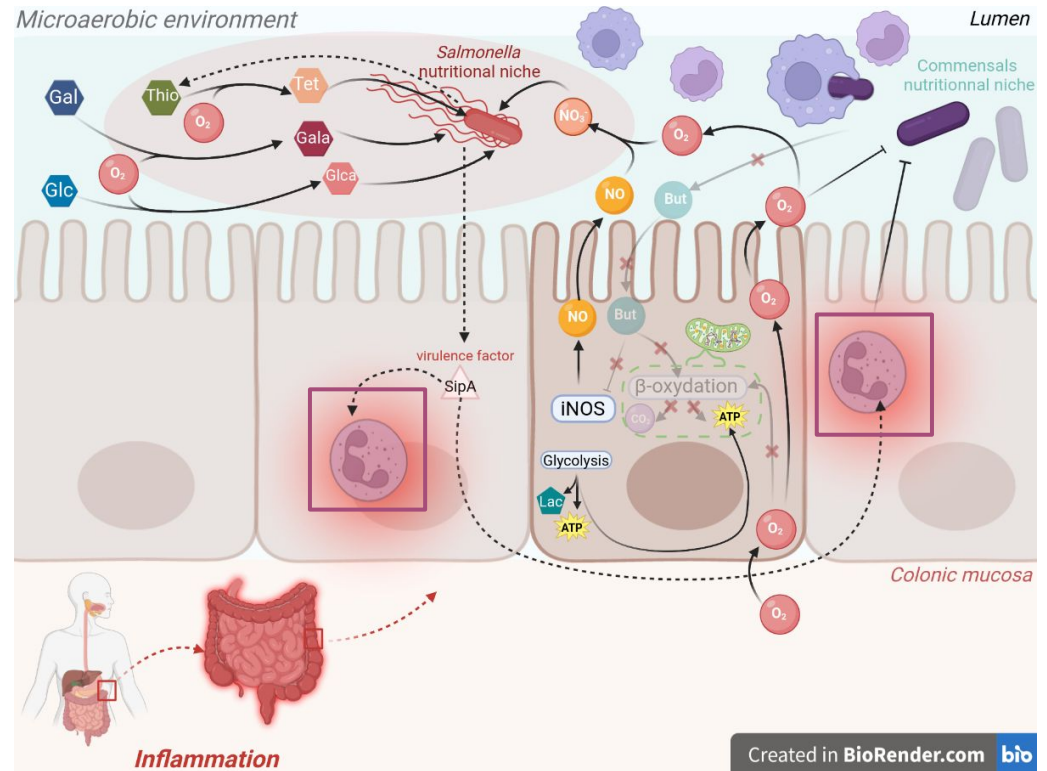
- Immune system is triggered by a **virulence factor** \Rightarrow **Inflammation**



Fabian Rivera-Chávez and Andreas J. Bäuml.
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Biological setting: Colonized gut

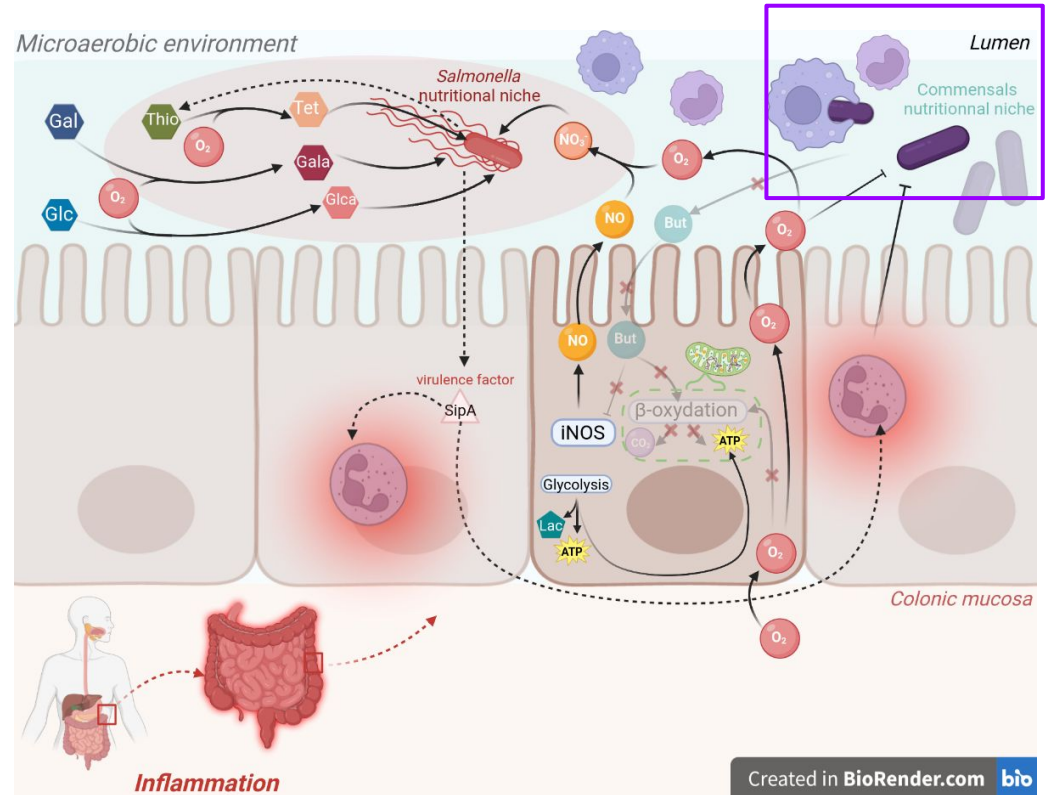
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Biological setting: Colonized gut

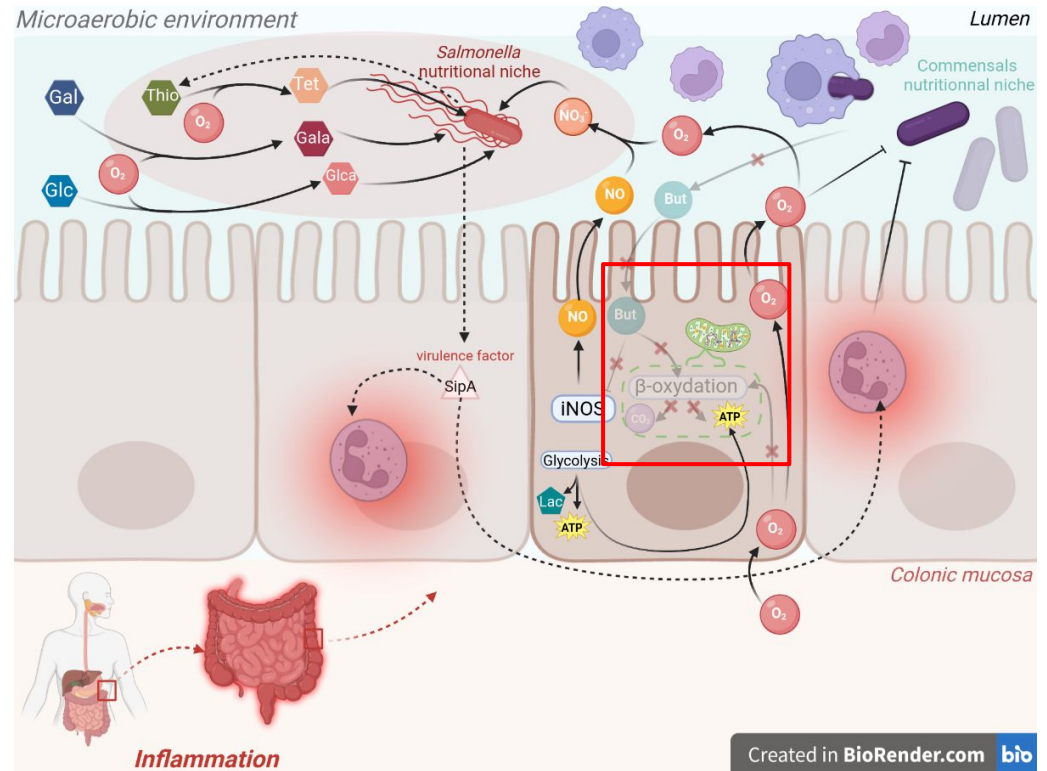
- Immune system is **triggered** by a **virulence factor** \Rightarrow **Inflammation**
- Infiltration of **neutrophils** in the lumen
- **Decrease** of **commensal bacteria** \Rightarrow **reduction** in butyrate production



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Biological setting: Colonized gut

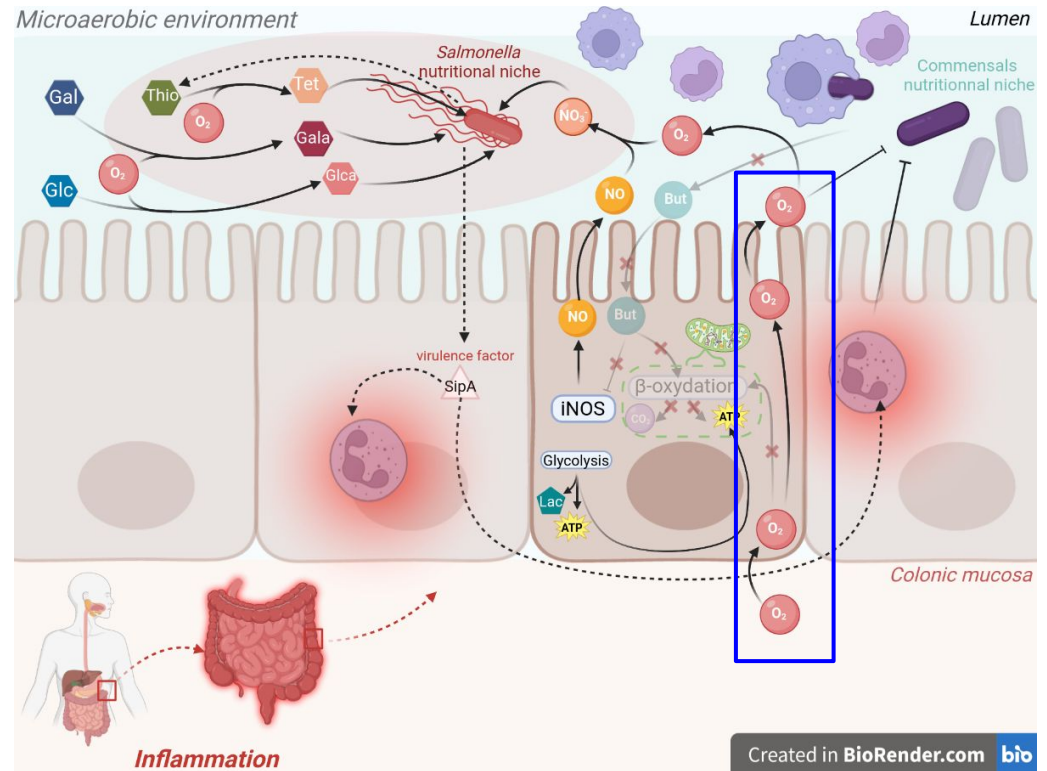
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Biological setting: Colonized gut

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- Lead to an **overflow** of **O₂** in lumen \Rightarrow Lumen is **microaerobic**

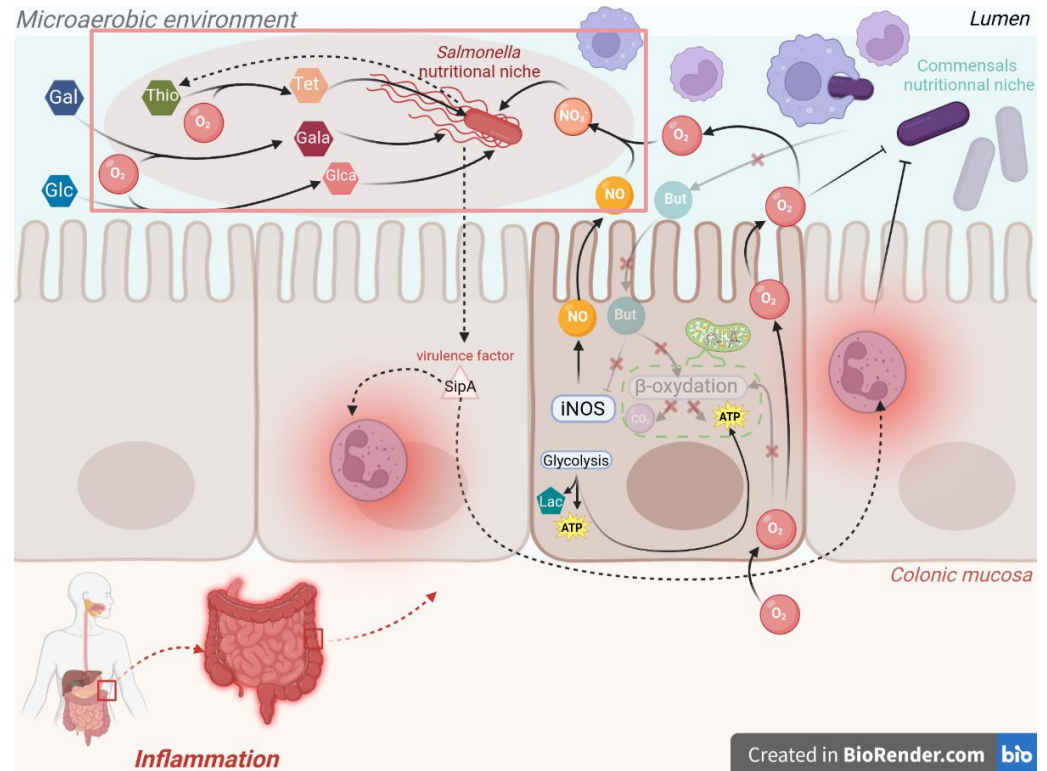


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Biological setting: Colonized gut

