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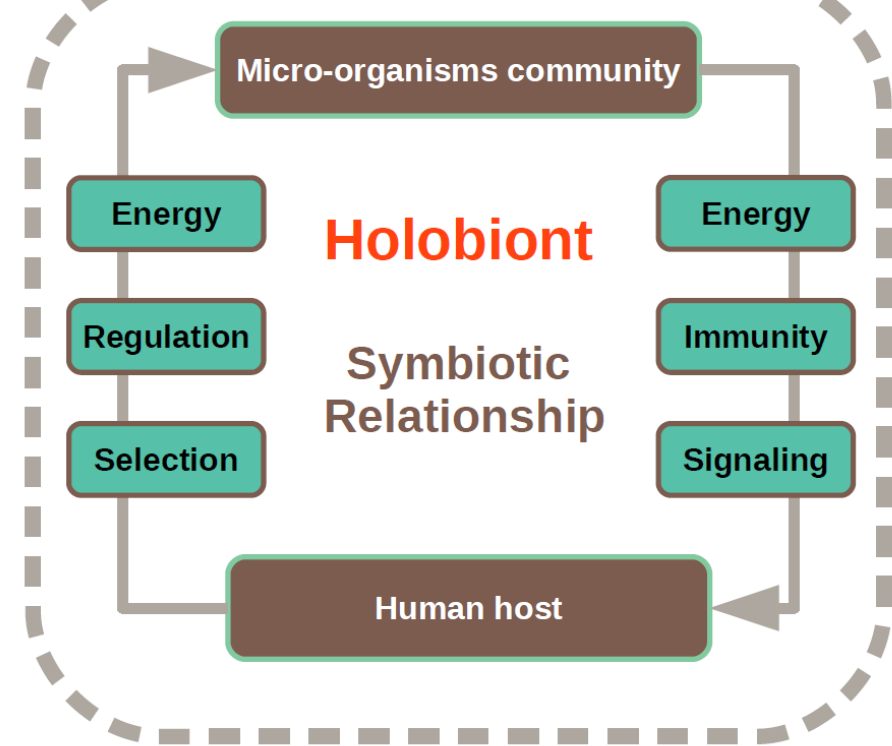
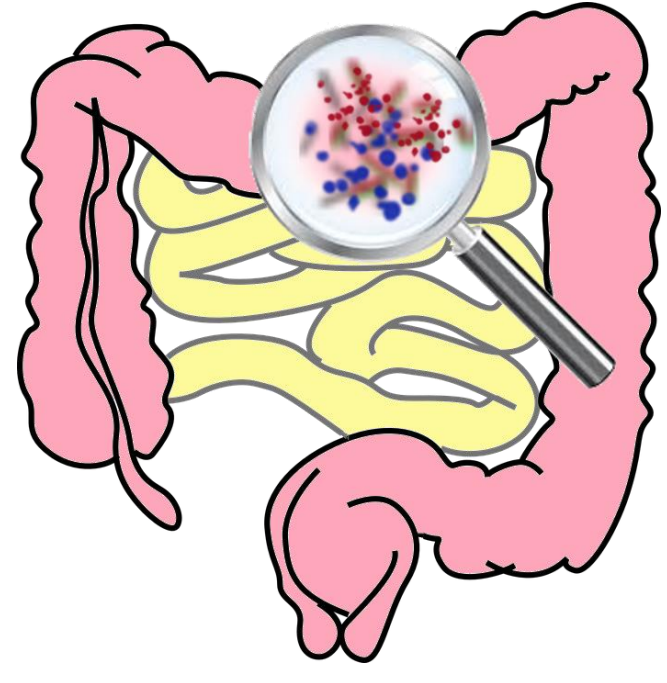
# A spatially structured model to investigate key drivers of the gut microbiota biogeography in humans

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## Colonic Microbiota



- Several thousands of microbial species
- Mostly located in the colon for man
- Main metabolic activity: dietary fiber fermentation, water production
- Impact on host health (animal, human) and performance (animal)

## Objectives

- Synthesize knowledge about the microbiota and its environment in a mathematical model
- Investigate the role of 4 key drivers of microbiota repartition and homeostasis in the colon: **fiber** level from host diet, **mucus** degradation, **viscosity gradients**, **peristalsis**

