Towards a Digital Twin of the Gut Microbiota: Multiscale Modeling and Host Interaction

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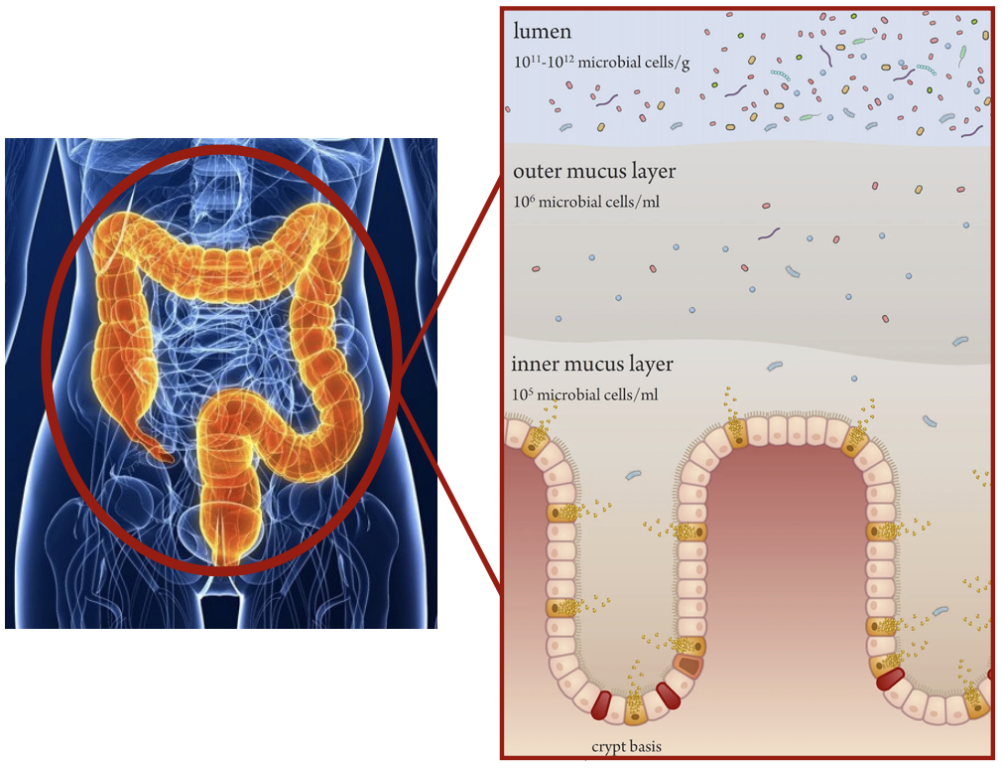
Outline

Biological context

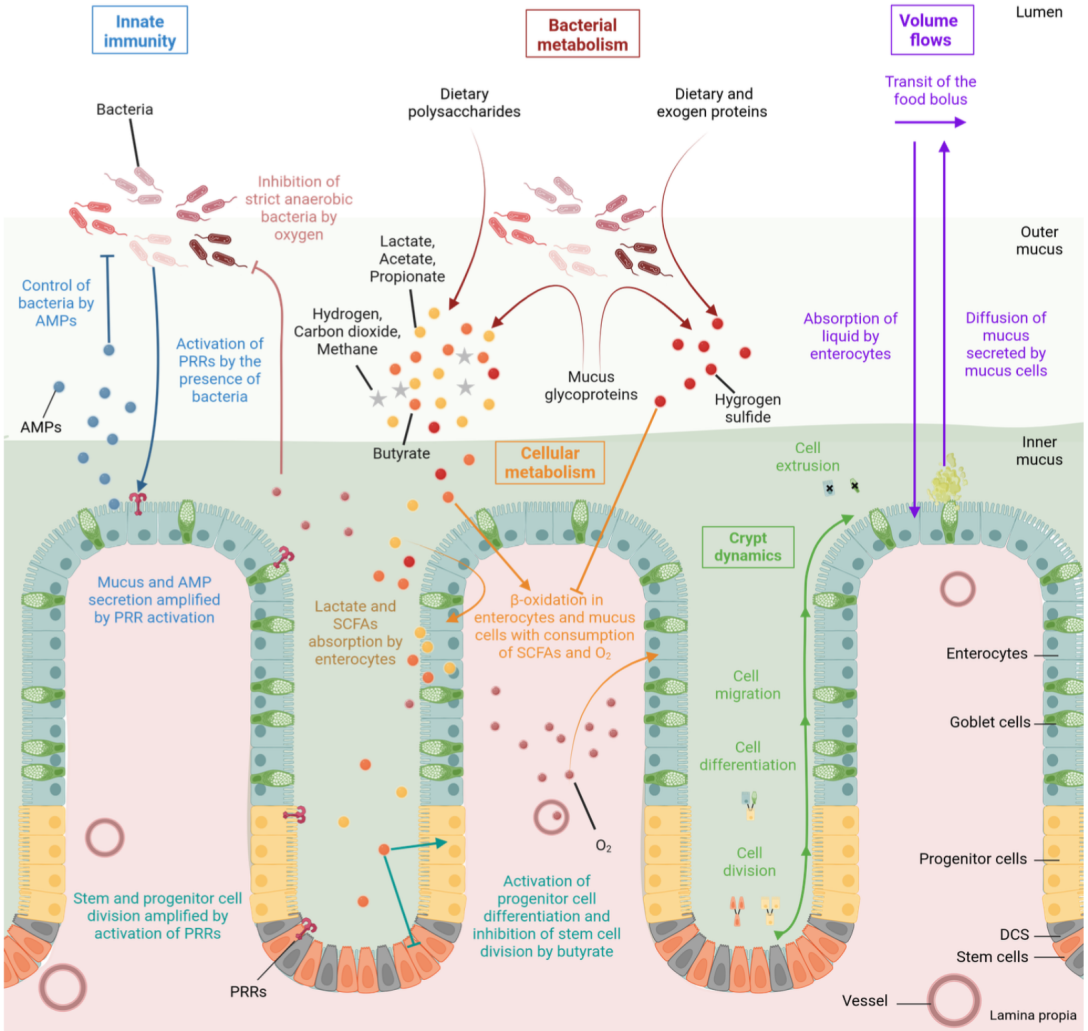
The gut microbiota:

- plays a vital role in many **physiological processes**,
- imbalance is linked to numerous **diseases**,
- hosts more than **500 bacterial species**.

