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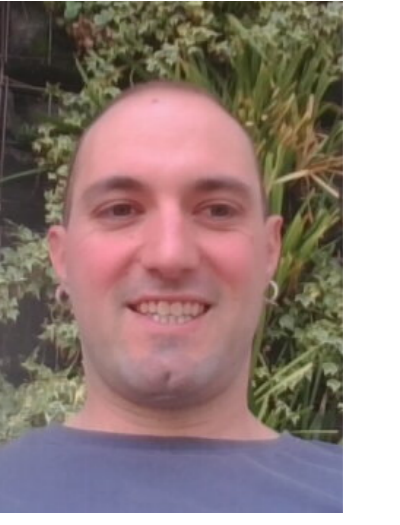
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Dynamic Flux Balance Analysis with Metamodels

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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 (ν) to produce or consume metabolites can be formalized in Flux Balance Analysis (FBA) [3].

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

- ν_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 $[c_{\min}, c_{\max}]$ are **fixed physical limits** to the flux ν .
- 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 ν^* obtained by (FBA)

$$\mathcal{F}: \mathbb{R}^{N^{up}} \rightarrow \mathbb{R}^{N_r} \\ c^{(up)} \mapsto \nu^*$$

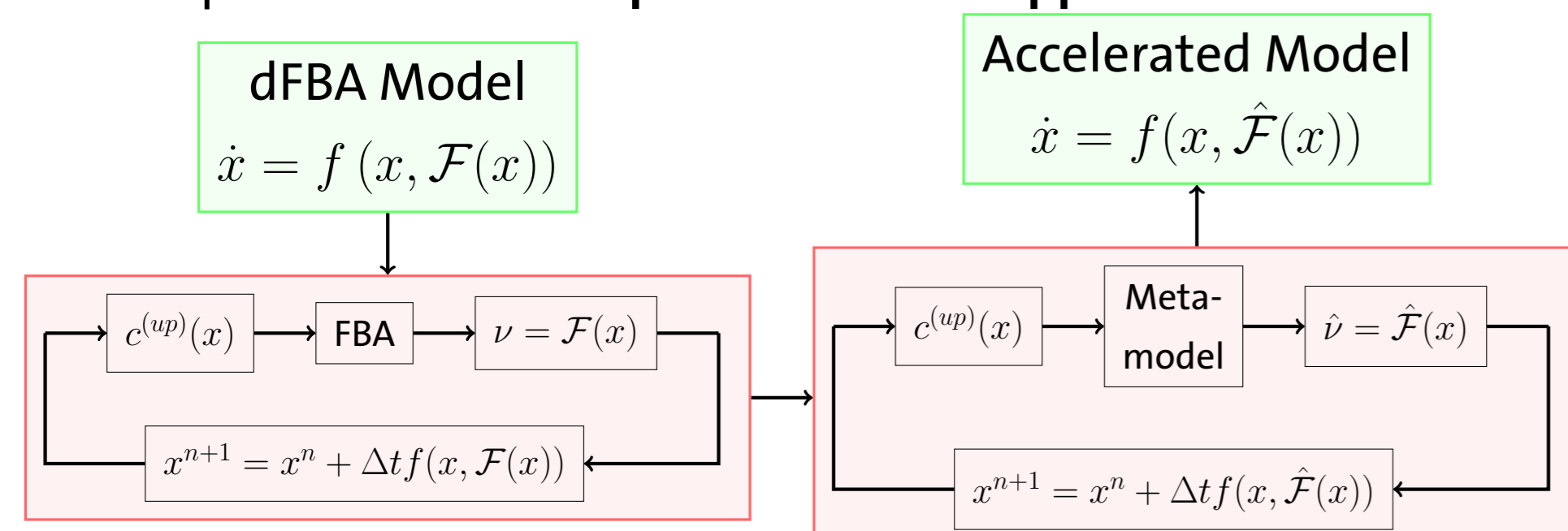
1.2 dFBA: FBA models through time

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 $\dot{x} = f(x, \mathcal{F}(x))$ (see diagram below).

