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Mathematical models in microbial ecology

Simon Labarthe

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Simon Labarthe. Mathematical models in microbial ecology. 2019. hal-03352423

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S.Labarthe

DynEnvie - MaIAGE - INRA Jouy en Josas

09/27/2019

Mathematical models in microbial ecology

1

Introduction

Why studying the microbiota ?

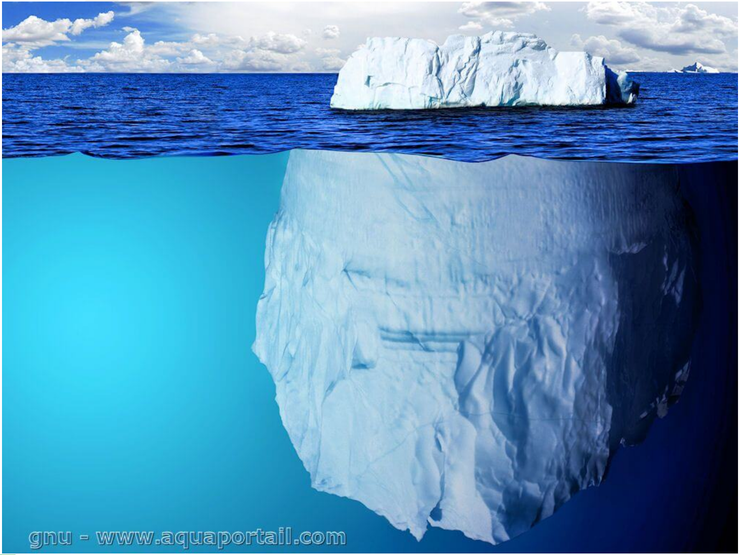
Omic data revolution

Microbiology before omic data

- Insulation
- Culture *in vitro*
- Functional phenotyping of individuals

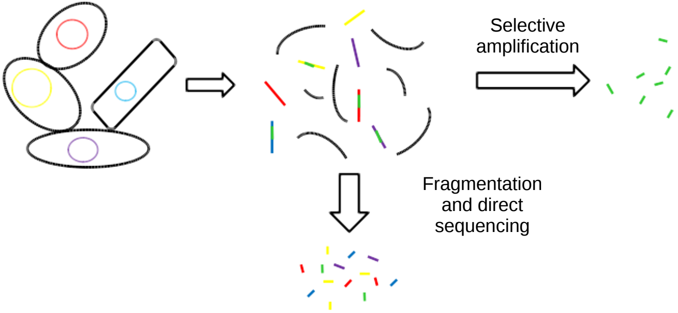
Studying a microbial ecosystem = studying individuals = reductionism

Omic data revolution



Omic data revolution

Microbiology after omic data



Adapted from S.Raguideau's thesis

Global view of microbial ecosystem = holism/system biology

Omic data revolution

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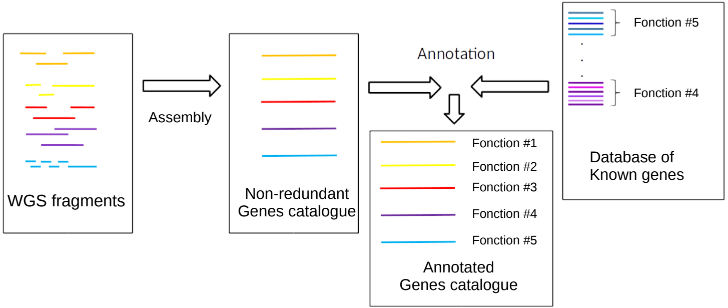

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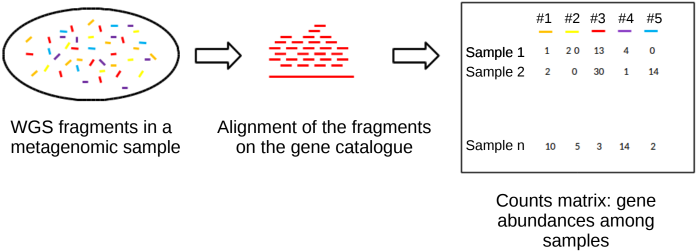

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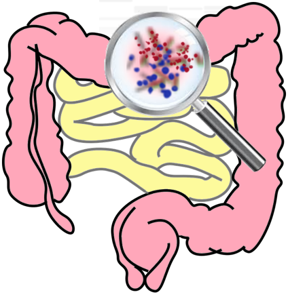
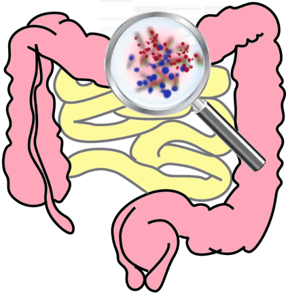
Human gut microbiota



Microbiote

- several thousands of microbial species
- 10 $\times$ the number of human cells
- metagenome $\Rightarrow$150 $\times$ the number of genes of human genomes

Human gut microbiota



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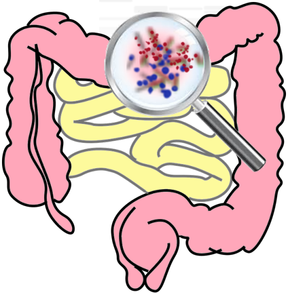
Microbial ecology

- Interactions ?
- Dysbiosis ?
- Colonization ?

