MIXTURE MODELS FOR PHOTOTROPHIC BIOFILMS AND GUT MICROBIOTA ECOLOGY

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OUTLINE

1. Introduction to mixture theory
2. Phototrophic biofilm
    - Biofilm in a nutshell
    - Mathematical model
    - Numerical method overview
    - Numerical results
    - Impact of harvest on productivity
    - Conclusion & Further work
3. Gut ecology
    - Gut's role
    - Generalisation toward a more detail model
    - Conclusion & Further work

THEORETICAL FRAMEWORK FOR MIXTURE THEORY

Consider a mixture of $K \geqslant 1$ constituents: $\mathbf{C}_k$, each constituent is describe by:

- Its volume fraction: $\phi_k(t,x) := \lim_{\mathbb{V}\to 0} \frac{\text{volume of } \mathbf{C}_k \text{ in } \mathbb{V}}{\text{volume of } \mathbb{V}}$
- Its speed $V_k(t,x)$
- Its mass density ρ_k (assumed constant)

Fundamental properties:

- Total volume conservation: $\sum_{k=1}^{K} \phi_k = 1$
- Mass balance equation:

$$\underbrace{\partial_t (\phi_k \rho_k) + \nabla_x \cdot \Big(\phi_k \rho_k V_k\Big)}_{\text{transport}} = \underbrace{\nabla_x \cdot \Big(\mathrm{D}_k \nabla_x (\phi_k \rho_k)\Big)}_{\text{diffusion}} + \underbrace{\Gamma_k}_{\text{exchanges}}$$

- Momentum conservation (*Force balance equation*):

$$\underbrace{\partial_t (\phi_k \rho_k V_k) + \nabla_x \cdot \Big(\phi_k \rho_k V_k \otimes V_k\Big)}_{\text{inertial terms}} = \underbrace{-\phi_k \nabla_x P}_{\text{pressure}} + \underbrace{\mathrm{F}_{\text{fric}} + \mathrm{F}_{\text{visc}} + \dots}_{\text{other forces}}$$

Advantages:

- Mesoscale
- Physical constraints included
- Different physical properties for each $\mathbf{C}_k$
- Interfaces without free boundary

Phototrophic biofilm

PHOTOTROPHIC BIOFILM

Phototrophic?

Biofilm using light and inorganic carbon source to growth.

(a) Rotating microalgae biofilm device
Hans C. Bernstein et al. 2014

Motivation:

Credible alternative for biofuels

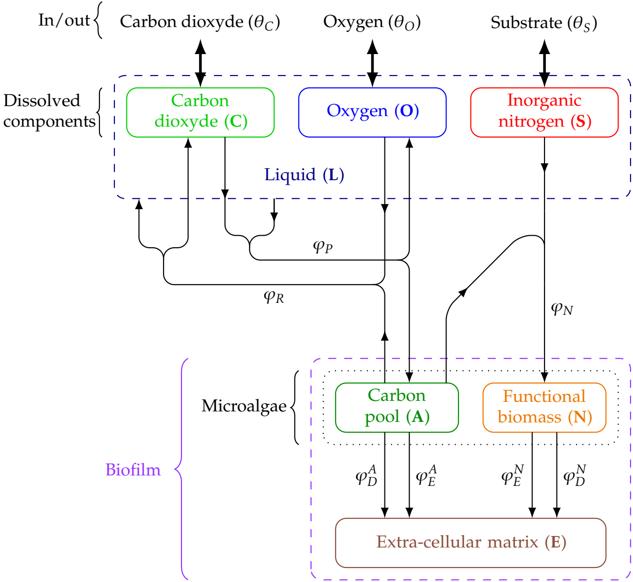
Why?

- High production yield for lipids,
- Easy to harvest (just scalp),
- A wide variety of species,
- Can develop in sea and oceans,
- Combined with wastewater treatment?

Objective:

Quantify the influence of growing conditions and harvest on productivity.

SCHEMATIC REPRESENTATION OF THE SYSTEM



MIXTURE FRAMEWORK – MASS BALANCE

- **Total volume conservation:** $A + N + E + L = 1$

- **Mass conservation for phase:**

$$\text{Microalgae}\left\{\begin{array}{ll}\text{Carbon pool:} & \partial_t A + \nabla_x \cdot (A \boldsymbol{V_M}) = \Gamma_A/\boldsymbol{\rho_M} \\ \text{Functional biomass:} & \partial_t N + \nabla_x \cdot (N \boldsymbol{V_M}) = \Gamma_N/\boldsymbol{\rho_M} \end{array}\right.$$

$$\begin{array}{ll}\text{Extracellular matrix:} & \partial_t E + \nabla_x \cdot (E \boldsymbol{V_E}) = \Gamma_E/\boldsymbol{\rho_E} \\ \text{Liquid:} & \partial_t L + \nabla_x \cdot (L \boldsymbol{V_L}) = \Gamma_L/\boldsymbol{\rho_L}\end{array}$$