→ Understanding host-gut microbiota interactions is crucial.



Magnified view of the colon showing lumen and double mucus layer.

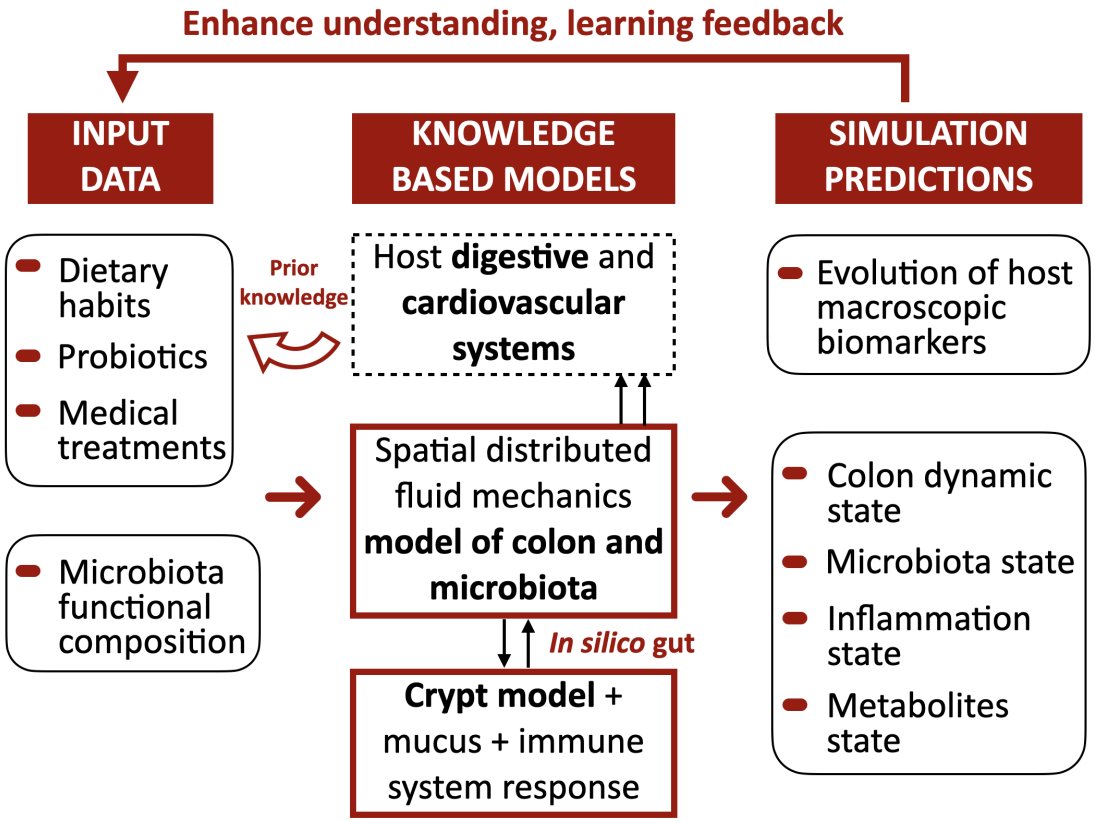


Biological representation of the main symbiotic mechanisms [1].

[1] *Haghebaert (2024)*.

Objective

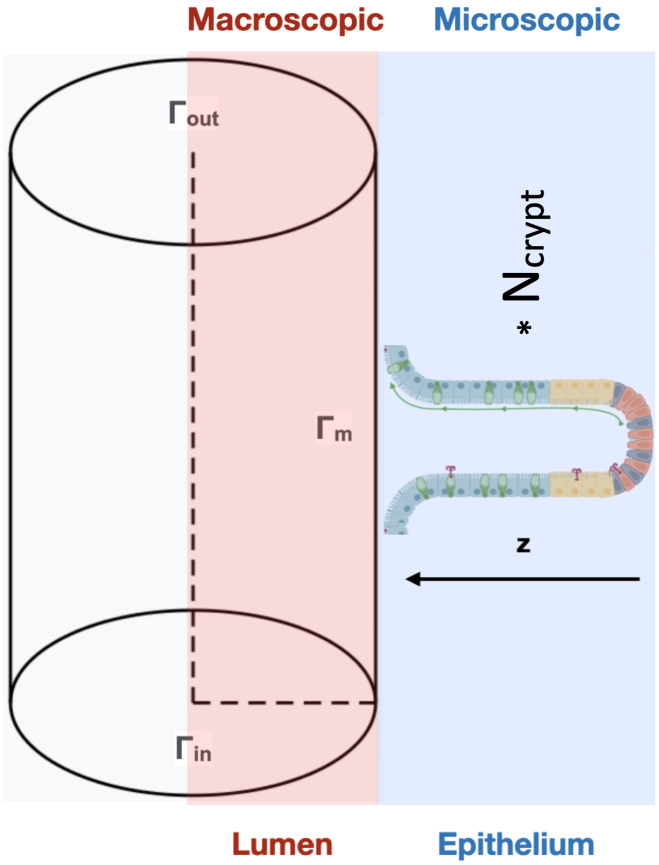
Establish a **computational framework** that integrates models at **different spatial scales** to simulate host-gut microbiota symbiosis:



Geometry

1. **Colon model** [2][3]:
   Cylindrical domain $\Omega_{colon} \subset \mathbb{R}^3$.
   By assuming **axisymmetry** in cylindrical coordinates, the problem is reduced to two dimensions.

2. **Crypt model** [4]:
   1D spatial domain $\Omega_{crypt} \subset \mathbb{R}$ with each cell located at $z \in [0, z_{max}]$.
   Assuming crypts are perfectly **synchronized**, only one crypt per section is modeled.



