Modéliser les interactions hôte-microbiote-pathogène : défis et perspectives

Béatrice Laroche
MaIAGE, INRAE IDF Jouy-en-Josas

Journée Chaire MMB
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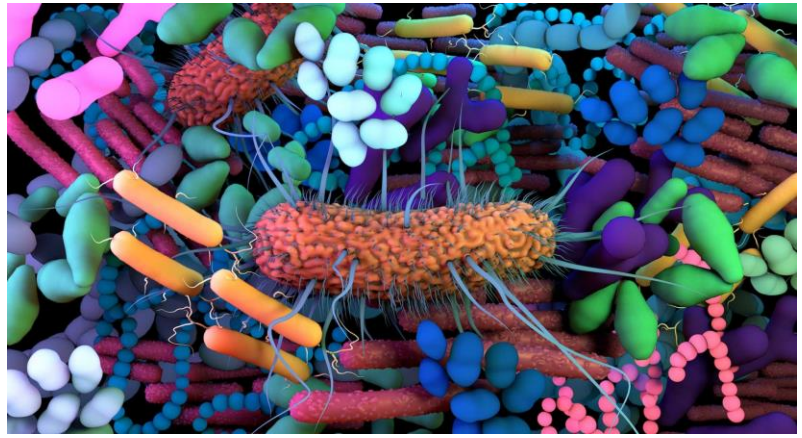
Outline

- Overview of host-microbiota interaction **in the large intestine**
- Crypt modelling
- Microbiota modelling
- Putting it all together
- Pathogen strategies
- Challenges and unsolved questions

Overview of host-microbiota interactions



Borrowed from https://www.gutmicrobiotaforhealth.com

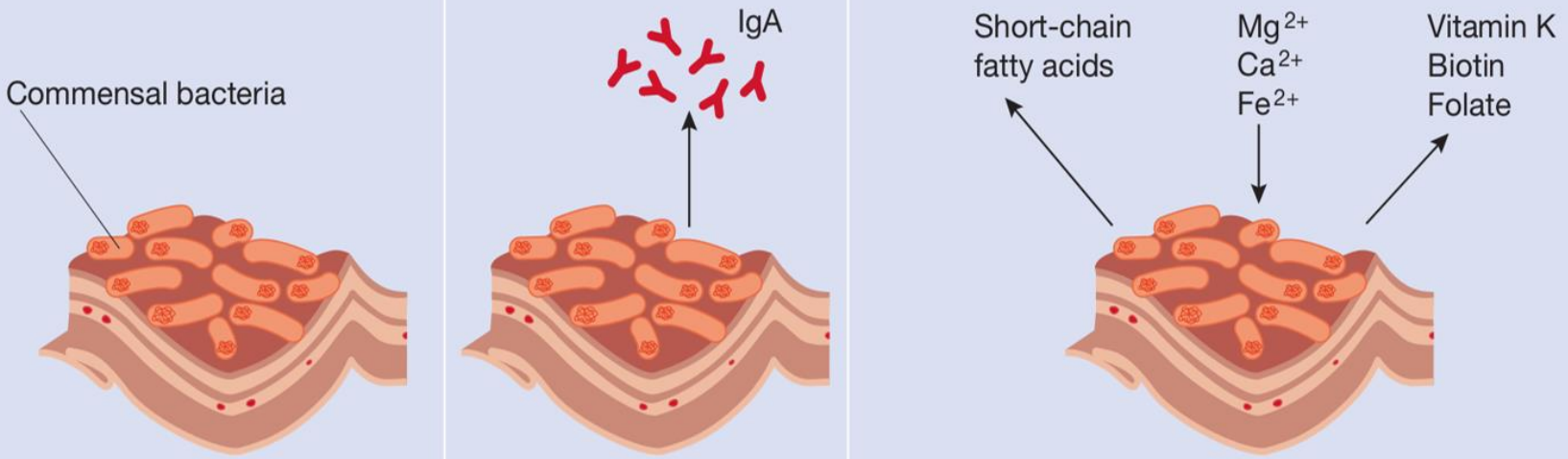
- Focus on monogastric mammals

  - Human, pigs, mice
  - Large intestine microbiota (very high density)
  - In human: mainly bacteria and some archaea (but also small fraction of yeasts, fungi…)

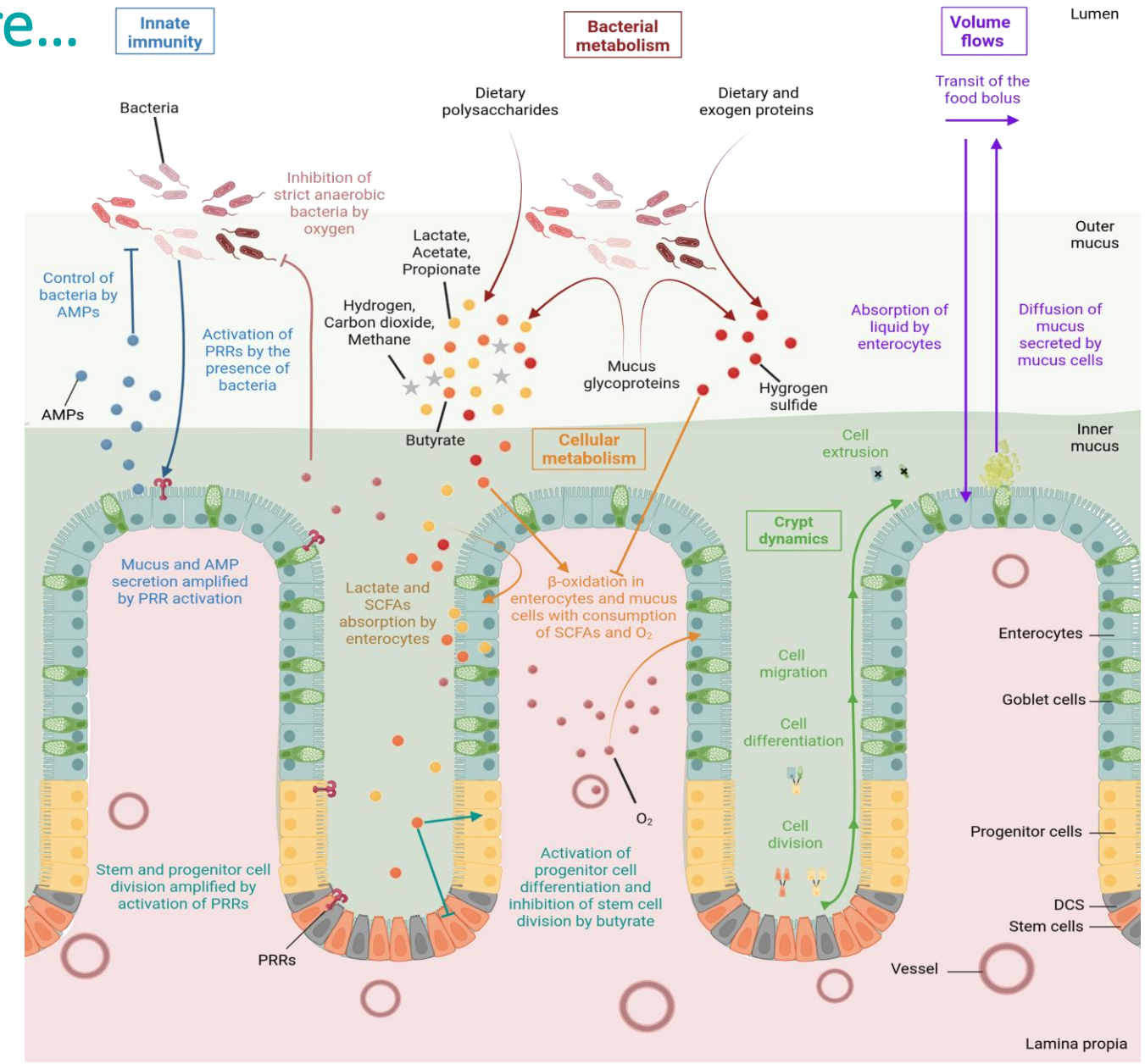
  - Acquisition during first 2-3 years in life,
  - Stable (but influenced by diet, drugs, health) ~1000 different species in one individual, « closed » ecosystem
  - Mostly anaerobic environment (anaerobes or facultatives anaerobes)
  - Reciprocal interaction with the host -> « holobiont »

Main role of intestinal microbiota in host health

Protective functions	Structural functions	Metabolic functions
Ecological barrier	**Immune System Education**	**Fermentation of non digestible dietary fibers**

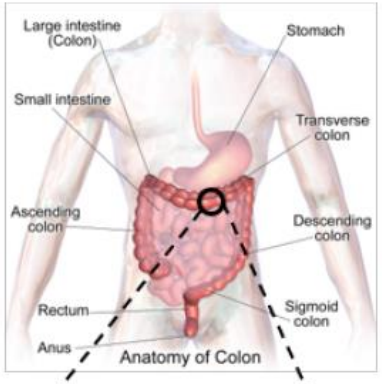


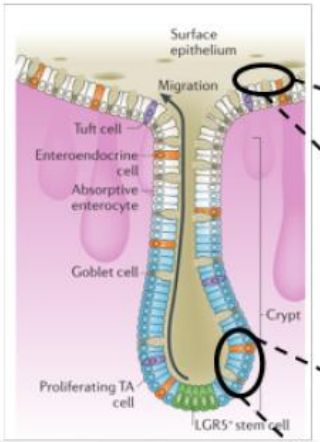
A complex global picture…



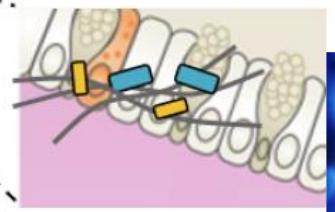
Borrowed from Haghebaert et al. (2023) JRSI, in press

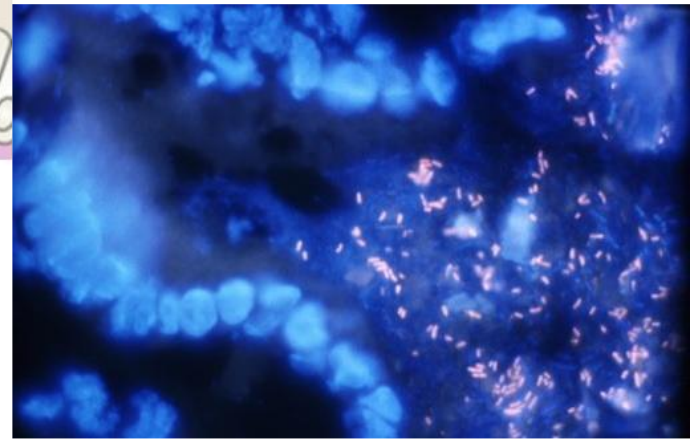
…and a highly multi-scale perspective

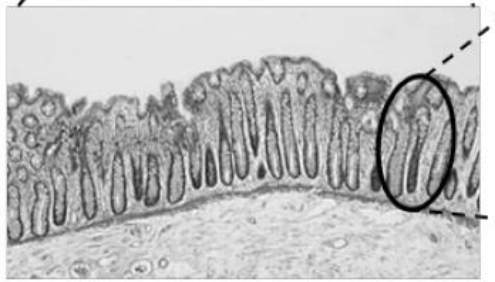




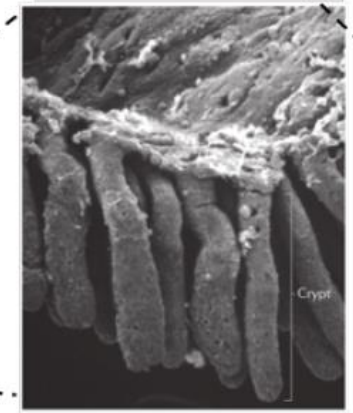
Bacteria attached to mucus 1 µm



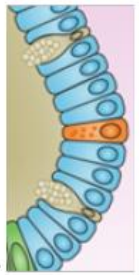




Intestinal mucosa
1,60 m (human colon)