- **Pseudo incompressibility:**

$$\nabla_x \cdot \Big((A+N)\,\boldsymbol{V_M} + E\,\boldsymbol{V_E} + L\boldsymbol{V_L} \Big) = \frac{\Gamma_A + \Gamma_N}{\boldsymbol{\rho_M}} + \frac{\Gamma_E}{\boldsymbol{\rho_E}} + \frac{\Gamma_L}{\boldsymbol{\rho_L}}$$

- **Dissolved components:**

$$\theta = \begin{cases} S & \text{Substrate} \\ C & \text{Carbon dioxide} \\ O & \text{Oxygen} \end{cases} \quad \partial_t\,(\theta \boldsymbol{L}) + \nabla_x \cdot (\theta \boldsymbol{L V_L}) = \underbrace{\nabla_x \cdot \Big(\mathcal{D}_\theta \boldsymbol{L} \nabla_x \theta \Big)}_{\text{diffusion}} + \frac{\Gamma_\theta}{\boldsymbol{\rho_L}}.$$

MIXTURE FRAMEWORK – FORCE BALANCE

- **Biological phases:** $\phi = A + N,\ E$

$$\partial_t\left(\phi\rho_\phi V_\phi\right) + \nabla_x\cdot\left(\phi_\phi\rho_\phi V_\phi\otimes V_\phi\right) = -\underbrace{\phi\nabla_x P}_{\text{Pressure}} + \underbrace{\boldsymbol{\nabla_x\left(\gamma_\phi\phi\right)}}_{\text{Elastic}} + \underbrace{\sum_{\ell\neq\phi} \boldsymbol{m_{\ell,\phi}\left(V_\phi - V_\ell\right)}}_{\text{Friction}} + \underbrace{\boldsymbol{\Gamma_\phi V_\phi}}_{\text{Exch.}}$$

- **Hypothesis:** Conservation of total momentum supply
- **Liquid phase:**

$$\partial_t\left(L\rho_L V_L\right) + \nabla_x\cdot\left(L\rho_L V_L\otimes V_L\right) = -\underbrace{L\nabla_x P}_{\text{Pressure}} - \underbrace{\sum_{\phi\neq L} \boldsymbol{m_{k,L}\left(V_L - V_\phi\right)}}_{\text{Friction}} - \underbrace{\sum_{\phi\neq L}\boldsymbol{\Gamma_\phi V_\phi}}_{\text{Exch.}}$$

SOURCE TERMS MODELLING

- **Construction of source terms:**
  1. Identify a biological mechanism

$$6CO_2 \quad + \quad 6H_2O \xrightarrow{\textit{photosynthesis}} C_6H_{12}O_6 \quad + \quad 6O_2$$

  2. Translate in term of considered components

$$\eta_C \underbrace{\text{Inorganic carbon}}_{\mathbf{C}} + \eta_L \underbrace{\text{Liquid}}_{\mathbf{L}} \xrightarrow[\psi_P]{\textit{Reaction rate}} \underbrace{\text{Carbon pool}}_{\mathbf{A}} + \eta_O \underbrace{\text{Oxygen}}_{\mathbf{O}}$$

  3. Express the information in the source terms:

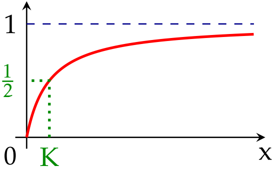
$$\Gamma_C = -\eta_C \psi_P + \dots \qquad \Gamma_A = \psi_P + \dots$$
$$\Gamma_L = -\eta_L \psi_P + \dots \qquad \Gamma_O = \eta_O \psi_P + \dots$$

- **Considered mechanisms:**

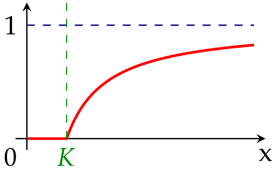
1. Photosynthesis
2. Respiration
3. Functional biomass synthesis
4. Extra-cellular matrix excretion
5. Mortality

REACTION RATES MODELLING: ψ

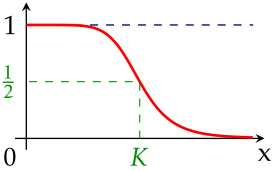
$$\psi := \prod_{i \geqslant 0} f_i(\phi) \qquad \begin{cases} f_i & \text{elementary functions} \\ \phi & \text{volume or mass fraction} \end{cases}$$



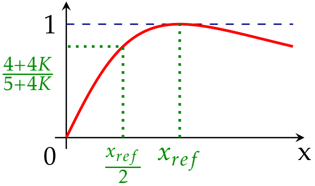
(b) Monod's law $f(x) = \frac{x}{K+x}$



(c) Droop's law $f(x) = \max\left\{0, 1 - \frac{K}{x}\right\}$



(d) Sigmoidal law $f(x) = \frac{1}{1+(x/K)^{\alpha}}$



(e) Haldane's law $f(x) = \frac{2(1+K)\tilde{x}}{\tilde{x}^2+2K\tilde{x}+1}$, $\tilde{x} = x/x_{ref}$

REACTION RATES MODELLING

- **Highly nonlinear reaction rates:**
  Example:

$$\psi_P = \mu_P \rho_M N \frac{C}{\mathcal{K}_C + C} \frac{(1+K_L)L}{\mathcal{K}_L + L} \frac{2(1+\mathcal{K}_I)\hat{I}}{\hat{I}^2 + 2\mathcal{K}_I \hat{I} + 1} \frac{\max\left\{0, 1 - \frac{Q_{min}}{\min\{Q, Q_{max}\}}\right\}}{Q_{max} - Q_{min}} \frac{1}{1 + \left(\frac{O}{\mathcal{K}_O}\right)^{\alpha}},$$

  - Received light intensity: $\hat{I}(z) = \frac{I_0}{I_{opt}} \exp\left(-\int_z^H \tau_L L + \tau_M (A+N+E)\, d\xi\right)$
  - Functional biomass quota: $Q = \frac{N}{N+A}$.

