

Mathematical models in microbial ecology Simon Labarthe

▶ To cite this version:

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

HAL Id: hal-03352423 https://hal.inrae.fr/hal-03352423

Submitted on 23 Sep 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



S.Labarthe

DynEnvie - MaIAGE - INRA Jouy en Josas 09/27/2019



Mathematical models in microbial ecology





1 Introduction Why studying the microbiota?





Microbiology before omic data

- Insulation
- Culture in vitro
- Functional phenotyping of individuals

Studying a microbial ecosystem = studying individuals = reductionism



Omic data revolution





S.Labarthe (MIA

Omic data revolution

Microbiology after omic data



Adapted from S.Raguideau's thesis

Global view of microbial ecosystem = holism/system biology



S.Labarthe (MIA)

Omic data revolution

Microbiology after omic data



Adapted from S.Raguideau's thesis

Global view of microbial ecosystem = holism/system biology



S.Labarthe (MIA)



Microbiology after omic data

		#1	#2	#3	#4	#5
	Sample 1	1	20	13	4	0
	Sample 2	2	0	30	1	14
WGS fragments in a Mignment of the fragments on the gene catalogue	Sample n	10	5	3	14	2

Counts matrix: gene abundances among samples

Adapted from S.Raguideau's thesis

Global view of microbial ecosystem = holism/system biology



S.Labarthe (MIA)

Human gut microbiota



Microbiote

- several thousands of microbial species
- 10 imes the number of human cells
- metagenome ⇒150 × the number of genes of human genomes



S.Labarthe (MIA)

Human gut microbiota



Microbiote

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

Microbial ecology

- Interactions ?
- Dysbiosis?
- Colonization ?

Human gut microbiota



Microbiote

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

Microbial ecology

- Interactions ?
- Dysbiosis?
- Colonization ?

'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

 \Rightarrow Microbiota impact on host glucidic and lipidic metabolism regulation



S.Labarthe (MIA)



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







Rivera Chavez et al. Mbio 2016

Barrier effect

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

 \Rightarrow Microbiota offers protection against pathogens.



S.Labarthe (MIA)





Bach, NEJM 2002

Involvement in immunity regulation

> Microbiota involved in immunity calibration during first years of life



S.Labarthe (MIA)



Micro-organisms community



S.Labarthe (MIA)



Micro-organisms community

Human host



S.Labarthe (MIA)







S.Labarthe (MIA)







S.Labarthe (MIA)







S.Labarthe (MIA)







S.Labarthe (MIA)







S.Labarthe (MIA)





Microbial ecology

- Interactions?
- Dysbiosis?
 - Colonization ?







Microbial ecology

- Interactions?
- Dysbiosis?
 - Colonization ?







Microbial ecology

- Interactions?
- Dysbiosis ?
- Colonization ?

Modeling bacterial populations in their environment





2 Mechanistic modeling for microbiology







S.Labarthe (MIA)

Maths models in microbial ecology

09/27/2019 10 / 26





S.Labarthe (MIA)

Maths models in microbial ecology

09/27/2019 10 / 26



3 <u>Mod</u>el presentation



S.Labarthe (MIA)

Maths models in microbial ecology

09/27/2019 11 / 26





S.Labarthe (MIA)





S.Labarthe (MIA)



Geometry

On
$$\Omega = \omega \times L$$

Mixture model.

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

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

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

S.Labarthe (MIA)

Maths models in microbial ecology



Geometry

On $\Omega = \omega \times L$

Mixture model.

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

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

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

Bathing solutes.

 $\mathit{I}_{\mathcal{S}}$: set of 8 solutes. No volume. $\widetilde{\mathit{u}} = \sum_{i \in \mathit{I}_{\mathcal{C}}} \mathit{c}_{i} \mathit{u}_{i}$

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

S.Labarthe (MIA)





Chemotactic speed

Keller-Segel model $\upsilon_{\textit{chem},i} = \nabla \Phi,$

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



S.Labarthe (MIA)



Chemotactic speed Keller-Segel model $v_{chem,i} = \nabla \Phi,$ $-\Delta \Phi = s_j - \frac{1}{|\omega|} \int_{\omega} rs_j(r) dr, \quad \nabla \Phi \cdot \eta = 0 \text{ on } \partial \Omega$ Stokes equation $\nabla p - \operatorname{div}(\mu D(\mu)) = 0$

$$abla p - \operatorname{div}(\mu D(u)) =$$
where $D(u) = rac{1}{2}(
abla u +
abla u^t)$,

S.Labarthe (MIA)

Maths models in microbial ecology



Chemotactic speed

Keller-Segel model

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

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

Stokes equation

$$abla p - \operatorname{div}(\mu(c)D(u)) = 0$$

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



Chemotactic speed

Keller-Segel model

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

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

Stokes equation

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

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

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



S.Labarthe (MIA)

Trophic

Interactions



Boundary conditions

• For c and s :

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

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

Physiological influx and mucosal exchanges γ_i . Outflow = transport.