$\Rightarrow$

Human gut microbiota



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Microbial ecology

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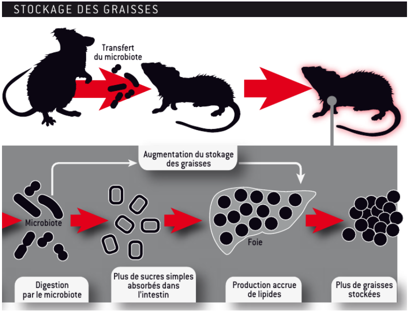
$\Rightarrow$

'Axenic/gnotobiotic individual' revolution

Animals grown in insulators $\Rightarrow$without microbiota

Metabolic diseases



Pour la Science, 01/2015

Microbiota/metabolic diseases

- Normal animal fat > axenic animal fat (40 %)
- Axenic animal + microbiota ⇒60 % increase of fat despite feeding reduction

⇒Microbiota impact on host glucidic and lipidic metabolism regulation

Gut/brain axis

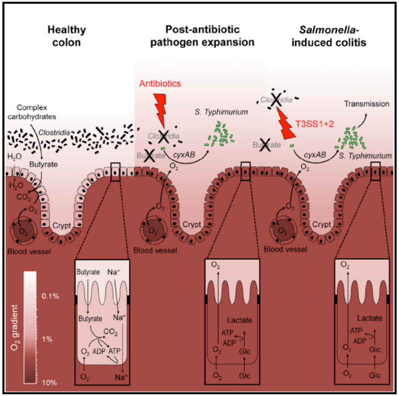
Pour la Science, 01/2015

Stress regulation

- Axenic animal more susceptible to stress
- Axenic animal + microbiota ⇒diminution of stress behavior, more social interactions
- For stressful animals : microbiota replacement ⇒less stress

⇒Microbiota impact on stress regulation. Microbiota also related to autistic spectrum syndroms

Immunity



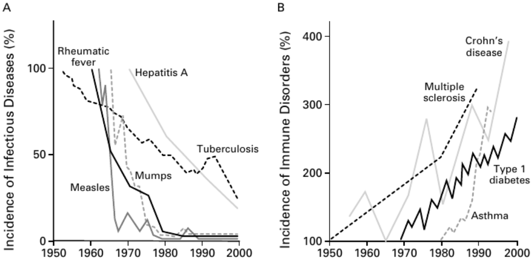
Rivera Chavez et al. Mbio 2016

Barrier effect

- Pathogen : hack of intestinal regulation mechanisms
- Microbiota involved in epithelial cell and inflammation regulation

⇒Microbiota offers protection against pathogens.

Immunity

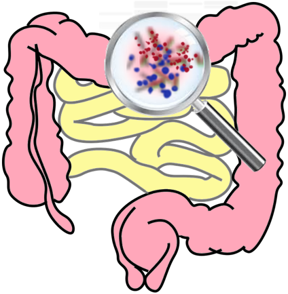


Bach, NEJM 2002

Involvement in immunity regulation

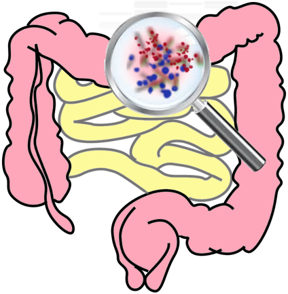
- Microbiota involved in immunity calibration during first years of life

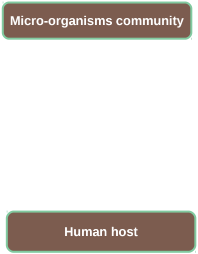
Host/microbiota interactions



Micro-organisms community

Host/microbiota interactions





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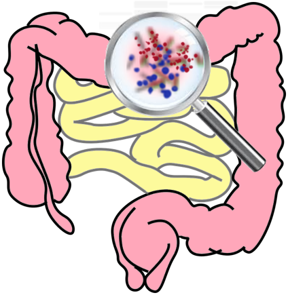

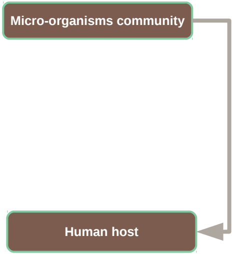

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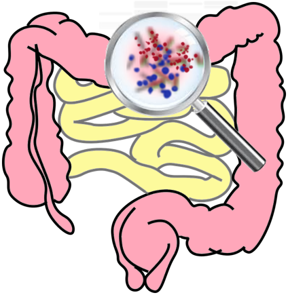

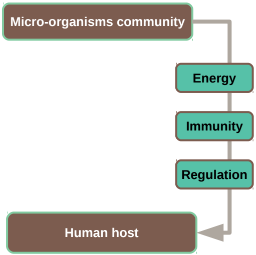

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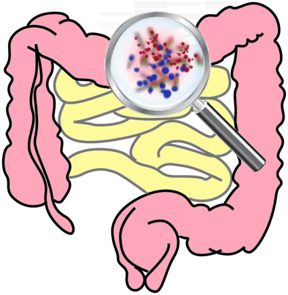

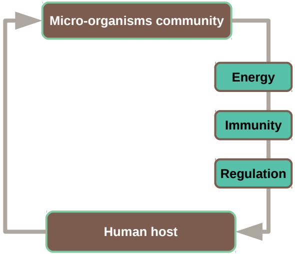

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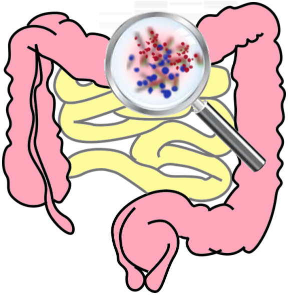

