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# cMFA for multi-omics data integration in microbial community models

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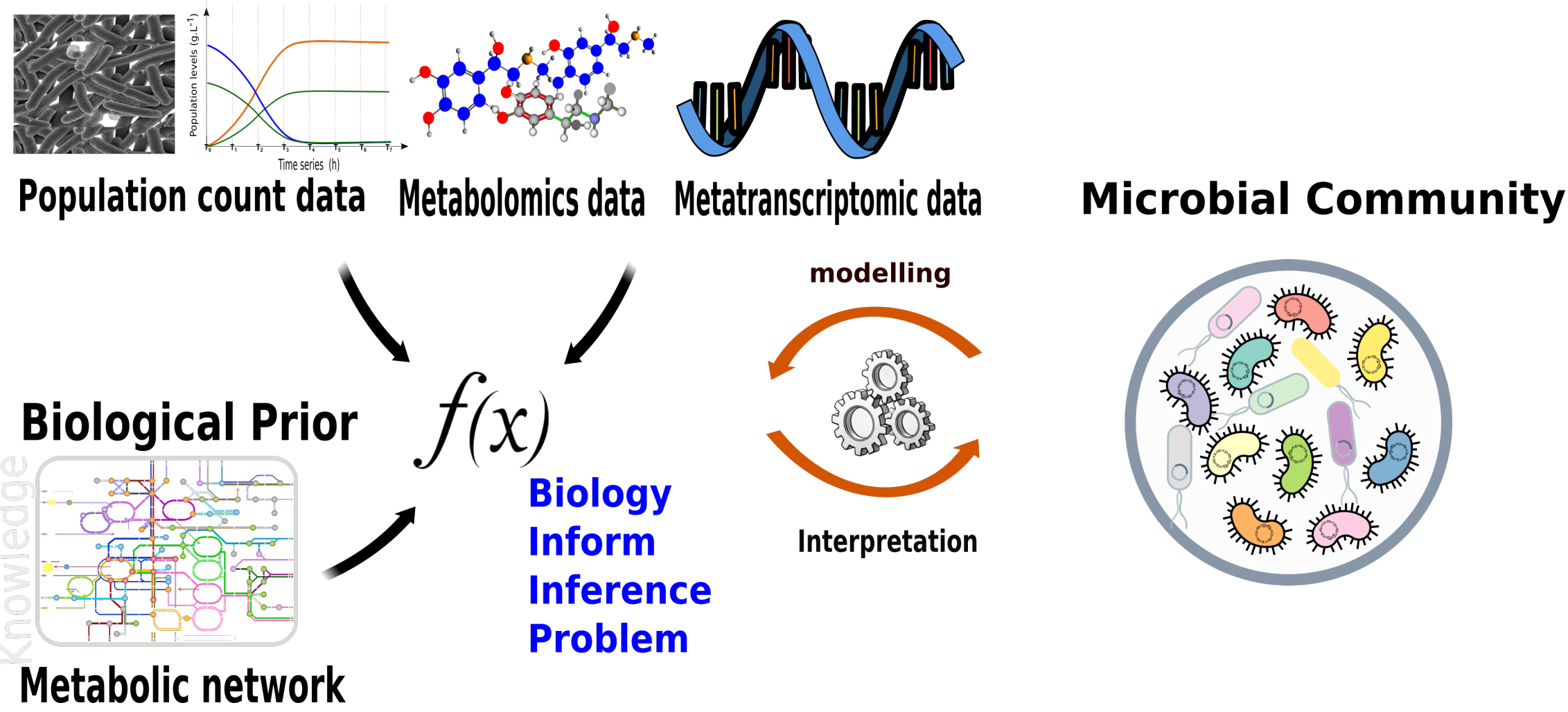
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## INTRODUCTION

### Biology-informed inference from multi-omics data



Understanding natural microbial communities presents significant challenges due to the complex interactions and metabolite exchanges between microorganisms. To gain deeper insights into these dynamics, we are focusing on:

- Developing mathematical models based on metabolic networks.
- Inferring metabolic fluxes using biology-informed high-dimensional analysis methods to integrate multi-omics data.