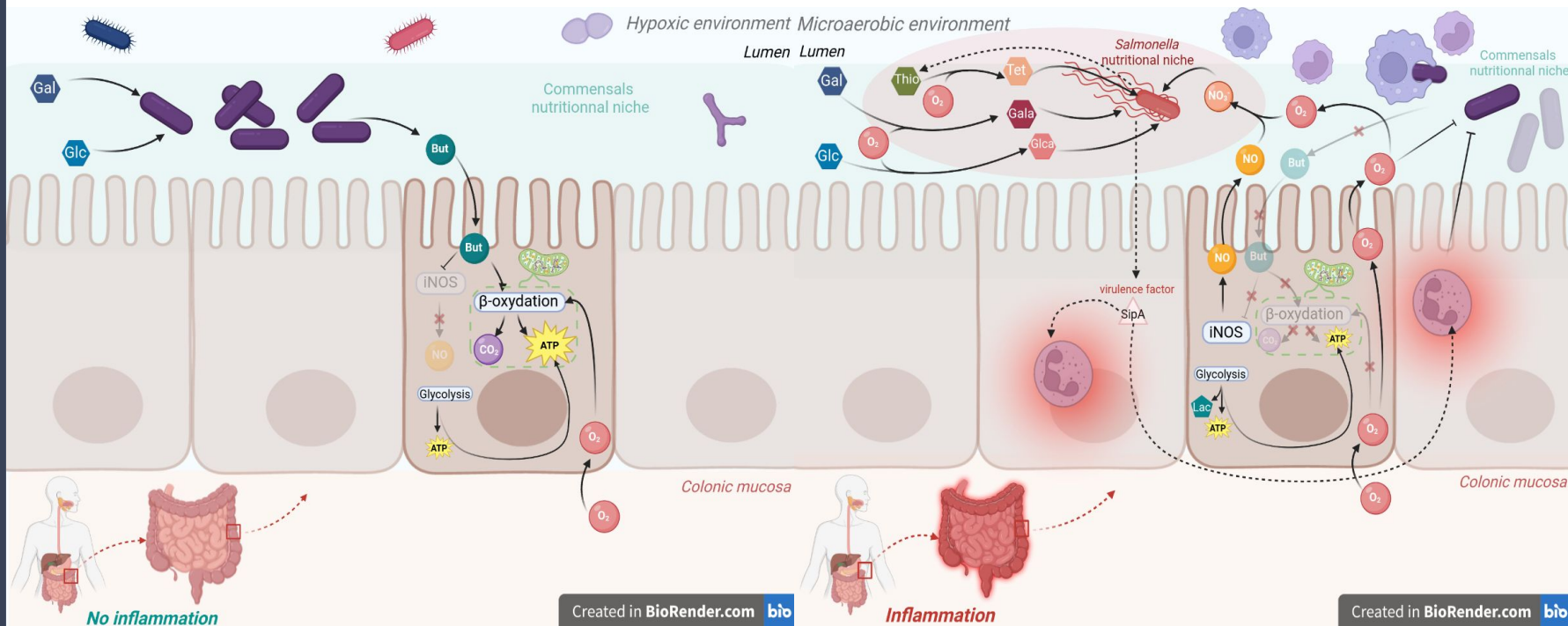
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- Infiltration of **neutrophils** in the lumen
- **Decrease** of **commensal bacteria** \Rightarrow **reduction** in butyrate production
- **TCA cycle** and the **ETC** activity is **reduced** \Rightarrow **ATP** production is **reduced**
- Lead to an **overflow** of **O₂** in lumen \Rightarrow Lumen is **microaerobic**
- **Oxidation** of metabolites favors an **oxidative niche** for *Salmonella*



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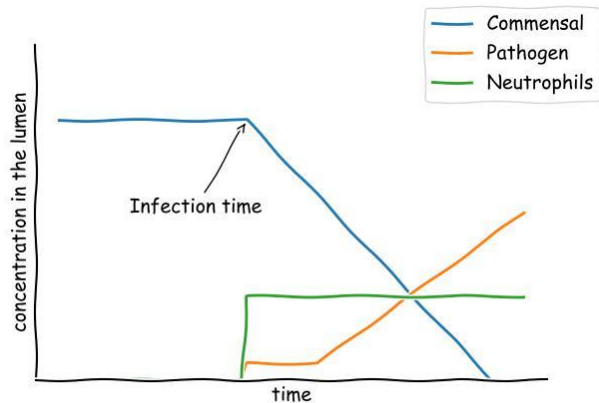
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Biological setting: Complete model

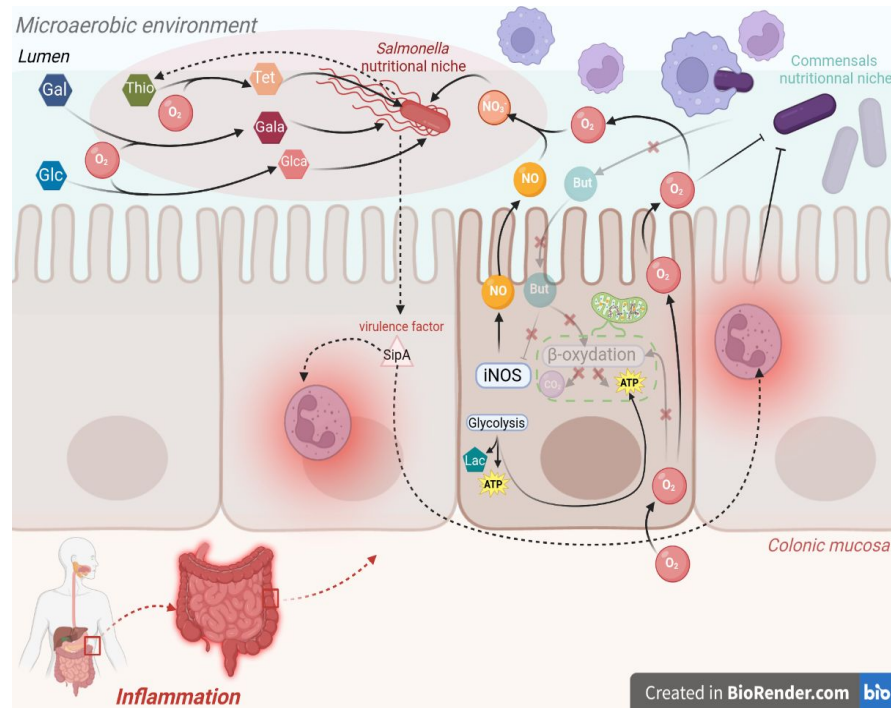


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Biological setting: Complete model

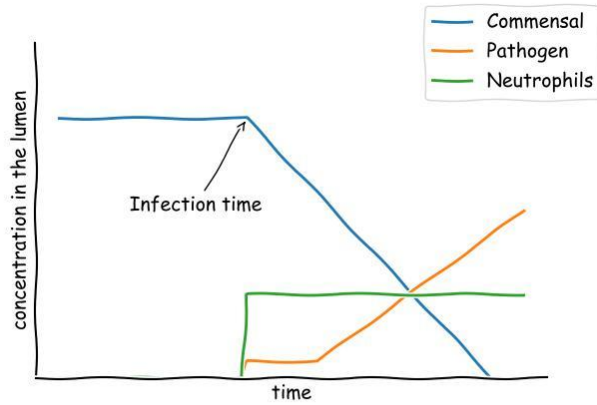


What we expect our model to produce

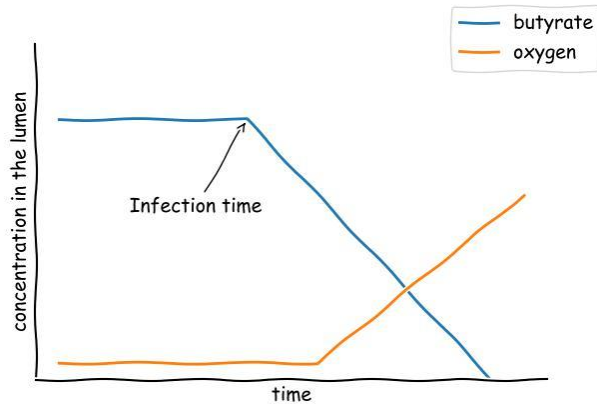


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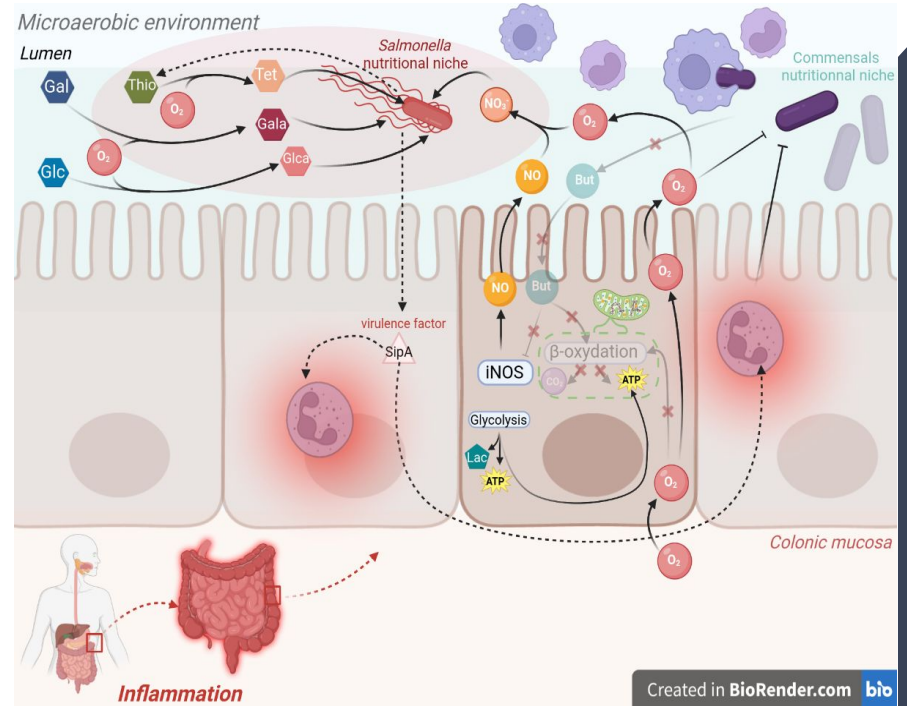
Biological setting: Complete model



What we expect our model to produce



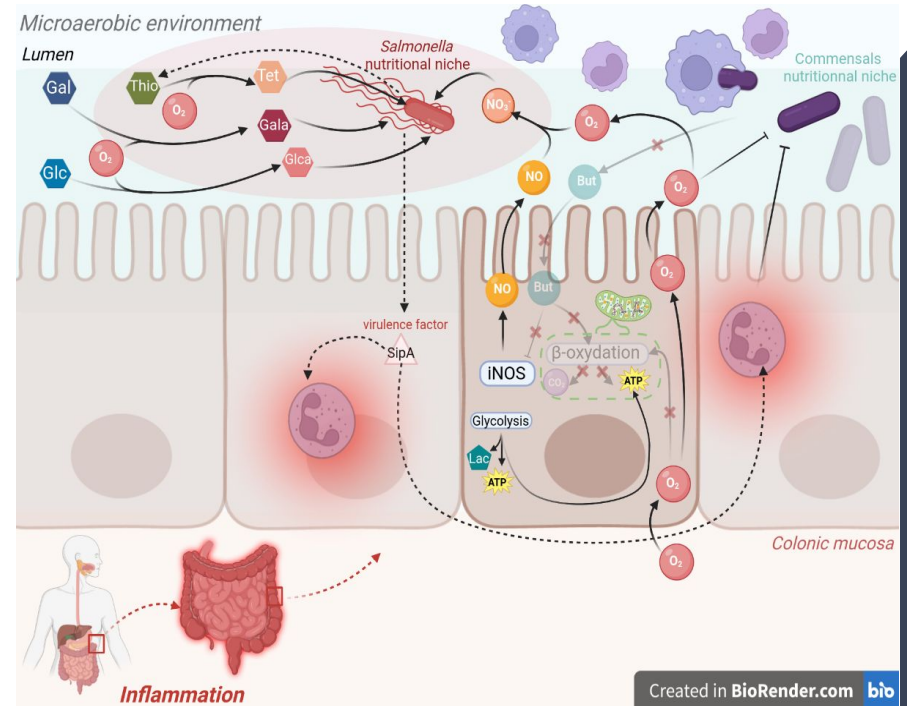
What we expect our model to produce



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Modelling choices

- Consider **Salmonella only** in the lumen
- Use of genome **scale metabolic models** to represent the metabolism of commensal bacteria, salmonella, and enterocytes



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Metabolic models

- Build a **host-microbiota-pathogen** system using 3 metabolic networks

Metabolic models

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1 Kocabaş K, et al. PLOS ONE. (2022)