Colonic crypt
50 x 250 µm 100 crypts / mm2



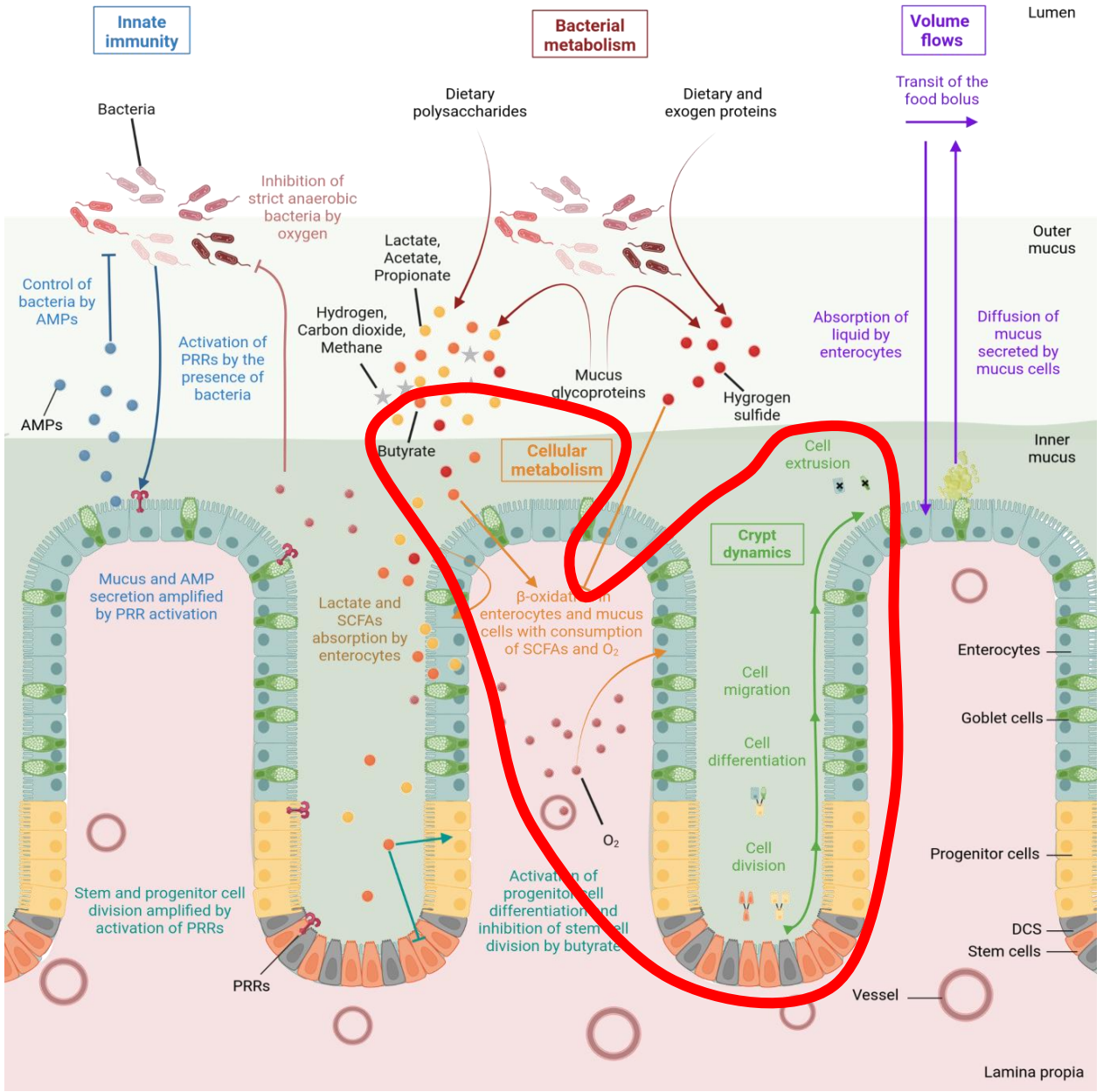
Colonic epithelial cells
10 µm 300 cells / crypt

Crypt modelling in the large intestine

PhD of Léo Darrigade,
co-supervision with S. Labarthe,
Collaboration with C. Cherbuy (MICALIS)

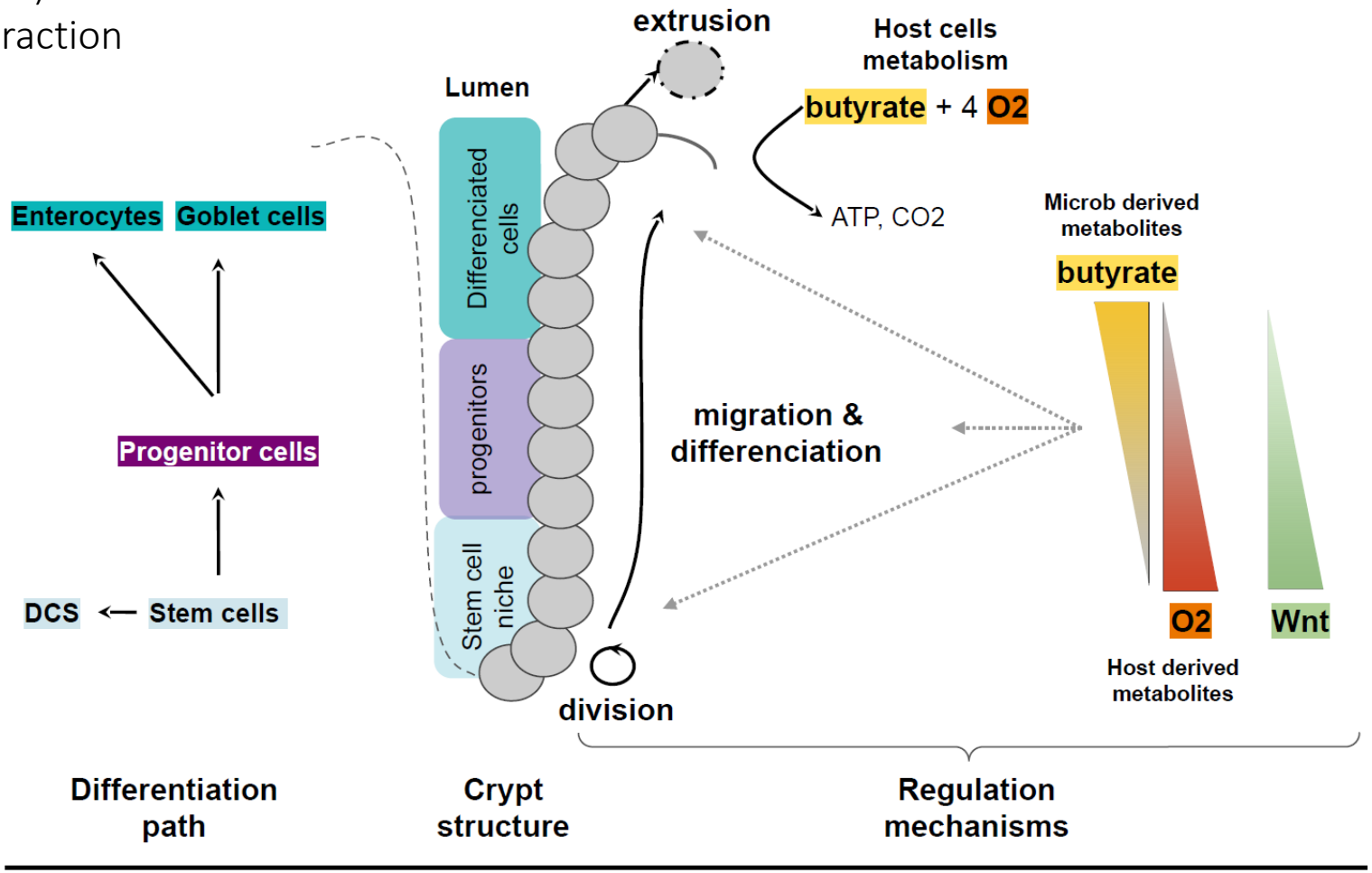
Objectives

- Build a healthy colonic crypt model
- Include microbial regulations
- Stochastic IBM with sound formulation
- Derive large population limit (PDEs)



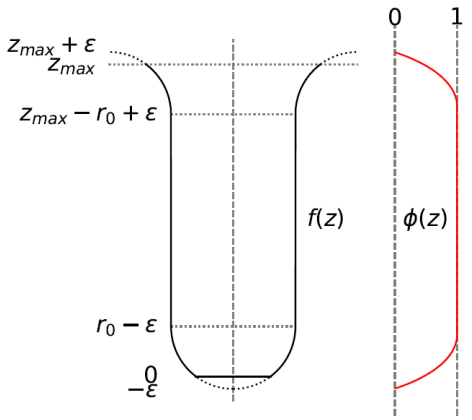
Modeling host-microbiota interactions at the colonic crypt scale

- Many models (Almet et al. 2020)
- Mostly small intestine, no interaction with the microbiota



Darrigade et al. 2022, J Math Biol

An IBM **PDMP** model



Deterministic evolution of cells and metabolites between stochastic events

State space

- 1D model $z \in [0, z_{max}]$
- A cell is a Dirac measure in $\mathscr{X} = [0, z_{max}] \times \mathscr{T}$ (position x cell type)
- A population of n epithelial cells in a crypt is in the set of positive finite
- atomic measures

$$\nu_t(dx) = \sum_{i=1}^{n} \delta_{x_i(t)}(dx) \quad \in \mathscr{M}_{P^+}(\mathscr{X})$$

- Typical cell diameter a

$$]0, z_{max}[_a :=]-a/2, z_{max} + a/2[$$

- Concentrations of oxygen and butyrate $\boldsymbol{c} = (c_o, c_b)$ defined on
- State space $H^1(]0, z_{max}[_a)^2 \times \mathscr{M}_{P^+}(\mathscr{X})$

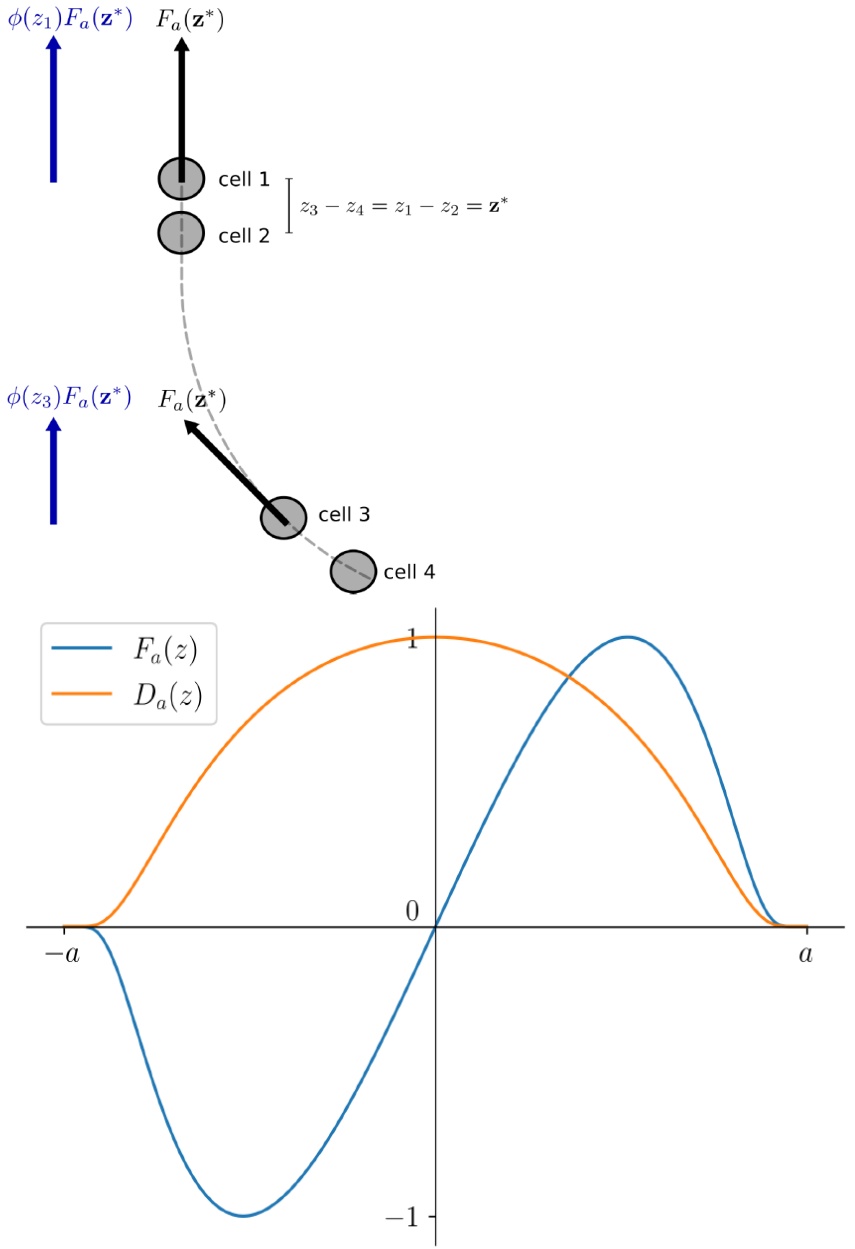
Deterministic motion

Cell-cell interaction

$$\frac{dz^i}{dt}(t) = \varphi\left(z^i(t)\right) \times (v_t \star F_a)\left(z^i(t)\right)$$

Except for DCS cells (no motion).

Shape of forces (blue curve) motivated by 1D reduction.