## Ongoing/future work

- Improve the description of bacterial population and host epithelium
- Adapt to other species: mouse, pig, chicken
- Simulate ecological phenomena, such as colonization, barrier effect against enteric pathogens (e. g. salmonella)

## A spatialized mixture model (El Bouthi et al. 2016; Labarthe et al., submitted)

**8 volume phases**, indexed by  $I_c = \{1, \dots, 8\}$ , liquid (l), mucus (m), dietary polysaccharides (pol), residues (r), 4 bacterial populations

•  $C_i$ : volume fraction of phase  $i$ ,  $\sum_{i \in I_c} c_i = 1$

**8 soluble metabolites (no volume)**, indexed by  $I_s = \{9, \dots, 16\}$ , monosaccharides, lactate, SCFA (acetate, propionate, butyrate), dissolved gas ( $H_2, CO_2, CH_4$ )

•  $C_j$ : concentration of metabolite  $j$ ,  $\sum_{i \in I_c} c_i = 1$

### 4 functional groups of bacteria (Munoz-Tamayo et al. 2010)

1 hydrolysis of fibers and mucus, sugar utilization  $\rightarrow$  SCFA, lactate,  $H_2$ ,  $CO_2$

2 lactate utilization  $\rightarrow$  SCFA,  $H_2$ ,  $CO_2$

3  $H_2$  utilization  $\rightarrow$  Acetate; 4  $H_2$  utilization  $\rightarrow$   $CH_4$

- growth limited by nutrient and volume availability
- growth, death, production, utilization rates gathered in source term  $F_i$  for population  $i$

### Chemotaxis

Keller-Segel model for chemotactic speed :  $v_{chem,i} = \nabla \Phi_i$

$$-\Delta \Phi_i = \sum_j \lambda_{ij} \left( c_j - \frac{1}{\pi R^2} \int_0^R r c_j(r) dr \right)$$

**Volume phases** ( $i = 1 \dots 8$ ): mass conservation volume fraction  $c_i$ , speed  $u_i = u + v_{chem,i}$

$$\partial_t c_i = F_i(c) - \text{div}(u_i c_i) + \text{div}(\sigma \nabla c_i)$$

boundary conditions: influx and epithelial excretion/absorption  $(-\sigma \nabla c_i + u_i c_i) \cdot \eta = \gamma_i$

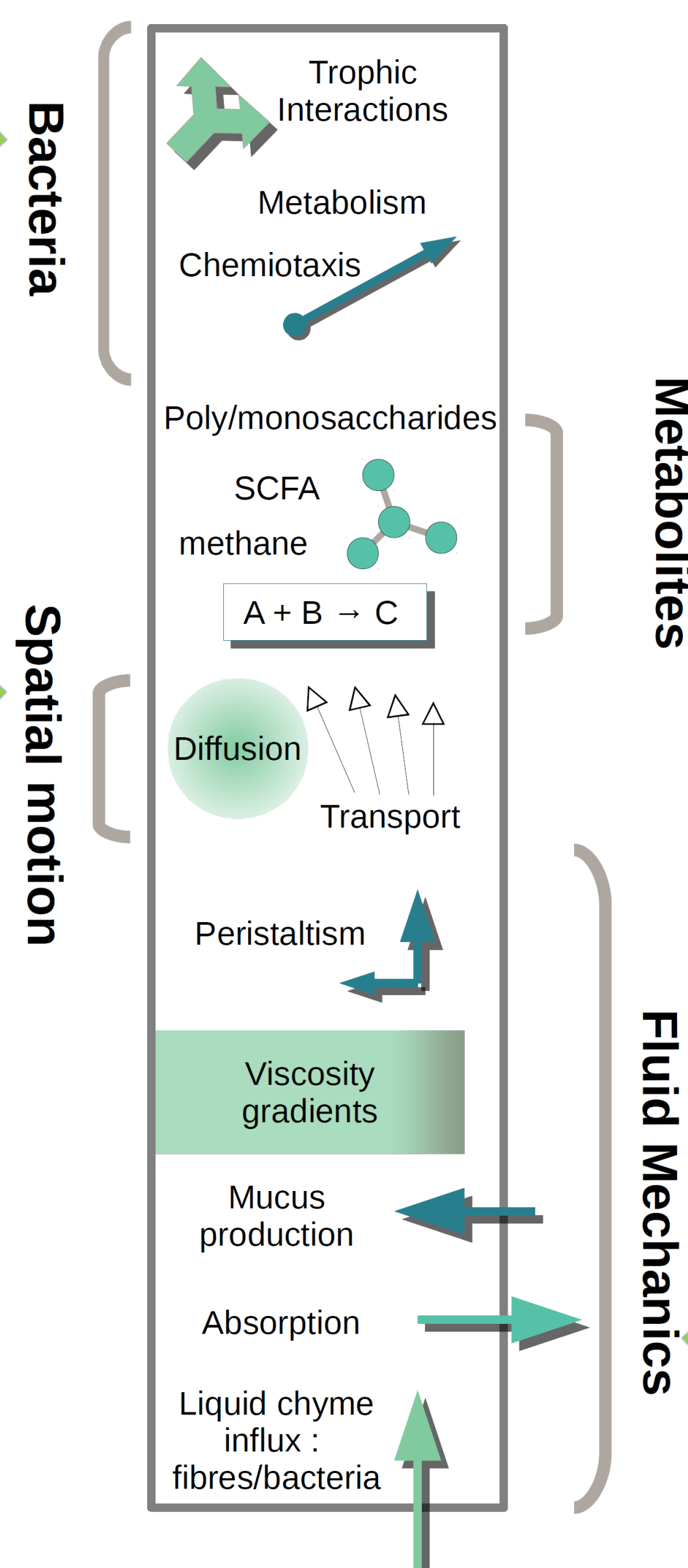
**Dissolved components** ( $j = 9 \dots 16$ ): same concentration  $c_j$  in all phases, speed  $\tilde{u} = \sum_{i \in I_c} u_i c_i$