N_{crypt}: crypt density per surface unit.

[2] *Labarthe (2019)*, [3] *Muñoz-Tamayo (2010)*, [4] *Darrigade (2022)*.

Colon model

Mass conservation

$$\begin{aligned}\partial_t f_i - \operatorname{div}(\sigma_i \nabla f_i) + \operatorname{div}(f_i u_i) &= F_i \\ \left(-\sigma_i \nabla f_i + f_i u_i\right)\cdot n &= \gamma_{f_i}\end{aligned}$$ **SOLID**

$$\begin{aligned}\partial_t c_j - \operatorname{div}(\sigma_j \nabla c_j) + \operatorname{div}(c_j u) &= G_j \\ \left(-\sigma \nabla c_j + c_j u\right)\cdot n &= \gamma_{c_j}\end{aligned}$$ **DISSOLVED**

Stokes model

$$\begin{cases} -\nabla\cdot(\mu(f)\varepsilon(u)) + \nabla p = 0 & \text{in } \Omega_{colon} \\ \nabla\cdot u = 0 & \text{in } \Omega_{colon} \end{cases}$$

$$\begin{cases} u\cdot n = -U_{in} & \text{on } \Gamma_{\text{in}} \\ u_r = \sum_{i\in I_c}\gamma_{f_i} + U_{\text{per},r} & \text{on } \Gamma_m \\ u_z = U_{\text{per},z} & \text{on } \Gamma_m \\ (-pI + \mu(f)\varepsilon(u))\cdot n = 0 & \text{on } \Gamma_{\text{out}} \end{cases}$$

where $\varepsilon(u) := \frac{1}{2}\left(\nabla u + \nabla u^\top\right)$

$$\mu(f) = \max\left(\mu_m(f_{hm}(x,z,t)), \mu_l(f_l(x,z,t))\right)$$

- $\mu_m(f_m) = \mu_{m,\min} + (\mu_{m,\max} - \mu_{m,\min})\dfrac{f_{hm}^{\alpha_m}}{f_{hm,\text{thr}}^{\alpha_m} + f_{hm}^{\alpha_m}}$
- $\mu_l(f_l) = \mu_{l,\max} - (\mu_{l,\max} - \mu_{l,\min})\dfrac{f_l^{\alpha_l}}{f_{l,\text{thr}}^{\alpha_l} + f_l^{\alpha_l}}$

Hard Mucus Layer

$$\partial_t f_{hm} - div(\sigma_{hm}\nabla f_{hm}) + div(f_{hm}u_{hm}) = F_{hm} \quad \text{in } \Omega_{colon}$$

$$\begin{cases} \left(-\sigma_{hm}\nabla f_{hm} + f_{hm}u_{hm}\right)\cdot n = 0 & \text{on } \Gamma_{in} \\ \left(-\sigma_{hm}\nabla f_{hm} + f_{hm}u_{hm}\right)\cdot n = -0.2\cdot q_m \cdot N_{crypt}\cdot \overline{N_{gc}} & \text{on } \Gamma_m \\ \left(-\sigma_{hm}\nabla f_{hm} + f_{hm}u_{hm}\right)\cdot n = 0 & \text{on } \Gamma_{out} \end{cases}$$

$$u_{hm} = \begin{bmatrix} U_a \\ 0 \end{bmatrix}, \qquad U_a = A_{top} + \frac{A_{bot} - A_{top}}{1 + e^{-k(f_{hm} - thr)}}$$

- *thr* is the region of the domain where the concentration of *hm* is sufficient to prevent penetration

Soft Mucus Layer

$$\partial_t f_{sm} - div(\sigma_{sm}\nabla f_{sm}) + div(f_{sm}u) = F_{sm} \quad \text{in } \Omega_{colon}$$

$$\begin{cases} \left(-\sigma_{sm}\nabla f_{sm} + f_{sm}u\right)\cdot n = -U_{in}f_{sm,in} & \text{on } \Gamma_{in} \\ \left(-\sigma_{sm}\nabla f_{sm} + f_{sm}u\right)\cdot n = -0.8\cdot q_m \cdot N_{crypt}\cdot \overline{N_{gc}} & \text{on } \Gamma_m \\ \left(-\sigma_{sm}\nabla f_{sm} + f_{sm}u\right)\cdot n = f_{sm}u\cdot n & \text{on } \Gamma_{out} \end{cases}$$

- q_m is the **mucus production rate** per Goblet cell
- N_{gc} is the total **number of Goblet cells** per crypt
- 20% of the total mucus produced corresponds to *hm*, 80% to *sm*
- *n* is the unit **outward normal vector** to $\partial\Omega_{colon}$

Repulsive force

- A new **one-way repulsive force** between Bacteria and Hard Mucus was incorporated:

$$\partial_t f_i - \operatorname{div}(\sigma_i \nabla f_i) + \operatorname{div}(f_i \underline{u_i}) = F_i \quad \text{in } \Omega_{colon}$$

$$\begin{cases} (-\sigma_i \nabla f_i + f_i u_i) \cdot n = -U_{\text{in}} f_{i,\text{in}} & \text{on } \Gamma_{\text{in}} \\ (-\sigma_i \nabla f_i + f_i u_i) \cdot n = 0 & \text{on } \Gamma_m \\ (-\sigma_i \nabla f_i + f_i u_i) \cdot n = f_i u_i \cdot n & \text{on } \Gamma_{\text{out}} \end{cases}$$

$$u_i = u + \begin{bmatrix} U_r \\ 0 \end{bmatrix}, \quad U_r = C_{top} + \frac{C_{bot} - C_{top}}{1 + e^{-k(f_{hm} - thr)}}, \qquad i \in Bact$$

- This force was **extended** to **all solid** components except mucus and liquid.

