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

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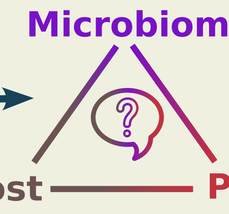
A route to digital twins of microbiomes

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.

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

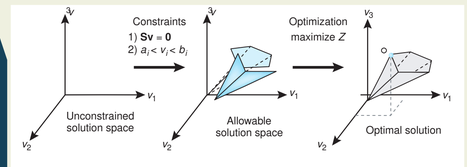


Figure 1: The conceptual basis of FBA
Figure adapted from Jeffrey D Orth, & al. 2010

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

Dynamic FBA (dFBA)[5]:

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

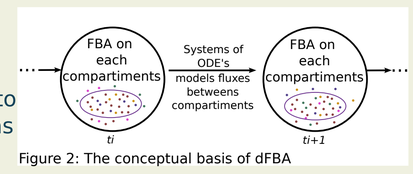


Figure 2: The conceptual basis of dFBA

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]

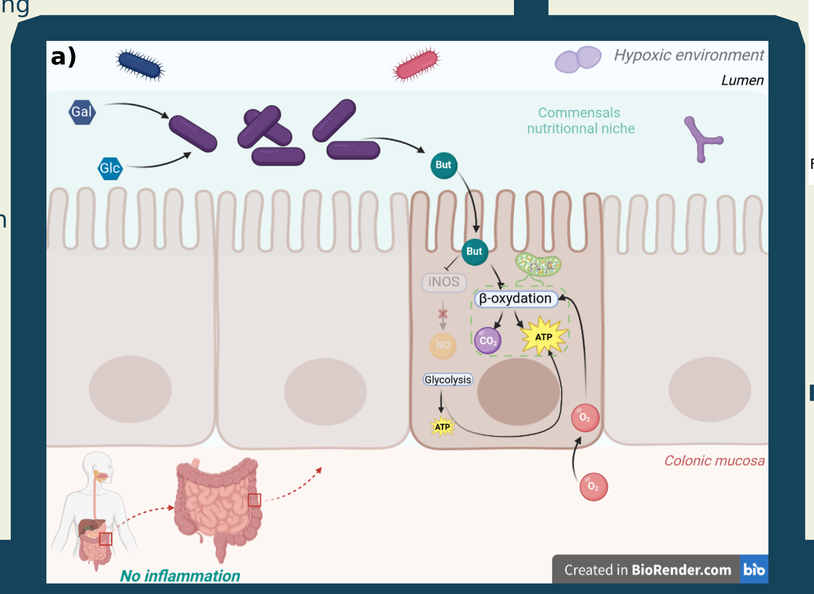
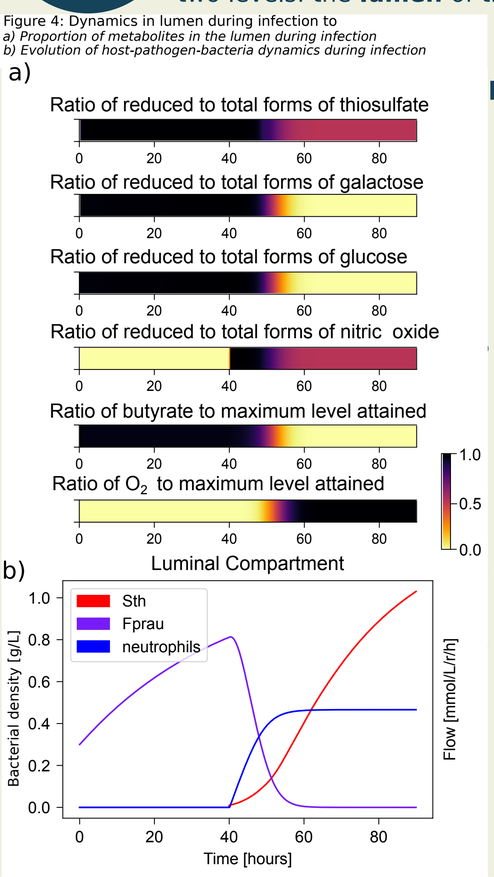


Figure 3:Mechanism of *Salmonella* Typhimurium infection
a) Healthy gut uncolonized by Salmonella, with commensal bacteria (purple) and enterocytes(brown) interactions
b) Salmonella-colonized intestine with Salmonella (red),commensal bacteria and enterocytes interactions
Created with BioRender.com

Simulations

Our simulations represent correctly the infection process on two levels: the **lumen** of the intestin 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_2 (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_2 (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

Dynamics in Enterocyte:

No infection(t0):

- Production of NO **inihibited by butyrate from** Fprau
- **Consumption** of butyrate an O_2 in TCA cycle and electron
- **Prodution** of energy (ATP) from butyrate

