# Dynamic Flux Balance Analysis with Metamodels

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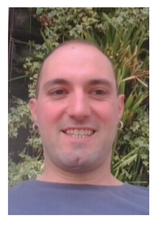

**About the presenter**: Mathematical Engineer (U. de Chile), Ph.D in Microbiology and Biotechnology at INRAE Laboratoire de Biotechnologie de L'Environnement (U. de Montpellier). Postdoctoral fellow at INRIA Bordeaux at the team unit PLEIADE. Interested in the interplay and integration between **bioprocess, microbial ecology, bioenergetics and genetic sequencing** from a dynamic **modelling** stance.
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## 1. Modeling of microbial metabolism through time

### 1.1 FBA models

**Genome sequencing** allows us to reconstruct the set of **possible reactions** within a cell. Deciding at which **rate** ($\nu$) to produce or consume **metabolites** can be formalized in **Flux Balance Analysis** (FBA) [3].

$$\begin{aligned} \nu^* := \arg\max \quad & \nu_b \\ s.t. & A\nu = 0 \\ & \nu \in [c_{\text{min}}, c_{\text{max}}] \\ & \nu_{up} \in [c^{(up)}, c_{\text{max}}] \end{aligned} \tag{FBA}$$

- $\nu_b$ represents the **biomass flux**. A **working hypothesis** is that cells maximize biomass formation.
- $A\nu = 0$ reflects the **mass balance** of genome-based reactions.
- The bounds $[c_{\text{min}}, c_{\text{max}}]$ are **fixed physical limits** to the flux $\nu$.
- The **environmental conditions** are reflected on the **variable uptake bounds** $c^{(up)}$ for the case of the $N^{up}$ **extracellular metabolites**. They depend on the **availability of metabolites**.

Let $\mathcal{F}$ be the function that maps the **constraints** $c^{(up)}$ to the optimal **flux** $v^*$ obtained by (FBA)

$$\begin{aligned} \mathcal{F}: \quad \mathbb{R}^{N^{up}} &\longrightarrow \mathbb{R}^{N_r} \\ c^{(up)} &\mapsto \nu^* \end{aligned}$$

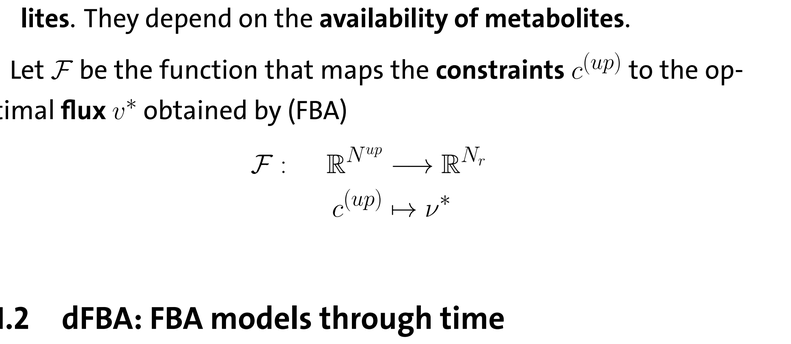
### 1.2 dFBA: FBA models through time

Extracellular metabolites change through time: One can include function $\mathcal{F}$ in a dynamic setting.

- If $x$ is the state variable representing the concentrations of extracellular metabolites varying in time, one can write $c^{(up)} = c^{(up)}(x)$.
- Abusing notation then $\mathcal{F}(c^{(up)}(x)) = \mathcal{F}(x)$.
- Time evolution is described by the system $\dot{x} = f\left(x, \mathcal{F}(x)\right)$ (see diagram below).