Deterministic motion

Reaction diffusion of metabolites (consumption by epithelial cells)

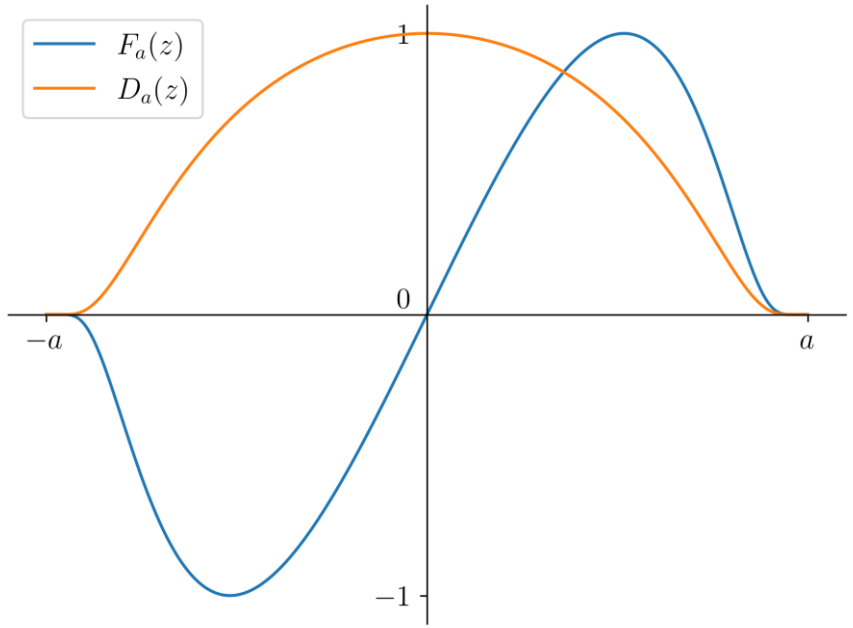
$$\partial_t c_i - \sigma_i \partial_{zz} c_i = -s_i \gamma_\beta^\infty \frac{c_o^4 c_b}{c_o^4 c_b + K_\beta^5} (\nu_t^{ent} + \nu_t^{gc}) * \psi_a(z)$$

i=oxygen or butyrate, s_i= stoichiometric coefficient

$$1 \text{ butyrate} + 4\ O_2 \longrightarrow \text{ energy} + \text{ byproducts}$$

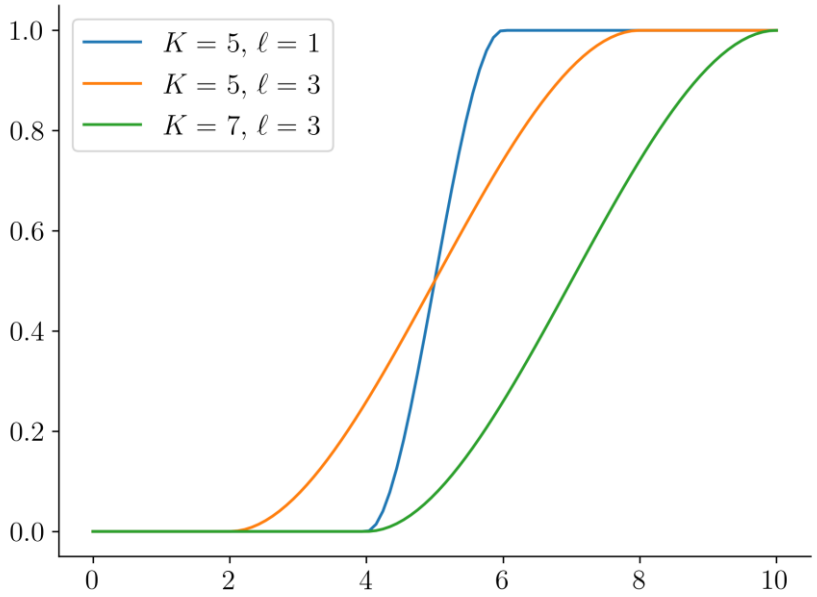
Boundary conditions for butyrate (symmetric for oxygen

$$c_b = c_{b,lum} \quad \text{at } z = z_{max} + \frac{a}{2}$$
$$\partial_z c_b = 0 \quad \text{at } z = -\frac{a}{2}$$



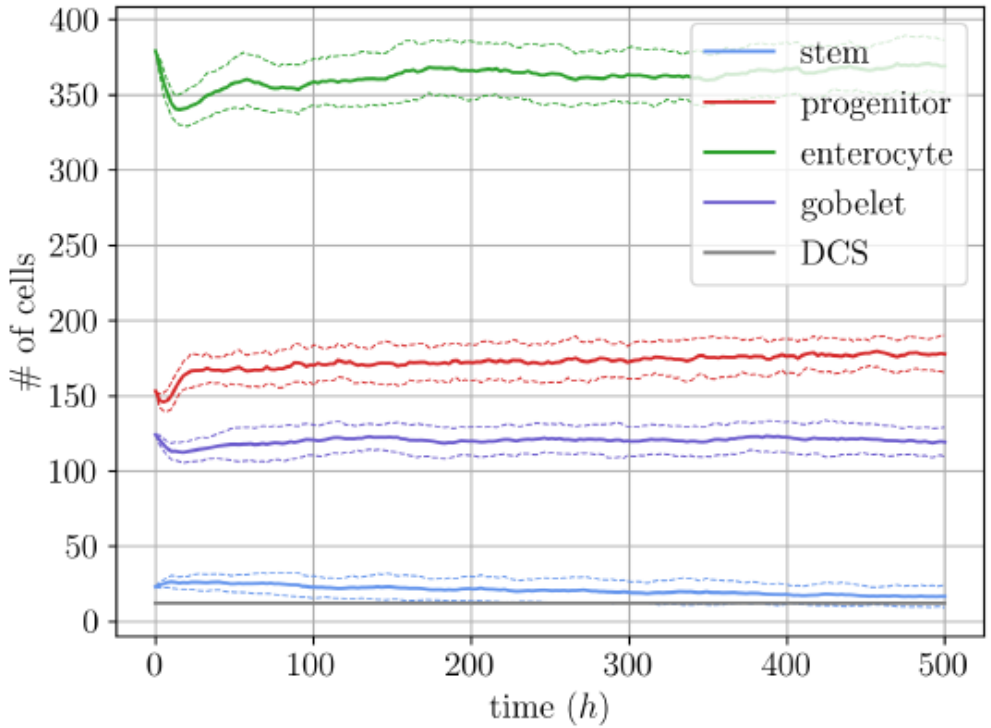
Stochastic jumps and regulations

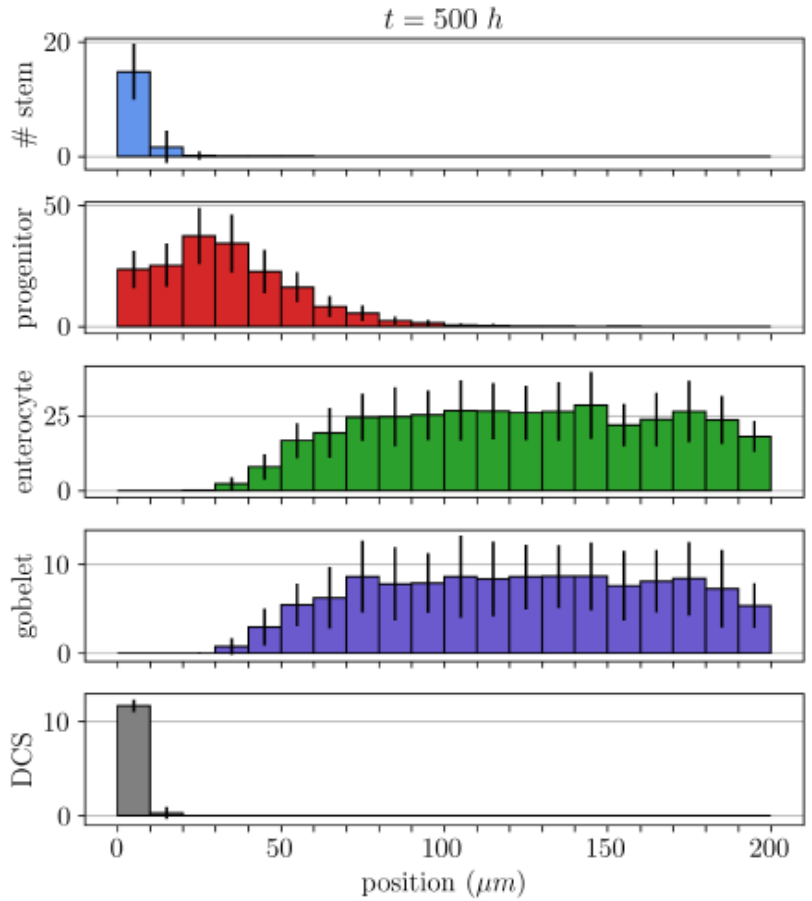
Jump type	Jump index (k)	Regulation pathway (j)		
		Butyrate [but]	Wnt [z]	Density [$dens$]
Stem cell division	div,sc	−	−	−
Progenitor division	div,pc	∅	−	−
Stem cell to progenitor differentiation	sc, pc	∅	+	∅
Progenitor to globlet cell differentiation	pc, gc	+	+	∅
Progenitor to enterocyte differentiation	pc, ent	+	+	∅
Goblet cell extrusion	ex, gc	∅	+	+
Enterocyte extrusion	ex, ent	∅	+	+



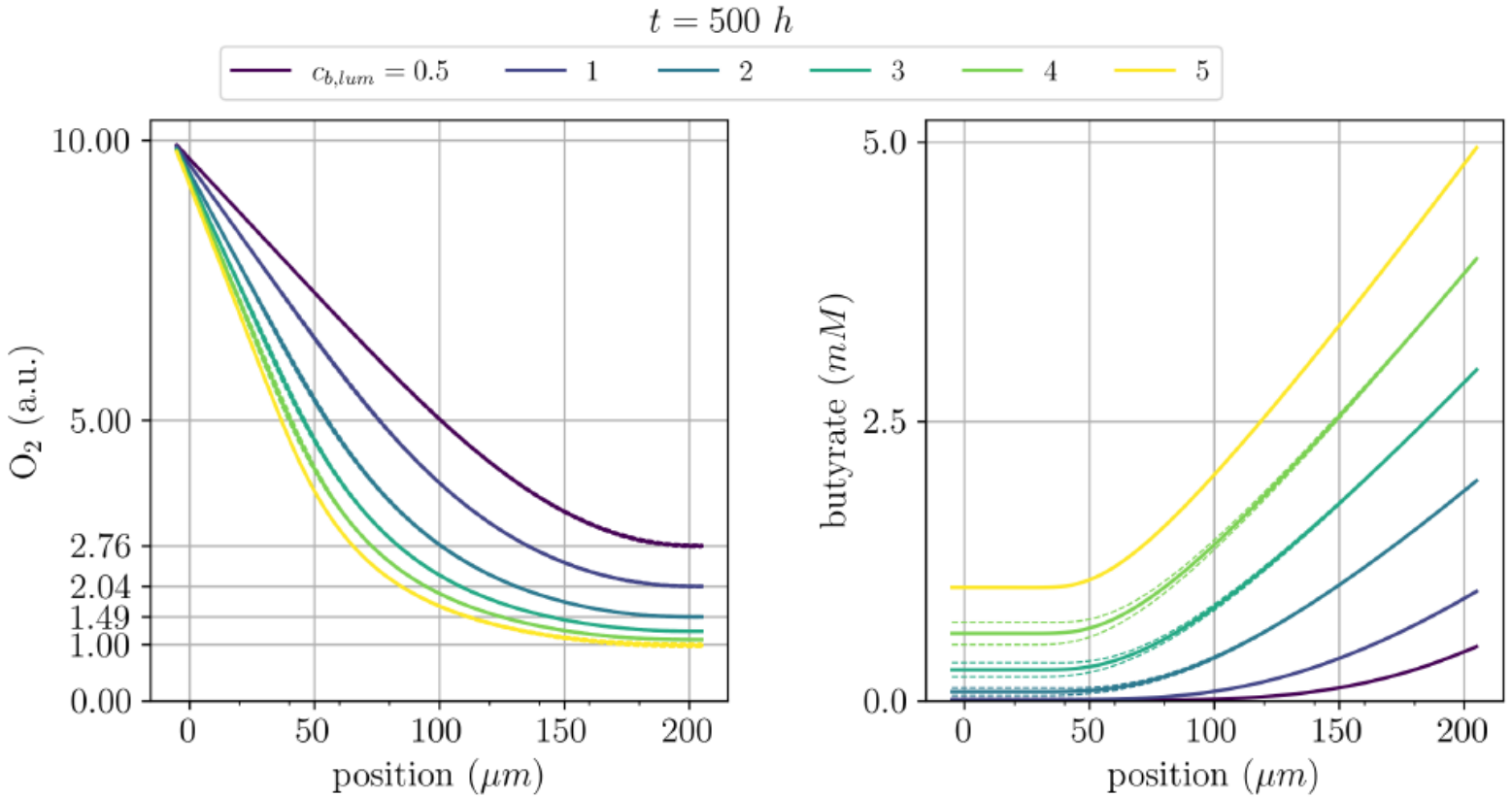
$$q_{\mathrm{div,sc}}(z, \ell, \mathbf{d}(\nu_t, z), \mathbf{c_b}(z)) = \overbrace{\mathbb{1}_{\{\ell=\mathrm{sc}\}}}^{\text{0 if not stem cell}} \times \overbrace{(1 - R(z, K_{\mathrm{div,sc}}[z], \kappa_{\mathrm{div,sc}}[z]))}^{\text{regulation by Wnt}} \times \overbrace{(1 - R(\mathbf{d}(\nu_t, z), K_{\mathrm{div,sc}}[dens], \kappa_{\mathrm{div,sc}}[dens]))}^{\text{regulation by density}} \times \underbrace{(1 - R(\mathbf{c_b}(z), K_{\mathrm{div,sc}}[but], \kappa_{\mathrm{div,sc}}[but]))}_{\text{regulation by butyrate}} .$$

PDMP simulation: individual based part





PDMP simulation: diffusion part, steady state.