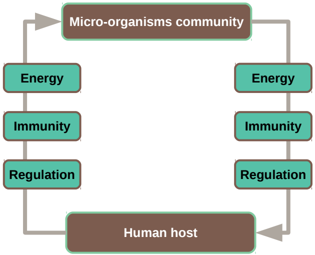

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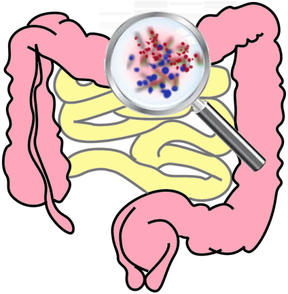

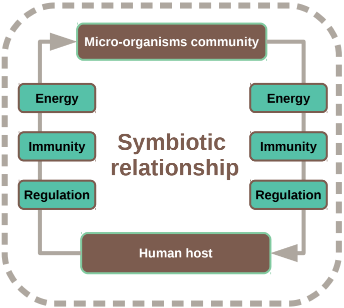

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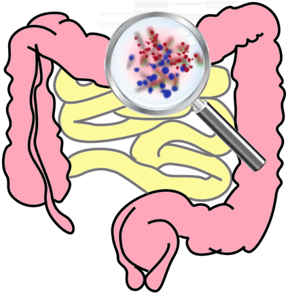
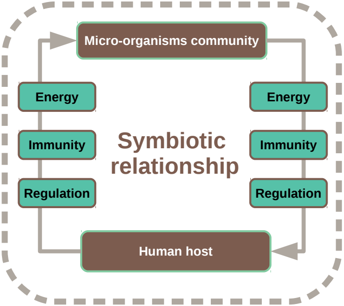


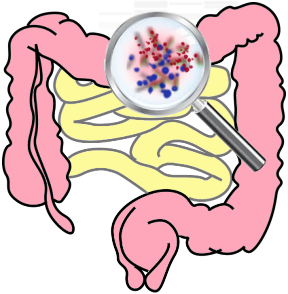


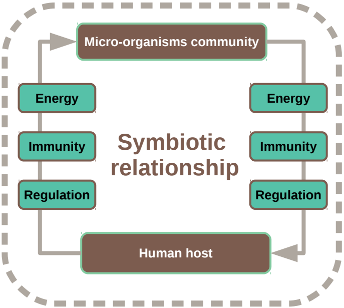
Microbial ecology

- Interactions ?
- Dysbiosis ?
- Colonization ?

⇒

Host/microbiota interactions





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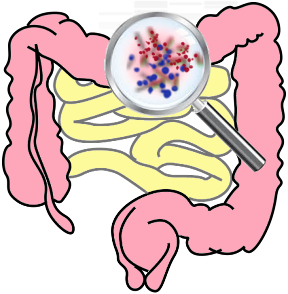

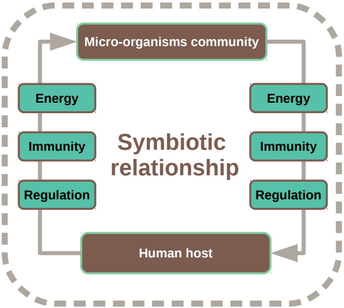

Microbial ecology

- Interactions ?
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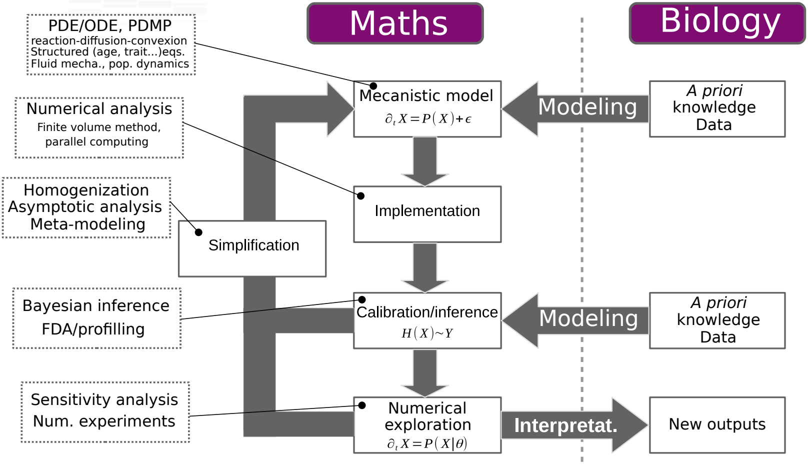
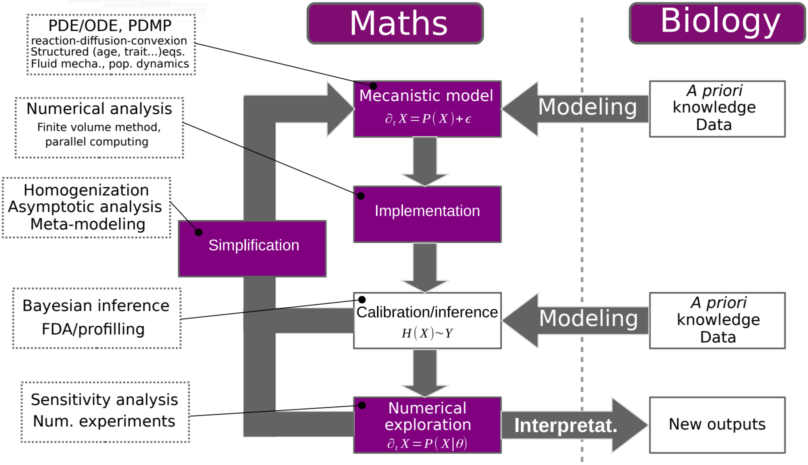
⇒ **Modeling bacterial populations in their environment**