- **Coupled mass balances:**

$$\partial_t A + \nabla_x \cdot (A V_M) = \frac{1}{\rho_M}\left(\psi_P - \psi_R - \eta_N^A \psi_N - \psi_E^A - \psi_D^A\right)$$

$$\partial_t (CL) + \nabla_x \cdot (CLV_L) - \nabla_x \cdot (\mathcal{D}_C L \nabla_x C) = \frac{1}{\rho_L}\left(\eta_R^C \psi_R - \eta_P^C \psi_P\right),$$

NUMERICAL METHOD OVERVIEW

- **Semi-implicit approach for the mass balance equations:**

$$\frac{(\theta L)^{n+1}-(\theta L)^{n}}{dt}+\nabla_x\cdot\left(\boldsymbol{\theta L V_L}\right)^{\boldsymbol{n}}=\nabla_x\cdot\left(D_\theta \boldsymbol{L^n}\nabla_x\frac{\boldsymbol{(\theta L)^{n+1}}}{\boldsymbol{L^n}}\right)+f\left(\boldsymbol{U^n}\right)-g\left(\boldsymbol{U^n}\right)\boldsymbol{(\theta L)^{n+1}}$$

$f(U)$ production terms & $g(U)\theta L$ consumption terms

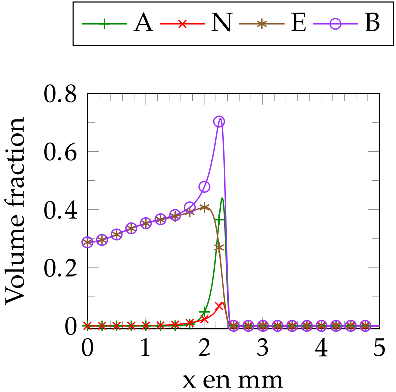
- **Chorin-Temam's projection method for the conservation of momentum:**
  1. Projection step for $V_\phi,\ \ \phi = M, E, L$:

$$\frac{\left(\phi V_\phi\right)^{n+\frac{1}{2}}-\left(\phi V_\phi\right)^{n}}{dt}+\nabla_x\cdot\left(\boldsymbol{\phi V_\phi\otimes V_\phi}\right)^{\boldsymbol{n}}$$

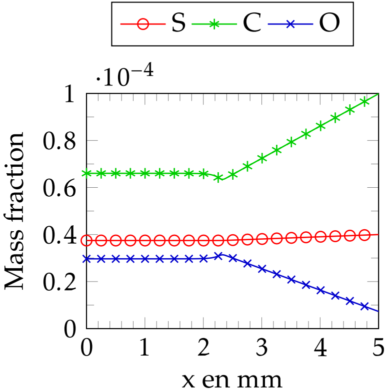
$$=\frac{1}{\rho_\phi}\left(-\nabla_x\left(\gamma_\phi\boldsymbol{\phi^n}\right)+\sum_{\phi'\neq\phi}m_{\phi,\phi'}\left(\boldsymbol{V_\phi-V_{\phi'}}\right)^{\boldsymbol{n+\frac{1}{2}}}+\left(\boldsymbol{\Gamma_\phi V_\phi}\right)^{\boldsymbol{n}}\right)$$

  2. Elliptic equation for P: Variable coefficients & Nonhomogeneous
  3. Correction step: $V_\phi^{n+1}=V_\phi^{n+\frac{1}{2}}-\dfrac{\Delta t}{\rho_E}\left(\nabla_X P\right)^{n+1}$