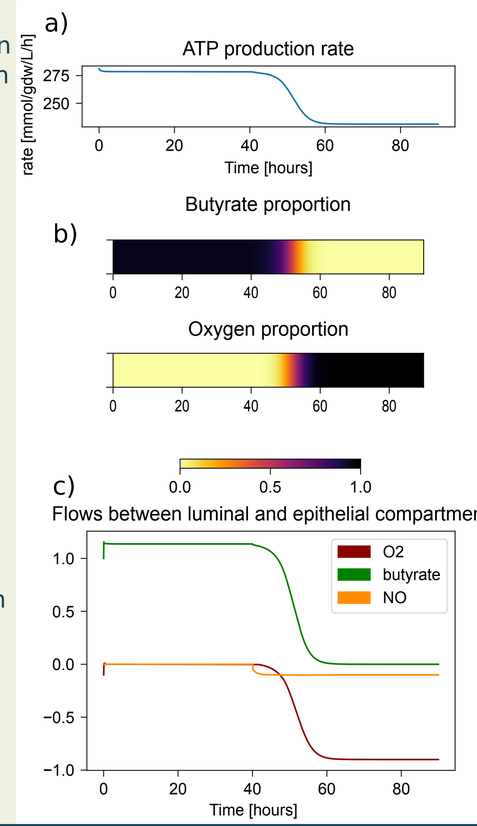
Infection(t40):

- **Production** of NO without its inihibition by butyrate
- **No consumption** of butyrate an O_2 in TCA cyle
- O_2 **leakage** to lumen
- **Reduction** in energy production (ATP)

Flow dynamics during infection:

- **Decline** of the butyrate flow causes by absence of production
- **Overflow** O_2 and NO in the lumen from enterocytes

Figure 5: Dynamics in enterocyte during infection
a) Evolution of the ATP production during infection
b) Proportion of O2 and butyaret in the enterocyte during infection
c) Evolution of flows between luminal and epithelial compartment

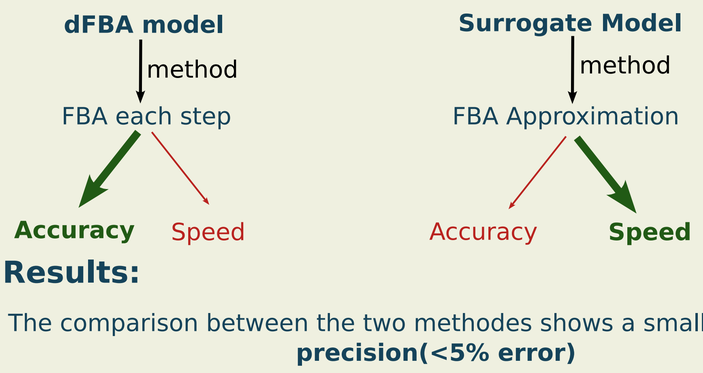


A surrogate to speed up simulations

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

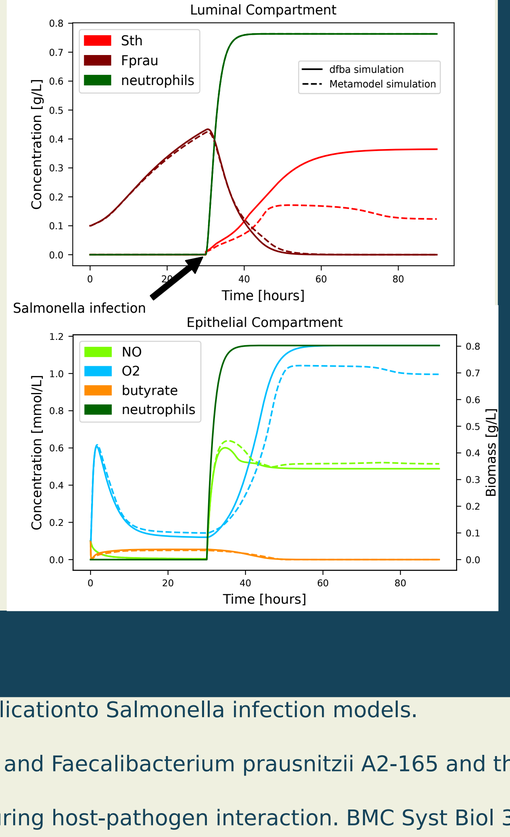


Our Results:

- ✓ 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

References

[1] Clémence Frioux et al. Accelerating metabolic models evaluation with statistical metamodels: applicationto Salmonella infection models. working paper or preprint, April 2022.
[2] 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
[3] Raghunathan 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
[4] 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
[5] Ove Øyås and Jörg Satellin . Genome-scale metabolic networks in time and space. Current Opinion in Systems Biology, 8:51–8, 2018.
[6] 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
[7] Sylvie Huet and Marie-Luce Taupin. Metamodel construction for sensitivity analysis. ESAIM: Proceedings and Surveys, 60:27–69, 2017.