1.3 Main goal

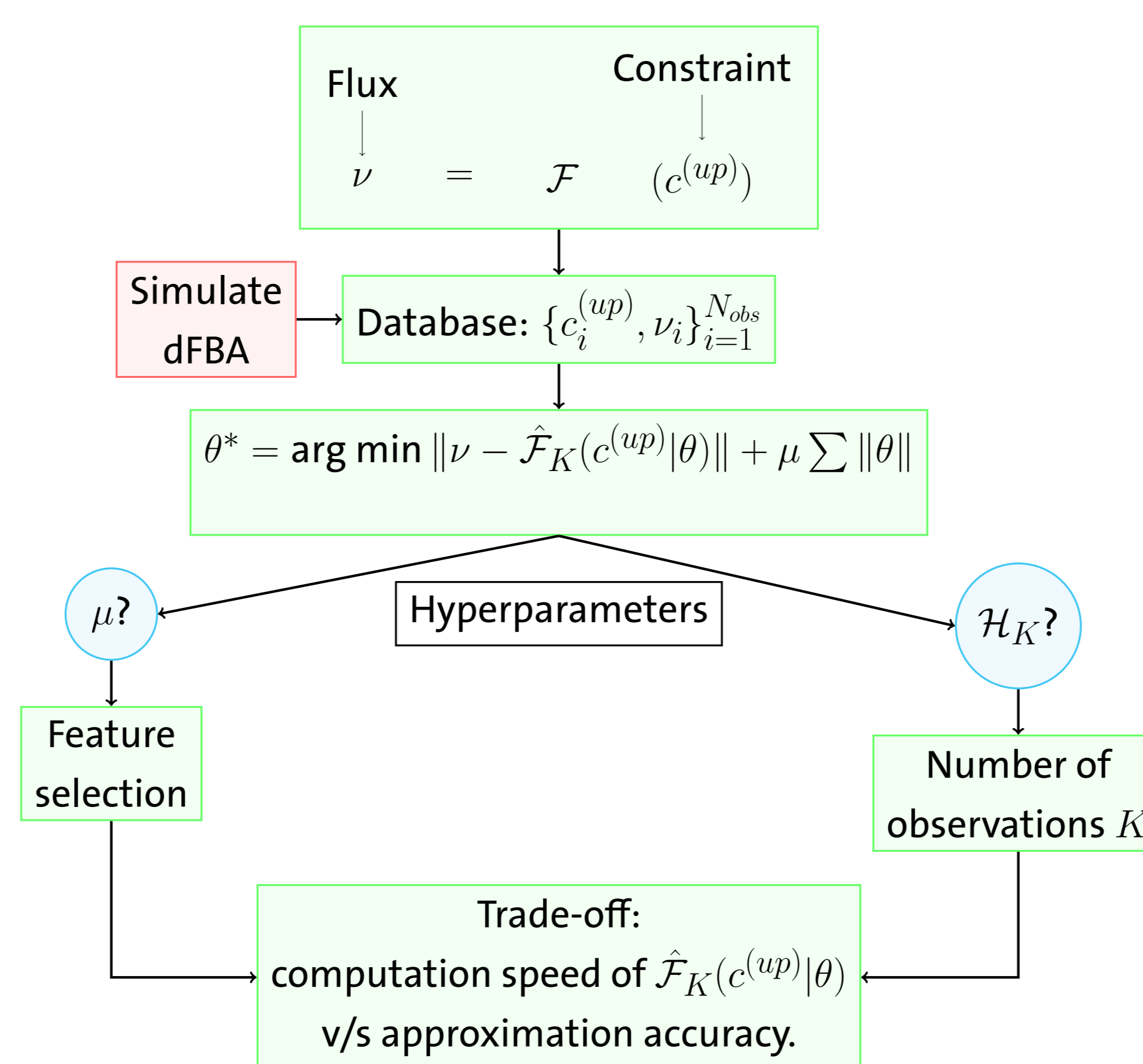
Evaluation of dFBA models can represent a high computational cost in various situations (large microbial community, parameter inference, sensitivity analysis, PDE resolution). It is then of interest to provide a **low-computational-cost approximate model**.