$$\partial_t c_j = F_j(c) - \text{div}(\tilde{u} c_j) + \text{div}(\sigma \nabla c_j)$$

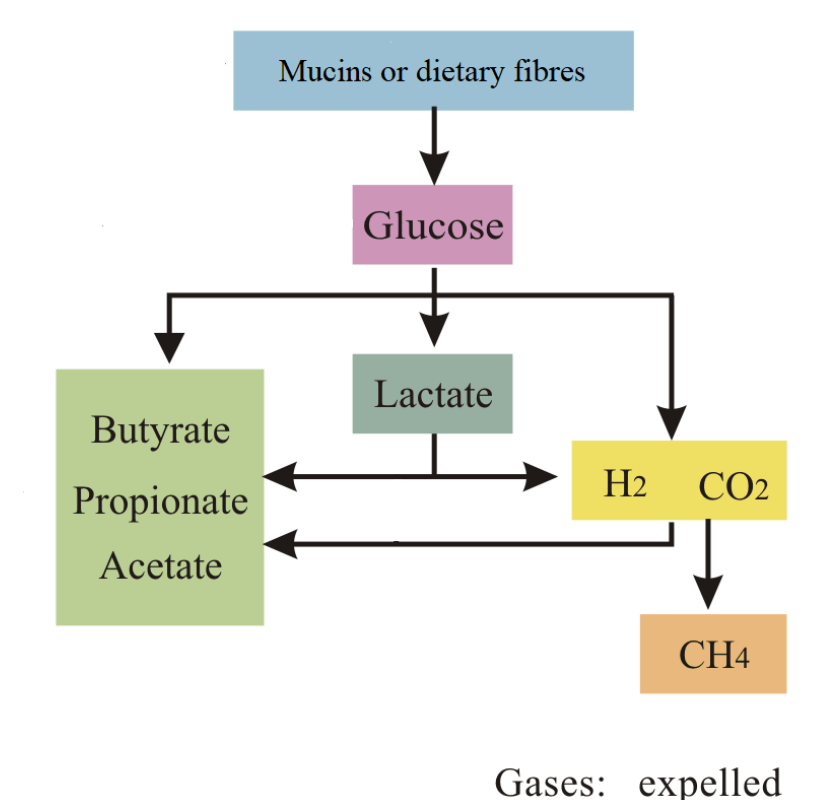
boundary conditions:  $(-\sigma \nabla c_j + \tilde{u} c_j) \cdot \eta = \gamma_j$