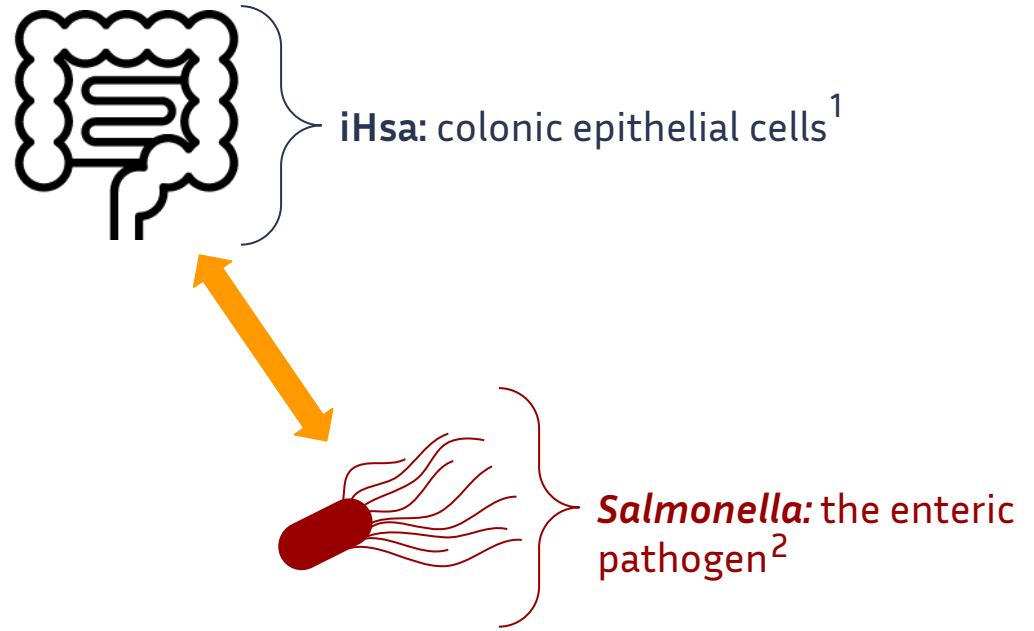
iHsa: colonic epithelial cells¹

Metabolic models

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Metabolic models

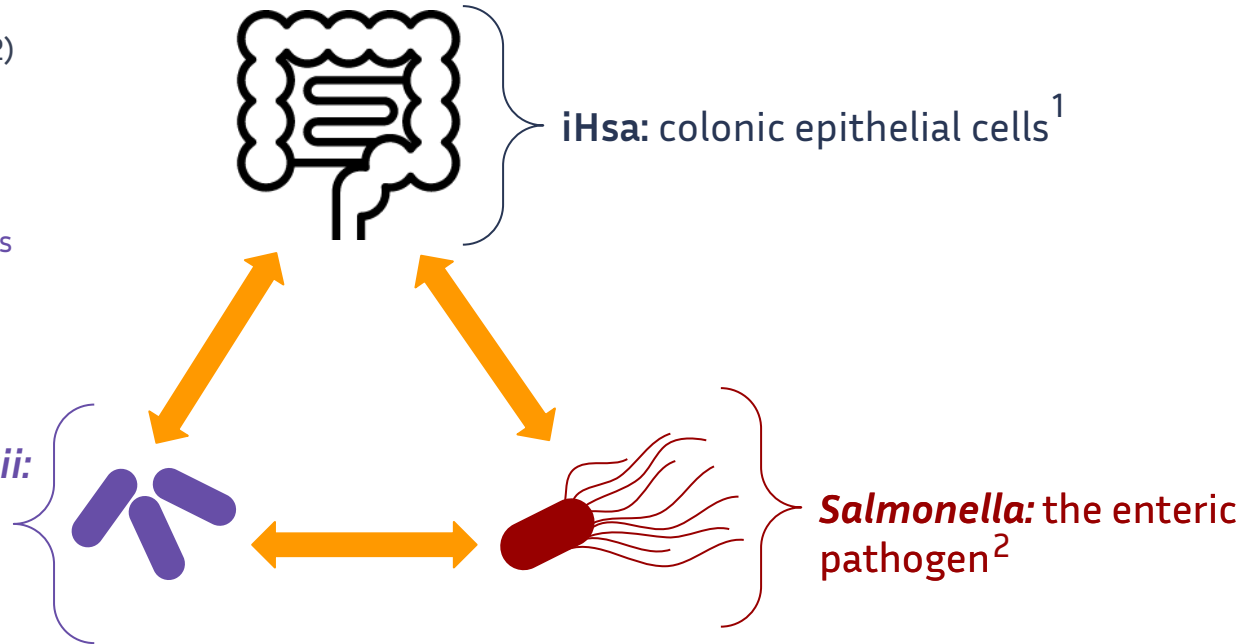
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Faecalibacterium prausnitzii:
butyrate-producing
commensal bacterium³



Metabolic models

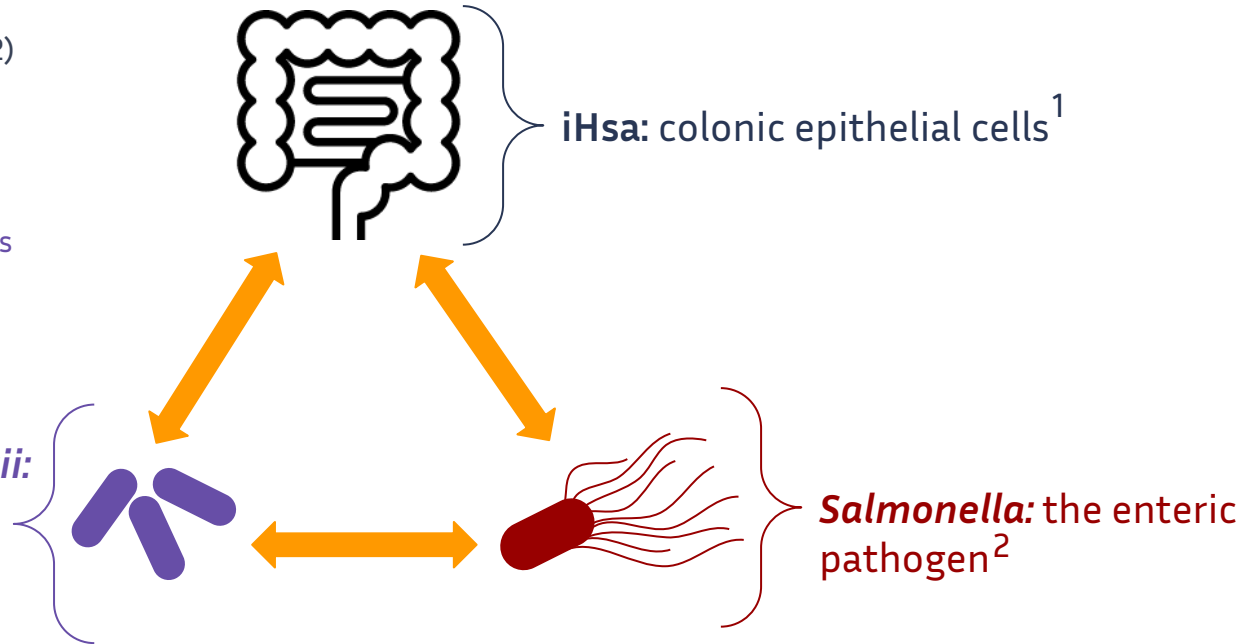
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What is a metabolic network ?

Metabolic networks

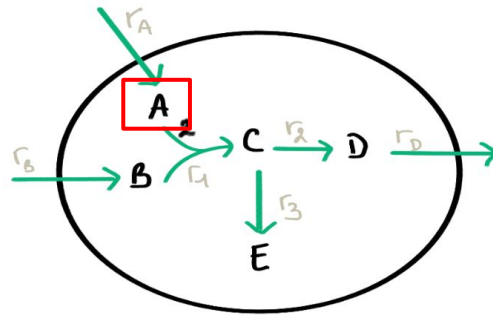
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Metabolic networks

- Set of metabolic and physical processes that determine the physiological and biochemical properties of a cell.
- Can be represent in a graph with **metabolites** as **nodes**

Metabolites (nodes)

A
B
C
D
E

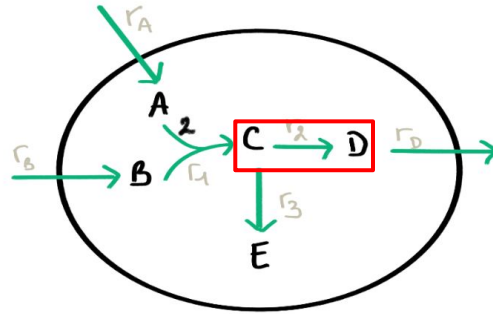


Metabolic networks

- Set of metabolic and physical processes that determine the physiological and biochemical properties of a cell.
- Can be represent in a graph with **metabolites** as **nodes** and **reactions** as **edges**

Metabolites (nodes)

A
B
C
D
E



Reactions (edges)

r1: $2A+B \rightarrow C$

r2: $C \rightarrow D$

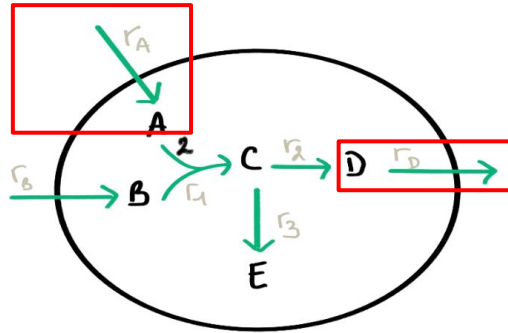
r3: $C \rightarrow E$

Metabolic networks

- Set of metabolic and physical processes that determine the physiological and biochemical properties of a cell.
- Can be represent in a graph with **metabolites** as **nodes** and **reactions** as **edges**

Metabolites (nodes)

A
B
C
D
E



Reactions (edges)

$r_1: 2A+B \rightarrow C$

$r_2: C \rightarrow D$

$r_3: C \rightarrow E$

r_A (IR)*: $\rightarrow A$

r_B (IR)*: $\rightarrow B$

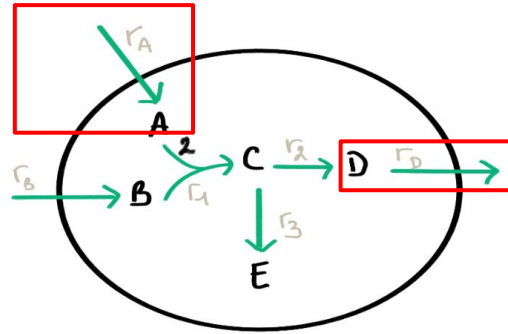
r_D (ER)*: $D \rightarrow$

Metabolic networks

- Set of metabolic and physical processes that determine the physiological and biochemical properties of a cell.
- Can be represent in a graph with **metabolites** as **nodes** and **reactions** as **edges**

Metabolites (nodes)

A
B
C
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E



Reactions (edges)

r1: $2A+B \rightarrow C$

r2: $C \rightarrow D$

r3: $C \rightarrow E$

rA (IR)*: $\rightarrow A$

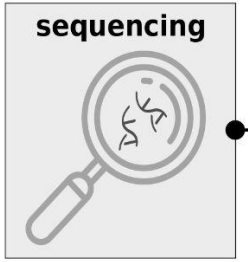
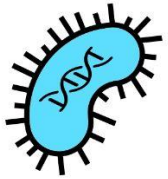
rB (IR)*: $\rightarrow B$

rD (ER)*: $D \rightarrow$

How to obtain a metabolic network ?

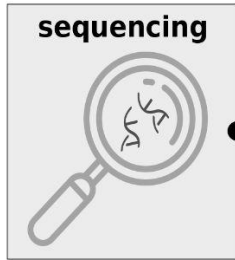
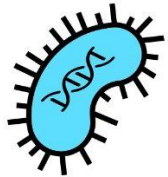
Workflow: metabolic network creation

Sequence reconstruction

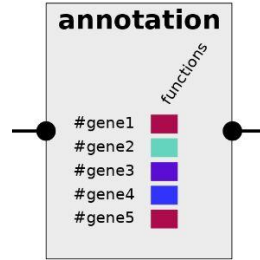


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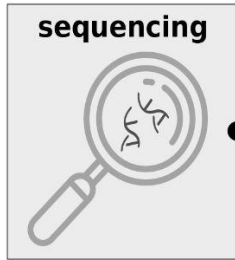
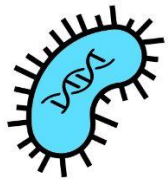


Assign functions to genes

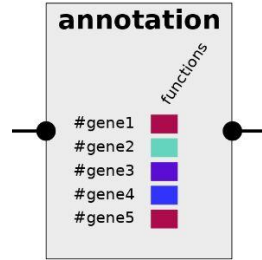


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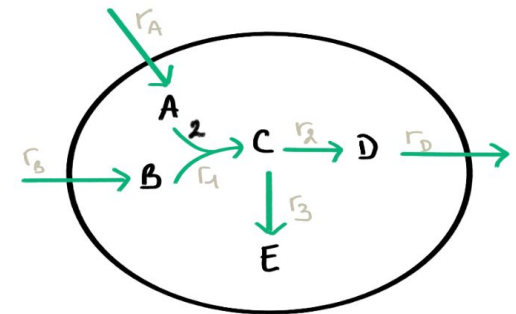
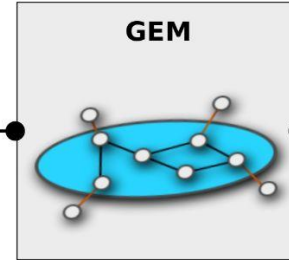
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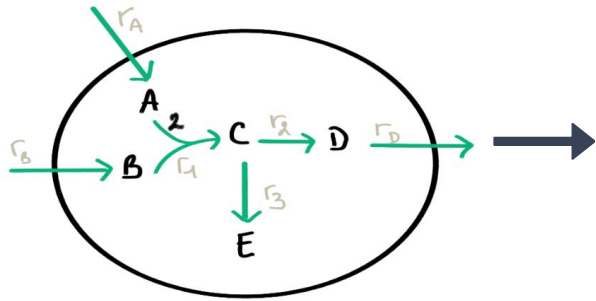
Assign functions to genes