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**.

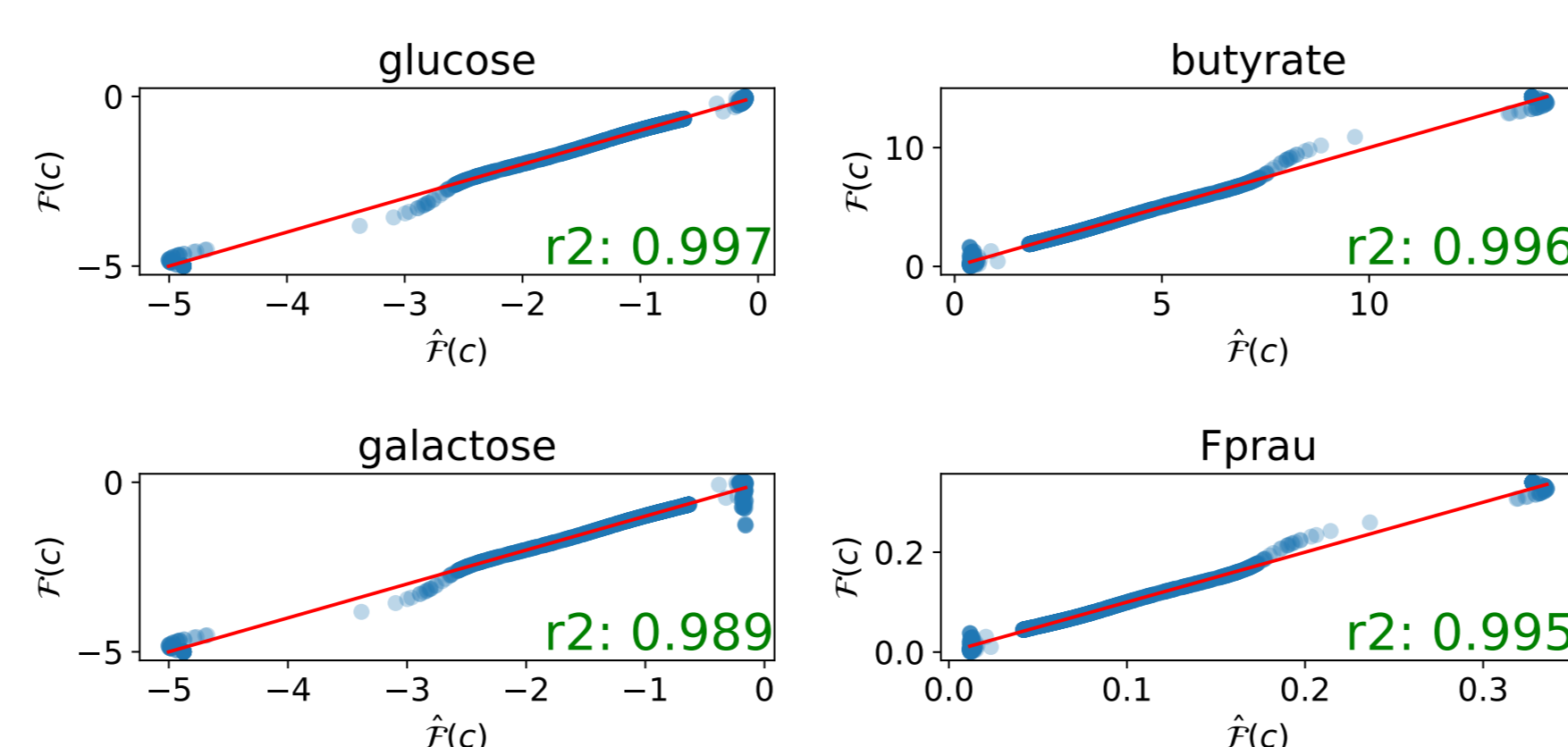
2. Metamodel of FBA

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 μ 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}