### Cylinder shape

radius  $R$ , length  $L$   
Coordinates  $(r, z)$



Reaction network for **Fiber and mucus** fermentation (Munoz-Tamayo et al. 2010)  
production, utilization rates gathered in source term  $F_i$  for metabolite  $i$



### Stokes model for the flow speed $u$ and pressure $p$

$$\nabla p - \text{div}(\mu(c)D(u)) = 0$$

where  $D(u) = \frac{1}{2}(\nabla u + \nabla u^T)$

**Variable viscosity  $\mu(c)$** : sigmoid function of mucus and non liquid phases

Volume conservation:  $\text{div}(u) = -\sum_{i \in I_c} \text{div}(v_{chem,i} c_i)$

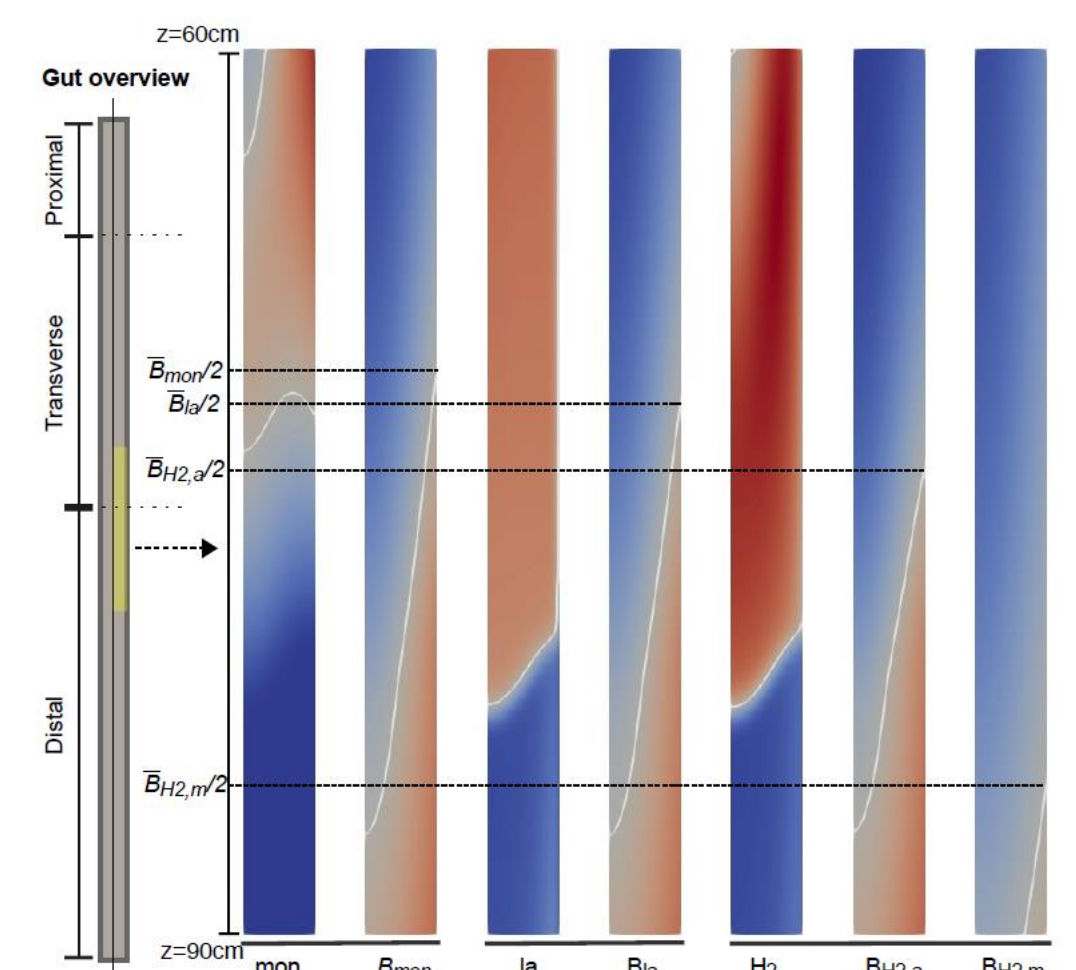
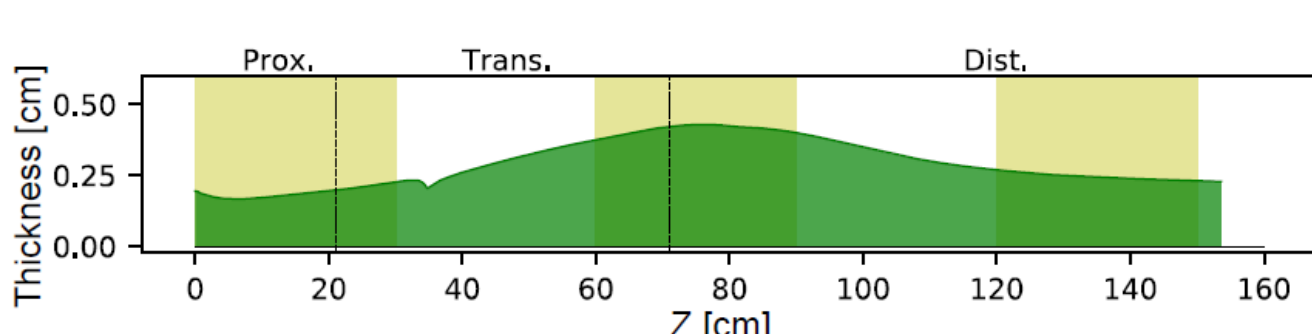
boundary condition  $u \cdot \eta = \sum_{i \in I_c} \gamma_i$  and  $u \cdot \tau = U_{per}$   
 $\eta$  unit normal vector,  $\tau$  unit tangent vector,  $U_{per}$  models peristalsis.