Coupling Colon-Crypt

COLON MODEL

$$\left(-\sigma_{AMPs}\nabla c_{AMPs} + c_{AMPs}u\right)\cdot n \quad = -q_{AMPs}\cdot N_{crypt}\cdot \overline{N_{ent}}$$

- q_{AMPs} is the diffusion of AMPs per Enterocyte

$$\left(-\sigma_{hm}\nabla f_{hm} + f_{hm}u_{hm}\right)\cdot n \quad = -0.2\cdot q_m\cdot N_{crypt}\cdot \overline{N_{gc}}$$

$$\left(-\sigma\nabla f_{sm} + f_{sm}u\right)\cdot n \quad = -0.8\cdot q_m\cdot N_{crypt}\cdot \overline{N_{gc}}$$

$$\left(-\sigma_{O_2}\nabla c_{O_2} + c_{O_2}u\right)\cdot n = -q_{O_2}\cdot c_{O_2}^{top}\cdot N_{crypt}$$

- $c_{O_2}^{top}$ is the oxygen concentration at the top of the crypt
- q_{O_2} is the oxygen diffusion per crypt.

$$\left(-\sigma\nabla f_l + f_l u\right)\cdot n \quad = q_l\cdot N_{crypt}\cdot fl\cdot \overline{N_{ent}}$$

- q_l is the water pumping per Enterocyte cell
- $\overline{N_{ent}}$ is the total number of Enterocyte cells in one crypt

$$\left(-\sigma_j\nabla c_j + c_j u\right)\cdot n = q_j\cdot N_{crypt}\cdot \overline{N_{ent}}\cdot c_j$$
$$\tilde{c_j}(Z_{max},t) = c_j(t) \qquad \text{in } \Omega_{Crypt}$$

- $j \in \{la, ac, pro, but, H_2S\}$
- $\tilde{c_j}$ is the concentration inside the crypt model

CRYPT MODEL [1]

Process of Cell Migration

$$\begin{cases} \partial_t\rho_l - W\partial_z(\phi(z)\rho_l\partial_z\rho) & = H_l(\rho_{sc},\rho_{pc},D\times\rho,z), \\ \rho_l(0,t) & = \rho_l^{bot}, \\ \partial_z\rho_l(Z_{max},t) & = 0, \end{cases}$$

where $l \in$ {sc, dcs, pc, gc, ent} is the cell type.

Time Evolution of Oxygen

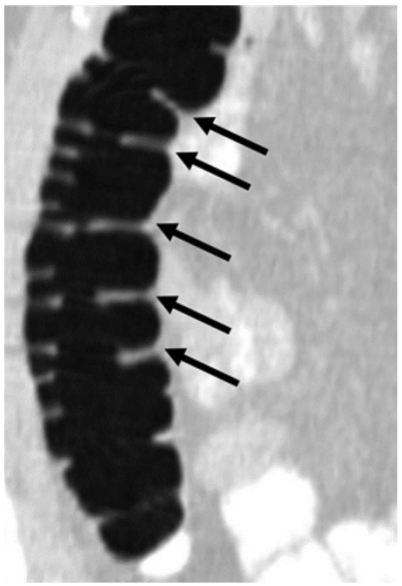
$$\begin{cases} \partial_t c_{O_2} - \sigma_{O_2}\partial zz c_{O_2} = -\sum_{i\in\mathcal{M}} s_{O_2,i}\beta(c_i, c_{O_2}, c_{\text{but}}, c_{H_2S}^L, \rho_{gc}+\rho_{ent}), \\ c_{O_2}(0,t) = c_{O_2}^{\text{bot}}, \\ \partial_z c_{O_2}(Z_{\max},t) = 0. \end{cases}$$

[1] *Haghebaert (2024).*

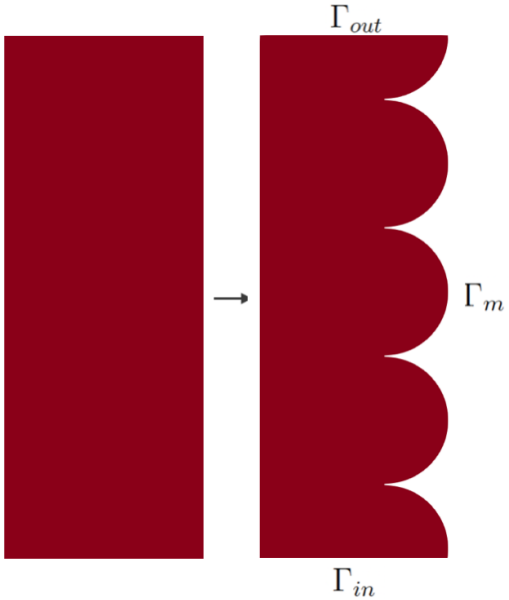
New Geometry

A **new geometrical representation** [5] of the colon was incorporated:

- the transition was handled, ensuring consistency and coherence,
- the model was adapted to the **non-straight lateral wall** Γ_m by recalibrating key parameters.



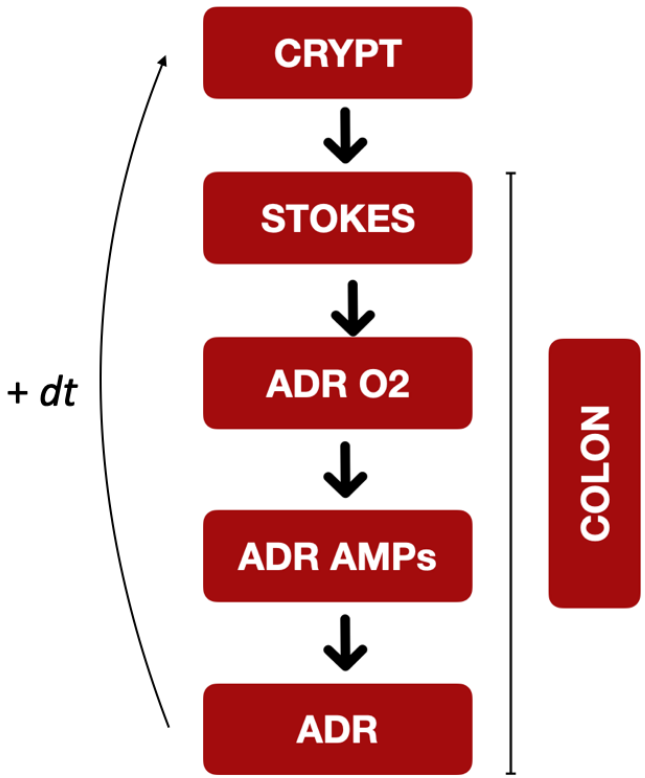
Colon with five haustral folds (black arrows) [5].