• For *u* :

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

S.Labarthe (MIA)

Source function & Model structure

$\mathsf{Ecology} \Rightarrow \mathsf{Trophic} \text{ interactions}$

Knowledge-based microbiota metabolic model (Muñoz Tamayo 2010)





S.Labarthe (MIA)

Source function & Model structure

$\mathsf{Ecology} \Rightarrow \mathsf{Trophic interactions}$

Knowledge-based microbiota metabolic model (Muñoz Tamayo 2010)



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

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



S.Labarthe (MIA)



4 Implementation







S.Labarthe (MIA)

Maths models in microbial ecology

09/27/2019 16 / 26



Principles

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





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

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

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

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 $u_{i,j+1/2} \ge 0$

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





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

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

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

Stokes formula + constant on cell

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

Linear system to be solved at each time step

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





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

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

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

Stokes formula $+\mbox{ constant}$ on cell

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

Time integration : Euler semi-implicit scheme

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





5 Simplifications



S.Labarthe (MIA)

Maths models in microbial ecology

09/27/2019 18 / 26





S.Labarthe (MIA)

Maths models in microbial ecology

09/27/2019 19 / 26



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 $\epsilon \Rightarrow$ cascade of simpler equations
- Get *f*₀, *f*₁, ...
- Prove rigorously that $||f (f_0 + \epsilon f_1 + ...)|| \le C\epsilon$ in a certain norm





aspect ratio $\epsilon = R/L$.



5.Labarthe (MIA

Maths models in microbial ecology



$$\nabla_{\epsilon} f := \begin{pmatrix} \partial_{r} f \\ \epsilon \partial_{z} f \end{pmatrix}, \quad D_{\epsilon}(u) := \begin{pmatrix} \partial_{r} u_{r} & \frac{1}{2} (\epsilon \partial_{z} u_{r} + \partial_{r} u_{z}) \\ \frac{1}{2} (\epsilon \partial_{z} u_{r} + \partial_{r} u_{z}) & \epsilon \partial_{z} u_{z} \end{pmatrix}$$
$$\operatorname{div}_{\epsilon}(u) := \frac{1}{r} \partial_{r}(ru_{r}) + \epsilon \partial_{z} u_{z}, \quad \operatorname{div}_{\epsilon}(M) := \begin{pmatrix} \frac{1}{r} \partial_{r}(rM_{11}) + \epsilon \partial_{z} M_{12} \\ \frac{1}{r} \partial_{r}(rM_{21}) + \epsilon \partial_{z} M_{22} \end{pmatrix}.$$



S.Labarthe (MIA

Asymptotic analysis

$$\nabla_{\epsilon} f := \begin{pmatrix} \partial_{r} f \\ \epsilon \partial_{z} f \end{pmatrix}, \quad D_{\epsilon}(u) := \begin{pmatrix} \partial_{r} u_{r} & \frac{1}{2} (\epsilon \partial_{z} u_{r} + \partial_{r} u_{z}) \\ \frac{1}{2} (\epsilon \partial_{z} u_{r} + \partial_{r} u_{z}) & \epsilon \partial_{z} u_{z} \end{pmatrix}$$
$$\operatorname{div}_{\epsilon}(u) := \frac{1}{r} \partial_{r}(ru_{r}) + \epsilon \partial_{z} u_{z}, \quad \operatorname{div}_{\epsilon}(M) := \begin{pmatrix} \frac{1}{r} \partial_{r}(rM_{11}) + \epsilon \partial_{z} M_{12} \\ \frac{1}{r} \partial_{r}(rM_{21}) + \epsilon \partial_{z} M_{22} \end{pmatrix}.$$