### Scientific Question:

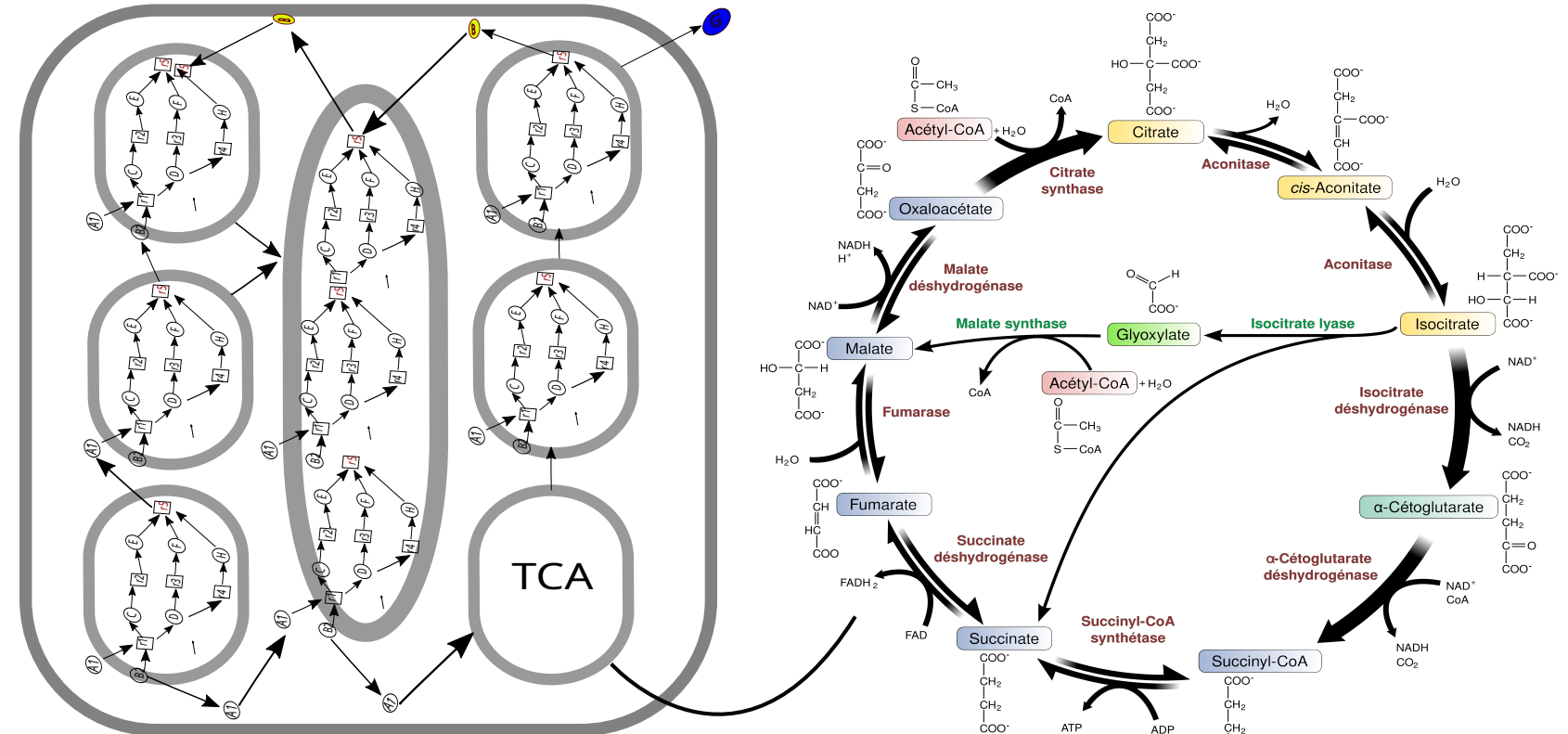
How can mathematical models help us better understand the functioning of microbial communities ?

- Internal flux reconstruction based on some external reaction rates.
- Estimating the contribution of each microorganism to the community.