NUMERICAL RESULTS

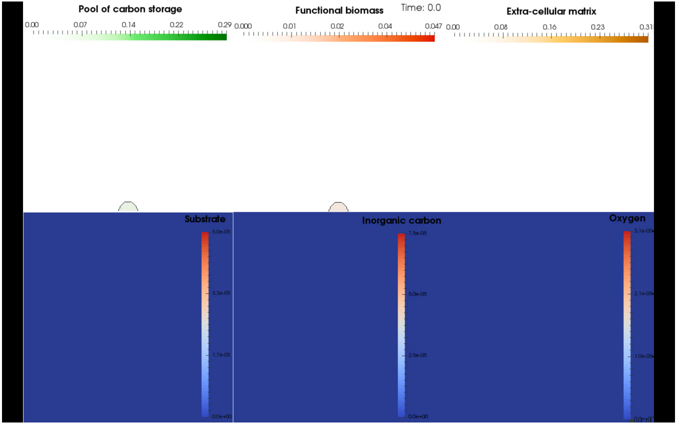


(f) Biofilm components after 90 days

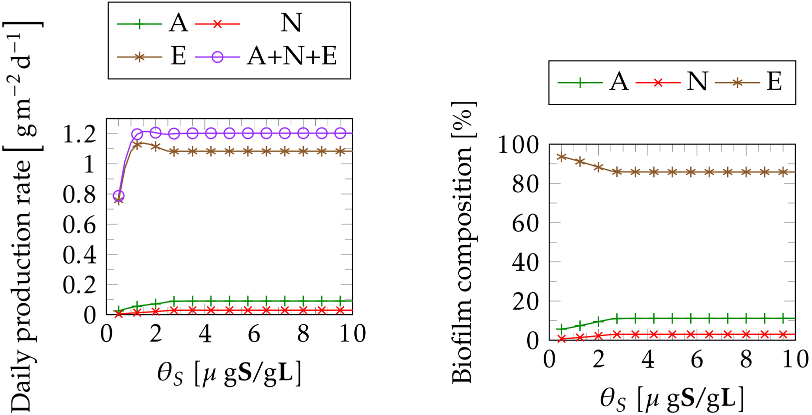


(g) Disolved components after 90 days

NUMERICAL SIMULATION IN 2D



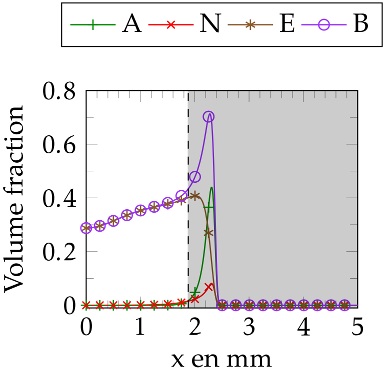
INFLUENCE OF THE SUBSTRATE SUPPLY NITROGEN



(h) Biofilm daily production rate with respect to θ_S after 90 days

(i) Biofilm composition with respect to θ_S after 90 days

HOW TO INCLUDE THE EFFECT OF THE HARVEST?



Initial model

Component dissolved provided at the top of the domain, ie: $x = 5mm$

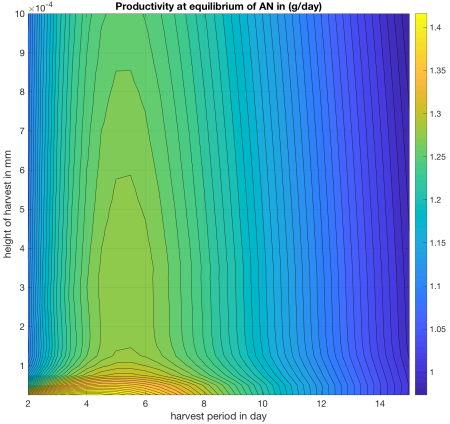
- Drawback: Unable to capture optimal harvest height and frequency,
- Why: The closer the biofilm front is to the source the higher the growth is.

Modified model

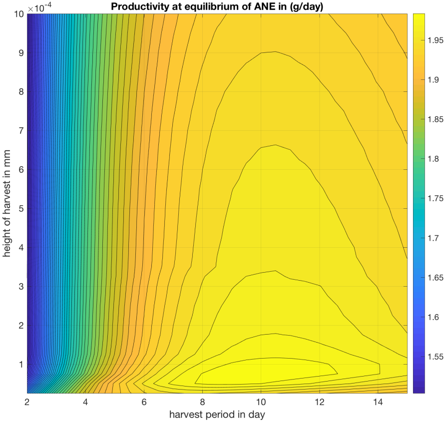
Use Henry's law for the inorganic carbon and oxygen supply:

- $\partial_t (CL) = \cdots - k_{L,C} (C - C^*) \mathbb{1}_{L>L_{min}}$
- $\partial_t (OL) = \cdots - k_{L,O} (O - O^*) \mathbb{1}_{L>L_{min}}$

HARVEST, WHAT HEIGHT AND FREQUENCY?



(j) Microalgae



(k) Whole biofilm

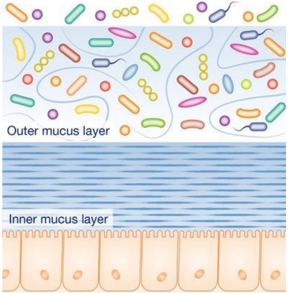
CONCLUSION & FURTHER WORK

- **Summary and results:**
  - Front velocity $\propto \sqrt{\text{Elastic tensor}}$,
  - Productivity $(g/D/m^2)$: model $\sim 1,13 \simeq$ experiments $\sim [1,2]$
  - Quantification of the substrat supply on productivity and composition
  - Role of dissolved components in the developpement of structures,
  - Quantification of limiting factors:
    - Influence of light,
    - Oxygen concentration
  - Optimal height and frequency for harvest.
- **On going work:** Impact of the harvest, what about the shape ?
- **Further work:**
  - Include the water flow,
  - Take into account the viscosity,
  - Calibration and comparison with experimental data.