2 Mechanistic modeling for microbiology

Modeling process

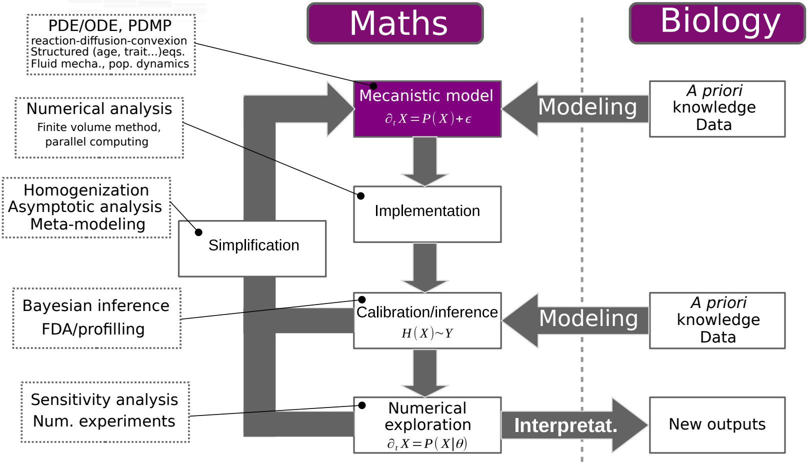


Modeling process

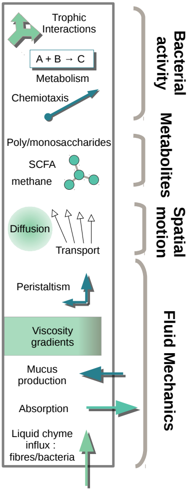


3 Model presentation

Modeling process



Model elements



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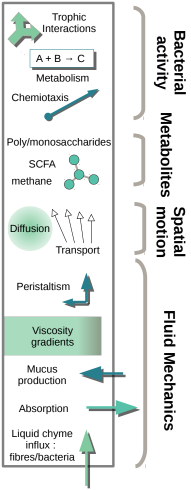


Geometry

On $\Omega = \omega \times L$

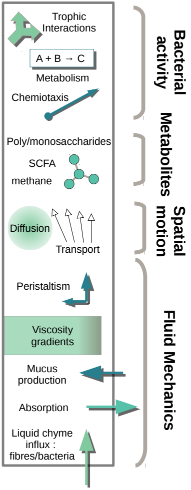
Mixture model.

I_C : set of 7 fluid components. c_i : volume fraction.

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

$$u_i = u + \upsilon_{chem,i}, \quad \sum_{i \in I_C} c_i = 1, \quad \sum_{i \in I_C} F_i = 0$$

Model elements



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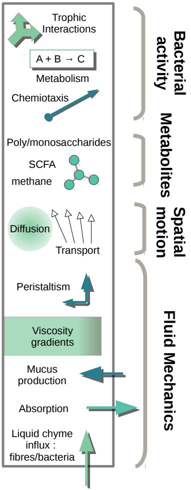
Bathing solutes.

I_S : set of 8 solutes. No volume. $\tilde{u} = \sum_{i \in I_C} c_i u_i$

$$\partial_t s_j = G_j(c,s) + \mathrm{div}(\sigma \nabla s_j) - \mathrm{div}(\tilde{u} s_j)$$

Model elements



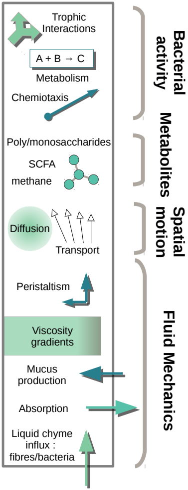
Chemotactic speed

Keller-Segel model

$$v_{chem,i} = \nabla\Phi,$$

$$-\Delta\Phi = s_j - \frac{1}{|\omega|}\int_\omega r s_j(r)dr, \quad \nabla\Phi\cdot\eta = 0 \text{ on } \partial\Omega$$

Model elements



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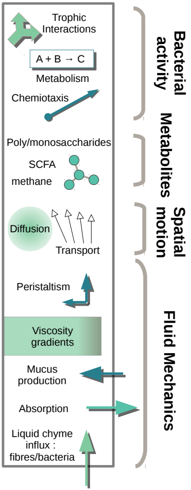
Stokes equation

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

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

Model elements



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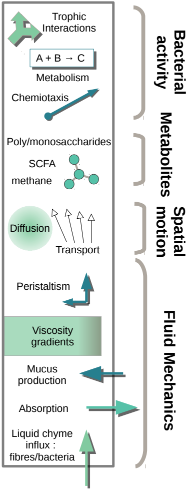
Stokes equation

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

μ depend on mucus (sigmoid function) and non liquid phases

Model elements



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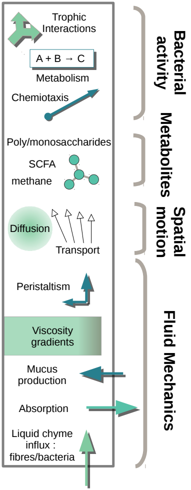
$$\partial_t c_i = F_i(c, s) + \mathrm{div}(\sigma \nabla c_i) - \mathrm{div}(u_i c_i), \quad \sum_{i \in I_C} c_i = 1, \sum_{i \in I_C} F_i = 0$$

$$\mathrm{div}(u) = -\sum_{i \in I_C} \mathrm{div}(\upsilon_{chem,i} c_i)$$

Model elements



Boundary conditions

- For c and s :

$$(-\sigma \nabla c_i + u c_i) \cdot \eta = \gamma_{c,i}$$

$$(-\sigma \nabla s_j + u s_j) \cdot \eta = \gamma_{s,j}$$

Physiological influx and mucosal exchanges γ_i. Outflow = transport.