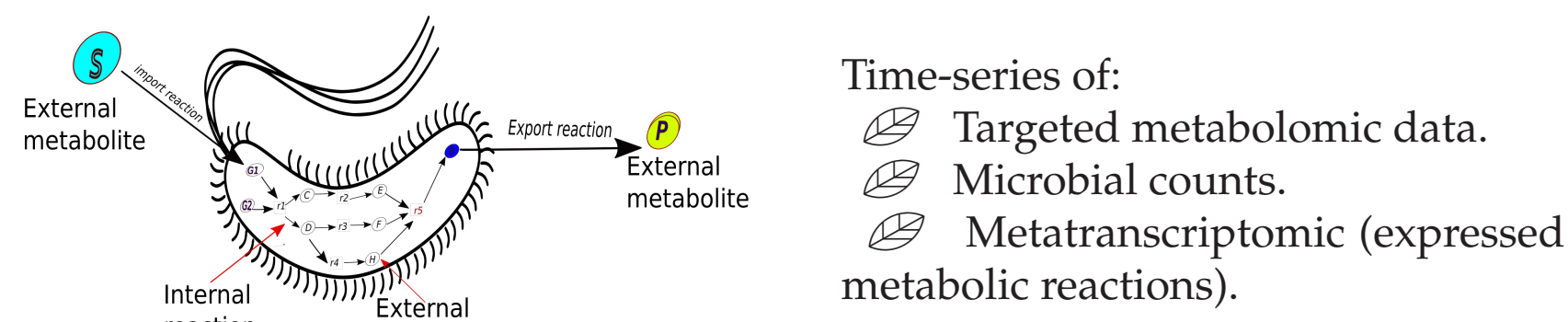
## COMMUNITY METABOLIC FLUX ANALYSIS (cMFA)

### METABOLIC NETWORK

A metabolic network refers to the interconnected set of biochemical reactions and pathways that occur within a cell or organism.



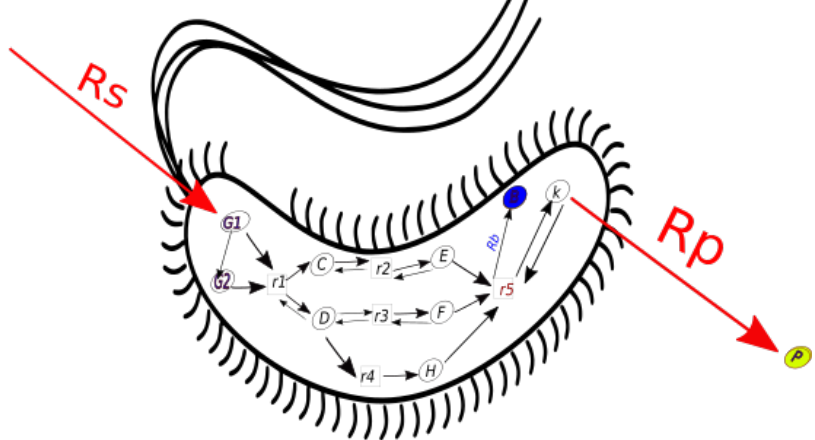
### INPUT DATA DESCRIPTION



Time-series of:  
 • Targeted metabolomic data.  
 • Microbial counts.  
 • Metatranscriptomic (expressed metabolic reactions).

### METABOLIC FLUX ANALYSIS (MFA)

Experimental technique used to estimate intracellular metabolic fluxes by analyzing metabolite production and consumption rates in a biological system, providing insights into the cell's core metabolism.



### COMMUNITY MFA (cMFA)

Find, for  $t \geq 0$ , for a set  $\mathcal{M}$  of  $N_m$  metabolites and for a set  $\mathcal{B}_m$  of  $N_b$  micro-organisms the flux vector

$\hat{\nu}(t) = (\nu^{(\hat{b}_1)}(t), \dots, \nu^{(\hat{b}_{N_b})}(t))$  of dimension  $N_r$  such that

$$\hat{\nu}(t) := \arg \min \sum_{m \in \mathcal{M}} \left\| R_{m,t} - \sum_{b \in \mathcal{B}_m} \chi_t^{(b)} \nu_{m,t}^{(b)} \right\|_2^2 + \lambda \mathcal{R}(\nu)$$