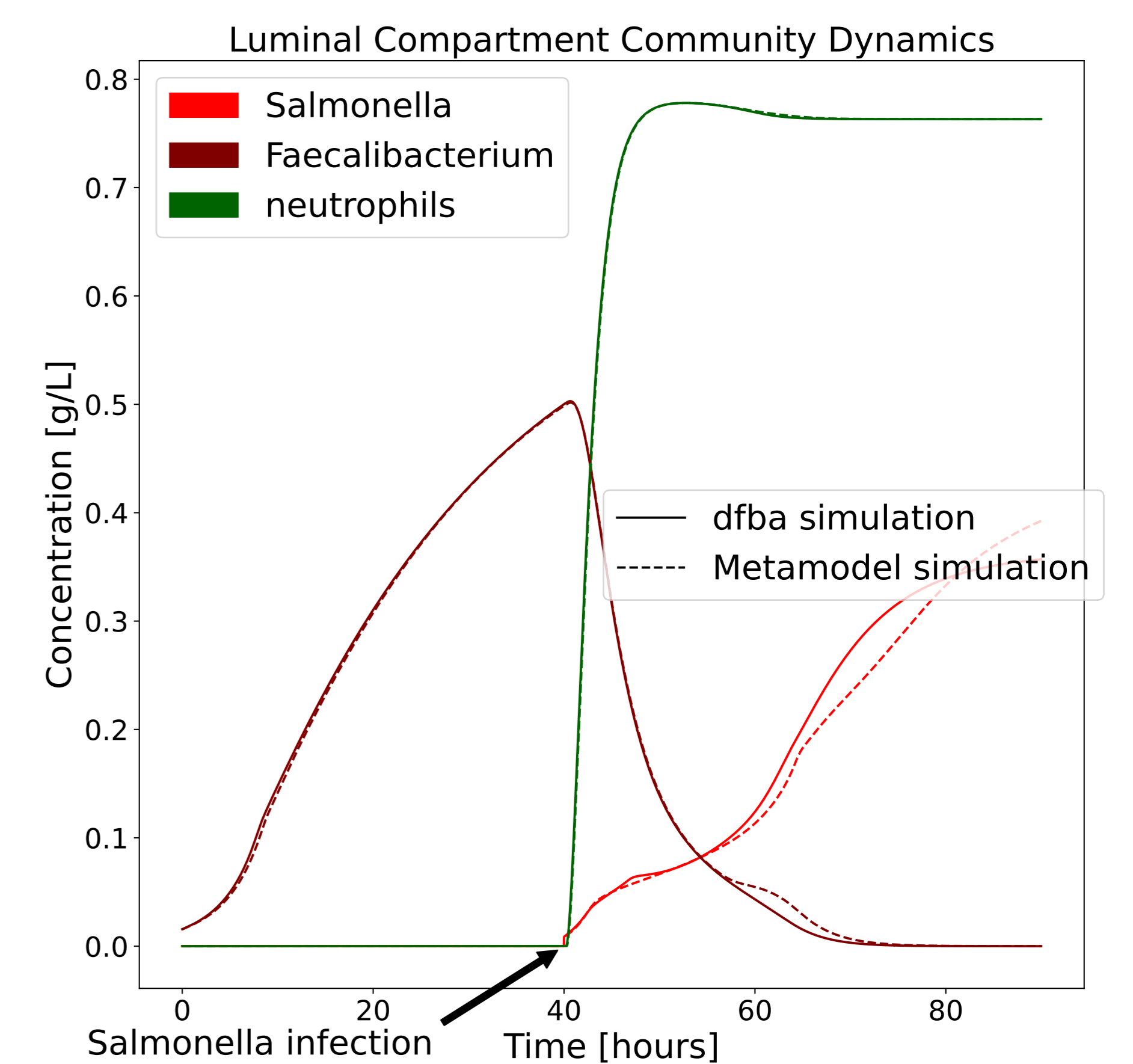


The metamodel outputs are plotted against the FBA model outputs on unseen constraints $c^{(up)}$.