Gut ecology

COLON & GUT MICROBIOTA IN A NUTSHELL

(l) Human gut



(m) Mucus layers & Microbiota

Gut's role

- Last stage of digestion,
- Body hydratation.

Gut's operating mechanisms

- **Microbiota:** *all the bacteria contained in the gut*
    - Fiber degradation,
    - Synthetize neuro-transmettors,
    - Pathogens domination,
    - Regulate immunity.
- **Host:**
    - Excretion of protective mucus layers,
    - By-products assimilation,
    - Water pumping: 90% of the gastric broth's water.

COLON & GUT MICROBIOTA IN A NUTSHELL

Motivations: Understand the complex symbiotic relationship between the host and its microbiota.

Why: Dysbiosis[1] is associated with many diseases such that metabolic, inflammatory, mental, autoimmune, …

Objectives: **Quantify the influence of mechanical, ecological and chemical mechanisms in the functioning of the gut.**

Context: Collaboration with scientists from Institut National de Recherche en Agronomie (INRA): B. Laroche & S. Labarthe.

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[1] Qualitative and functional alteration of the microbiota.

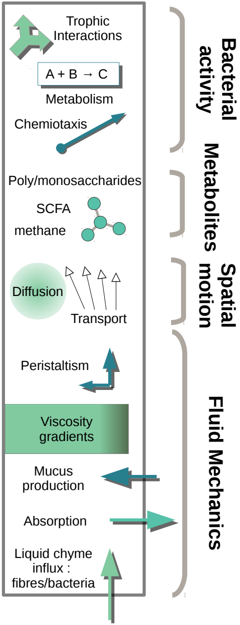
MODEL COMPLEXITY FOR THE GUT ECOLOGY

Aim of the model

- Describe the microbiota in its physical environment,
- Understand how bacteria remain in the colon and resist the overcoming flow,
- Study the ecology of bacteria in competition in the gut.

Features of the model

- Hydrodynamical description: luminal flow, water pumping, viscosity gradient, mucus structure, …
- Spatial behaviour: **chemotaxis**, **peristaltism**, …
- **Metabolic description** of the digestion process:
  - Dissolved metabolites,
  - Different bacteria communities.



Trophic Interactions

A + B → C

Metabolism

Chemiotaxis

Poly/monosaccharides

SCFA

methane

Diffusion

Transport

Peristaltism

Viscosity gradients

Mucus production

Absorption

Liquid chyme influx : fibres/bacteria

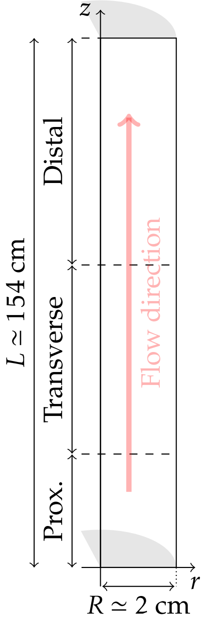
Bacterial activity

Metabolites

Spatial motion

Fluid Mechanics

GEOMETRY AND UNKNOWNS



Mixture model with

- **8 fluid components:**
  1. mucus,
  2. indigestible residuals,
  3. liquid chyme,
  4. polysaccharides
  5. bacteria $\mathcal{B}_{mon}$,
  6. bacteria $\mathcal{B}_{la}$,
  7. bacteria $\mathcal{B}_{H_2a}$,
  8. bacteria $\mathcal{B}_{H_2m}$.
- **8 dissolved compounds:**
  1. monosaccharides,
  2. lactate,
  3. hydrogen,
  4. acetate
  5. butyrate,
  6. propionate,
  7. methane,
  8. carbon dioxyde.
- A common velocity field, with a correction for bacteria,
- The hydrostatic pressure

MIXTURE THEORY FRAMEWORK

- **Fluid components:** $\phi_i = \textit{Volume fractions},\ i \in [\![1,8]\!]$

Mass balance	$\partial_t \phi_i + \nabla_x \cdot (\phi_i \mathrm{V}_i) - \nabla_x \cdot (\sigma \nabla_x \phi_i) = \mathcal{F}_i$
Total volume conservation	$\sum_{i \in [\![1,8]\!]} \phi_i = 1$
Velocity, $v_i = \textit{chemotactic speed}$	$\mathrm{V}_i = \mathrm{V} + v_i$
Phase transfert constraint	$\sum_{i=1}^{8} \mathcal{F}_i = 0$
Incompressibility	$\nabla_x \cdot \left(\mathrm{V} + \sum_{i=1}^{8} \phi_i v_i \right) = 0$

- **Solutes:** $\mathcal{S}_i = \textit{concentration},\ i \in [\![1,8]\!]$

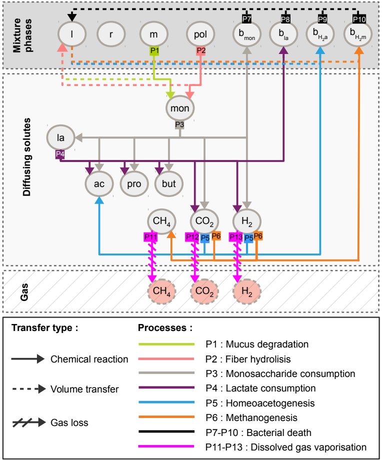
Mass balance	$\partial_t \mathcal{S}_i + \nabla_x \cdot \left(\mathcal{S}_i \widetilde{\mathrm{V}} \right) - \nabla_x \cdot (\sigma_i \nabla_x \mathcal{S}_i) = \mathcal{G}_i$
Mixture average velocity	$\widetilde{\mathrm{V}} = \sum_{i=1}^{8} \phi_i \mathrm{V}_i$