Asymptotic analysis using the aspect ratio  $\varepsilon = \frac{R}{L} \ll 1$  leads to simplification and efficient implementation with Matlab

## Results (Labarthe et al., submitted)

Reference model: peristalsis off, chemotaxis off

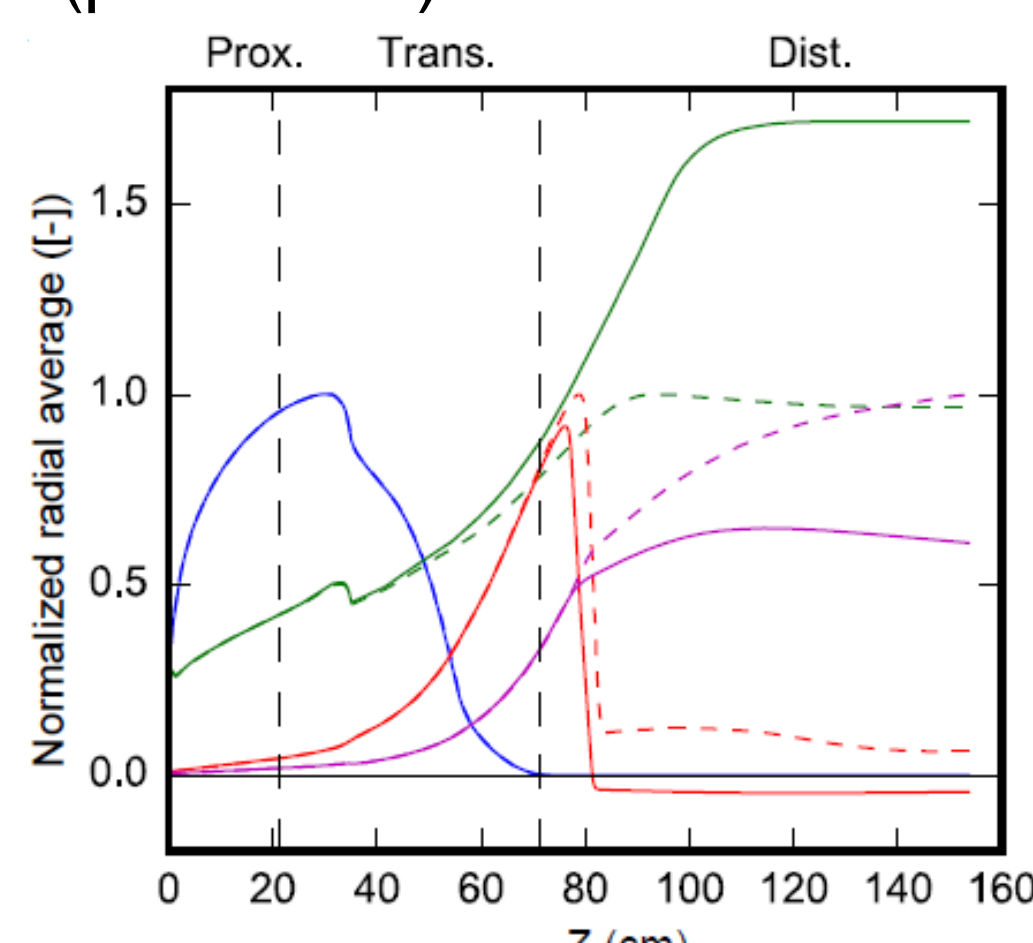
Maximum value of each output used to scale the graphs, output shown in dashed lines.