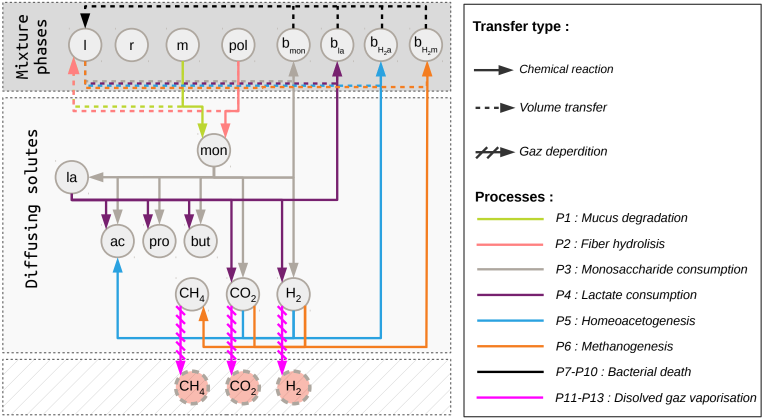
- For u :

$$u \cdot \eta = \sum_{i \in I_C} \gamma_{c,i}, \quad u \cdot \tau = U_{per} \text{ or } 0$$

Source function & Model structure

Ecology ⇒Trophic interactions

Knowledge-based microbiota metabolic model (*Muñoz Tamayo 2010*)



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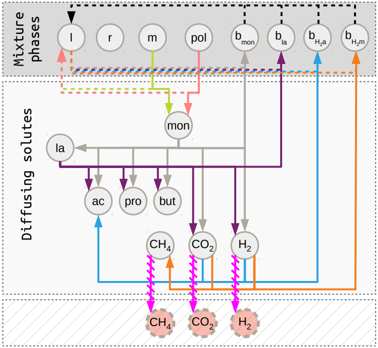


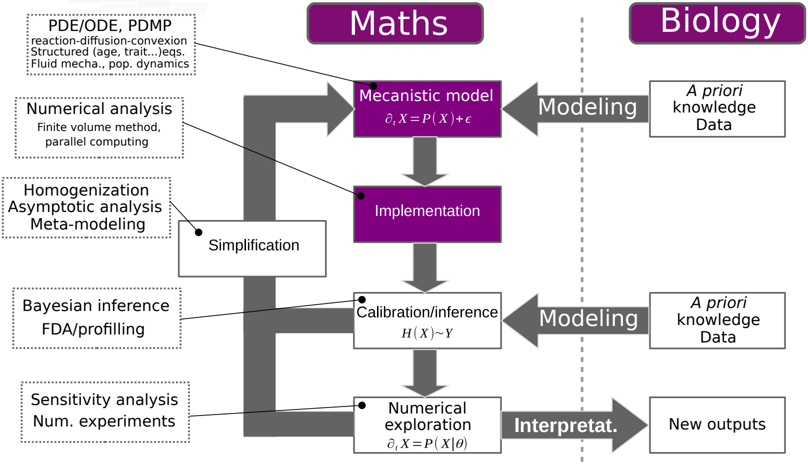
$$F_i(c, s) = \mu_{max,ij} \frac{c_i s_j}{K_{max,ij} + s_j} c_l$$

- Volume transfers
- Inihibition by volume disponibility c_l ⇒logistic term

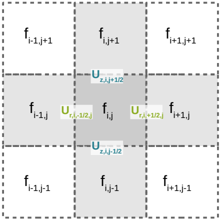
4

Implementation

Modeling process



Finite volume method

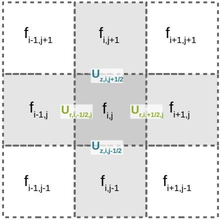


Principles

- **Space discretization :** Solution approximate with piecewise constant functions on mesh cells
- Equation integration on each mesh cell
- **Flux approximation** $\Rightarrow$linear system
- **Time discretization**

Finite volume method

$$\partial_t f - \text{div}(\sigma \nabla f + uf) = F$$



Space discretization : Intregration on $\Omega_{i,j}$

$$\partial_t \int_{\Omega_{i,j}} f dx - \int_{\Omega_{i,j}} \text{div}(\sigma \nabla f + uf) dx = \int_{\Omega_{i,j}} F dx$$

Stokes formula + constant on cell

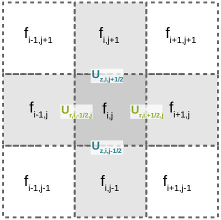
$$\Delta r \Delta z \partial_t f_{i,j} - \int_{\partial \Omega_{i,j}} (\sigma \nabla f + uf) \cdot \eta ds = \Delta r \Delta z F_{i,j}$$