- **Stokes equation:** – Viscosity $\mu(\mathcal{M}, \mathcal{L})$ depending on mucus and liquid
  – P pressure

$$\nabla_x \cdot \left(\mu(\mathcal{M}, \mathcal{L}) \left(\nabla_x \mathrm{V} + \nabla_x \mathrm{V}^T \right) \right) - \nabla_x \mathrm{P} = 0.$$

METABOLIC MODEL: MODELLING SOURCE TERMS

Knowledge-based microbiota metabolic model: *Muñoz Tamayo et al. JTB 2010*



- **Petersen matrix,**
- **Complex reaction rates including:** inhibition, limitation mechanisms, . . .
- **General form:**

$$\mathcal{F}_i(\phi,\mathcal{S}) = \sum \mu_{max} \frac{\mathcal{S}_j \phi_i}{\mathrm{K}_j + \mathcal{S}_j}$$

CHEMOTACTIC SPEED

Observations:

- Chemotactic speed ~ 1 cm/day
- Gut half average surface inflow ~ 40 cm/day

Consequence: Chemotactic speed $\ll$ Gut average inflow

Hypothesis: Consider only the radial chemotactic speed

Keller-Segel model:

$$v_i = \sum_j \lambda_{i,j} \nabla_r \psi_j \qquad \text{and} \qquad -\Delta \psi_j = \mathcal{S}_j - \frac{1}{R} \int_0^R \mathcal{S}_j(r,z) \cdot dr$$

whith	$\lambda_{i,j}$	chemosensitivity coefficient of $\mathcal{B}_i$ to $\mathcal{S}_j$,
	ψ_j	chemotactic potential of $\mathcal{S}_j$,
	R	gut radius,
	$\nabla \psi_j \cdot \vec{n} = 0$	boundary condition.

BOUNDARY CONDITIONS: IN/OUT & PERISTALTISM

- **Mucosal exchanges:** robin boundary conditions

$$\Big(\phi_i \mathrm{V}_i - \sigma \nabla_x \phi_i\Big) \cdot \vec{n} = \gamma_{\phi_i}$$
$$\Big(\mathcal{S}_i \widetilde{\mathrm{V}} - \sigma_i \nabla_x \mathcal{S}_i\Big) \cdot \vec{\eta} = \gamma_{\mathcal{S}_i}$$

  where γ is the exchange rate which depends on the local composition.

- **Peristaltism:**

$$\mathrm{V} \cdot \vec{n} = \sum_{i \in [\![1,8]\!]} \gamma_{\phi_i} + \mathrm{V}_{per} \cdot \vec{n} \qquad \text{and} \qquad \mathrm{V} \cdot \vec{\tau} = \mathrm{V}_{per} \cdot \vec{\tau}$$

  with V_{per} is the velocity peristaltism induced.

Notation: $\vec{n}$ *normal unit vector,*
$\vec{\tau}$ *tangential unit vector.*

MODEL SIMPLIFICATION

- **Realistic hypothesis:** Aspect ratio $\varepsilon = \frac{R}{L} \ll 1$.

- **Model simplification method:**
  - Use series expansion in ε, ie. $f = f_0 + \varepsilon f_1 + \dots$
  - Keep only the first orders.

- **Simplified mass balance**

$$\partial_t \phi_i + \nabla_x \cdot (\phi_i \mathrm{U}) + \frac{1}{r}\partial_r (r\phi_i u_{i,r}) - \frac{1}{r}\partial_r (r\sigma\partial_r\phi_i) = \mathcal{F}_i$$

$$\partial_t \mathcal{S}_i + \widetilde{\mathrm{U}} \cdot \nabla_x \mathcal{S}_i - \frac{1}{r}\partial_r (r\sigma_i\partial_r\mathcal{S}_i) = \mathcal{G}_i$$

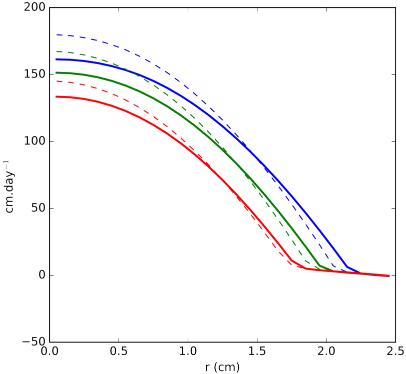
- **Simplified Stokes and Keller-Segel equations**
  - Can be solved exactly

  ⇒ Explicit formulas for the velocities U and $u_{i,r}$ depending on: rehology, peristaltism, inflow and pumping.