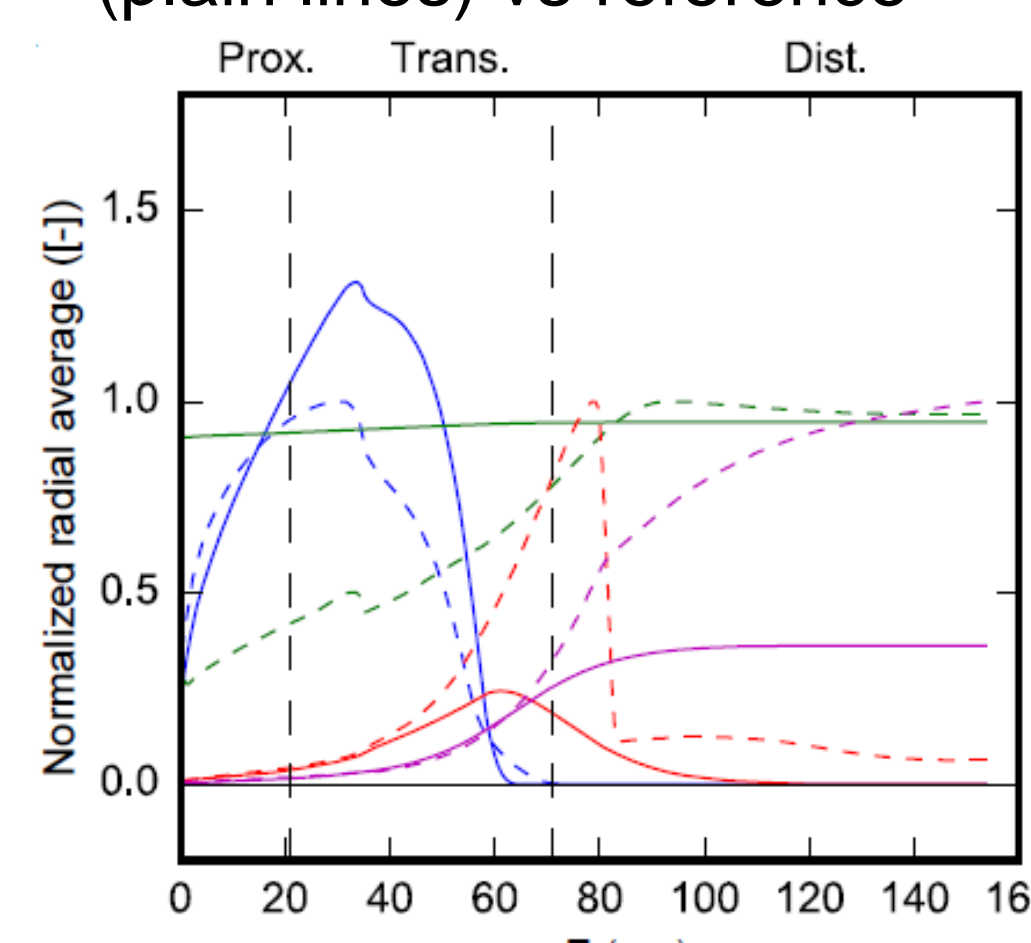
Sensible order of magnitude compared to literature

### Influence of key parameters: mucus degradation and mixture viscosity strongly influence the bacterial repartition and density