Effect of luminal concentration of butyrate

Deterministic large population limit

Strong form for measures with densities: self aggregation equation

$$\partial_t \rho_l + \partial_z \Big(\phi \rho_l (\rho * F_a) \Big) = \sum_{k \in \mathscr{E} \setminus Div} \eta_{k,l} q_k^\infty q_k(z, l, \mathbf{d}(\rho, z), \mathbf{c_b}(z))$$
$$+ \sum_{k \in Div} \eta_{k,l}(z - \lambda(z)) q_k^\infty q_k(z - \lambda(z), l, (d \times \rho * D_a)(z - \lambda(z)), \mathbf{c_b}(z - \lambda(z))$$

Formal limit when the cell diameter a goes to zero: PME-like equations

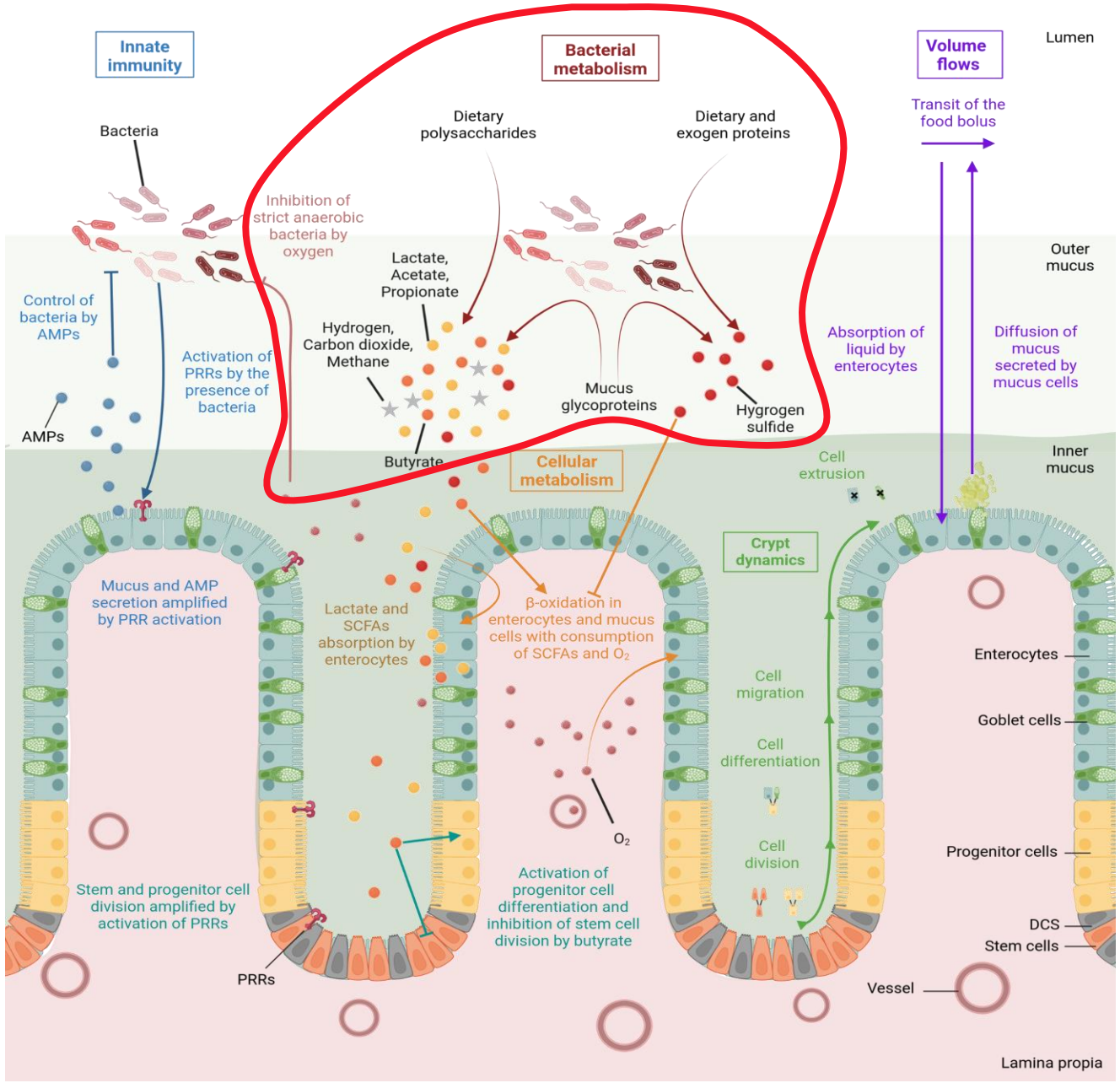
$$\partial_t \rho_l - W \partial_z (\phi(z) \rho_l \partial_z \rho) = \sum_k \varepsilon_{k,l} q_k^\infty q_k(z, l, D\rho, c_b)$$

Used for model analysis and coupling with larger scales (microbiota, host immune response)
PhD of Marie Haghebaert, help from M. Ribot (Univ. Orleans).

Microbiota modelling

- A functional approach
- Literature or expert driven
- Or data driven

PhD of R. Muñoz-Tamayo (2009)
PhD of S. Raguideau (2016)
PhD of M. Haghebaert (2023)



Microbiota modelling

- 5 Functional populations

Muñoz-Tamayo et al. , JTB 2010

Haghebaert et al., JRSI, to appear

B_{mon}, B_{la}, B_{H_2a}, B_{H_2m}, B_{H_2S}

Homo.Symbiosus, Joel Doré

- Split according to oxygen sensitivity?

Here oxygen represents the effect of inflammation

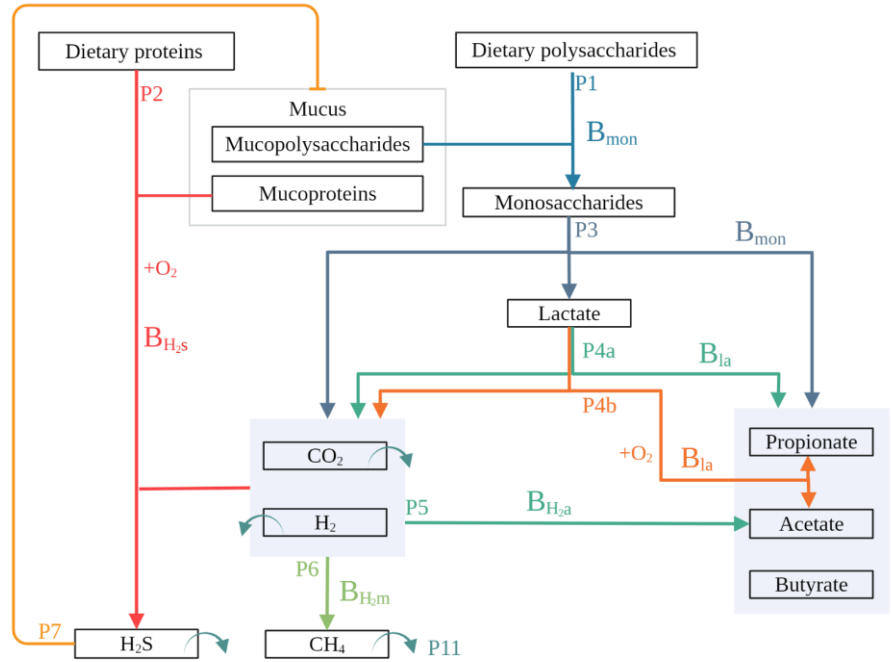
Metabolic processes :

P1 : Polysaccharide degradation
P2 : Protein degradation (cysteine catabolism + sulfate reduction)
P3 : Monosaccharides consumption
P4a : Consumption of lactate (fermentation)
P4b : Consumption of lactate (oxidation)
P5 : Acetogenesis
P6 : Methanogenesis (pH dependent)
P7 : H_2S toxicity on mucus
P11 : Gas transfer

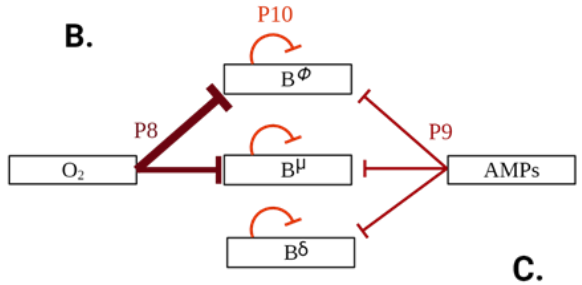
regulatory processes :

P8 : Bacterial death due to O2 sensitivity level
P9 : Bacterial death due to AMPs
P10 : Bacterial natural death

A.



B.



C.

Sensitivity to inflammation

Processes	High	Moderate	Low
P1, P3	B^{Φ}_{mon}	B^{μ}_{mon}	
P2			$B^{\delta}_{H_2S}$
P4a	B^{Φ}_{la}	B^{μ}_{la}	
P4b			B^{δ}_{la}
P5	$B^{\Phi}_{H_2a}$		
P6	$B^{\Phi}_{H_2m}$		

Deriving fiber & glycoprotein degradation functions organization from data

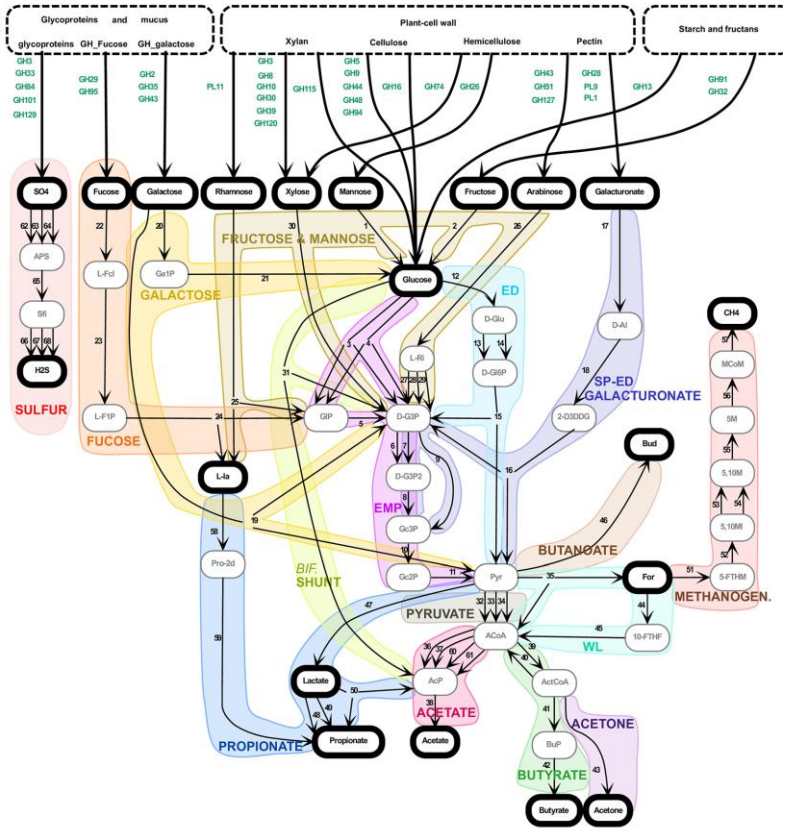
- Method based on constrained Non negative matrix factorization (NMF)