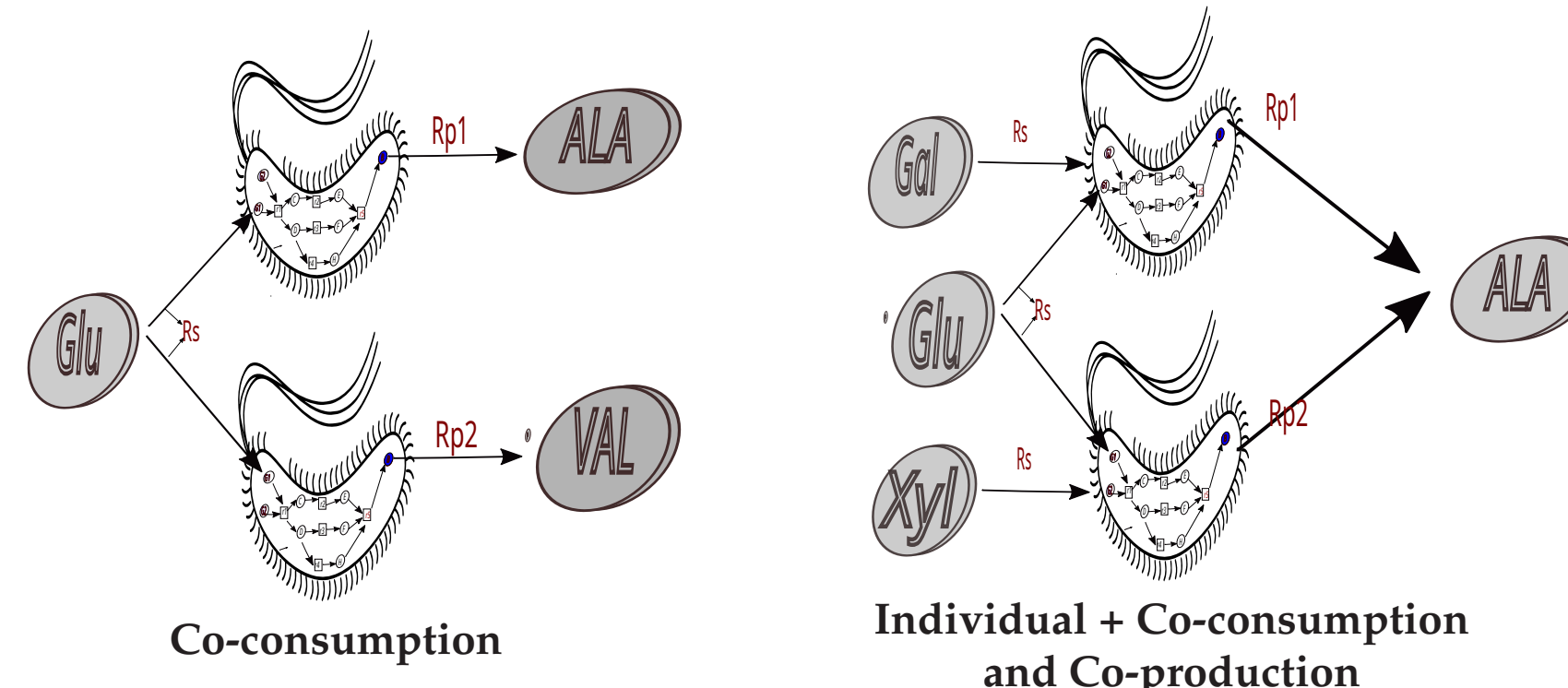
ST :  $\begin{cases} S^{(b)} \cdot \nu^{(b)} = 0, \text{ for } b \in \mathcal{B}_m \\ C_{min}^{(b)} \leq \nu^{(b)} \leq C_{max}^{(b)}, \text{ for } b \in \mathcal{B}_m \end{cases}$