Generation of metabolic network



Metabolic network and fluxes



Stoichiometric Matrix

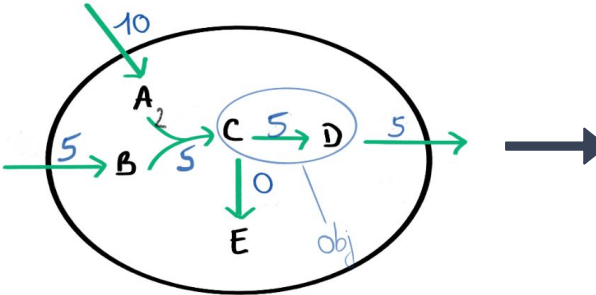
$$S = \begin{matrix} & \nu_A & \nu_B & \nu_C & \nu_D & \nu_E \\ \begin{matrix} A \\ B \\ C \\ D \\ E \end{matrix} & \begin{vmatrix} 1 & 0 & -2 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & -1 & 0 \\ 0 & 0 & 0 & 1 & 0 & -1 \\ 0 & 0 & 0 & 0 & 1 & 0 \end{vmatrix} \end{matrix}$$

Fluxes [mmol][L]⁻¹[h]⁻¹

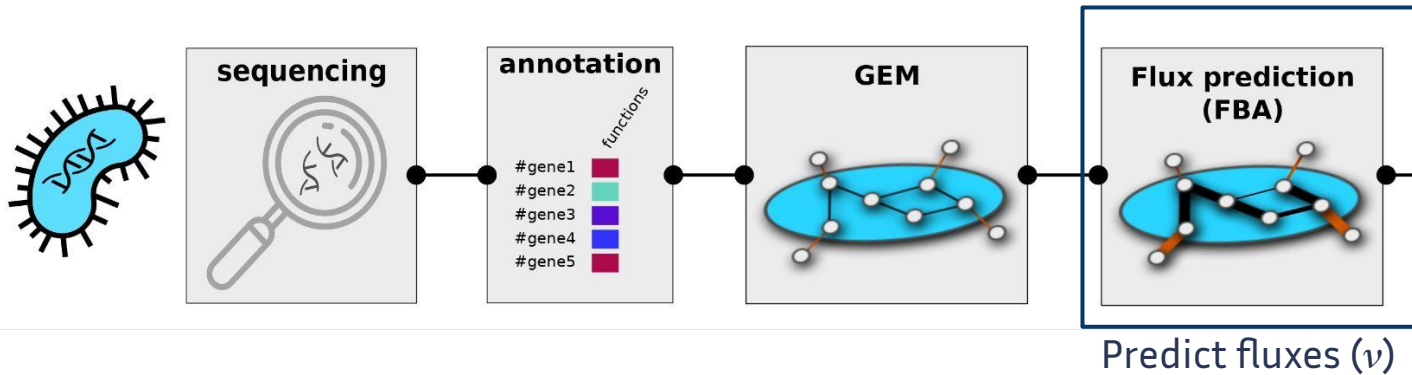
$$\nu = \begin{pmatrix} \nu_{rA} \\ \nu_{rB} \\ \nu_{r1} \\ \nu_{r2} \\ \nu_{r3} \\ \nu_{rD} \end{pmatrix} = \begin{pmatrix} -10 \\ -5 \\ 2 \\ 5 \\ 0 \\ 5 \end{pmatrix}$$

The multiplication gives us the rate of production or consumption of each metabolite.

$$S \cdot \nu = \frac{d}{dt} \begin{pmatrix} [A] \\ [B] \\ [C] \\ [D] \end{pmatrix}$$



Workflow: metabolic model and FBA



Flux Balance Analysis Hypothesis:

- **Quasi-steady state** at the interior of cells
- Physical **constraints** of the fluxes.
- Objective **function**
- **Exchange reactions** constrained by available metabolites

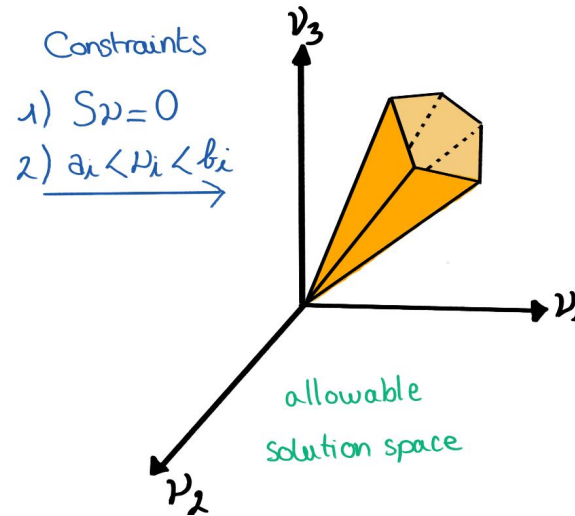
Flux Balance Analysis

Quasi-steady state : Intracellular metabolites concentration are considered constant

$$S \cdot v = \frac{d}{dt} \begin{pmatrix} [A] \\ [B] \\ [C] \\ [D] \end{pmatrix} = 0$$

Constraint: Fluxes are bounded (enzyme capacity)

$$a_i \leq v_i \leq b_i$$



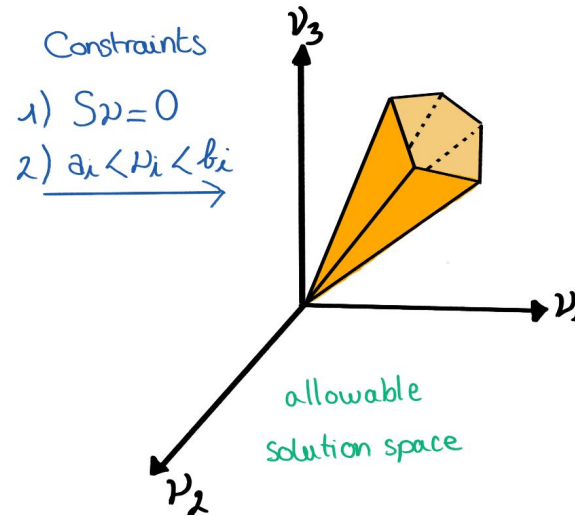
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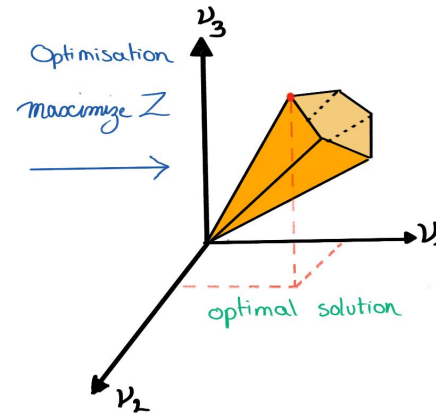
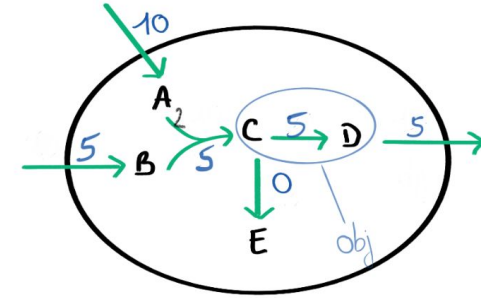
$$a_i \leq v_i \leq b_i$$



How to choose one solution among them?

Flux Balance Analysis

What does the cell search to do?

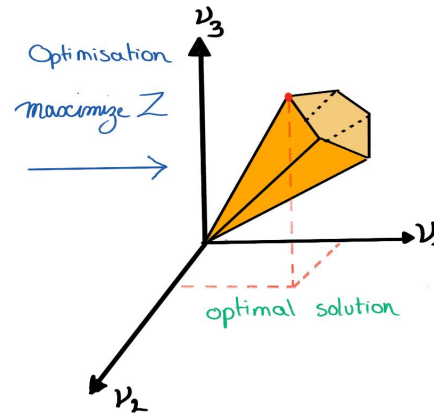
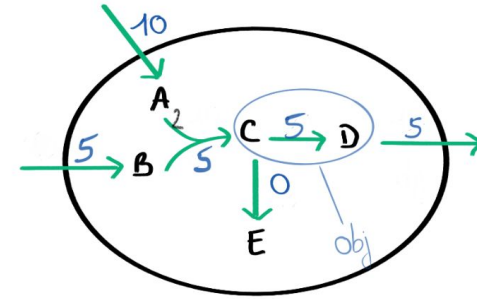


Flux Balance Analysis

What does the cell search to do?

Objective function:

-Choose a reaction (or a combination of them) to be maximized.

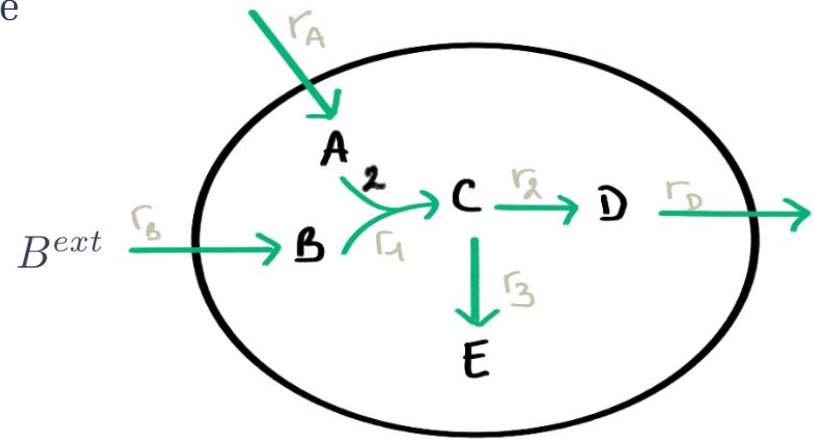


Flux Balance Analysis

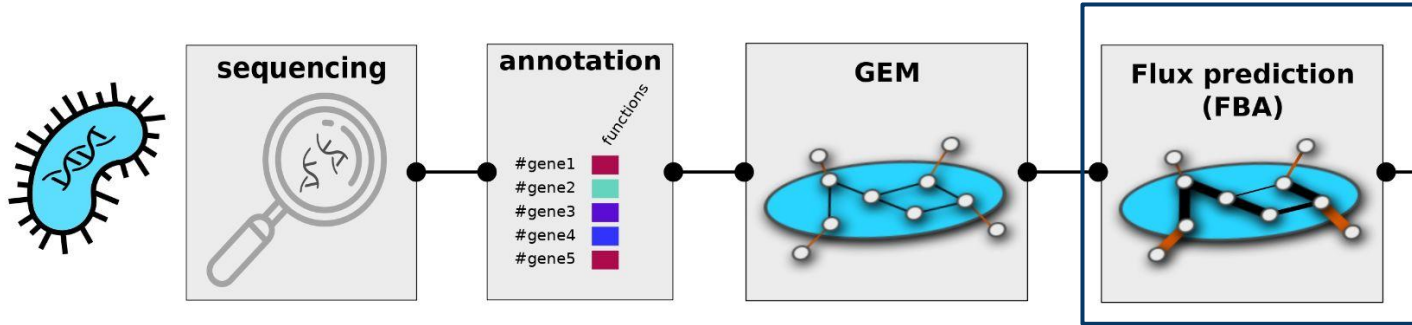
Uptake reactions:

- They bring metabolites into the cell (r_A and r_B)
- Uptake flux is bounded by the metabolite availability

$$c^{up}([B^{ext}]) \leq \nu_B^{up} \leq 0$$



Workflow: metabolic model and FBA

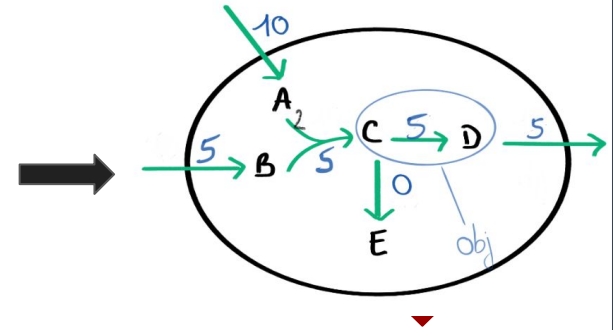


Predict fluxes (v)

$$\begin{array}{c}
 \pi_A \quad \pi_b \quad \pi_4 \quad \pi_2 \quad \pi_3 \quad \pi_D \\
 \begin{array}{c}
 A \\
 B \\
 C \\
 D \\
 E
 \end{array}
 \begin{array}{|c|}
 \hline
 \begin{array}{cccccc}
 1 & 0 & -1 & 0 & 0 & 0 \\
 0 & 1 & -1 & 0 & 0 & 0 \\
 0 & 0 & 1 & -1 & -1 & 0 \\
 0 & 0 & 0 & 1 & 0 & -1 \\
 0 & 0 & 0 & 0 & 1 & 0
 \end{array}
 \hline
 \end{array}
 = S
 \end{array}$$