3. dFBA case study

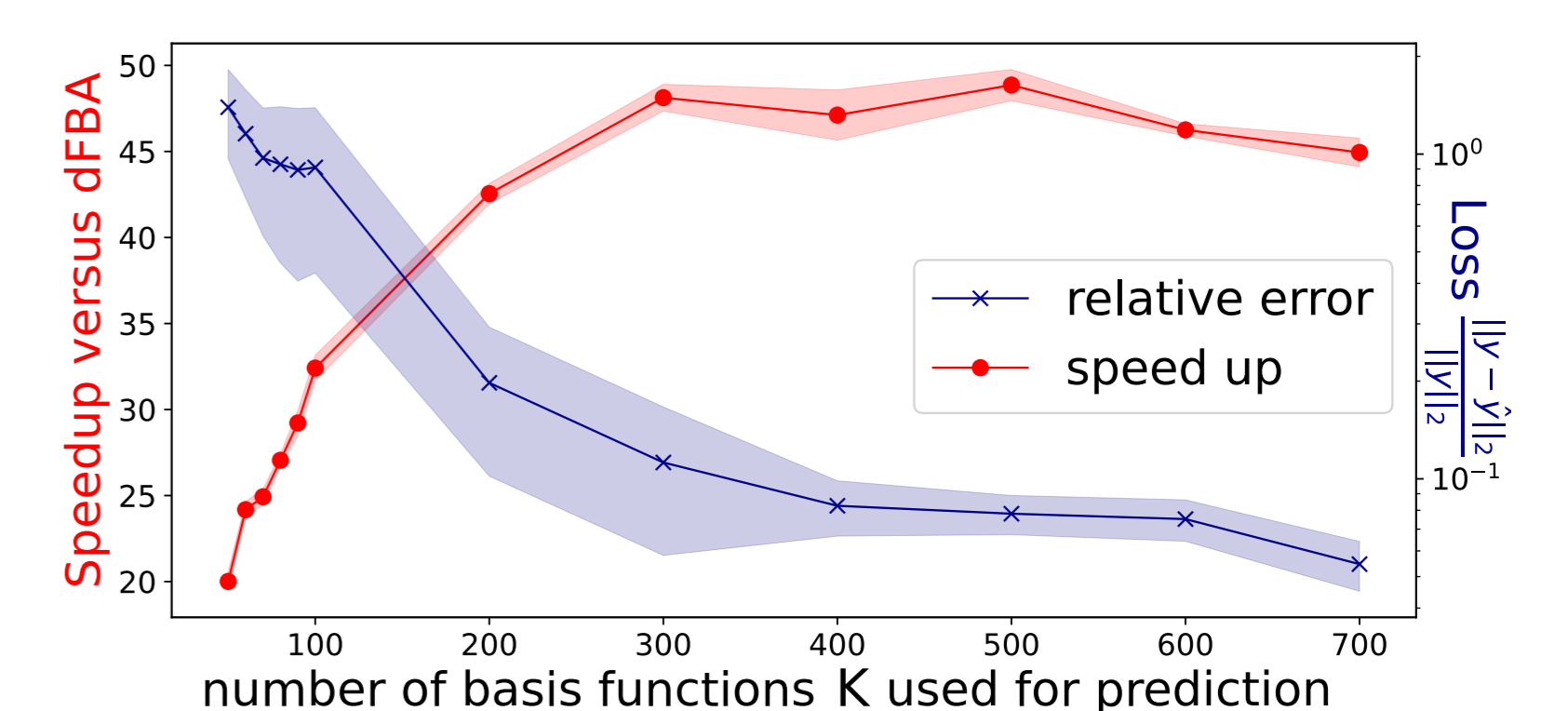
We use a dynamical system that models the infection of Salmonella in a host. It includes two different FBA, one for *Salmonella* and another one for commensal bacteria represented by *Faecalibacterium Prauznitzii*. For a more detailed view on the model we refer to the **poster 161** entitled "Modelling 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 μ : for low K and fixed μ , 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

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