On $\partial \Omega_{i,j+1/2}$, if $u_{i,j+1/2} \geq 0$

$$\int_{\partial \Omega_{i,j}} (\sigma \nabla f + uf) \cdot \eta ds = \Delta r (\sigma \frac{f_{i,j+1} - f_{i,j}}{\Delta z} + u_{i,j+1/2} f_{i,j})$$

Finite volume method

$$\partial_t f - \mathrm{div}(\sigma \nabla f + uf) = F$$



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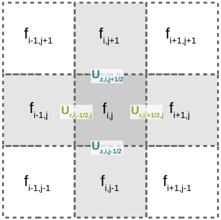
Linear system to be solved at each time step

$$\partial_t f_{i,j} + A f_{i,j} = F_{i,j}$$

Finite volume method

$$\partial_t f - \mathrm{div}(\sigma \nabla f + uf) = F$$



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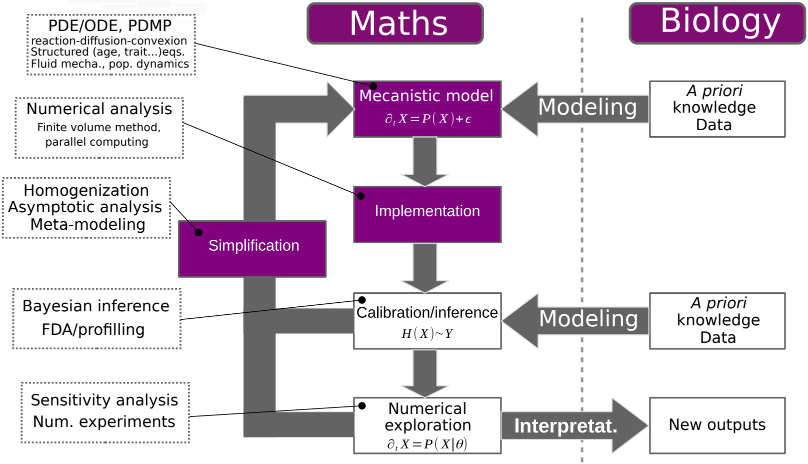
Time integration : Euler semi-implicit scheme

$$\frac{f_{i,j}^{n+1} - f_{i,j}^{n}}{\Delta t} + A f_{i,j}^{n+1} = F_{i,j}^{+,n} - F_{i,j}^{-,n+1}$$

$$\left(I + \Delta t (A + F_{i,j}^{-,n+1})\right) f_{i,j}^{n+1} = f_{i,j}^{n} + \Delta t F_{i,j}^{+,n}$$

5 Simplifications

Modeling process



Asymptotic analysis

Principles

- **Adimensioning :** $\Rightarrow$small parameter ϵ (Ansatz)
- Seek (**formal**) solution in the form $f = f_0 + \epsilon f_1 + \epsilon^2 f_2 ...$
- **Inject** that expression in the equation
- **Identify** the elements with same power of ϵ $\Rightarrow$cascade of simpler equations
- Get f_0, f_1, ...
- **Prove rigorously** that $\|f - (f_0 + \epsilon f_1 + ...)\| \leq C\epsilon$ in a certain norm

Asymptotic analysis

aspect ratio $\epsilon = R/L$.

Asymptotic analysis

Adimensionning the differential operators

$$\nabla_\epsilon f := \begin{pmatrix} \partial_r f \\ \epsilon \partial_z f \end{pmatrix}, \quad D_\epsilon(u) := \begin{pmatrix} \partial_r u_r & \frac{1}{2}(\epsilon \partial_z u_r + \partial_r u_z) \\ \frac{1}{2}(\epsilon \partial_z u_r + \partial_r u_z) & \epsilon \partial_z u_z \end{pmatrix}$$

$$\mathrm{div}_\epsilon(u) := \frac{1}{r}\partial_r(r u_r) + \epsilon \partial_z u_z, \quad \mathrm{div}_\epsilon(M) := \begin{pmatrix} \frac{1}{r}\partial_r(r M_{11}) + \epsilon \partial_z M_{12} \\ \frac{1}{r}\partial_r(r M_{21}) + \epsilon \partial_z M_{22} \end{pmatrix}.$$

Asymptotic analysis

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Stokes system + Keller Seigel

$$\frac{1}{\epsilon} \nabla_\epsilon p - \mathrm{div}_\epsilon(\mu D_\epsilon(u)) = 0$$

$$\mathrm{div}_\epsilon(u) = -\epsilon \, \mathrm{div}_\epsilon\Big(\sum_{i \in I_C} f_i \sum_{j \in I_C \cup I_S} \lambda_{i,j} \nabla_\epsilon(\Phi_j)\Big)$$

$$\frac{1}{\epsilon} \mathrm{div}_\epsilon(\nabla_\epsilon \Phi_j) = \frac{1}{\epsilon}\left(c_j - 2\int_0^1 s c_j(s,z) ds\right)$$