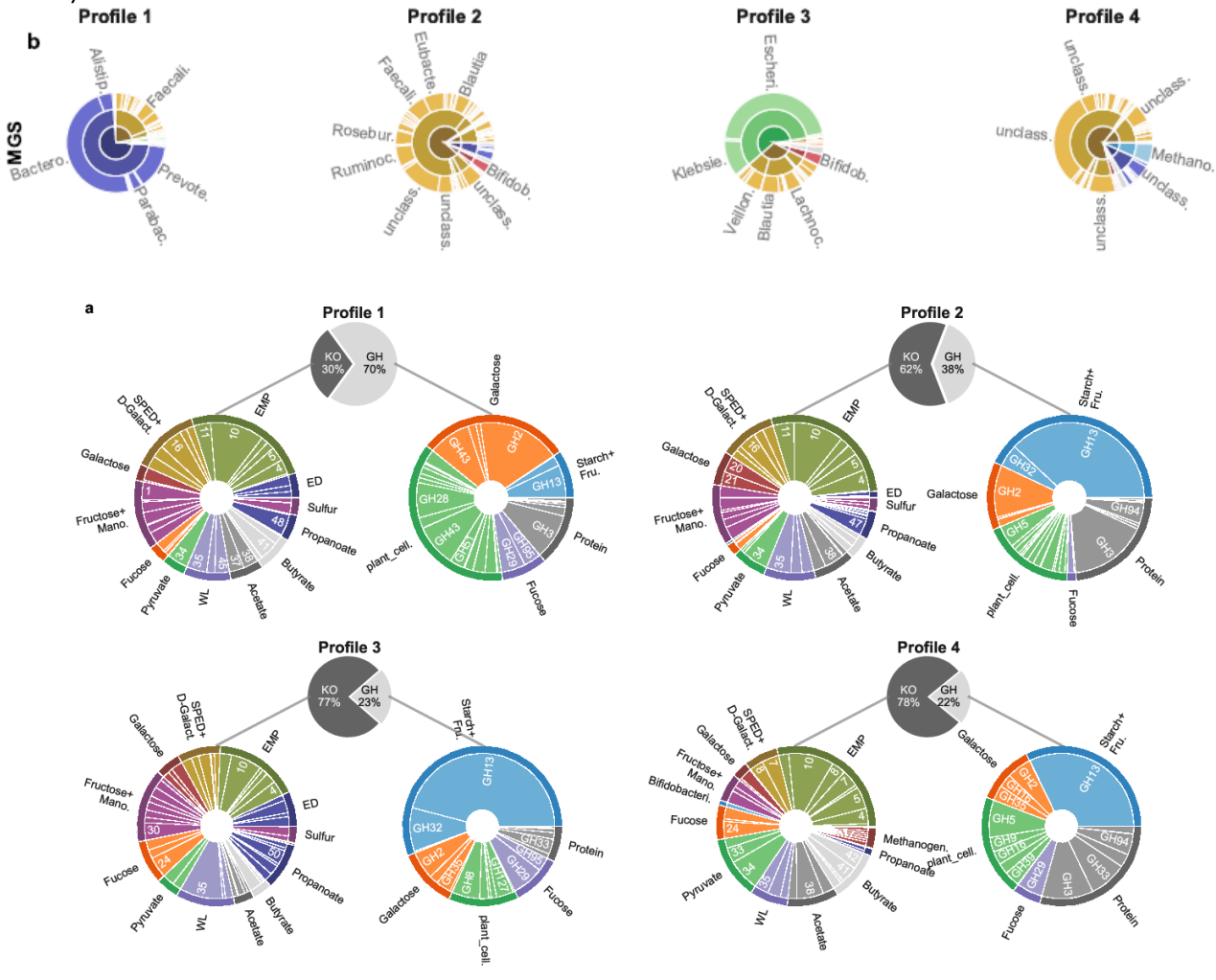
(Raguideau et al. PloS Comp. Biol. 2016)

- Further inference on 1153 samples & validation on 2571 samples

from 5 external cohorts (Labarthe et al. Microbiome 2023)

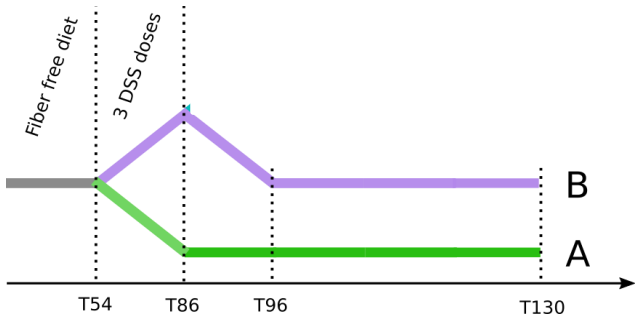
- Gene count matrices from shotgun data

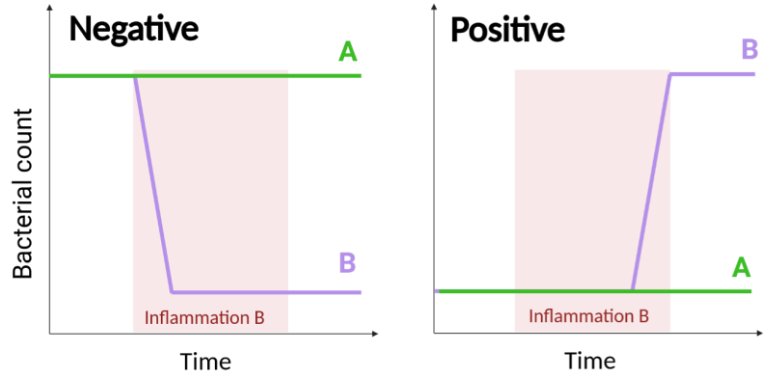




Deriving bacterial group sensitivity to inflammation from data

- Objective : combine metabolic functions and sensitivity to inflammation.
- Method:
  - Data from MAVA experiment, control group (A) vs DSS inflammed group (B)
  - Cluster bacteria with similar time curve in each rat -> identical response to environment
  - Analyse groups and compare behavior in A and B





Homo.Symbiosus, Joel Doré

Bacterial curve classification

- Compute a pairwise (dis-)similarity matrix : two species are close if their growth rates are close in each host -> cosine dissimilarity between s_i and s_j

  - H host number
  - s_i^h curve, proportions of species s_i in individual h
  - ω^h number of samples (time points) for h

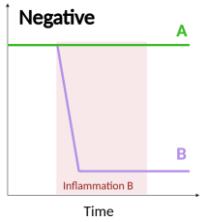
$$D(s_i, s_j) = 1 - \frac{1}{\sum_{h=1}^{H} \omega^h} \sum_{h=1}^{H} \omega^h \frac{\left\langle s_i^h, s_j^h \right\rangle}{\left|\left|s_i^h\right|\right| \times \left|\left|s_j^h\right|\right|}$$

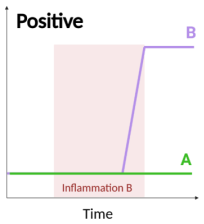
- Stochastic Block Model (R package Blockmodels, Leger, 2016).

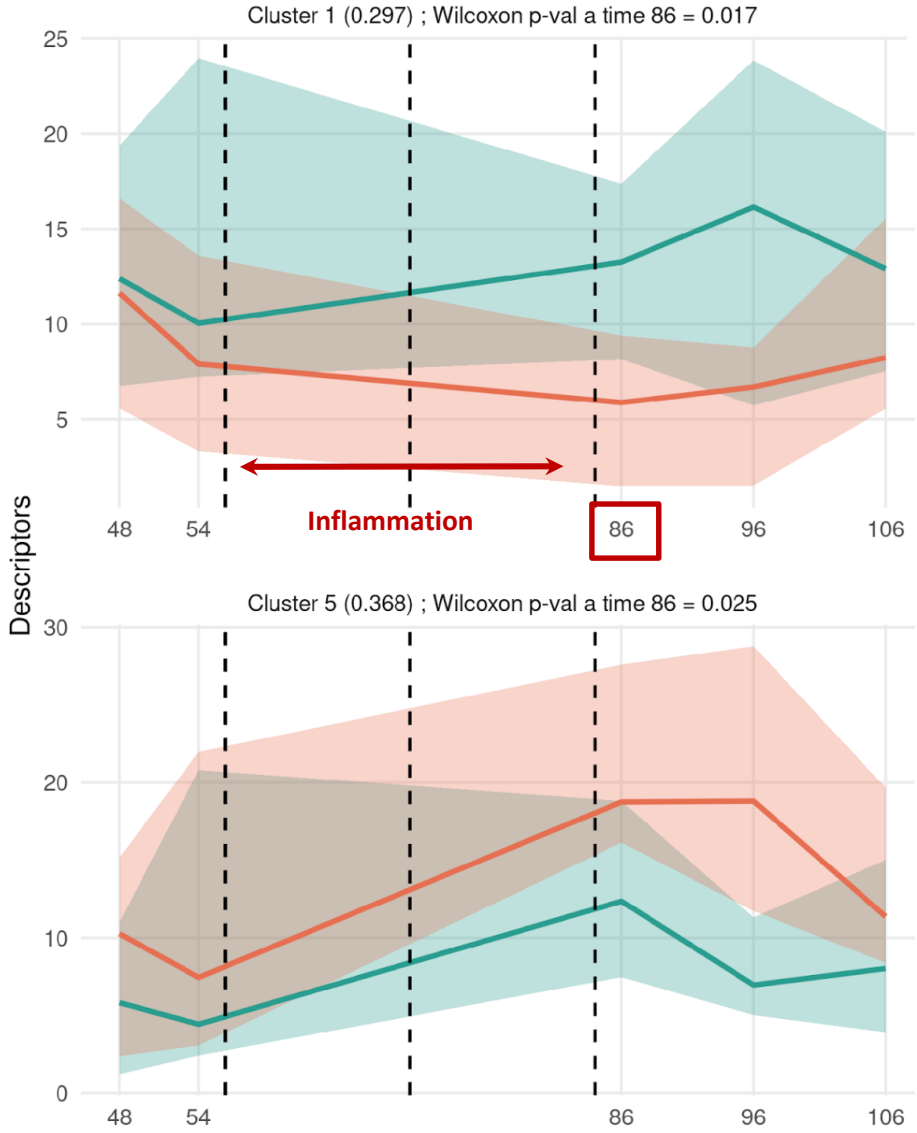
Deriving bacterial group sensitivity to inflammation from data

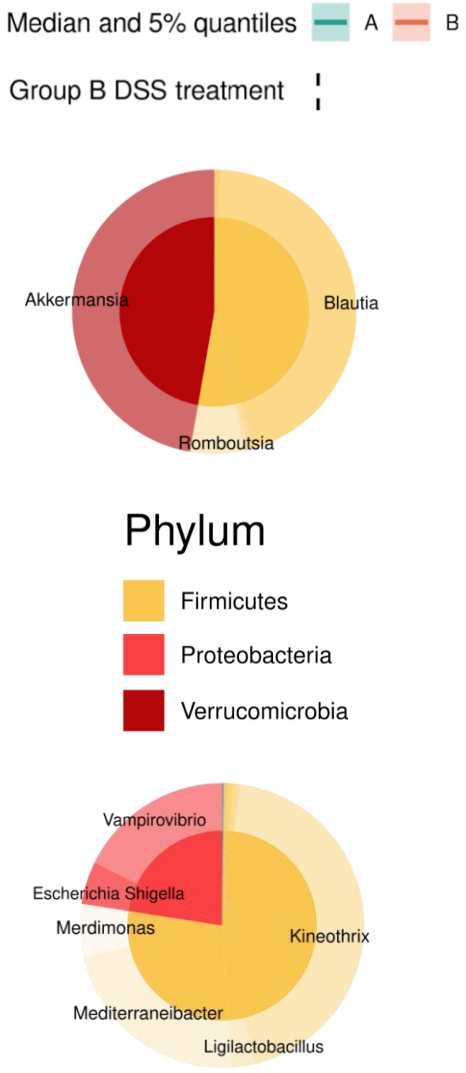
Translation in the model

- inflammation ~ rise of oxygen (Rivera-Chavez et al., 2017),
- 3 levels for the sensitivity to inflammation, impacting bacterial group death rate,
- raffinement of bacterial functional groups.