Stokes system + Keller Seigel

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

$$\operatorname{div}_{\epsilon}(u) = -\epsilon \operatorname{div}_{\epsilon}(\sum_{i \in I_{C}} f_{i} \sum_{j \in I_{C} \cup I_{S}} \lambda_{i,j} \nabla_{\epsilon}(\Phi_{j}))$$

$$\frac{1}{\epsilon} \operatorname{div}_{\epsilon}(\nabla_{\epsilon} \Phi_{j}) = \frac{1}{\epsilon} \left(c_{j} - 2 \int_{0}^{1} sc_{j}(s, z) ds \right)$$





$$\nabla_{\epsilon} f := \begin{pmatrix} \partial_{r} f \\ \epsilon \partial_{z} f \end{pmatrix}, \quad D_{\epsilon}(u) := \begin{pmatrix} \partial_{r} u_{r} & \frac{1}{2} (\epsilon \partial_{z} u_{r} + \partial_{r} u_{z}) \\ \frac{1}{2} (\epsilon \partial_{z} u_{r} + \partial_{r} u_{z}) & \epsilon \partial_{z} u_{z} \end{pmatrix}$$
$$\operatorname{div}_{\epsilon}(u) := \frac{1}{r} \partial_{r}(ru_{r}) + \epsilon \partial_{z} u_{z}, \quad \operatorname{div}_{\epsilon}(M) := \begin{pmatrix} \frac{1}{r} \partial_{r}(rM_{11}) + \epsilon \partial_{z} M_{12} \\ \frac{1}{r} \partial_{r}(rM_{21}) + \epsilon \partial_{z} M_{22} \end{pmatrix}.$$

Stokes system + Keller Seigel \Rightarrow spatial decoupling

$$\frac{1}{\epsilon} \nabla_{\epsilon} p - \operatorname{div}_{\epsilon}(\mu D_{\epsilon}(u)) = 0 \qquad \qquad U_{z} = U_{z,s} + \epsilon U_{z,s}^{(1)} + \cdots, \qquad U_{r} = U_{r,s} + \epsilon U_{r,s}^{(1)} + \cdots \\ \operatorname{div}_{\epsilon}(u) = -\epsilon \operatorname{div}_{\epsilon}(\sum_{i \in I_{C}} f_{i} \sum_{j \in I_{C} \cup I_{S}} \lambda_{i,j} \nabla_{\epsilon}(\Phi_{j})) \qquad \qquad \partial_{r} p = 0 \Rightarrow p(r, z) = P(z), \\ \frac{1}{\epsilon} \operatorname{div}_{\epsilon}(\nabla_{\epsilon} \Phi_{j}) = \frac{1}{\epsilon} \left(c_{j} - 2\int_{0}^{1} \operatorname{sc}_{j}(s, z) ds\right) \qquad \qquad \frac{1}{r} \partial_{r}(r U_{r,s}) = 0 \Rightarrow U_{r,s} = 0$$



S.Labarthe (MIA

Asymptotic analysis

$$\nabla_{\epsilon} f := \begin{pmatrix} \partial_{r} f \\ \epsilon \partial_{z} f \end{pmatrix}, \quad D_{\epsilon}(u) := \begin{pmatrix} \partial_{r} u_{r} & \frac{1}{2} (\epsilon \partial_{z} u_{r} + \partial_{r} u_{z}) \\ \frac{1}{2} (\epsilon \partial_{z} u_{r} + \partial_{r} u_{z}) & \epsilon \partial_{z} u_{z} \end{pmatrix}$$

$$\operatorname{div}_{\epsilon}(u) := \frac{1}{r} \partial_{r}(ru_{r}) + \epsilon \partial_{z} u_{z}, \quad \operatorname{div}_{\epsilon}(M) := \begin{pmatrix} \frac{1}{r} \partial_{r}(rM_{11}) + \epsilon \partial_{z} M_{12} \\ \frac{1}{r} \partial_{r}(rM_{21}) + \epsilon \partial_{z} M_{22} \end{pmatrix}.$$

Stokes system + Keller Seigel \Rightarrow spatial decoupling

(1)



S.Labarthe (MIA

Maths models in microbial ecology

(1)

Asymptotic analysis

$$\nabla_{\epsilon} f := \begin{pmatrix} \partial_{r} f \\ \epsilon \partial_{z} f \end{pmatrix}, \quad D_{\epsilon}(u) := \begin{pmatrix} \partial_{r} u_{r} & \frac{1}{2} (\epsilon \partial_{z} u_{r} + \partial_{r} u_{z}) \\ \frac{1}{2} (\epsilon \partial_{z} u_{r} + \partial_{r} u_{z}) & \epsilon \partial_{z} u_{z} \end{pmatrix}$$
$$\operatorname{div}_{\epsilon}(u) := \frac{1}{r} \partial_{r}(ru_{r}) + \epsilon \partial_{z} u_{z}, \quad \operatorname{div}_{\epsilon}(M) := \begin{pmatrix} \frac{1}{r} \partial_{r}(rM_{11}) + \epsilon \partial_{z} M_{12} \\ \frac{1}{r} \partial_{r}(rM_{21}) + \epsilon \partial_{z} M_{22} \end{pmatrix}.$$