Left: without mucus degradation (plain lines) vs reference



Right: without viscosity gradient (plain lines) vs reference

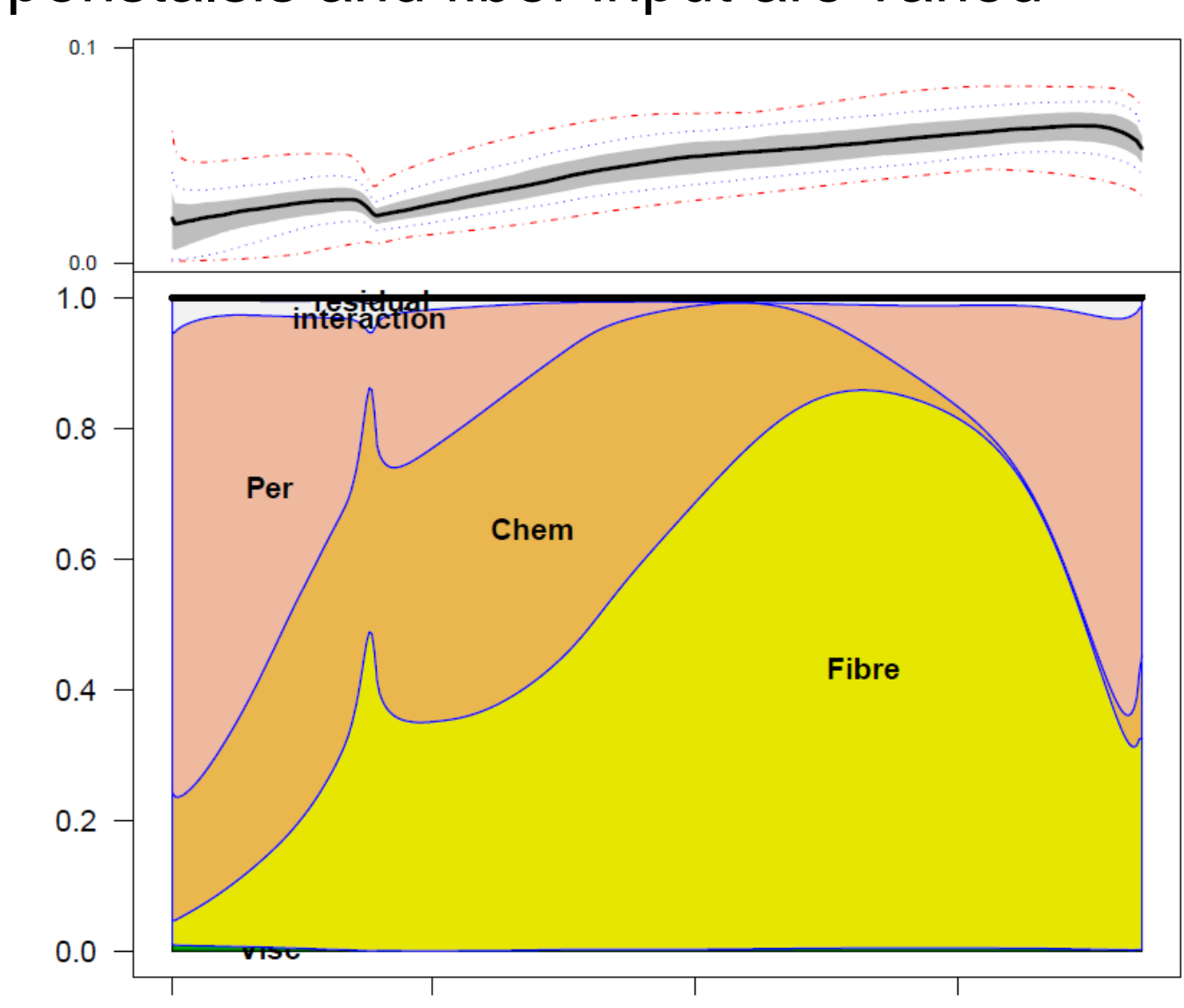


Polysaccharide density (blue), bacterial activity (red), Mixture viscosity (green), bacteria density (magenta)

### Global sensitivity analysis

of radial average bacterial density

First order Sobol indices computed with R package Multisensi; top: output distribution when the level of viscosity gradient, chemotaxis, peristalsis and fiber input are varied



The gut motility is preponderant in the proximal part, while the fiber levels is the main driver in the transverse and distal compartments.