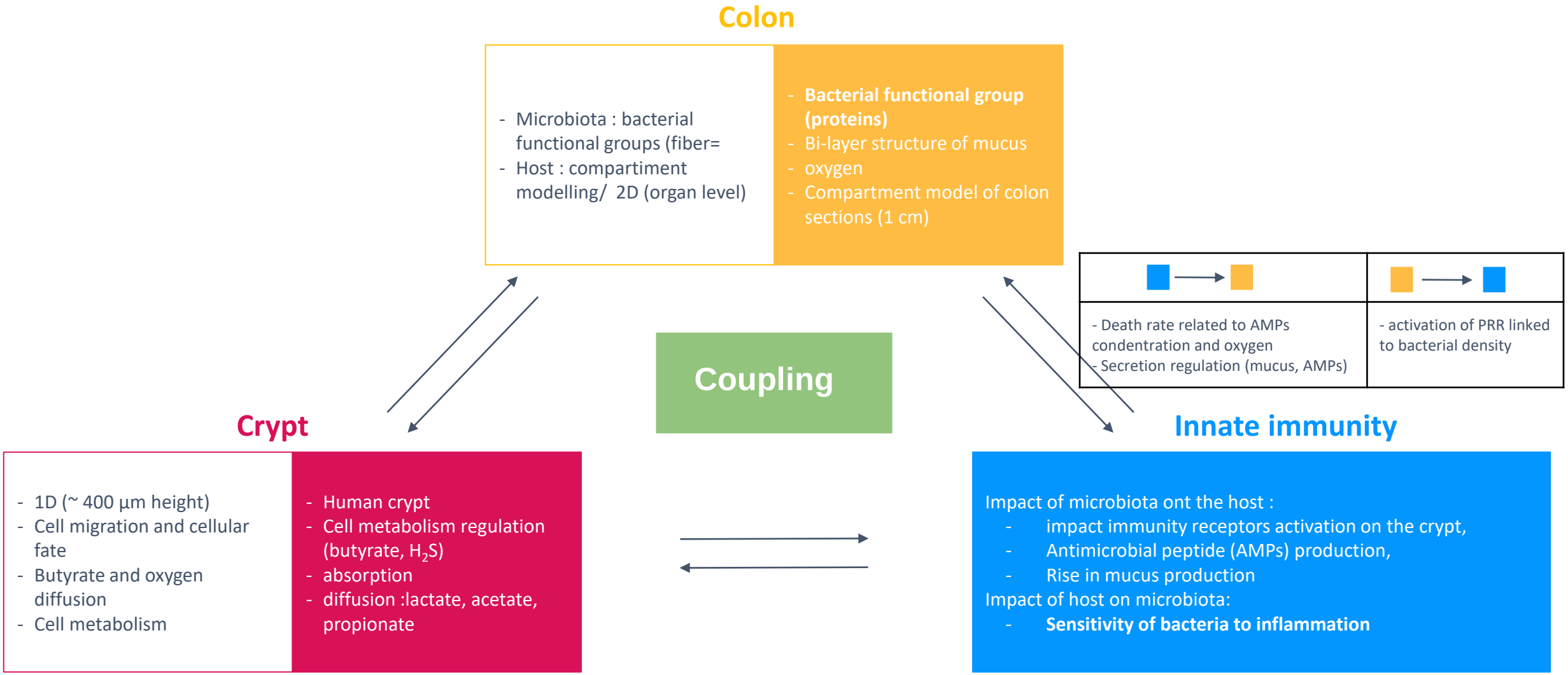




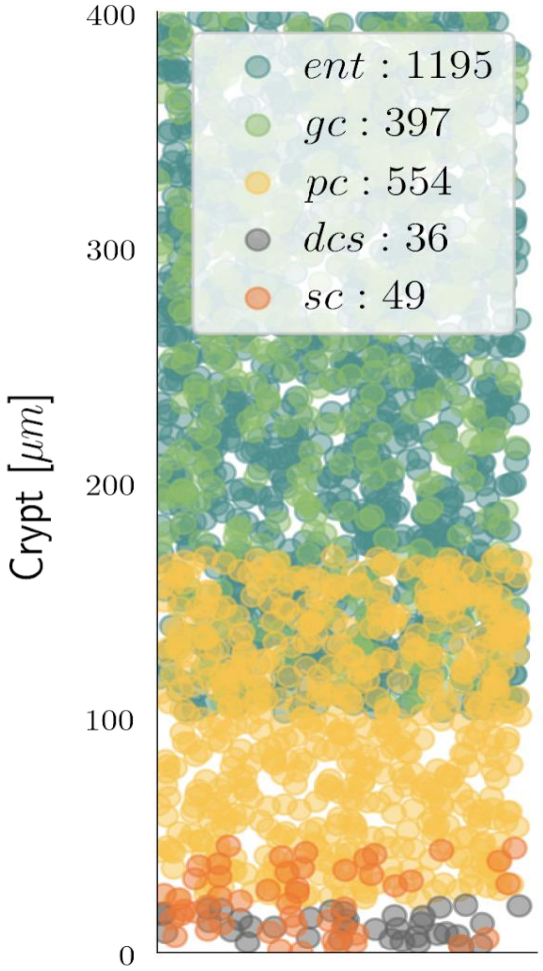




Putting it all together



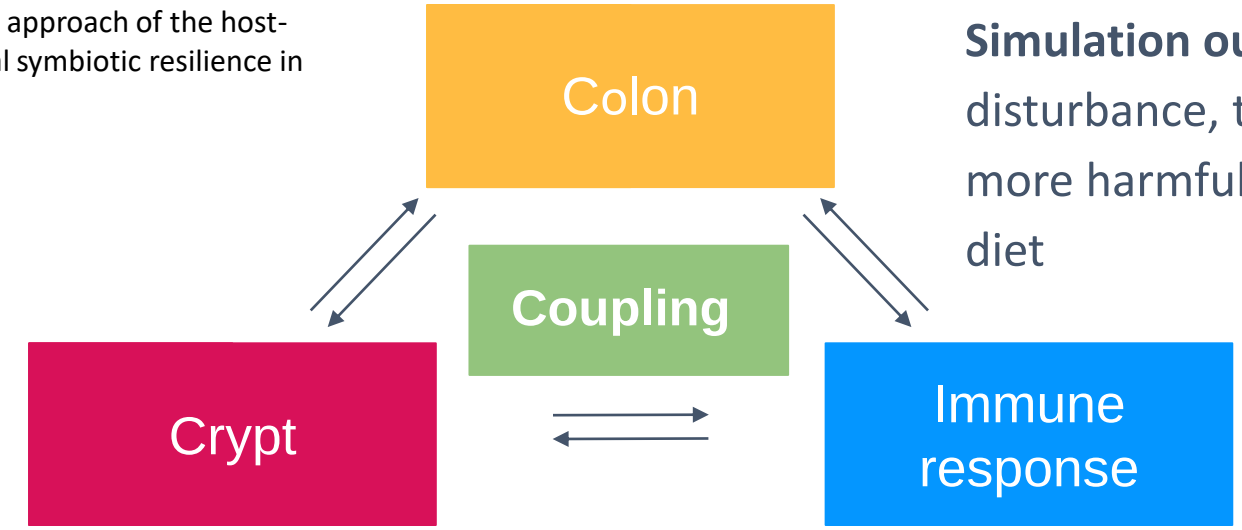
Validation on known biomarkers in the litterature



Biomarkers	References
Oxygen gradient	(Rivera-Chavez et al. 2017)
Concentrations and ratio acetate : propionate : butyrate in Lumen & crypt bottom	(Cummings et al., 1987) (Martin-Gallausiaux et al. 2021)
H_2S concentration in the lumen <1mM	(Blachier et al., 2021)
Cellular densities (space structure and cell counts)	(Bravo et al, 2013) (Darrigade et al. 2022)
Decreasing transit speed	
Composition and volume of bacterial populations	(Labarthe et al.,2018)
…	

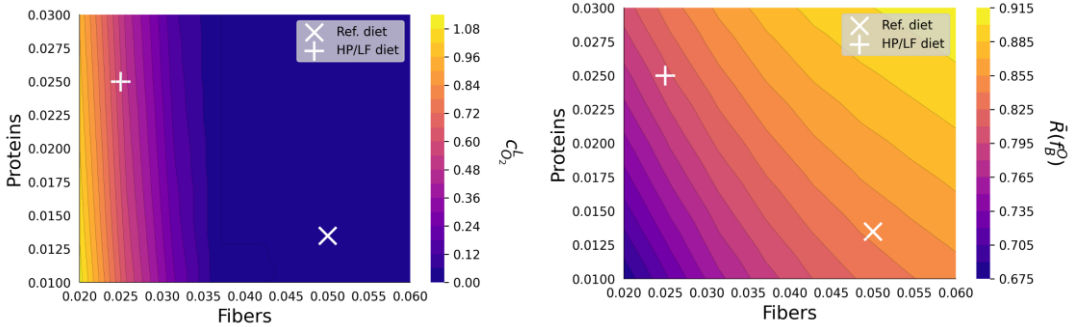
Simulating Diet impact on resilience

Haghebaert M et al. A mechanistic modelling approach of the host-microbiota interactions to investigate beneficial symbiotic resilience in the human gut, 2024. to appear in *JRSI*

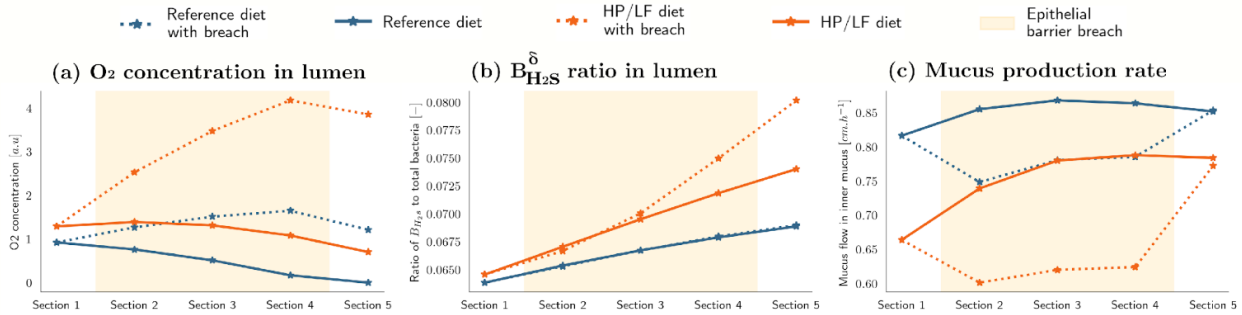


Simulation outcome : for an identical disturbance, the HP/LF diet induces more harmful effects than the reference diet

Impact of fiber/protein supply on the model steady state.



Impact of diet when simulting a breach in the epithlium



Impact of disturbances on microbiota: MAVA experiment

Inspired by « critical transition » theory:

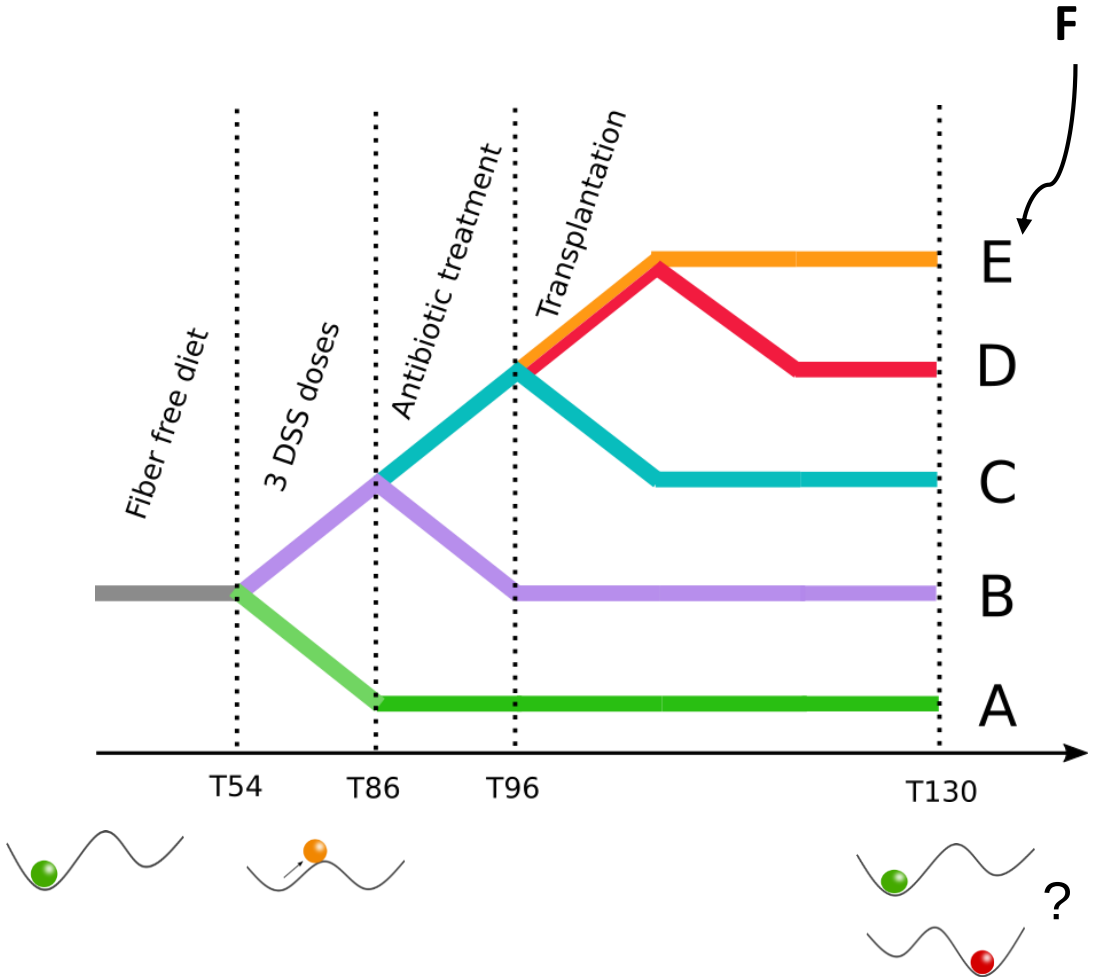
- Drive the host-microbiota system near a « critical point »

(disturbed diet, inflammation)

- Apply a strong perturbation (antibiotic)
- Group D & E: microbiota transplantation

Can we quantify the deviation of treated groups (B,C,D,E) from control and donnor groups (A,F)?