Mesh obtained using Salome and Gmsh softwares.

[5] *Thompson (2016).*

Resolution scheme



Computational scheme for each time step:

1. The **crypt** model is solved.
2. The **colon** model is solved.

   ADR equations for *AMPs* and O_2 are solved **separately** because:
   - their **concentrations** are orders of magnitude **higher** than those in the lumen,
   - they are **neither produced nor consumed** during reactions.

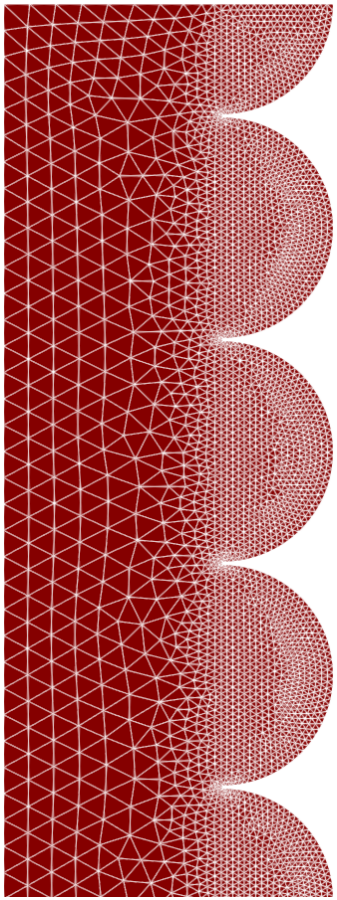
→ This separate resolution approach enhances convergence.

Numerical methods

The system of equations has been discretized and solved using the **FEniCS** framework [6].

Numerical methods used:

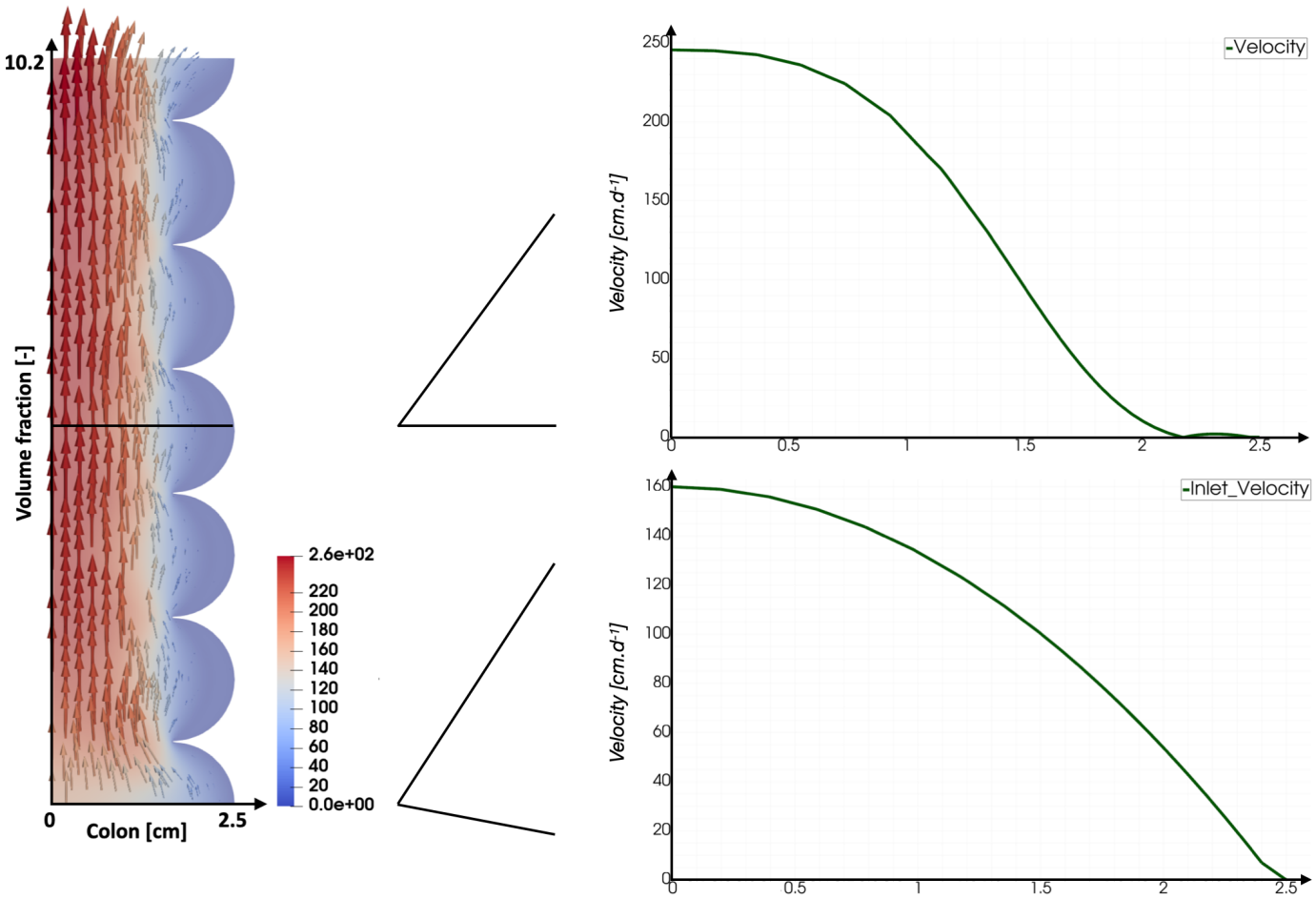
- *Crypt model*: **Explicit Kinetic Diffusive (EDK) Scheme**.
  A regular discretization is adopted [1].
- *Colon model*: **iterative Krylov solver** with preconditioners.
  A **triangular mesh** with **local refinement** is adopted.