Asymptotic analysis

Adimensionning the differential operators

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Stokes system + Keller Seigel ⇒spatial decoupling

$$\frac{1}{\epsilon}\nabla_\epsilon p - \mathrm{div}_\epsilon(\mu D_\epsilon(u)) = 0$$

$$\mathrm{div}_\epsilon(u) = -\epsilon\, \mathrm{div}_\epsilon\Big(\sum_{i \in I_C} f_i \sum_{j \in I_C \cup I_S} \lambda_{i,j} \nabla_\epsilon(\Phi_j)\Big)$$

$$\frac{1}{\epsilon}\mathrm{div}_\epsilon(\nabla_\epsilon \Phi_j) = \frac{1}{\epsilon}\left(c_j - 2\int_0^1 s c_j(s,z) ds\right)$$

$$U_z = U_{z,s} + \epsilon U_{z,s}^{(1)} + \cdots, \quad U_r = U_{r,s} + \epsilon U_{r,s}^{(1)} + \cdots$$

$$\partial_r p = 0 \Rightarrow p(r,z) = P(z),$$

$$\frac{1}{r}\partial_r(r U_{r,s}) = 0 \Rightarrow U_{r,s} = 0$$

Asymptotic analysis

Adimensionning the differential operators

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Stokes system + Keller Seigel $\Rightarrow$spatial decoupling

$$\frac{1}{\epsilon}\nabla_\epsilon p - \mathrm{div}_\epsilon(\mu D_\epsilon(u)) = 0$$

$$\mathrm{div}_\epsilon(u) = -\epsilon\, \mathrm{div}_\epsilon(\sum_{i\in I_C} f_i \sum_{j\in I_C\cup I_S} \lambda_{i,j} \nabla_\epsilon(\Phi_j))$$

$$\frac{1}{\epsilon}\mathrm{div}_\epsilon(\nabla_\epsilon \Phi_j) = \frac{1}{\epsilon}\left(c_j - 2\int_0^1 s c_j(s,z) ds\right)$$

$$U_z = U_{z,s} + \epsilon U_{z,s}^{(1)} + \cdots, \quad U_r = U_{r,s} + \epsilon U_{r,s}^{(1)} + \cdots$$

$$\partial_z P(z) + \frac{1}{r}\partial_r(r\mu\partial_r U_{z,s}) = 0$$

$$\partial_z U_{z,s} + \frac{1}{r}\partial_r(r U_{r,s}^{(1)}) = -\frac{1}{r}\partial_r(r \sum_{i\in I_C} f_i \sum_{j\in I_C\cup I_S} \lambda_{i,j}(\Upsilon))$$

Asymptotic analysis

Adimensionning the differential operators

$$\nabla_\epsilon f := \begin{pmatrix} \partial_r f \\ \epsilon \partial_z f \end{pmatrix}, \quad D_\epsilon(u) := \begin{pmatrix} \partial_r u_r & \frac{1}{2}(\epsilon\partial_z u_r + \partial_r u_z) \\ \frac{1}{2}(\epsilon\partial_z u_r + \partial_r u_z) & \epsilon \partial_z u_z \end{pmatrix}$$

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Stokes system + Keller Seigel ⇒spatial decoupling

$$\partial_z P(z) + \frac{1}{r}\partial_r(r\mu\partial_r U_{z,s}) = 0 \Rightarrow r\mu\partial_r U_{z,s} = -\partial_z P(z) r^2 \Rightarrow U_{z,s} = -P(z)\int_r^1 \frac{s}{\mu} ds + U_{per}(z)$$

$$\partial_z U_{z,s} + \frac{1}{r}\partial_r(rU^{(1)}_{r,s}) = -\frac{1}{r}\partial_r(r\sum_{i\in I_C} f_i \sum_{j\in I_C\cup I_S} \lambda_{i,j}(\Upsilon)) \Rightarrow \partial_z \int_0^1 rU_{z,s}(z,r)dr = -\sum_i \gamma_i(z)$$

$$\partial_z(\kappa(z)\partial_z P(z)) = \sum_{i\in I_C} \gamma_{f,i}^{(0)} + \frac{1}{2}\partial_z U_{per}, \quad \text{where} \quad \kappa(z) := \int_0^1 r\Lambda(r,z)dr$$

Simplifications

Explicit formulas

Including all the key features of fluid mechanics :

$$u_{s,z} = -\underbrace{\frac{\Lambda(r,z)}{\kappa(z)}}_{\text{Rheology}} \left(R \int_0^z \sum_{i \in I_b} \underbrace{\gamma_i(R,s)}_{\text{Pumping}} ds + R^2 \underbrace{U_{z,in}}_{\text{Inflow}} + \underbrace{U_{per}(z)}_{\text{Peristaltism}} \right) + \underbrace{U_{per}(z)}_{\text{Peristaltism}}$$

$$\text{where } \Lambda(r,z) := \int_r^1 \frac{s}{\mu^{(0)}(s,z)} ds, \quad \kappa(z) := \int_0^1 r\Lambda(r,z) dr$$

$$u_{s,r} = \left(-\frac{1}{r} \int_0^r s\partial_z u_{s,z}(s,z) ds - \underbrace{\sum_{i \in I_b} b_i \sum_{j \in I_b \cup I_s} \lambda_{i,j} \Upsilon_j(r,z)}_{\text{Peristaltism}} \right).$$

Simplifications

Simplified system

$$\sum_{i \in I_C} f_i = 1$$

$$\partial_t f_i^{(0)} - \frac{1}{r}\partial_r(r\sigma^{(0)}\partial_r f_i^{(0)}) + \mathrm{div_r}(u_s f_i^{(0)}) + \frac{1}{r}\partial_r(r\vartheta_i f_i^{(0)}) = F^{(0)}$$

$$\partial_t c_j^{(0)} - \frac{1}{r}\partial_r(r\theta^{(0)}\partial_r c_j^{(0)}) + \tilde{u}\cdot\nabla_\mathrm{r}\, c_j^{(0)} = G^{(0)}.$$