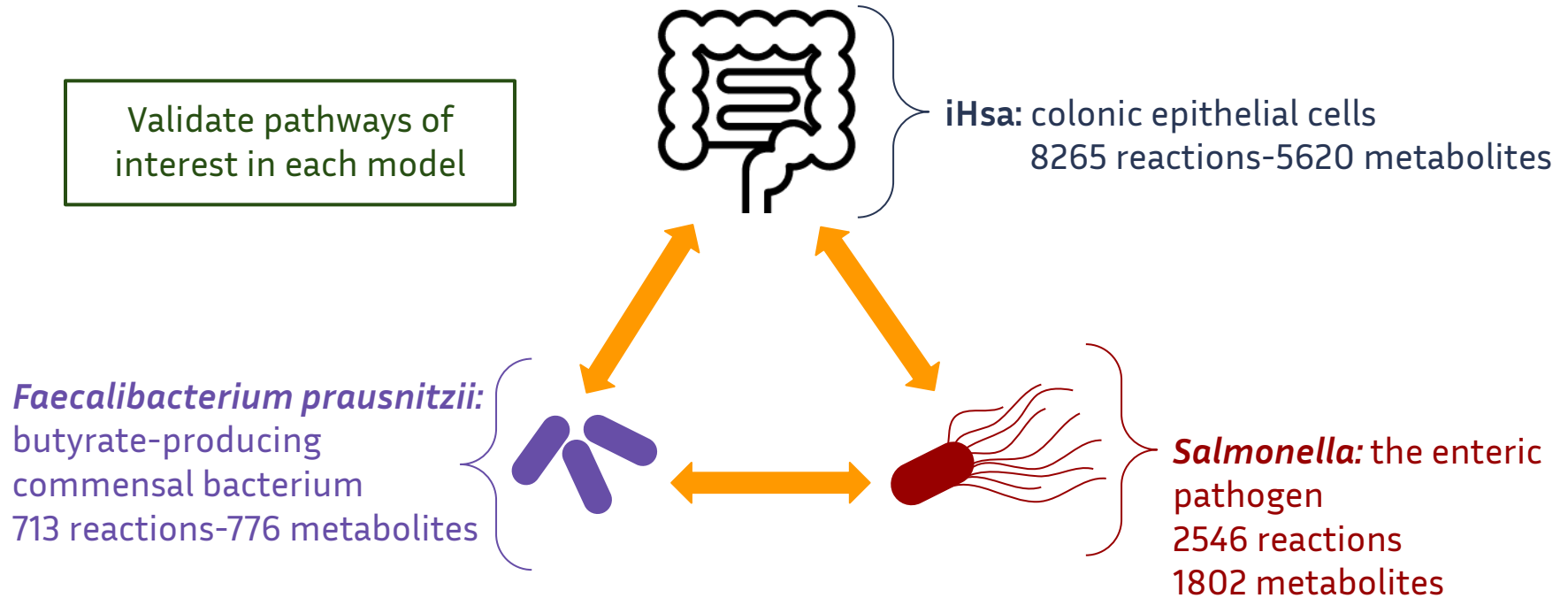


$$\begin{array}{l}
 \max \quad v^{choice} \\
 s.t. \quad S v = 0 \\
 v \in [a, b] \\
 v_{up} \in [c^{(up)}, 0]
 \end{array}$$



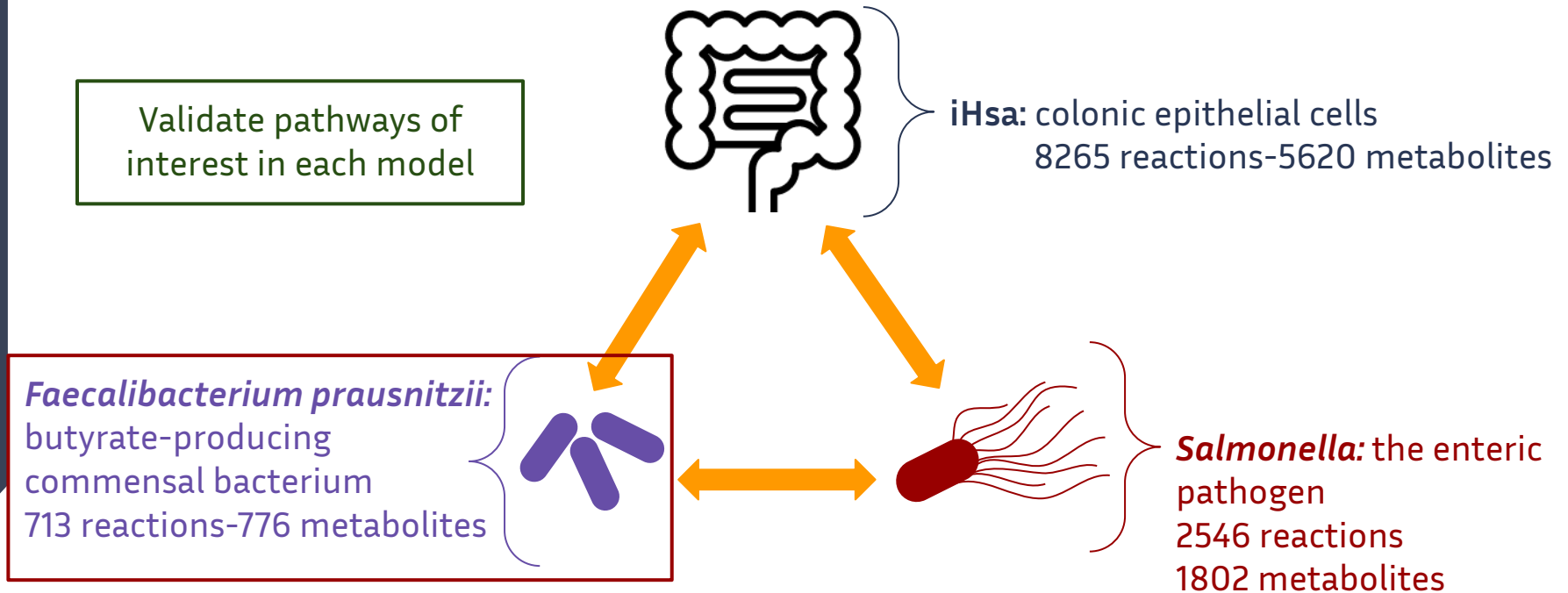
Metabolic model:

- Build a **host-microbiota-pathogen** system using 3 metabolic networks



Metabolic model:

- Build a **host-microbiota-pathogen** system using 3 metabolic networks



Metabolic model: Fprau

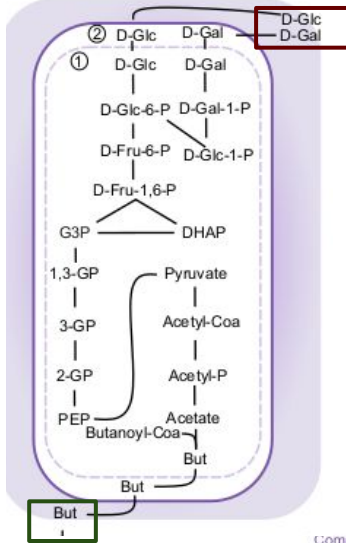


- Objective function:
- Biomass

Metabolic model: Fprau

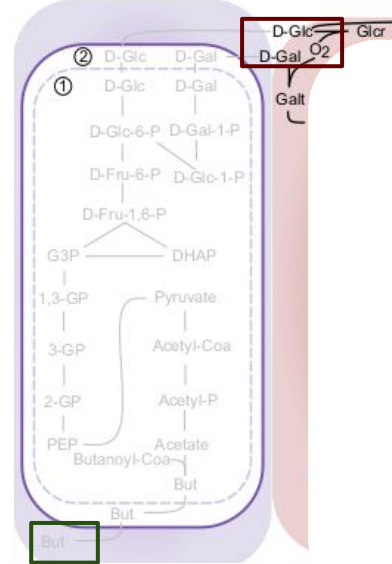


Healthy conditions



Commensal Bacteria

Infection conditions

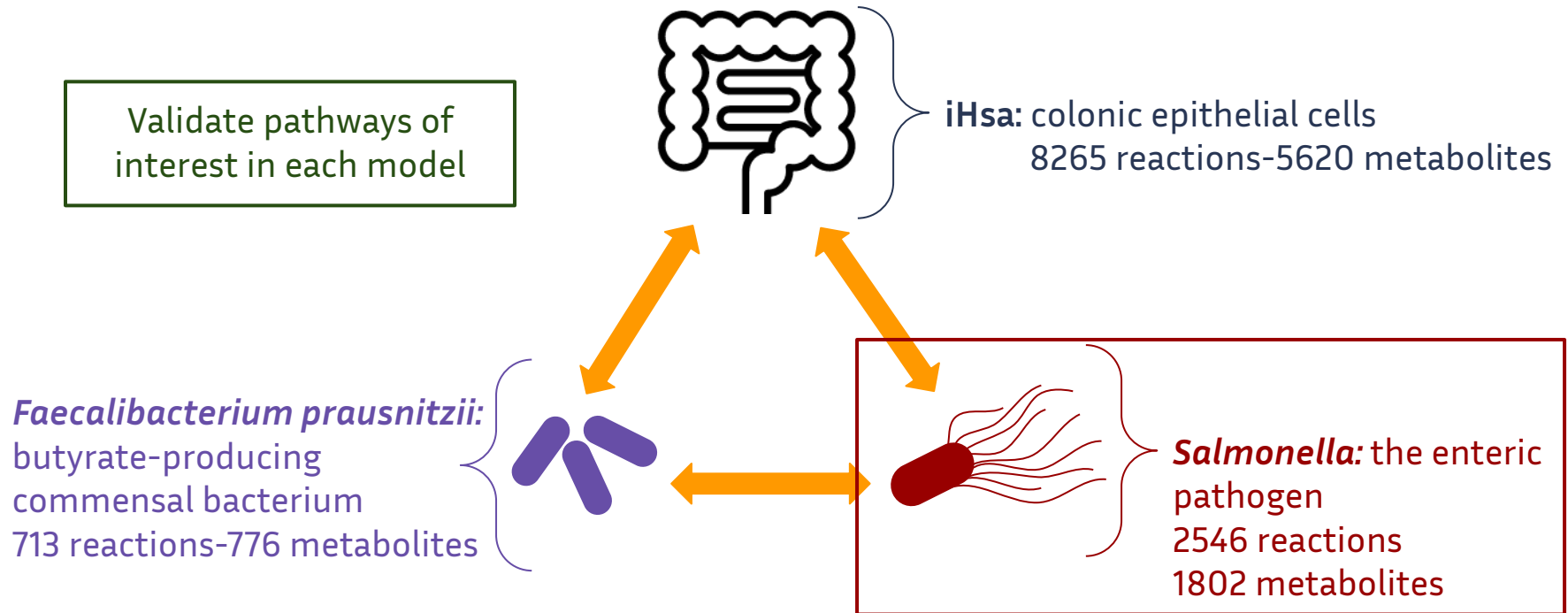


- ① cytosol
 - ② periplasm
 - ③ mitochondria
 - ④ intermembrane space
 - ⑤ mitochondrial inner membrane
 - ⑥ matrix
- high activity
 - - - medium activity
 . . . low activity

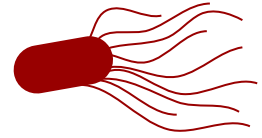
- Objective function:
 - Biomass
- Uptake metabolites of interest:
 - Glucose/Galactose
- Output metabolites of interest:
 - Butyrate

Metabolic model:

- Build a **host-microbiota-pathogen** system using 3 metabolic networks

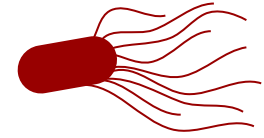


Metabolic model: *Salmonella*



- Objective function:
 - Biomass

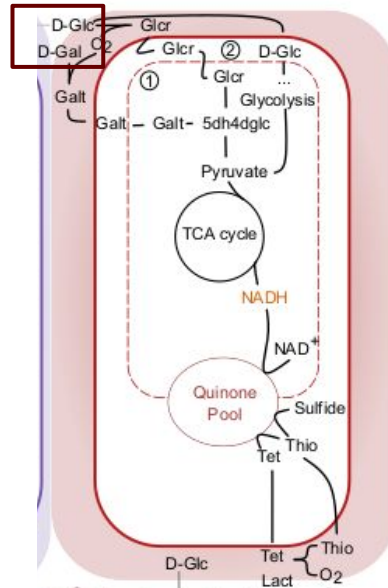
Metabolic model: *Salmonella*



Infection conditions

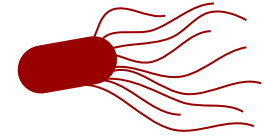
Salmonella

- ① cytosol
 - ② periplasm
 - ③ mitochondria
 - ④ intermembrane space
 - ⑤ mitochondrial inner membrane
 - ⑥ matrix
- high activity
— medium activity
— low activity



- Objective function:
 - Biomass
- Uptake metabolites of interest:
 - Glucose/Galactose

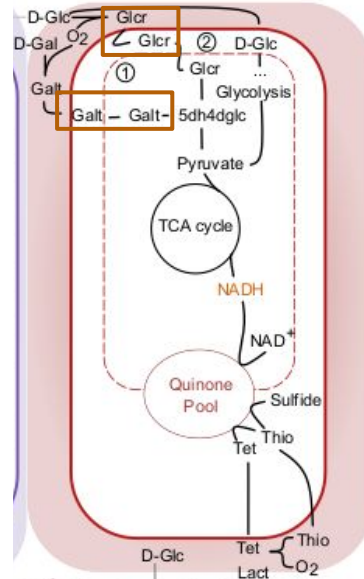
Metabolic model: *Salmonella*



Infection conditions

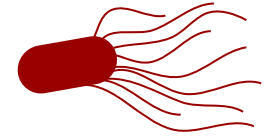
Salmonella

- ① cytosol
 - ② periplasm
 - ③ mitochondria
 - ④ intermembrane space
 - ⑤ mitochondrial inner membrane
 - ⑥ matrix
- high activity
— medium activity
— low activity