### 1.3 Main goal

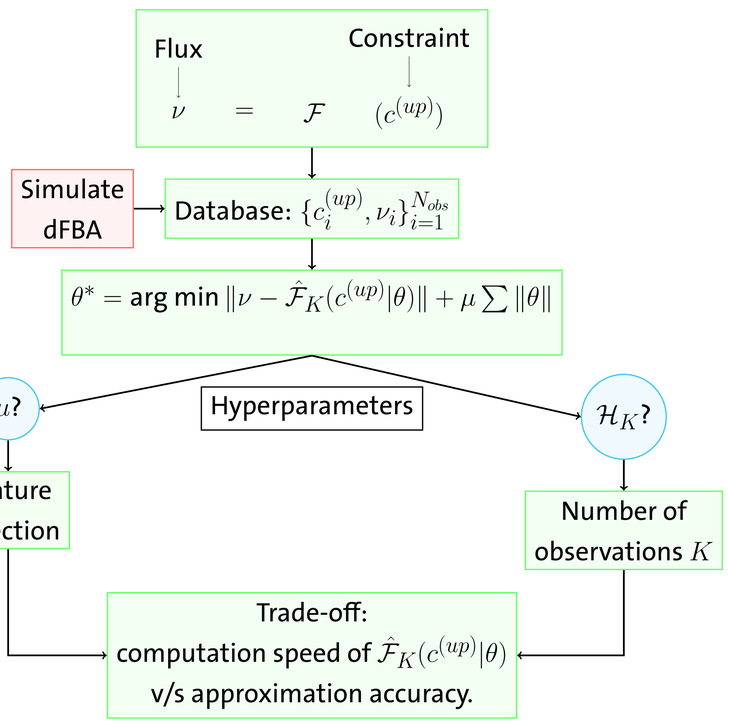
Evaluation of dFBA models can represent a high computational cost in various situations (large microbial community, parameter inferecence, sensitivity analysis, PDE resolution). It is then of interest to provide **a low-computational-cost approximate model**.




In a usual dFBA, an optimization problem (FBA) must be solved at each time step of the numerical integration. The idea is to replace it (right diagram) with a metamodel at the price of accuracy. The problem becomes a **trade-off** between **speed-up** and **accuracy**.

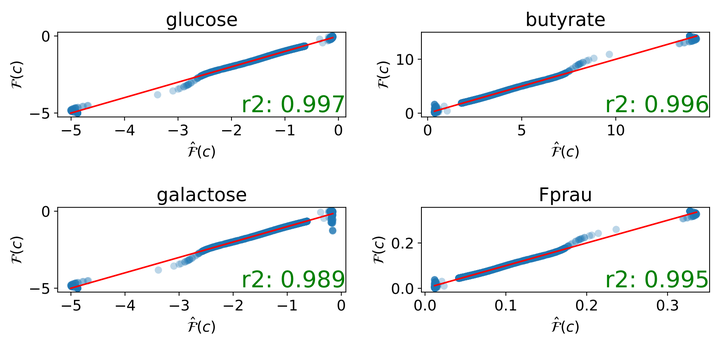
## 2. Metamodel of FBA

FBA is approximated using an ANOVA-Reproducing Kernel Hilbert Space techniques (RKHS) [2]. This method allows to perform **simultaneously feature selection and model approximation** to focus the computational budget on sensitive variables.




Hyperparameter $\mu$ selection performed on unseen points and $\mathcal{H}_K$ on new dFBA computations. For the selected parameters, the metamodel of FBA presents a good fit.