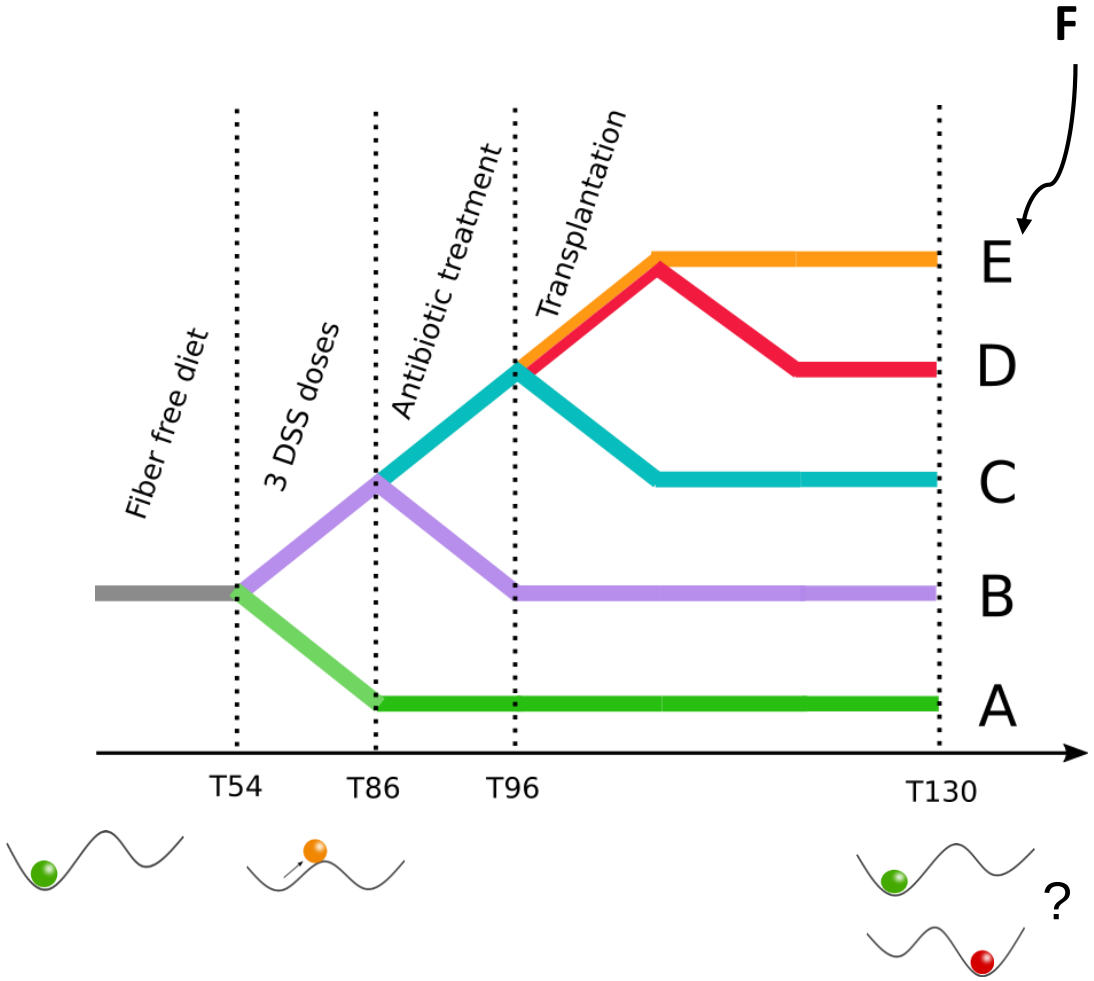
Do they come back to their initial composition?



Impact of disturbances on microbiota: MAVA experiment

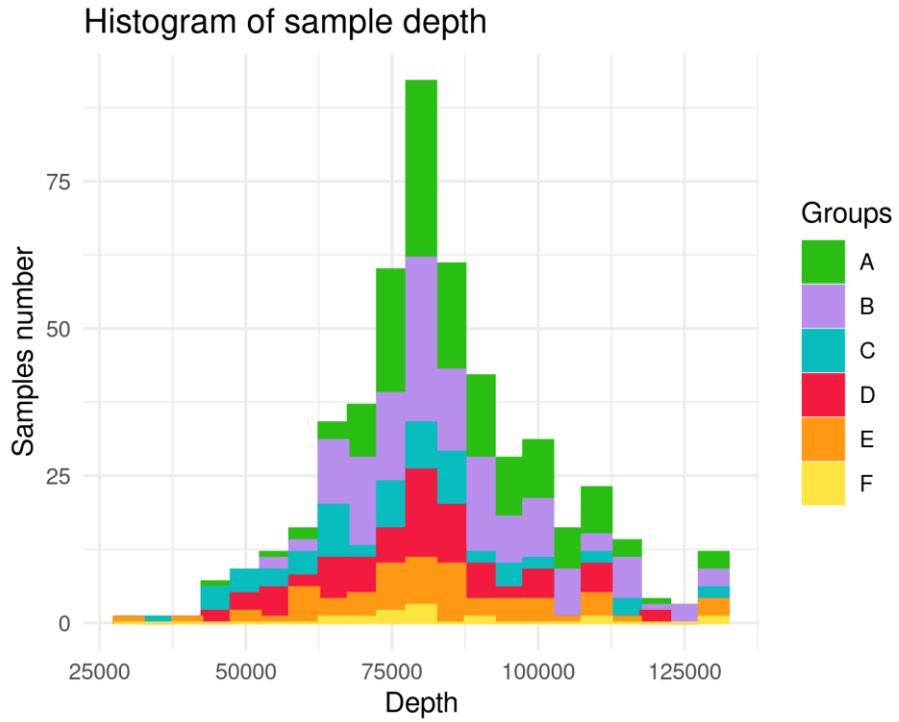
- Only ~10 rats per group
- 16 or 8 time points, missing data,
- ~ 800 bacterial species (OTU).
- Standard characterizations (Dakos et al.) not applicable

  - Built a statistical model of the control group
  - Compute the deviation of perturbed rats from this model.



A statistical model of the control group

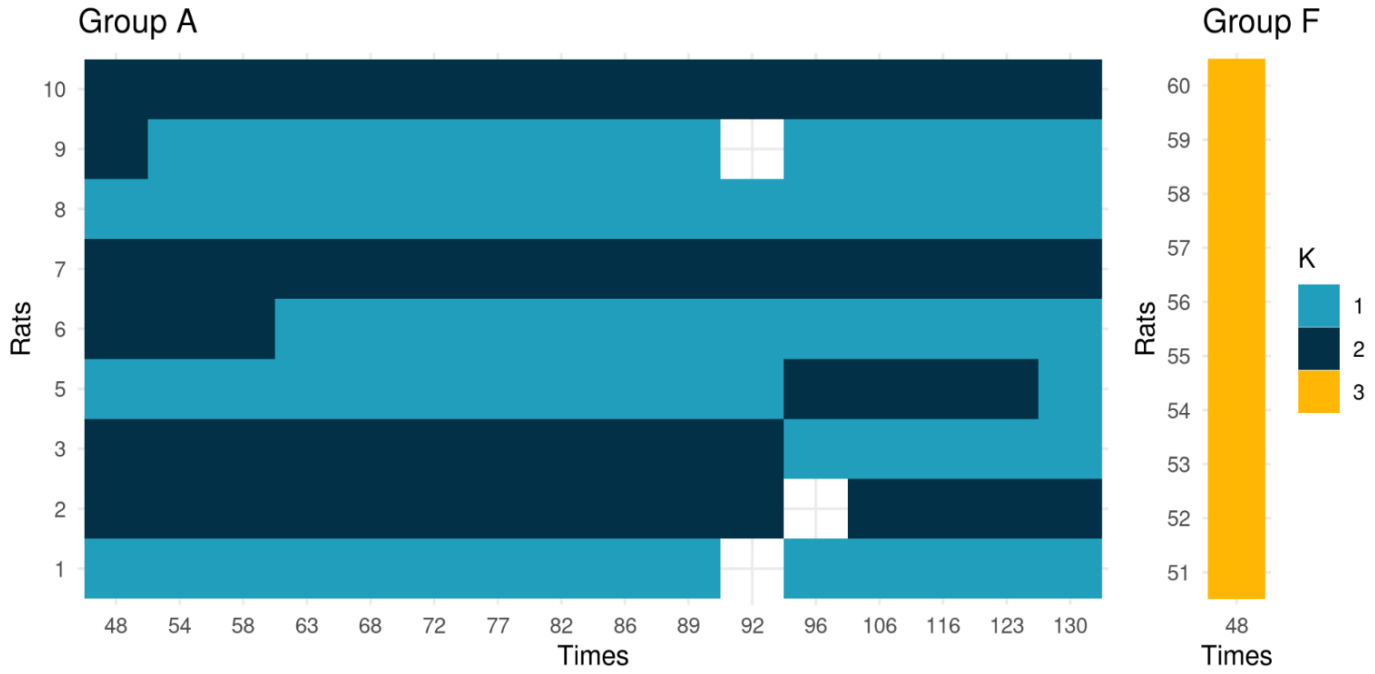
- Use of Dirichlet Multinomial Mixture (DMM) model (Holmes et al., 2012) :
  - Well adapted for bacterial count data
  - Sparse, overdispersed
  - Heterogeneous sample depths
  - R Package *DirichletMultinomial* (Morgan M, 2023)



A statistical model of the control group

- Selection and fit of DMM model on samples from group A et F (regardless of time structure)
- 3 components

k	π_k
1	0.497
2	0.437
3	0.066

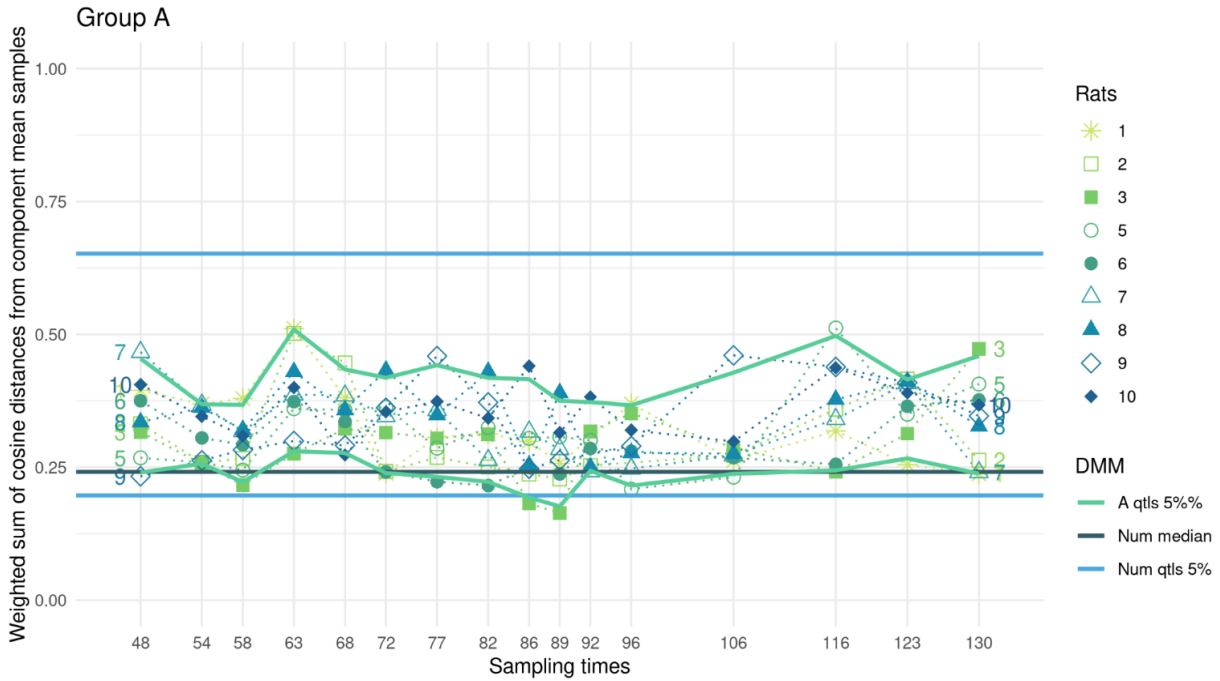


Sample deviation from « control » model

- Simulate model et compute the empirical mean per component (taking into account depth distribution)
- Compute the distribution of weighted cosine dissimilarity to the expected composition of each mixture component:

$$D_{DMM}(\boldsymbol{Y^J}) = \sum_{k=1}^{K} D_{cos}(\boldsymbol{Y^J}, \boldsymbol{E_k^J})\pi_k$$

- Visualization of experimental samples dissimilarities

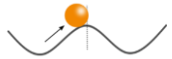


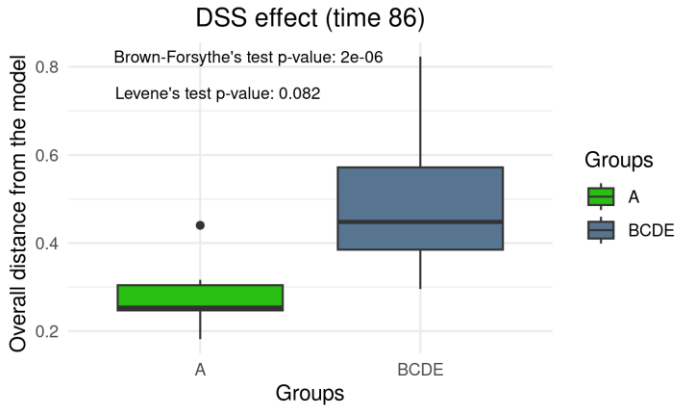
Dissimilarity analysis for treated rat groups