- Objective function:
 - Biomass
- Uptake metabolites of interest:
 - Glucose/Galactose
 - Glucarate/Galactarate

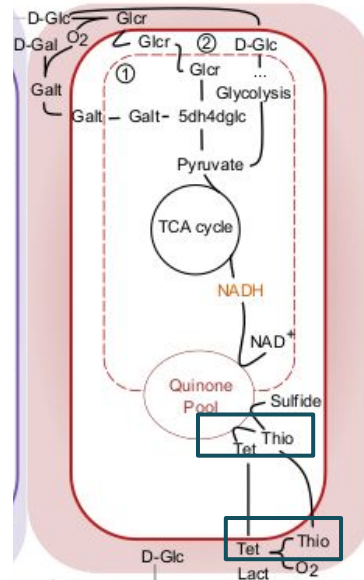
Metabolic model: *Salmonella*



Infection conditions

Salmonella

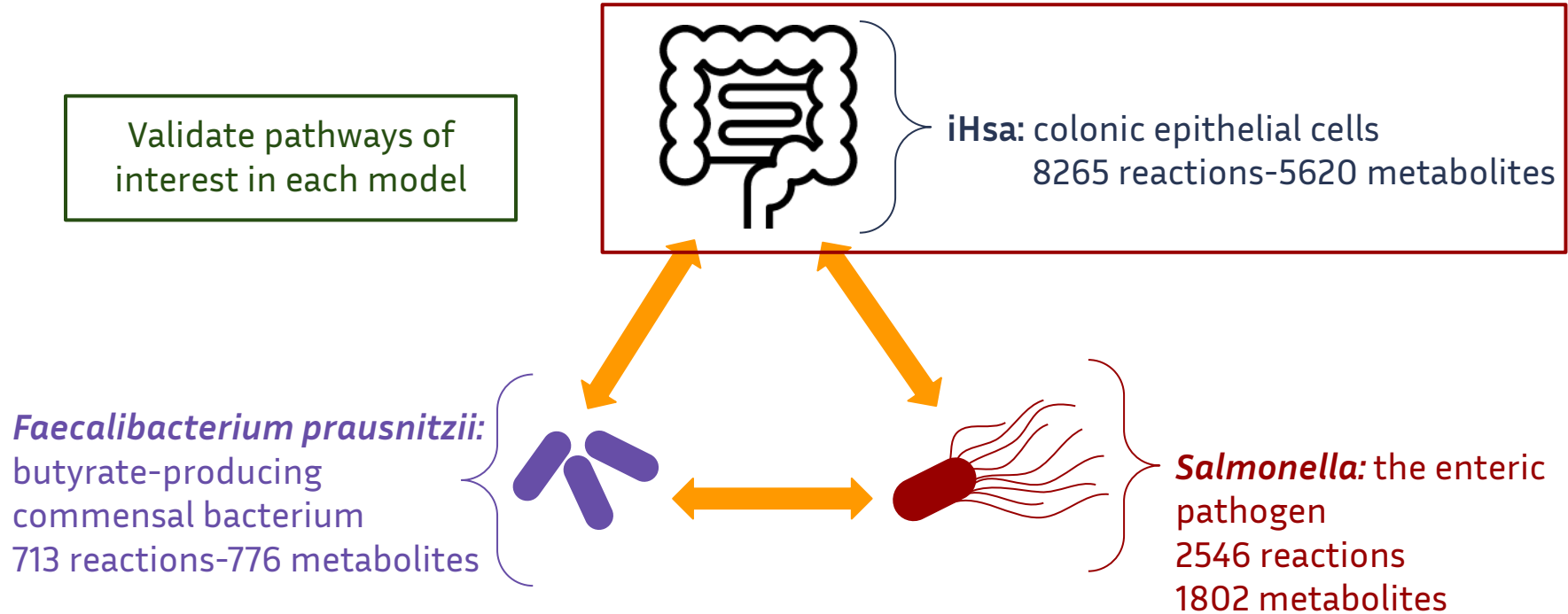
- ① cytosol
 - ② periplasm
 - ③ mitochondria
 - ④ intermembrane space
 - ⑤ mitochondrial inner membrane
 - ⑥ matrix
- high activity
— medium activity
— low activity



- Objective function:
 - Biomass
- Uptake metabolites of interest:
 - Glucose/Galactose
 - Glucarate/Galactarate
 - Thiosulfate/Tetrathionate

Metabolic model:

- Build a **host-microbiota-pathogen** system using 3 metabolic networks



Metabolic model: Enterocyte

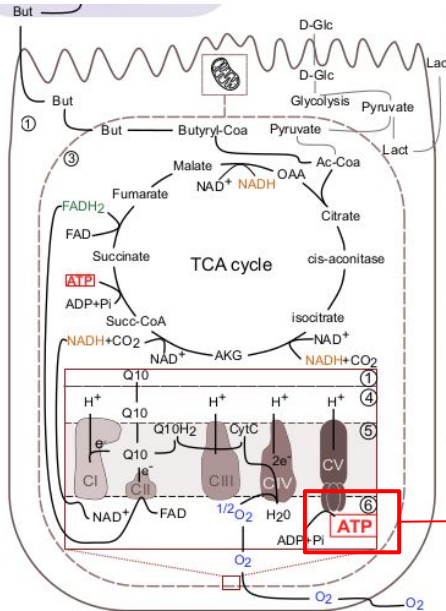


- Objective function:
 - Butyrate has **no impact** on the biomass production

Metabolic model: Enterocyte



Healthy conditions



ATP synthase of the mitochondria,
cell the production of energy

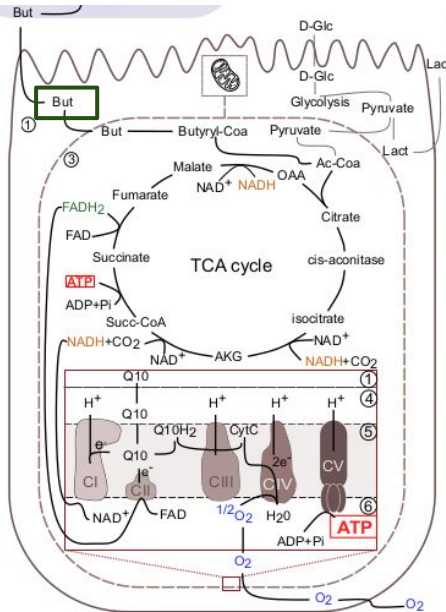
- ① cytosol
 - ② periplasm
 - ③ mitochondria
 - ④ intermembrane space
 - ⑤ mitochondrial inner membrane
 - ⑥ matrix
- high activity
 - - - medium activity
 ... low activity

- Objective function:
 - Butyrate has **no impact** on the biomass production
 - Set up the **ATP synthase**

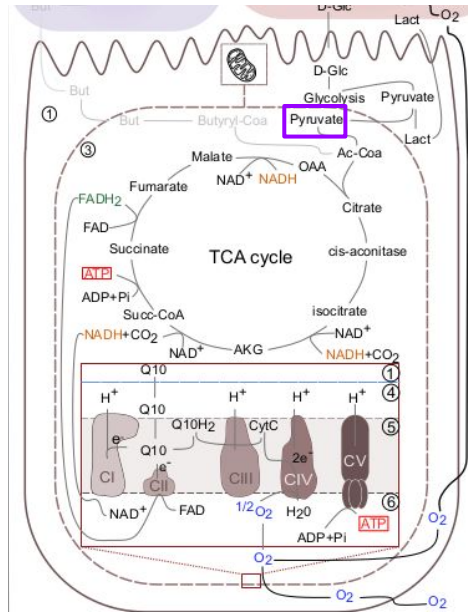
Metabolic model: Enterocyte



Healthy conditions



Infection conditions



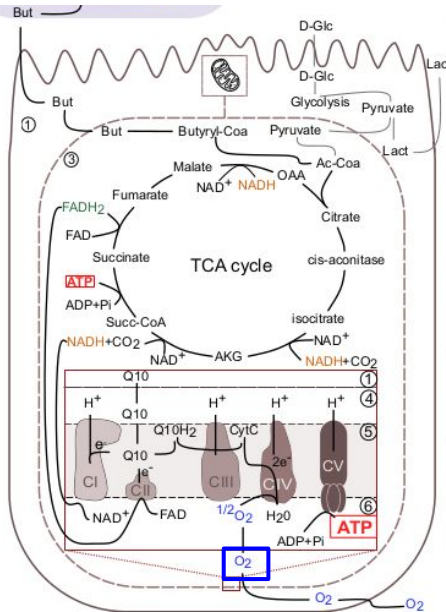
- ① cytosol
 - ② periplasm
 - ③ mitochondria
 - ④ intermembrane space
 - ⑤ mitochondrial inner membrane
 - ⑥ matrix
- high activity
 medium activity
 low activity

- Objective function:
 - Butyrate has **no impact** on the biomass production
 - Set up the **ATP synthase**
- Uptake/Output metabolites of interest:
 - **Butyrate** (uptake)
 - **Pyruvate** (uptake)

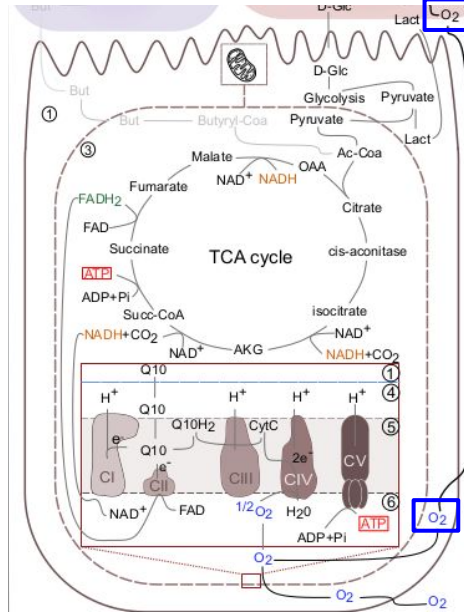
Metabolic model: Enterocyte



Healthy conditions



Infection conditions



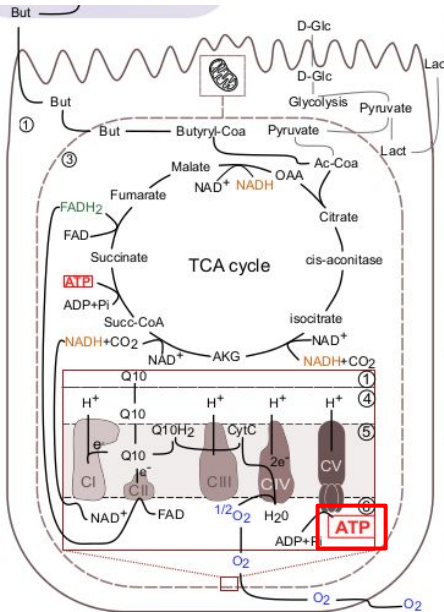
- ① cytosol
 - ② periplasm
 - ③ mitochondria
 - ④ intermembrane space
 - ⑤ mitochondrial inner membrane
 - ⑥ matrix
- high activity
 medium activity
 low activity

- Objective function:
 - Butyrate has **no impact** on the biomass production
 - Set up the **ATP synthase**
- Uptake/Output metabolites of interest:
 - **Butyrate** (uptake)
 - **Pyruvate** (uptake)
 - **O₂** (uptake in healthy condition and output in infection condition)

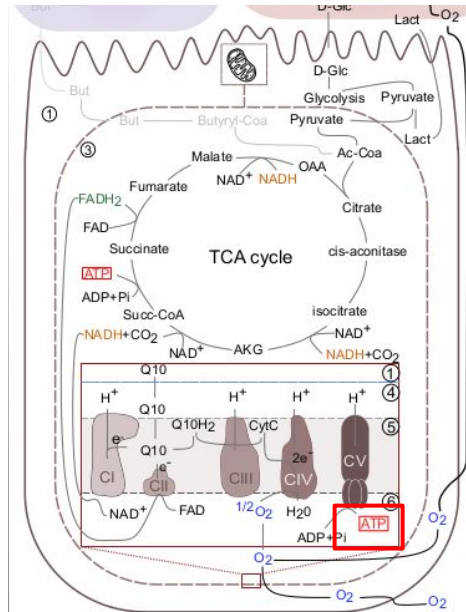
Metabolic model: Enterocyte



Healthy conditions



Infection conditions



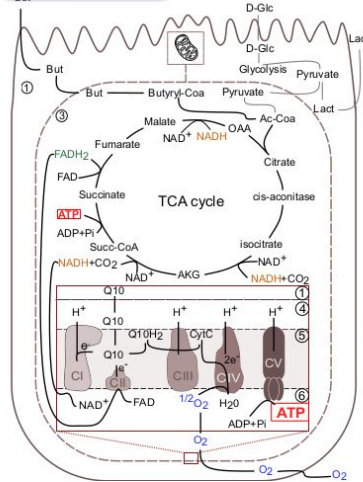
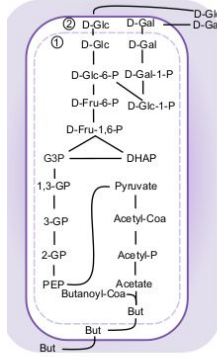
- ① cytosol
 - ② periplasm
 - ③ mitochondria
 - ④ intermembrane space
 - ⑤ mitochondrial inner membrane
 - ⑥ matrix
- high activity
 - - - medium activity
 ... low activity