**Figure 1:** Comparison of the metamodel $\hat{\mathcal{F}}$ and $\mathcal{F}$

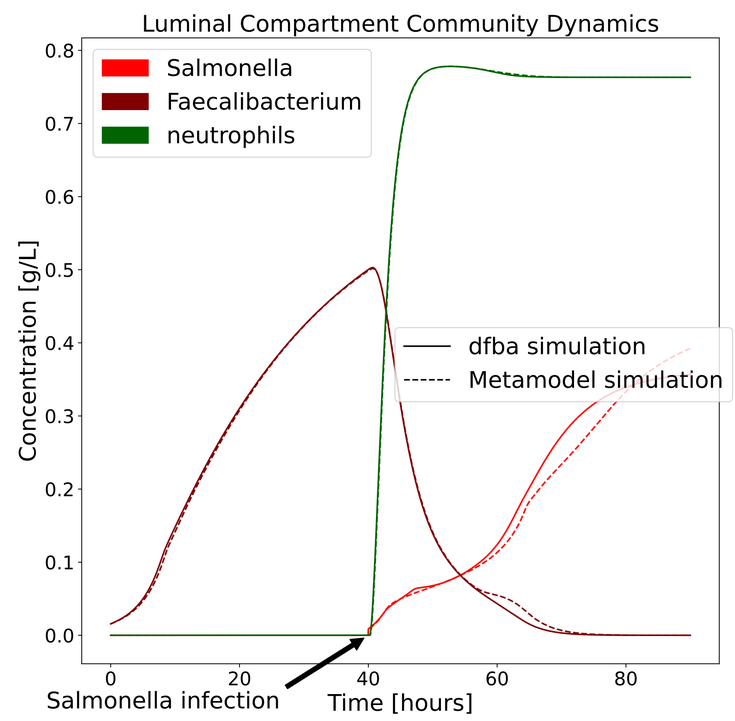



The metamodel outputs are plotted against the FBA model outputs on unseen constraints $c^{(up)}$.

## 3. dFBA case study

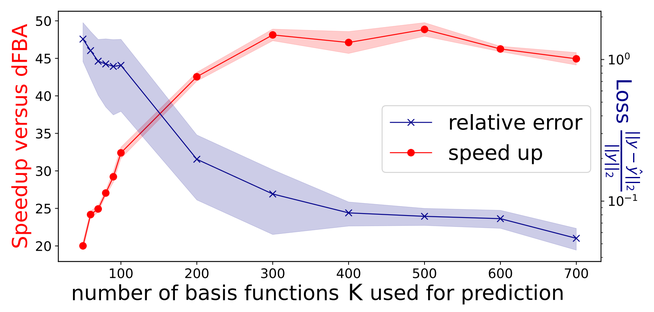
We use a dynamical system that models the infection of Salmonella in a host. It includes two different FBA, one for *Salmonella* and another one for commensal bacteria represented by *Faecalibacterium Prauznitzii*. For a more detailed view on the model we refer to the **poster 161** entitled "Modelling the dynamics of Salmonella infection in the gut at the bacterial and host levels" and to our article [1].

**Figure 2:** The ecological dynamics of both dFBA and the accelerated model




The same system ODE is solved with $\mathcal{F}$ (plain lines) or $\hat{\mathcal{F}}$ (dotted lines).

**Figure 3:** Trade-off between speed-up and relative error.




The trade-off "speed-up/accuracy" is tuned by $K$, but also by $\mu$: for low $K$ and fixed $\mu$, a higher number of features are retained $\Rightarrow$ impaired speed-up.

## 4. Take-Home Message

- dFBA models can be accelerated by a metamodel with a speed-up of 47 and satisfactory accuracy (7%).
- ANOVA-RKHS allows at the same time to accurately estimate the problem and select feature.
- Perspective: Other dimensional reduction techniques are being studied to improve speed-up.

## References

[1] Clémence Frioux, Sylvie Huet, Simon Labarthe, Julien Martinelli, Thibault Malou, David James Sherman, Marie-Luce Taupin, and Pablo Ugalde-Salas. Accelerating metabolic models evaluation with statistical metamodels: application to Salmonella infection models. working paper or preprint, April 2022.

[2] Sylvie Huet and Marie-Luce Taupin. Metamodel construction for sensitivity analysis. *ESAIM: Proceedings and Surveys*, 60:27–69, 2017.

[3] Jeffrey D Orth, Ines Thiele, and Bernhard Ø Palsson. What is flux balance analysis? *Nature Biotechnology*, 28(3):245–248, 2010.