Stokes system + Keller Seigel \Rightarrow spatial decoupling

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

$$\partial_{z} U_{z,s} + \frac{1}{r} \partial_{r} (r U_{r,s}^{(1)}) = -\frac{1}{r} \partial_{r} (r \sum_{i \in I_{C}} f_{i} \sum_{j \in I_{C} \cup I_{S}} \lambda_{i,j}(\Upsilon)) \Rightarrow \partial_{z} \int_{0}^{1} r U_{z,s}(z,r) dr = -\sum_{i} \gamma_{i}(z)$$
$$\partial_{z} (\kappa(z) \partial_{z} P(z)) = \sum_{i \in I_{C}} \gamma_{f,i}^{(0)} + \frac{1}{2} \partial_{z} U_{per}, \quad \text{where} \quad \kappa(z) := \int_{0}^{1} r \Lambda(r,z) dr$$





Explicit formulas

Including all the key features of fluid mechanics :

$$u_{s,z} = -\underbrace{\frac{\Lambda(r,z)}{\kappa(z)}}_{\text{Rheology}} \left(R \int_{0}^{z} \sum_{i \in I_{b}} \underbrace{\gamma_{i}(R,s)}_{\text{Pumping}} ds + R^{2} \underbrace{U_{z,in}}_{\text{Inflow}} + \underbrace{U_{per}(z)}_{\text{Peristaltism}} \right) + \underbrace{U_{per}(z)}_{\text{Peristaltism}}$$
where $\Lambda(r,z) := \int_{r}^{1} \frac{s}{\mu^{(0)}(s,z)} ds$, $\kappa(z) := \int_{0}^{1} r \Lambda(r,z) dr$

$$u_{s,r} = \left(-\frac{1}{r} \int_{0}^{r} s \partial_{z} u_{s,z}(s,z) ds - \underbrace{\sum_{i \in I_{b}} b_{i} \sum_{j \in I_{b} \cup I_{s}} \lambda_{i,j} \Upsilon_{j}(r,z)}_{\text{Peristaltism}} \right).$$





Simplified system

$$\begin{split} &\sum_{i \in I_{C}} f_{i} = 1 \\ &\partial_{t} f_{i}^{(0)} - \frac{1}{r} \partial_{r} (r \sigma^{(0)} \partial_{r} f_{i}^{(0)}) + \operatorname{div}_{r} (u_{s} f_{i}^{(0)}) + \frac{1}{r} \partial_{r} (r \vartheta_{i} f_{i}^{(0)}) = F^{(0)} \\ &\partial_{t} c_{j}^{(0)} - \frac{1}{r} \partial_{r} (r \theta^{(0)} \partial_{r} c_{j}^{(0)}) + \tilde{u} \cdot \nabla_{r} c_{j}^{(0)} = G^{(0)}. \\ &\vartheta_{i} = \left(\sum_{j \in I_{S} \cup I_{C}} \lambda_{i,j} \Upsilon_{j}, 0 \right) \\ &\Upsilon_{j}(r, z) = - \left(\frac{1}{r} \int_{0}^{r} s c_{j}^{(0)}(s, z) ds - \frac{r}{R^{2}} \int_{0}^{R} s c_{j}^{(0)}(s, z) ds \right) \end{split}$$

Speed up $\simeq 70$



.Labarthe (MIA

numerical assessment

Assessment of the accuracy of the approximation

Radial distribution of longitudinal speed





S.Labarthe (MIA

Maths models in microbial ecology



Assessment of the accuracy of the approximation



Radial distribution of radial speed



S.Labarthe (MIA

Maths models in microbial ecology



Assessment of the accuracy of the approximation



Radial distribution of mucus



S.Labarthe (MIA

Maths models in microbial ecology

numerical assessment

Assessment of the accuracy of the approximation



Radial distribution of bacteria



S.Labarthe (MIA

Maths models in microbial ecology



6 Numerical exploration



S.Labarthe (MIA)

Maths models in microbial ecology





S.Labarthe (MIA)

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 $\theta_i \Rightarrow$ model run
- Compute sensitivity criteria : Sobol Index, PRCC,...

$$S_{ heta}(z) := rac{Var(\mathbb{E}(B(z)| heta))}{Var(B(z))}$$

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



S.Labarthe (MIA) Maths models in microbial ecology







S.Labarthe (MIA)