- Objective function:
 - Butyrate has **no impact** on the biomass production
 - Set up the **ATP synthase**
- Uptake/Output metabolites of interest:
 - **Butyrate** (uptake)
 - **Pyruvate** (uptake)
 - **O₂** (uptake in healthy condition and output in infection condition)
- Production metabolites of interest:
 - **ATP** (stable in healthy conditions and decreased in infection conditions)

Complete model



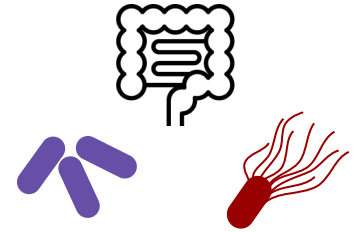
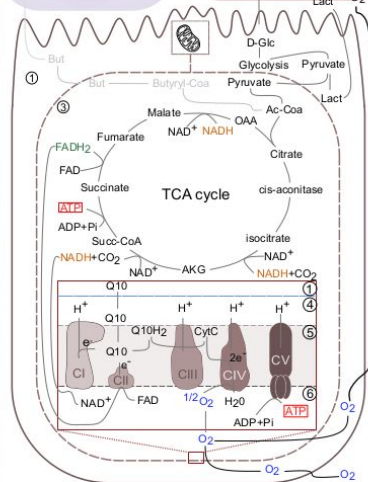
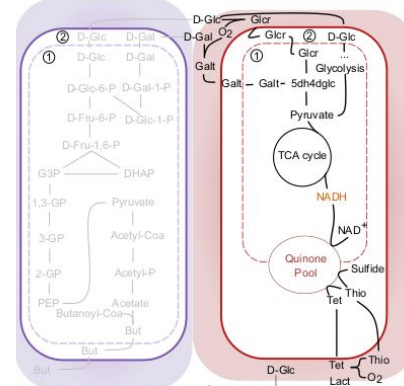
Healthy conditions



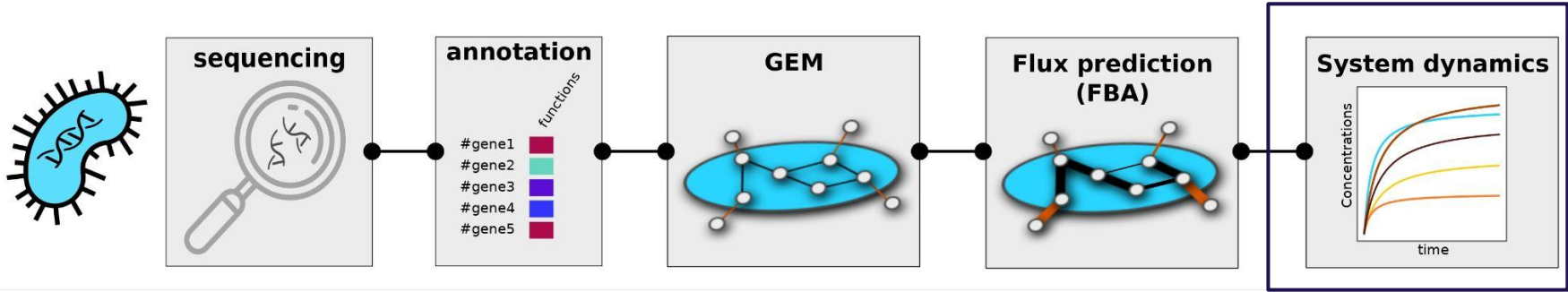
- Commensal Bacteria
Enterocytes
Salmonella
- ① cytosol
 - ② periplasm
 - ③ mitochondria
 - ④ intermembrane space
 - ⑤ mitochondrial inner membrane
 - ⑥ matrix

- high activity
- medium activity
- low activity

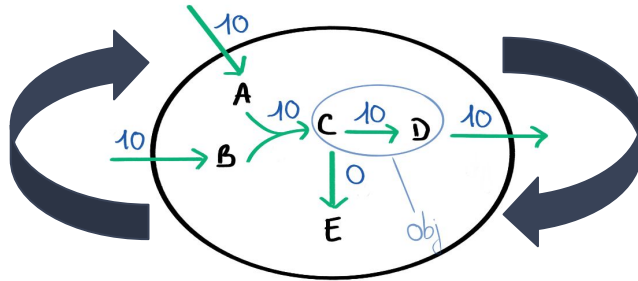
Infection conditions



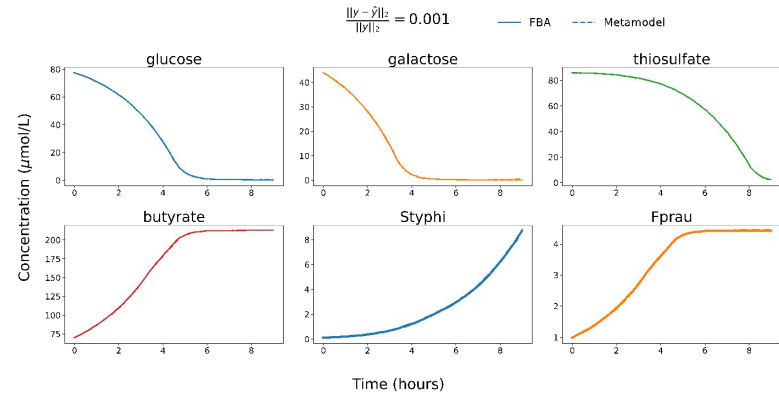
Workflow



Simulation at each time step



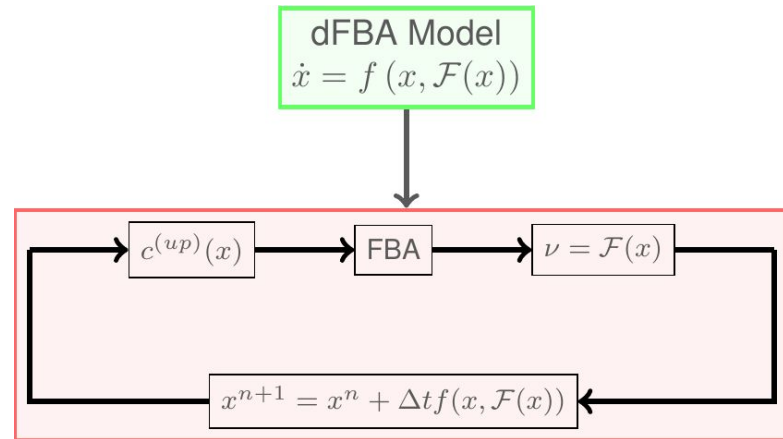
Predict the dynamics



Dynamic FBA

Let \mathcal{F} be the function that maps the **constraints** $c^{(up)}$ to the optimal **flux** v^* obtained by **FBA**

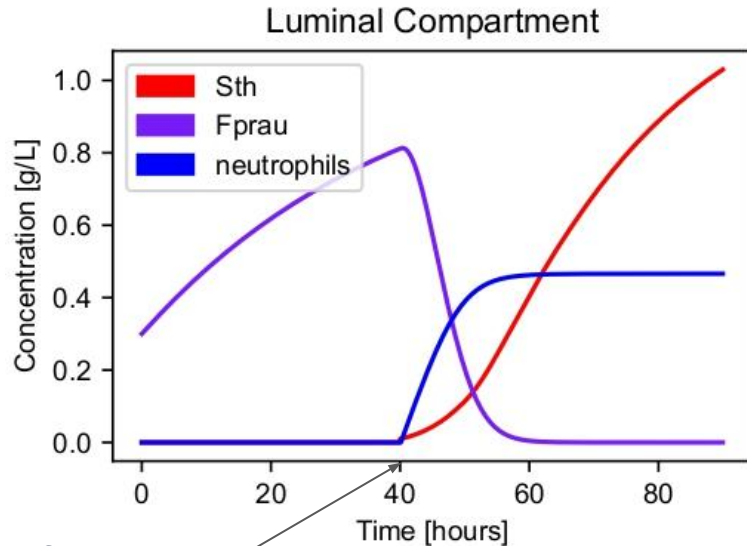
$$\mathcal{F} : \mathbb{R}^{N^{up}} \longrightarrow \mathbb{R}^{N_r}$$
$$c^{(up)} \mapsto v^*$$



Dynamic Model

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

Results

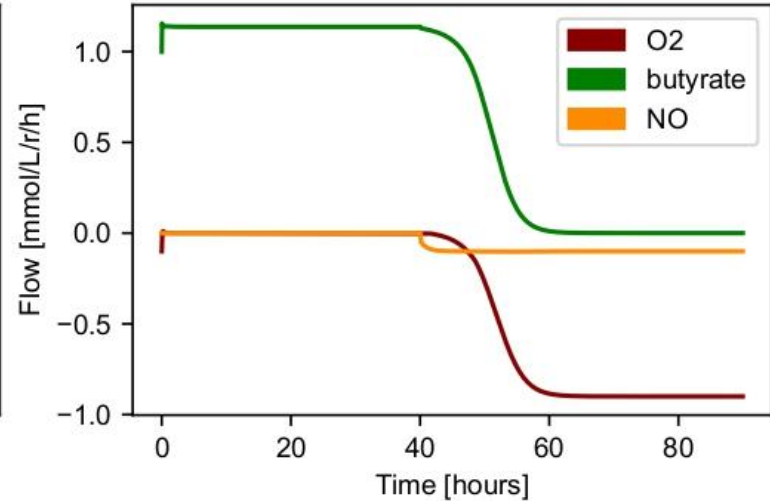


Infection time



Time [hours]

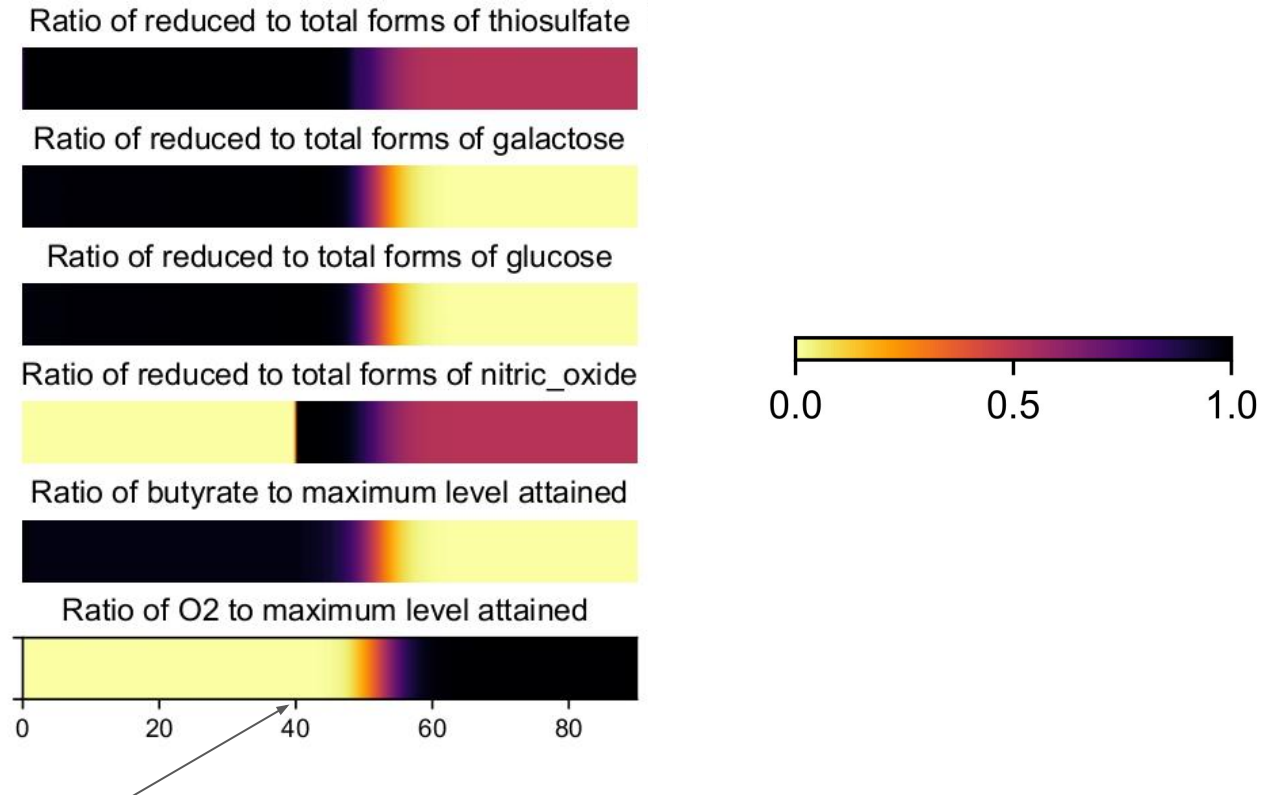
Flows between luminal and epithelial compartm



Flow [mmol/L/r/h]