Colon mesh.

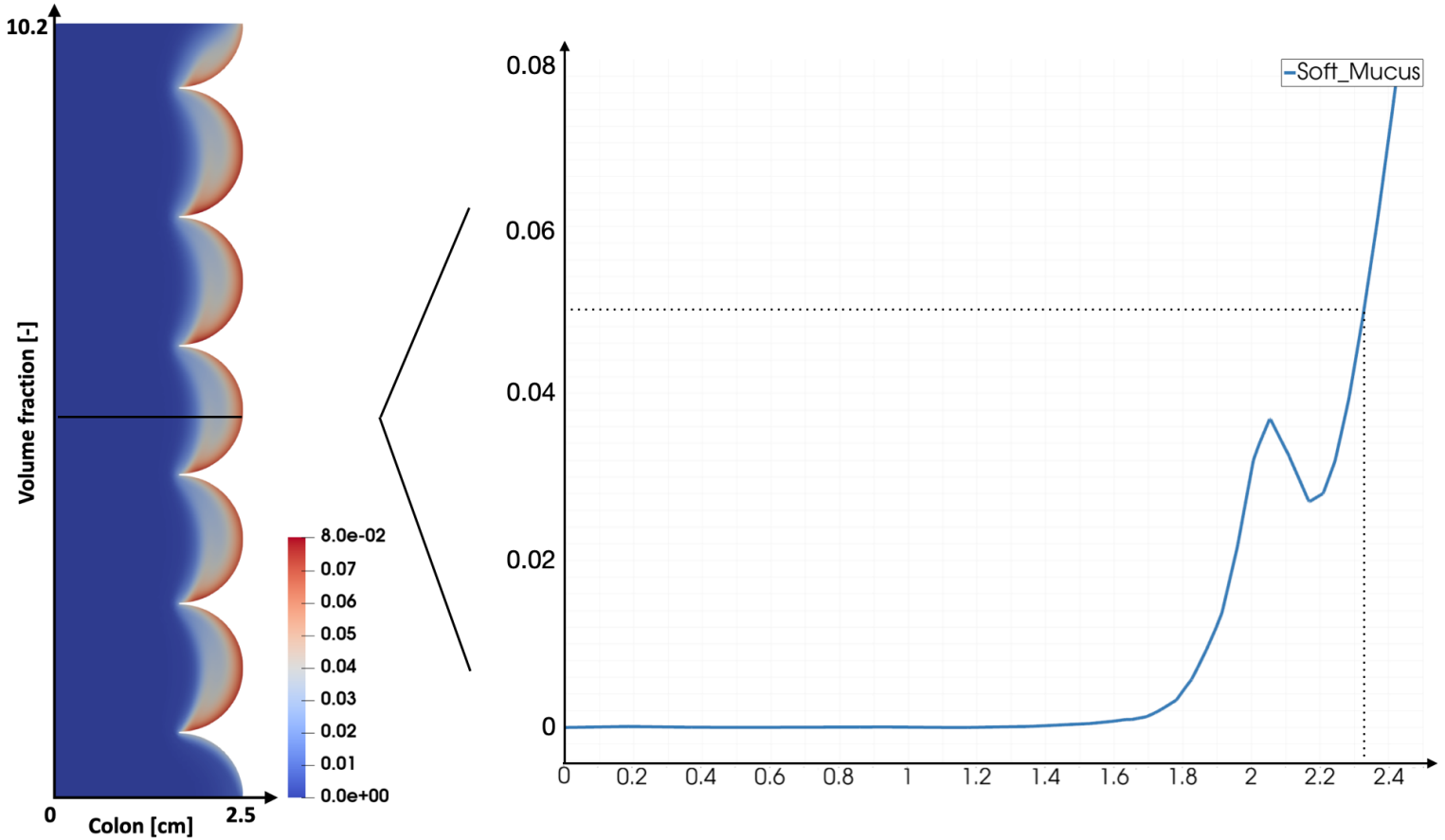
[1] *Haghebaert (2024)*, [6] *Baratta (2023)*.