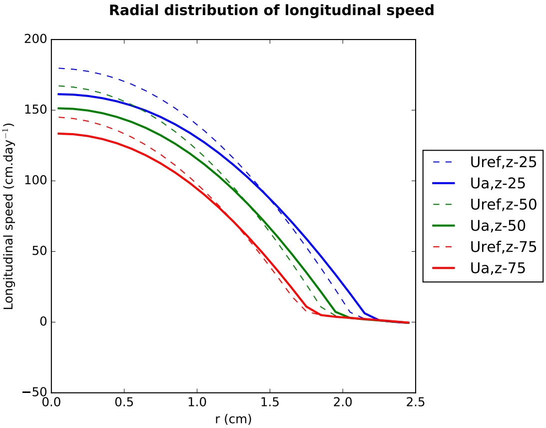
$$\vartheta_i = \left(\sum_{j \in I_S \cup I_C} \lambda_{i,j}\Upsilon_j, 0\right)$$

$$\Upsilon_j(r,z) = -\left(\frac{1}{r}\int_0^r s c_j^{(0)}(s,z)ds - \frac{r}{R^2}\int_0^R s c_j^{(0)}(s,z)ds\right)$$

Speed up $\simeq 70$

numerical assessment

Assessment of the accuracy of the approximation



numerical assessment

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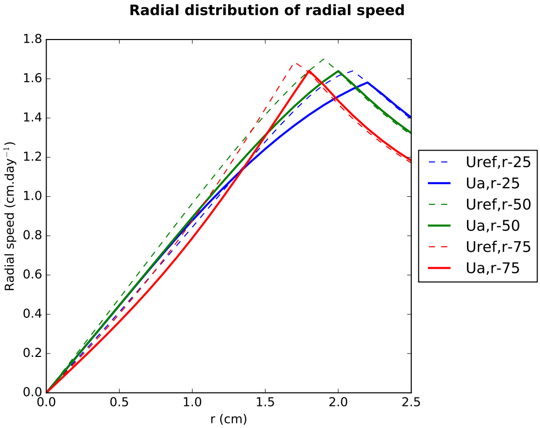

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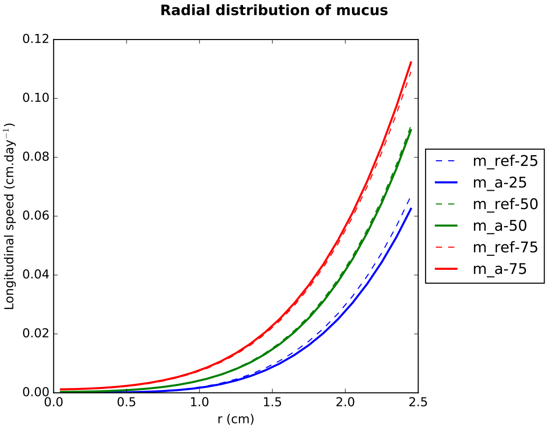

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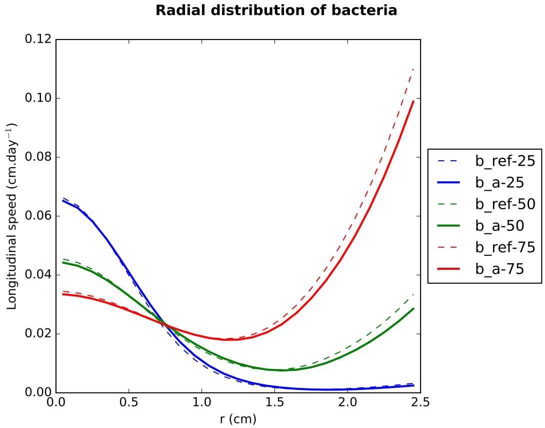
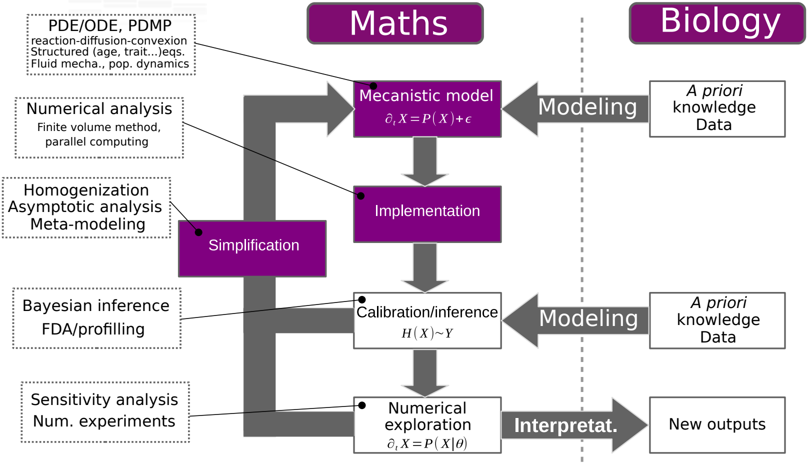


6 Numerical exploration

Modeling process



Sensitivity analysis

Principles

- **Experimental plan :** define a discrete exploration of the parameter space $(\theta_i)i \in I$
- **Construction of the model response :** for each parameter set θ_i $\Rightarrow$model run
- **Compute sensitivity criteria** : Sobol Index, PRCC,...

$$S_\theta(z) := \frac{Var(\mathbb{E}(B(z)|\theta))}{Var(B(z))}.$$

where $B(z) = \sum_{i \in I_B} \frac{2}{R^2} \int_0^R rc_i(r,z)\,\mathrm{d}r$

Sensitivity analysis