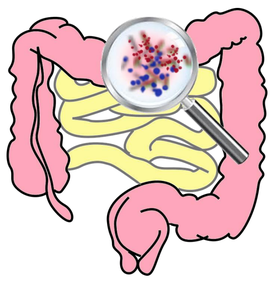
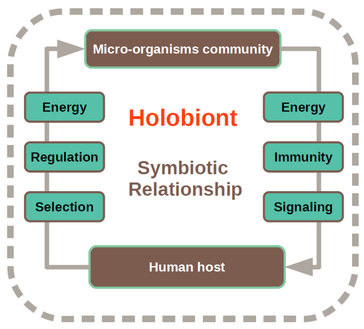
A spatially structured model to investigate key drivers of the gut microbiota biogeography in humans

S. Labarthe*, B. Polizzi**, T. Phan†, T. Goudon‡, M. Ribot† and B. Laroche*

*MaIAGE, INRA, Univ. Paris Saclay, France, **IMFT, Univ Paul Sabatier, Toulouse, France,
†MAPMO, Univ Orleans, France, ‡ LJAD, Univ Côte d'Azur, France.

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

- Synthetize 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 → SCFA, lactate, H2, CO2
2 lactate utilization → SCFA, H2, CO2
3 H2 utilization → Acetate; 4 H2 utilization → CH4

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

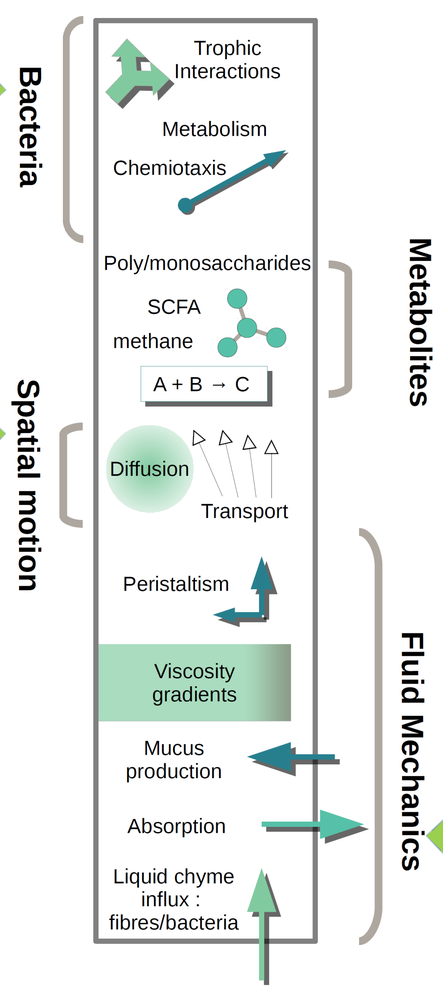
Chemotaxis

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

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

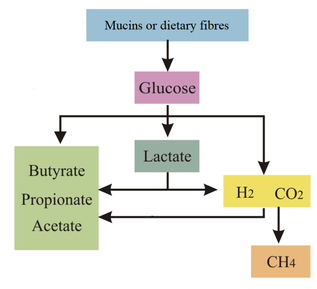
Cylinder shape

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



Volume phases ($i = 1 \dots 8$): mass conservation

volume fraction c_i, speed $u_i = u + v_{chem,i}$

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

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

Dissolved components (j = 9 ... 16): same

concentration c_j in all phases, speed $\tilde{u} = \sum_{i \in I_c} u_i c_i$

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

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

Stokes model for the flow speed u and pressure p

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

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

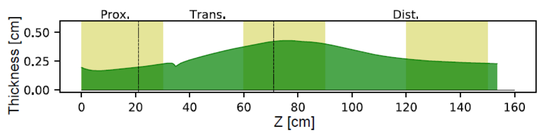
Variable viscosity $\mu(c)$: sigmoid function of mucus and non liquid phases
Volume conservation: $div(u) = -\sum_{i \in I_C} div(v_{chem,i} c_i)$

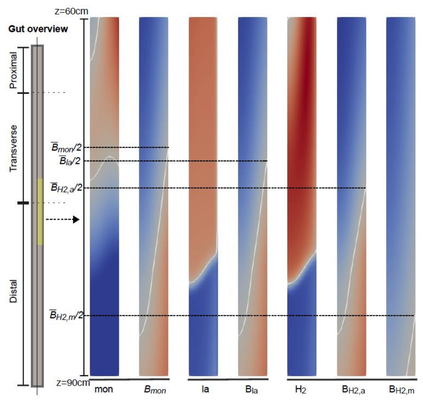
boundary condition $u \cdot \eta = \sum_{i \in I_C} \gamma_i$ and $u \cdot \tau = U_{per}$
η unit normal vector , τ unit tangent vector,
U_{per} models peristalsis.

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.

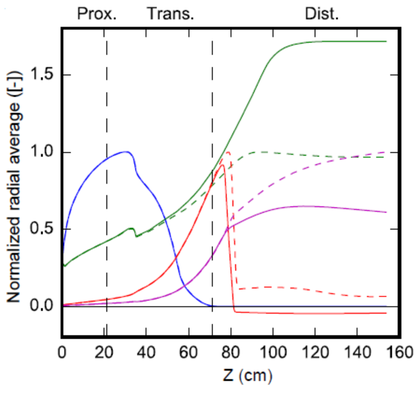




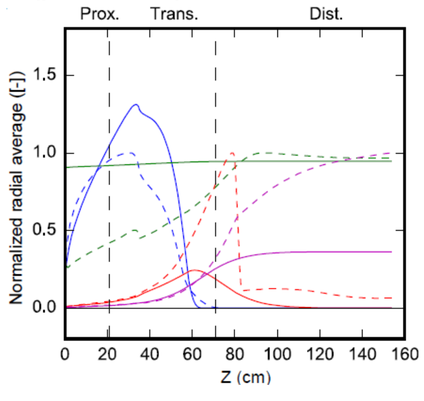
Sensible order of magnitude compared to literature

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

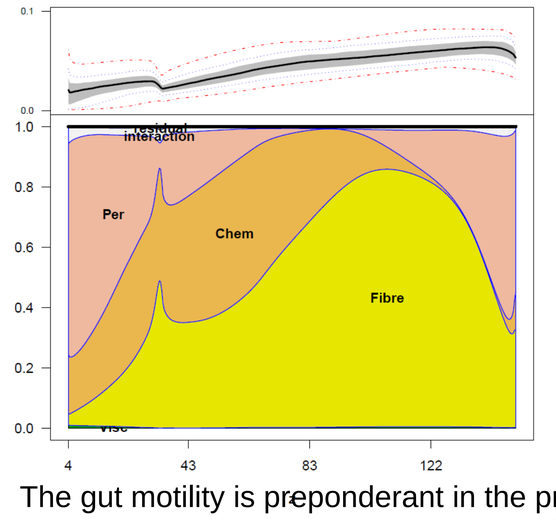


Polysaccharide density (blue), bacterial activity (red), Mixture viscosity (green), bacteria density (magenta)

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 compartiments.