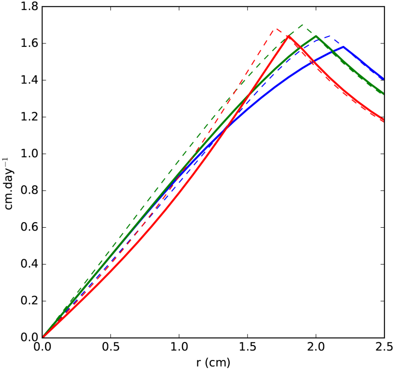
- **Speed up factor $\sim$ 70.**

COMPARISON BETWEEN FULL AND SIMPLIFIED MODEL

DISCREPANCIES BETWEEN VELOCITIES



(n) Radial distribution of longitudinal speed

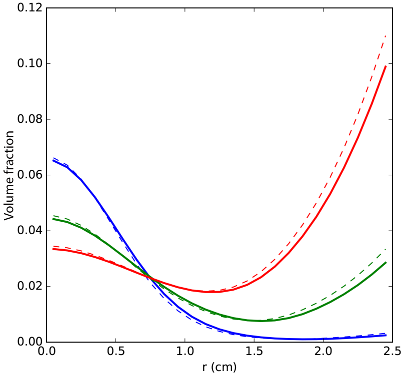


(o) Radial distribution of radial speed

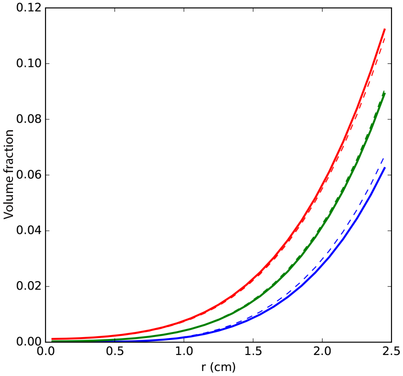
z in cm	−25	−50	−75
Reduce model	- - - -	- - - -	- - - -
Full model	——	——	——

COMPARISON BETWEEN FULL AND SIMPLIFIED MODEL

DISCREPANCIES IN COMPOSITION



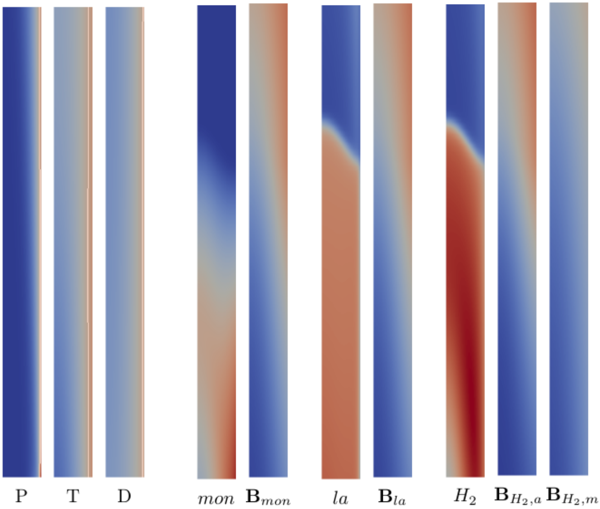
(p) Radial distribution of bacteria



(q) Radial distribution of mucus

z in cm	-25	-50	-75
Reduce model	- - - -	- - - -	- - - -
Full model	——	——	——

PERSISTENCE OF THE MUCUS LAYER & SPATIAL STRUCTURE

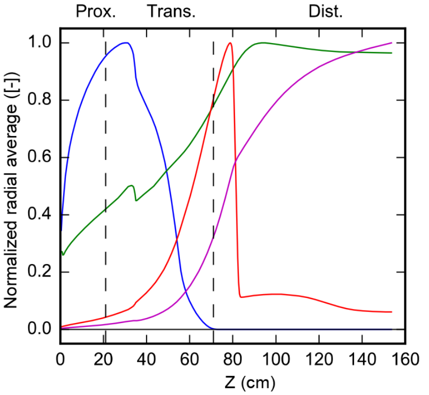


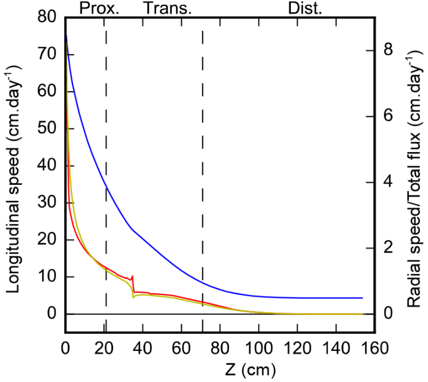
(a) Mucus distribution

(b) Distribution of microbial densities and their corresponding substrate in the transverse colon