Velocity



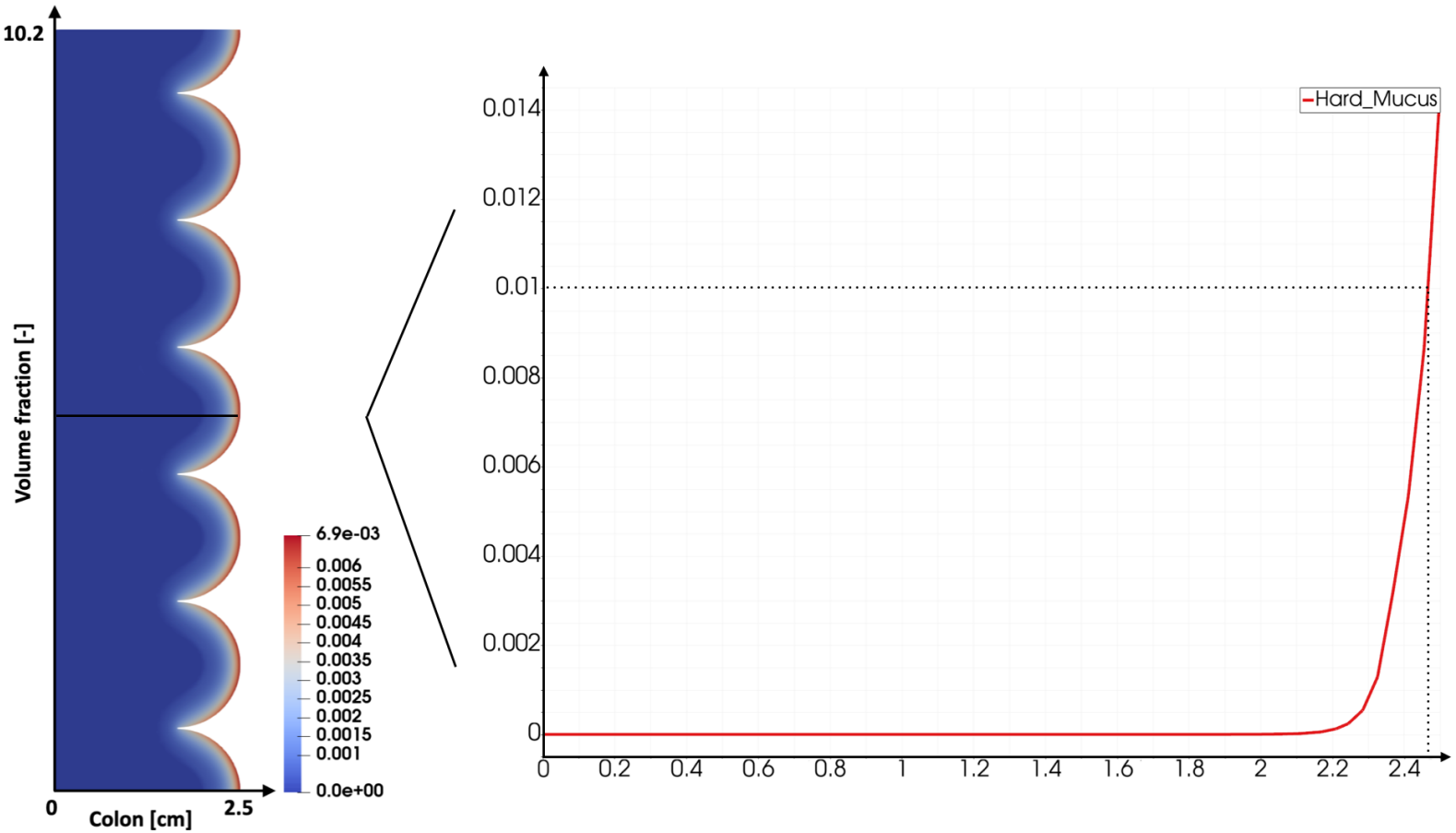
Velocity with vector field representing flow direction and radial sections.

Soft Mucus



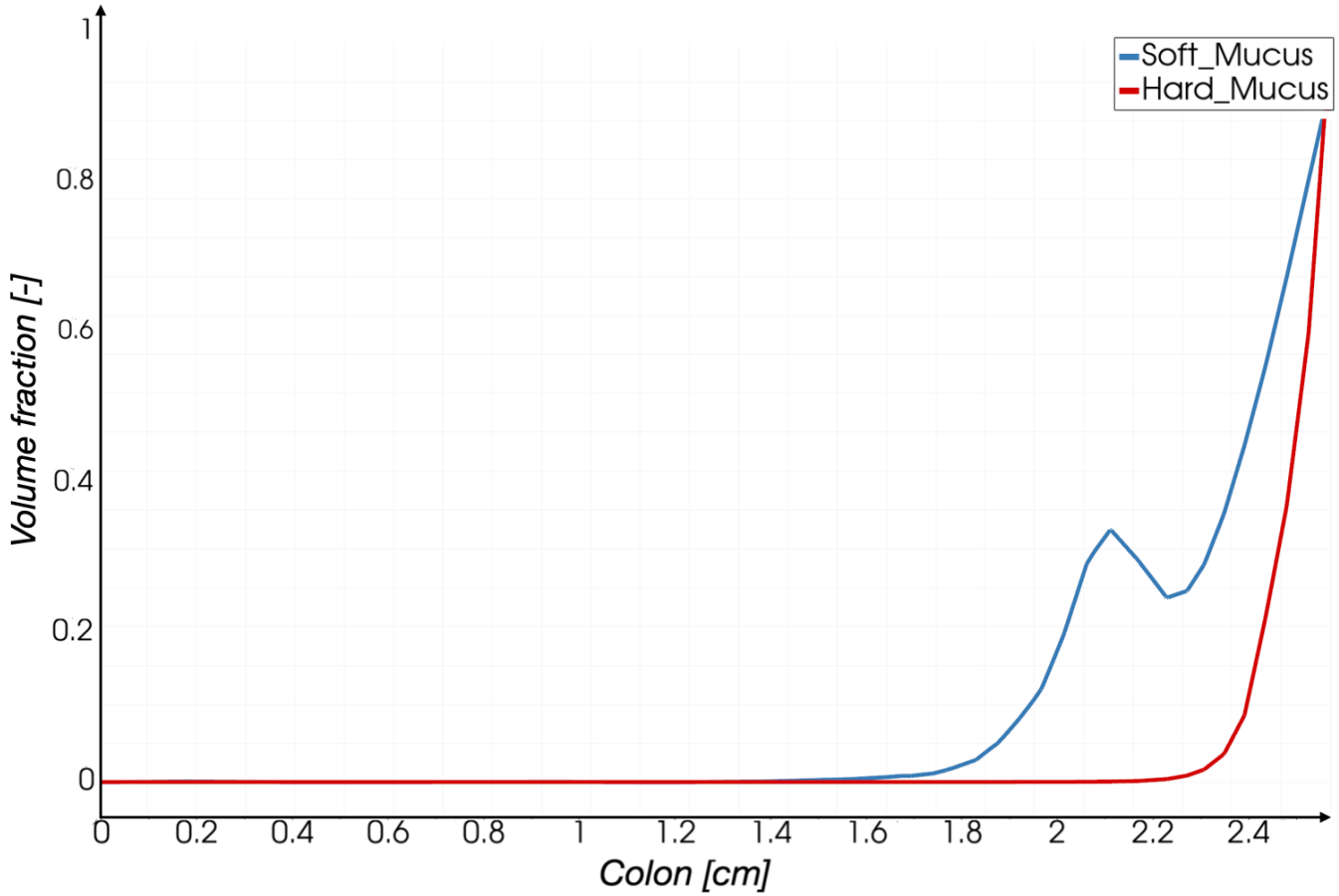
Soft Mucus distribution, with max value $\approx 8 \cdot 10^{-2}$ *and thickness* ≈ 0.17 *cm.*