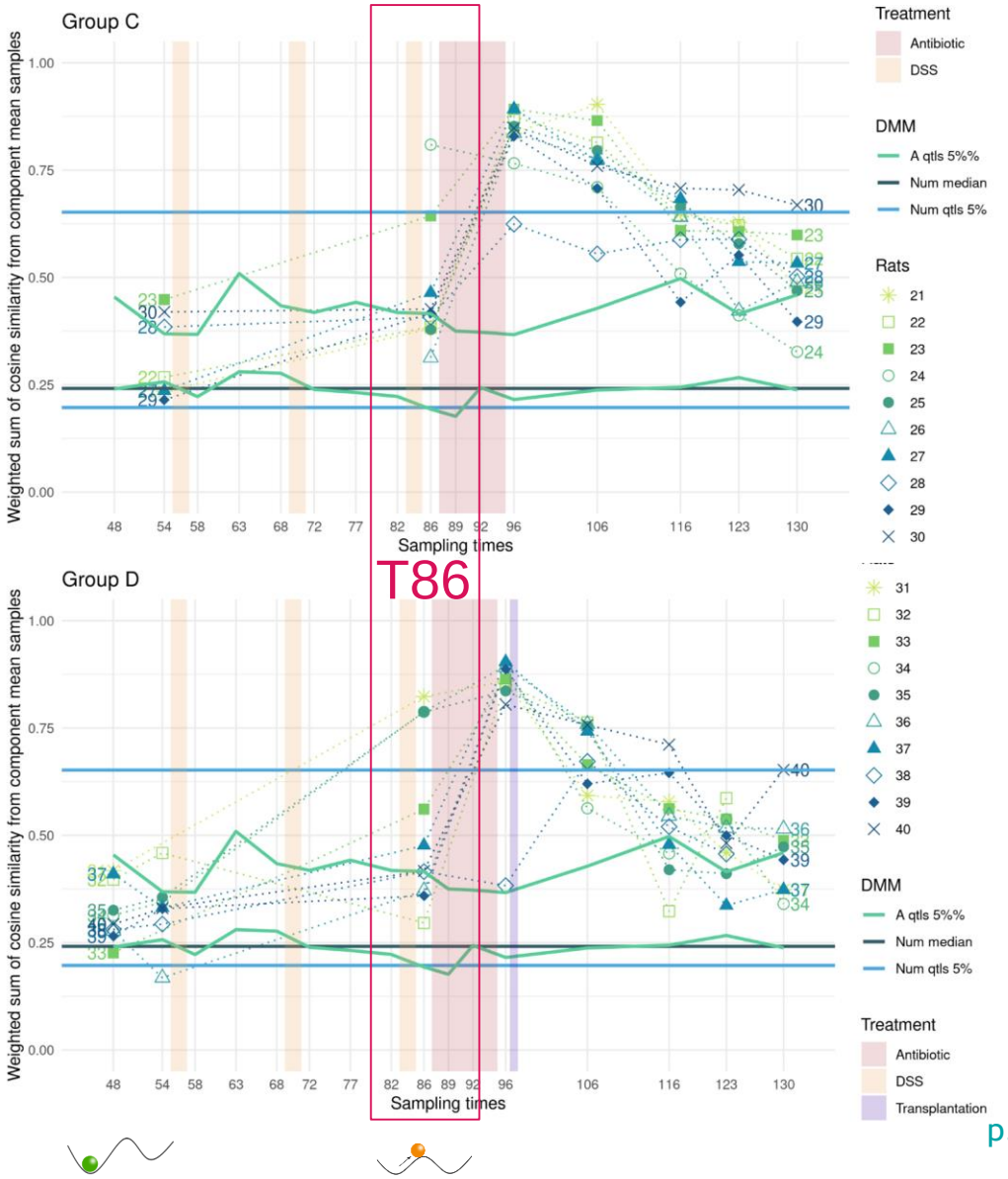
- Fraction of individual in the 95% **empirical** interquantile computed on group A samples on T130 :

Groupe	Pourcentage
B	70 %
C	20%
D	50%
E	44%

- Rise in dissimilarity variance on T86







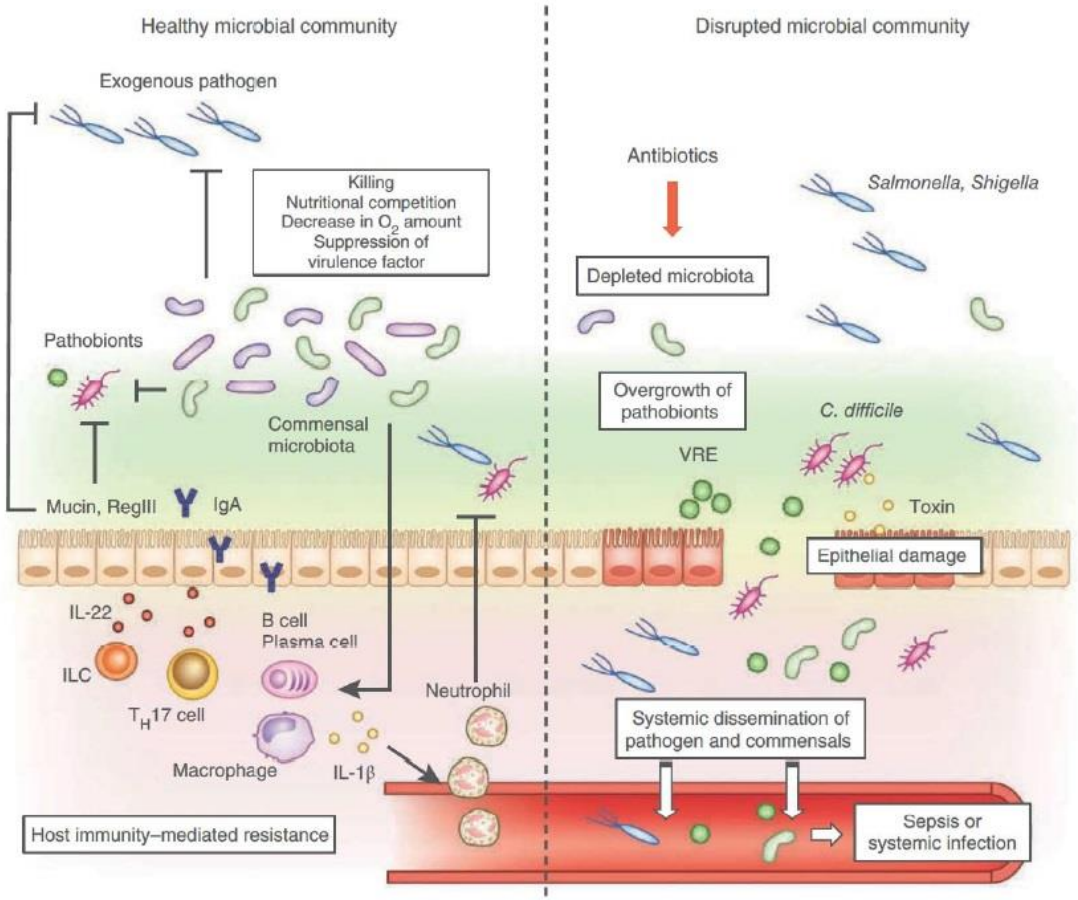
Pathogen strategies

- Pathogen and pathobionts are controlled by host barrier effect

- Chemical warfare
- Niche competition
- Mucus barrier & immune system control

- Main pathogens: Salmonella, Shigella, EHEC, VRE, C. Difficile

- Pathogen « objective » = reach the epithelium, translocate and induce a systemic infection

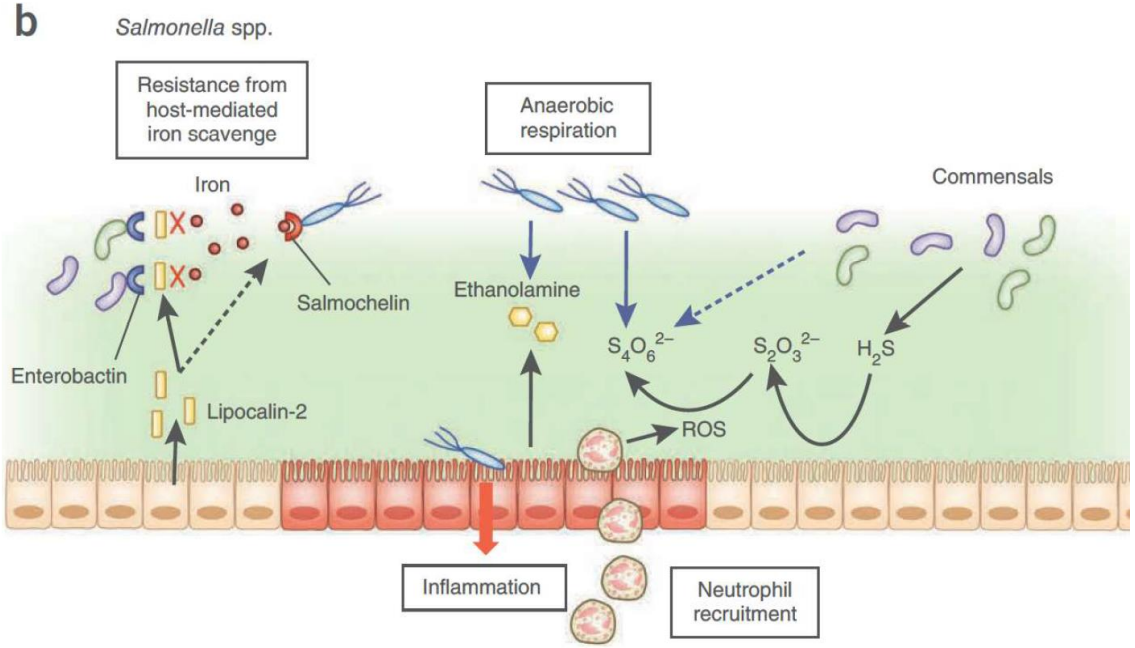


Kamada et al. (2013). Control of pathogens and pathobionts by the gut microbiota. *Nature immunology*

Pathogen strategies

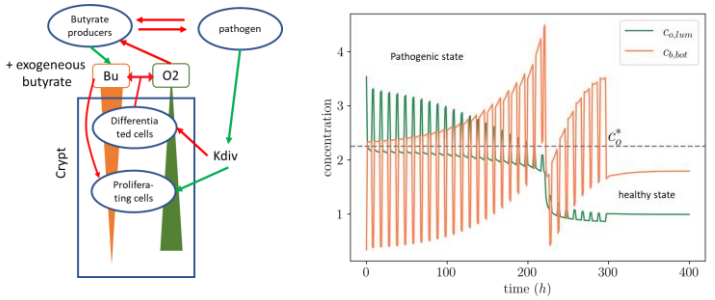
- Pathogen evolve and develop strategies to overcome commensal microbiota and host protection

- Use specific nutritional ressources (e.g. galactose, ethanolamine for EHEC)
- Localize to distinct niches (e.g. adhesion to inner mucus layer for C. Difficile)
- Escape host control on common ressource such as iron (Salmonella, EHEC, Klebsiella)
- Promote and exploit host inflammation to overgrowth competitors (Salmonella, E. Coli, C. Rodentium)



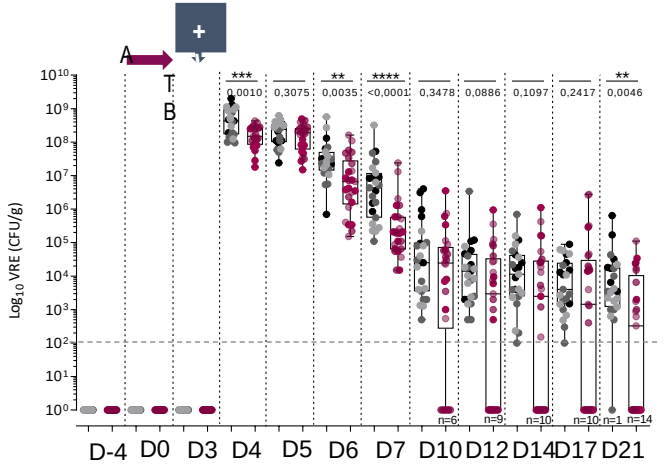
Ongoing work

- Model based simple simulations (eg C. Rodentium and hyperplasia in crypts), mouse crypt model,



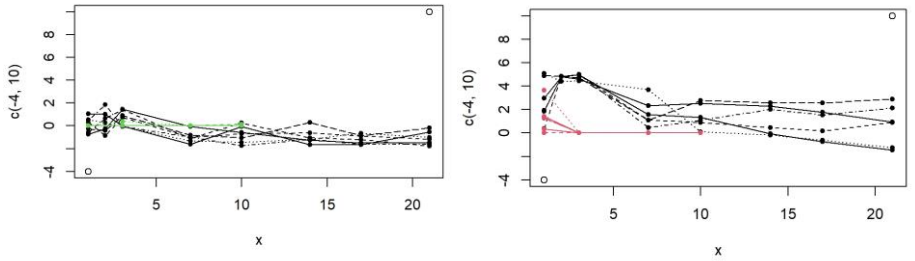
- Consortia design against VRE overgrowth (L. Rigottier and P. Serror, Micalis, INRAE)

mice experiments, VRE levels in un-treated (black-gray) or treated (light & dark pink) mice with A 7 species selected consortium.



- Understand heterogeneity in Salmonella infection in livestock for young individual (P. Velge and F. Kempf, ISP, INRAE)

poultry or here piglets, black = logCFU salmonella in feces, colored = Il1-beta cytokine level. Left « low shedders », right « high shedders ».



Main challenges

- How could we deal with microbiota richness in models?
  (e.g. Spragge et al. Science 2023, and work by K. Foster)
- A more evolutive point of view?
- Find the appropriate complexity level?
- Impact?
  - Consortia design
  - Food design
  - Transplantation
- Computational challenge