REFERENCE STATE

WITHOUT CHEMOTAXIS & PERISTALTISM

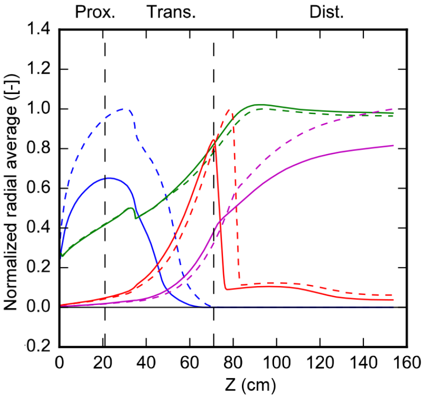




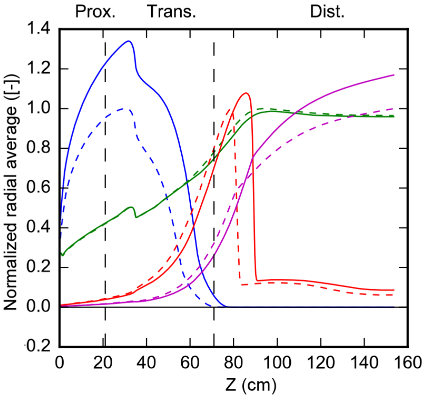
- — Polysaccharid density
- — Mixture viscosity
- — Bacterial activity
- — Total bacteria density

- — Longitudinal speeds
- — Radial speed
- — Total flux: $\sum_{i \in [\![1,8]\!]} \gamma_{\phi_i}$

IMPACT OF THE DIET



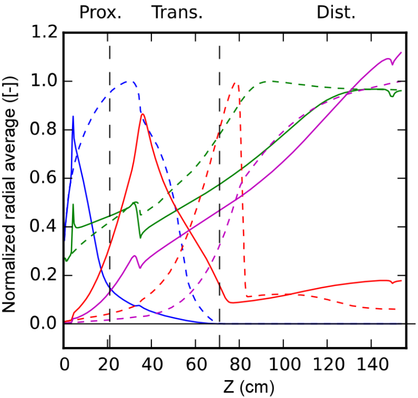
(r) Low fibre diet



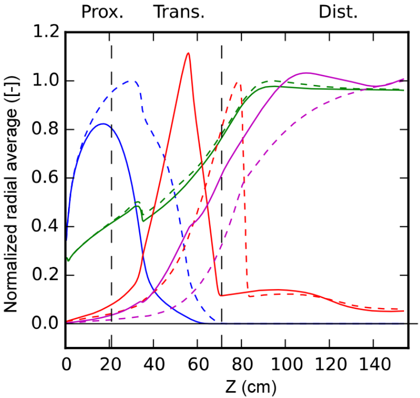
(s) Hight fibre diet

Curve	Poly. density	Mixt. viscosity	Bact. activity	Total bact. density
Reference	- - - -	- - - -	- - - -	- - - -
Low/Hight	——	——	——	——

IMPACT OF PERISTALTIMS & CHEMOTACTISM



(t) Impact of peristaltims

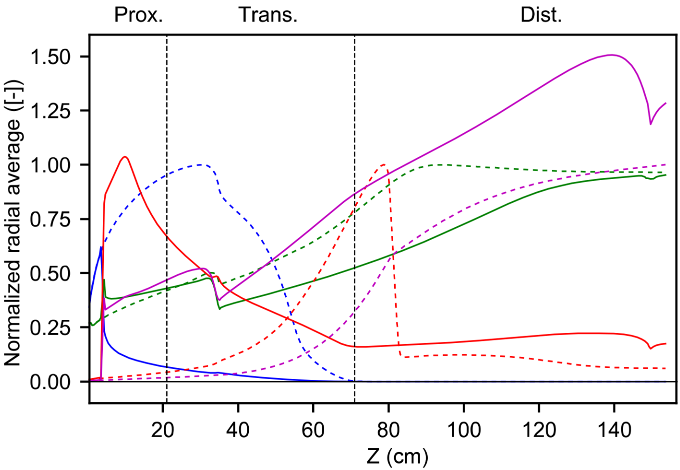


(u) Impact of chemotactism

Curve	Poly. density	Mixt. viscosity	Bact. activity	Total bact. density
Reference	- - - -	- - - -	- - - -	- - - -
Per./Chemo.	—	—	—	—

ALL MECHANISMS COMBINED

PERISTALTIMS & CHEMOTACTISM



Curve	Poly. density	Mixt. viscosity	Bact. activity	Total bact. density
Reference	- - - -	- - - -	- - - -	- - - -
Per./Chemo.	——	——	——	——

CONCLUSION & FURTHER WORK

Main results

- Coupled fluid mechanics-Population dynamics model.
- Simplified fluid mechanics.
- Assessment of the spatial structure of the gut microbiota.
- Chemotaxis has an impact on the gut's spatial structure and ecology.
- Quantification of the impact of peristaltism.

Mathematical perspectives

- Rigorous proof of the formal computations for the asymptotic limit

Modelling perspectives

- Include pathogens invasion
- Include drug delivery & immune response
- Different timescales for the source terms (slow-fast dynamics)

Thank you for your attention!

Questions?

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- Simon LABARTHE, INRA
- Beatrice Laroche, INRA

References:

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- **A mathematical model to investigate the key drivers of the biogeography of the colon microbiota,** *Simon Labarthe, Bastien Polizzi, Thuy Phan, Thierry Goudon, Magali Ribot, Béatrice LAROCHE.* Journal of Theoretical Biology - In revision,