Hard Mucus



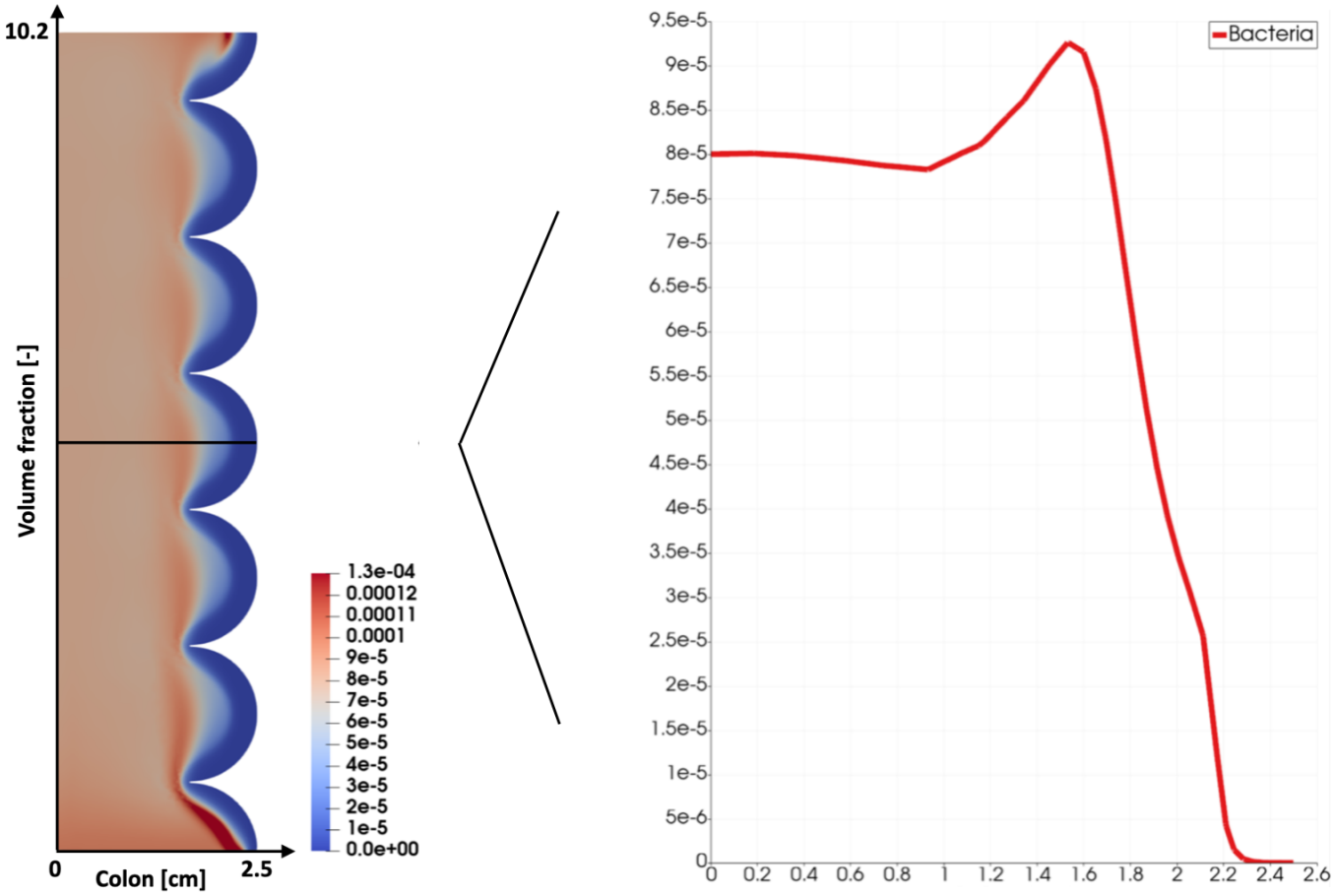
Hard Mucus distribution, constrained near Γ_m *with a thickness* ≈ 0.03 *cm.*

Comparison Soft - Hard



Comparison between Soft and Hard Mucus layer radial section normalized.

Bacteria



Monosaccharide-associated bacterial volume fraction and its radial section.

Conclusion

Conclusions:

- Successfully **coupled** macro[2] and micro[1]-scale models.
- Successfully integrated **new biological features** and improved anatomical **accuracy**.
- **Results** are **consistent** with established biological knowledge and existing models [1] [2].

Future perspectives:

- Enhance the computational efficiency by developing **Model Order Reduction techniques** and **Sensitivity Analysis**.
- Enable parameter estimation and biological **data integration**.

→ This work lays the foundation for **predictive, data-integrated model** (digital twin) of the gut microbiota.

[1] *Haghebaert (2024)*, [2] *Labarthe (2019)*.

Thanks for the attention!

Any questions?

References

[1] Marie Haghebaert et al. "A mechanistic modelling approach of the host–microbiota interactions to investigate beneficial symbiotic resilience in the human gut". In: *Journal of the Royal Society Interface* 21.215 (2024), p. 20230756.

[2] Simon Labarthe et al. "A mathematical model to investigate the key drivers of the biogeography of the colon microbiota". In: *Journal of theoretical biology* 462 (2019), pp. 552–581.

[3] Rafael Muñoz-Tamayo et al. "Mathematical modelling of carbohydrate degradation by human colonic microbiota". In: *Journal of theoretical biology* 266.1 (2010), pp. 189–201.

[4] Léo Darrigade et al. "A PDMP model of the epithelial cell turn-over in the intestinal crypt including microbiota-derived regulations". In: *Journal of Mathematical Biology* 84.7 (2022), p. 60.

[5] Atalie C Thompson et al. "Taller haustral folds in the proximal colon: A potential factor contributing to interval colorectal cancer". In: *Journal of Colon and Rectal Cancer* 1.1 (2016), pp. 45–54.

[6] Igor A Baratta et al. "DOLFINx: the next generation FEniCS problem solving environment". In: (2023).