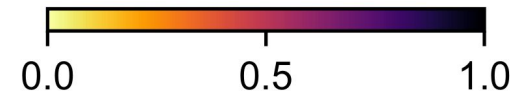
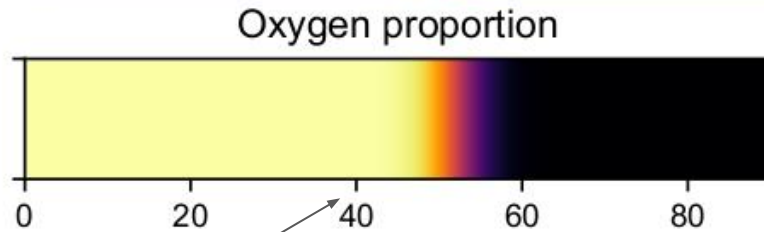
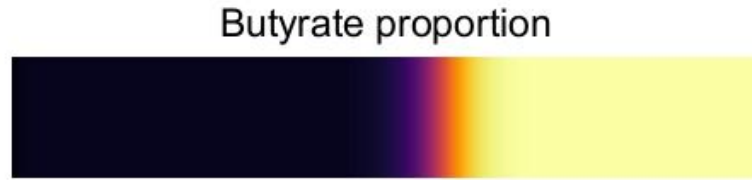
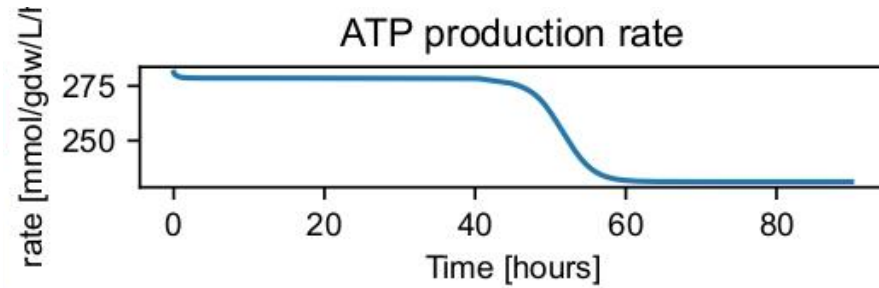
Time [hours]

Results: Luminal Compartment



Infection time

Results Epithelial Compartment

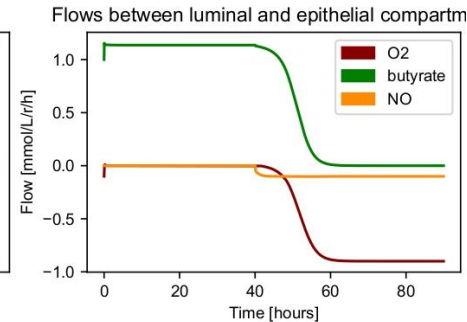
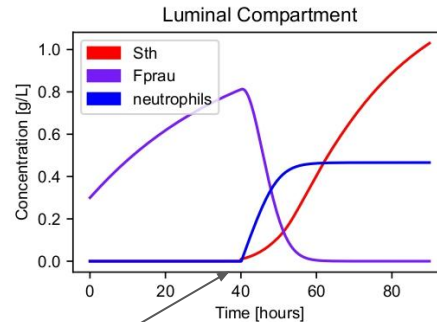
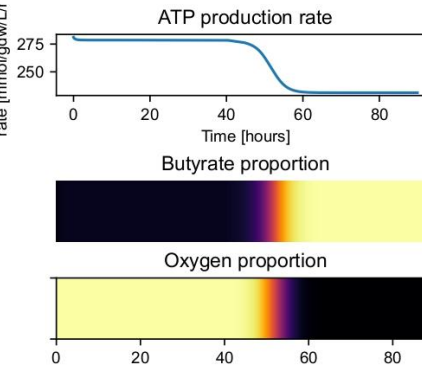
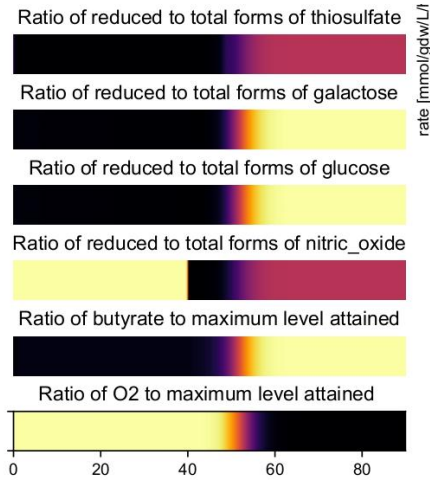


Infection time



Results

Big
computational
workload!



Infection time

Surrogate Model

- A surrogate model consists of **approximating** a function by another one, in order to gain computation time.
- **Statistical Learning:** Methods to reconstruct a function describing an unknown underlying distribution from a set of observations.

Surrogate Model

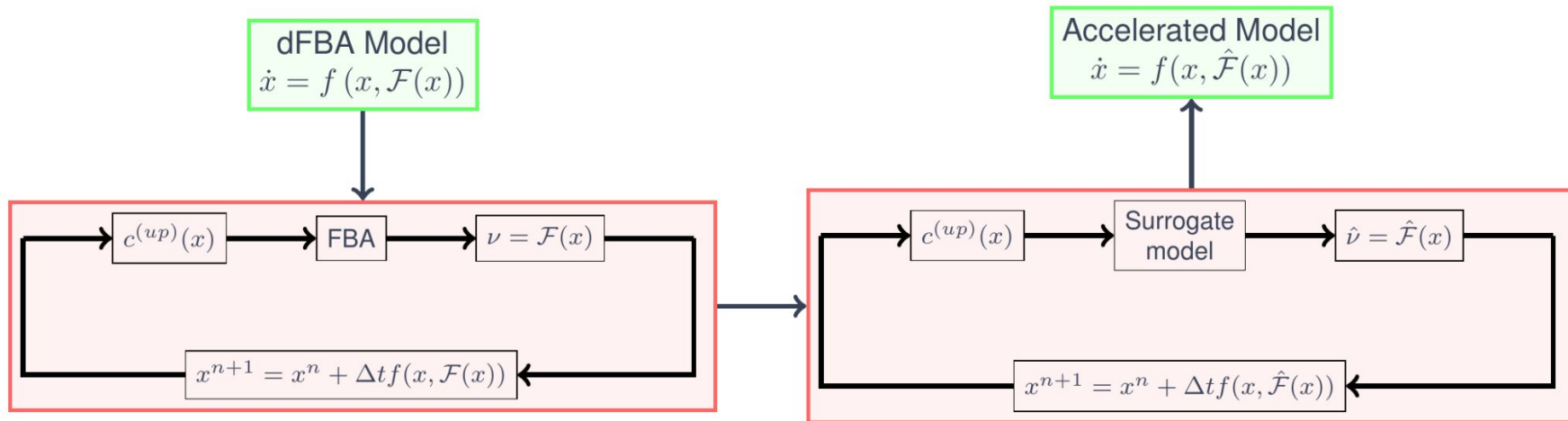
- A surrogate model consists of **approximating** a function by another one, in order to gain computation time.
- **Statistical Learning:** Methods to reconstruct a function describing an unknown underlying distribution from a set of observations.

- But we already know the function! $\mathcal{F} : \mathbb{R}^{N^{up}} \longrightarrow \mathbb{R}^{N_r}$
 $c^{(up)} \mapsto \nu^*$

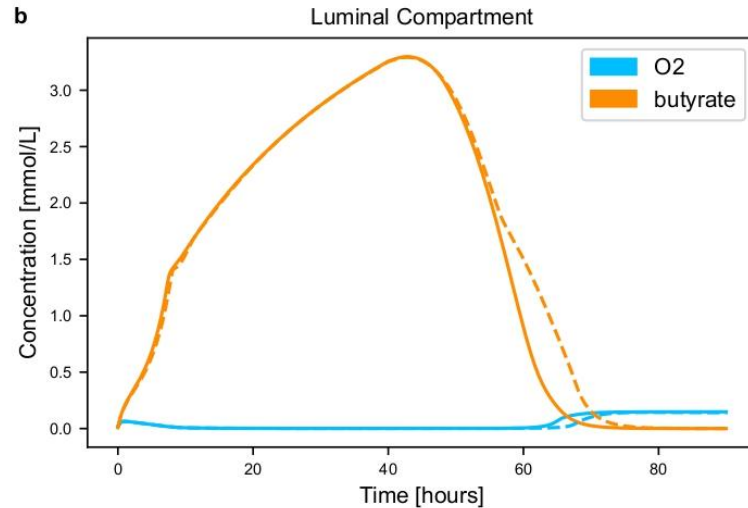
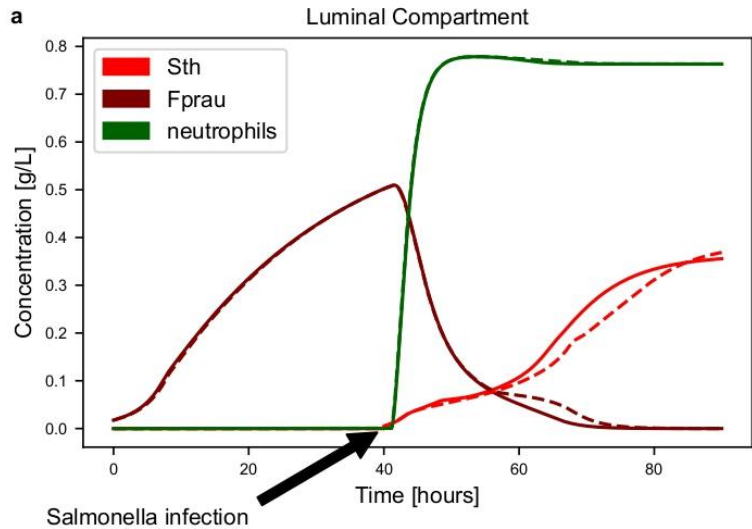


1. Generate a database of observations
2. Construct a surrogate model
3. Replace the original function

Speeding up the dynamic model

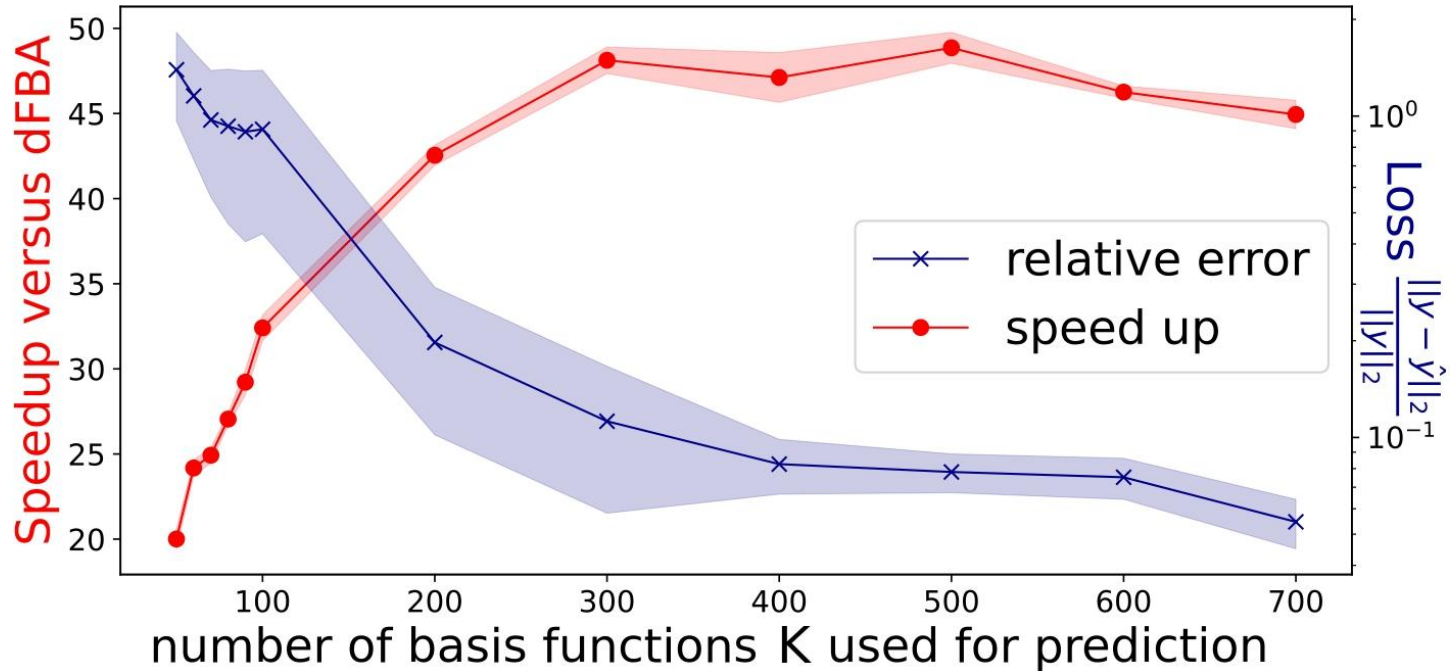


Speeding up the dynamic model



Original model —
Surrogate model - - - -

Speeding up the dynamic model



Conclusion

- Success at efficiently **capturing** and **predicting** the metabolic roles of **each** partner in the infection at the **cost of limited loss in accuracy**

Conclusion

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- A **mechanistic** and **accurate** metabolic model of a complex system involving a human metabolic network

Conclusion

- 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

Take-Home Message


Our model **paves the way** to a **more systematic** use of metabolic models as descriptors of **microbe-microbe** and **host-microbe** interactions during dysbiosis

Perspectives


Perspectives

- **Optimize** the speed-up and the accuracy \Rightarrow **Benchmark** of other metamodel


Perspectives

- **Optimize** the speed-up and the accuracy \implies **Benchmark** of other metamodel
-  Add **spatialization** to our model

Perspectives

- **Optimize** the speed-up and the accuracy \implies **Benchmark** of other metamodel
-  **Add spatialization** to our model
- Model of dysbiosis to model implying *E. coli* to **compete** with *Salmonella*

Perspectives

- **Optimize** the speed-up and the accuracy \implies **Benchmark** of other metamodels
-  **Add spatialization** to our model
- Model of dysbiosis to model implying *E. coli* to **compete** with *Salmonella*
- **Generalize** the approach to other ecosystems which functions are **important** for dynamics of the community

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Thank you for your attention !