### Regression problem is:

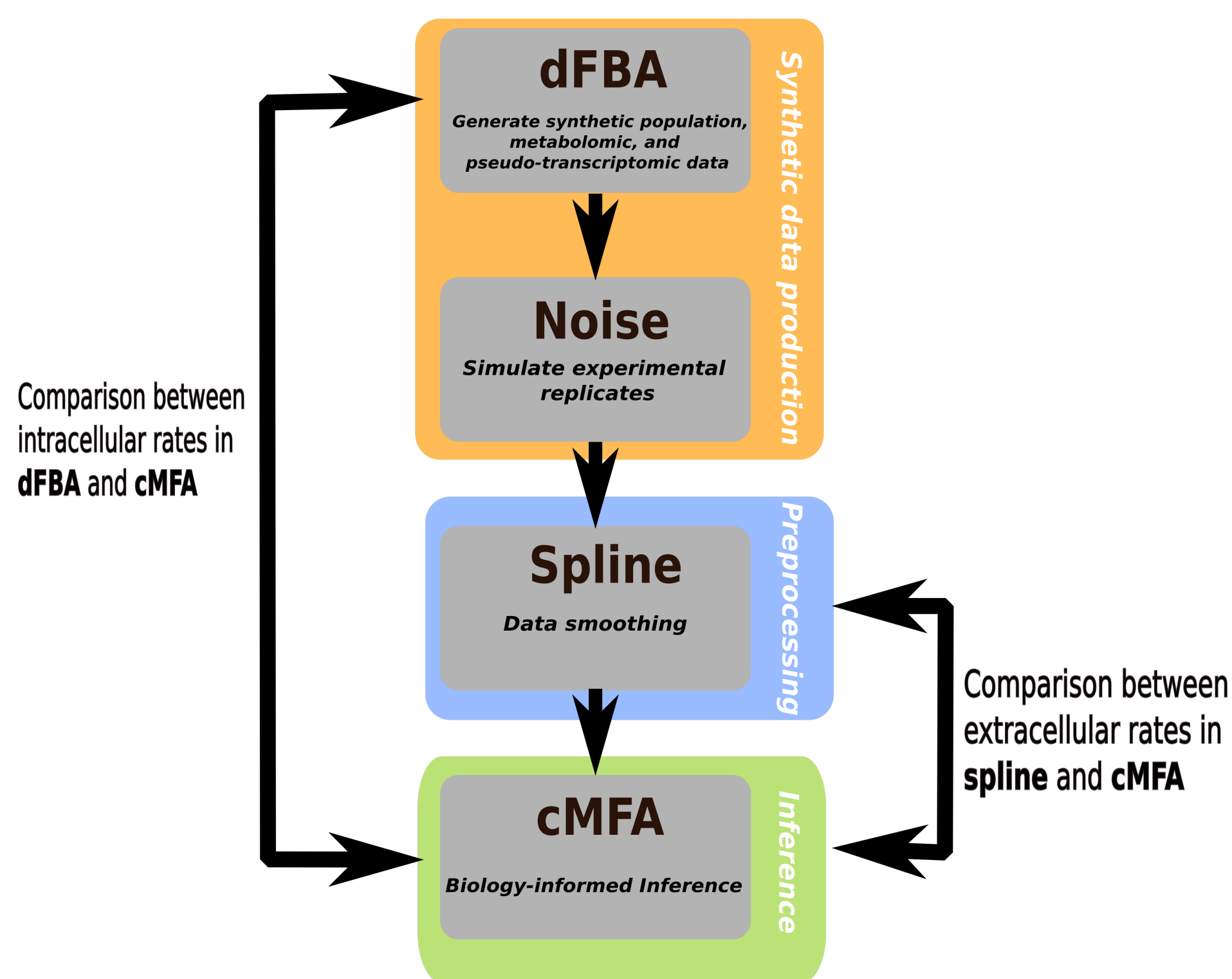
- High-dimensional ( $N_r \sim 5000$ )
- Highly-underdetermined ( $N_r \gg N_m$ )
- Biology-informed ( $S^{(b)}$ )
- Constrained by metatranscriptomics (where  $C_{min}^{(b)} = C_{max}^{(b)} = 0$ )
- Regularized by ridge ( $\mathcal{R}(\nu) = \|\nu\|_2^2$ ) or lasso ( $\mathcal{R}(\nu) = \|\nu\|_1$ ) penalty

### CO-CULTURE DEFINITION

Biological situation of E. coli to produce amine acids and ALA super producer



### BENCHMARK METHODOLOGY



### GENERATING DATA: dFBA

Dynamic Flux Balance Analysis (dFBA) is an extension of traditional Flux Balance Analysis (FBA), which is a mathematical modeling approach used in systems biology to predict the flow of metabolites through metabolic networks.

$$\begin{aligned} \partial_t b_i &= B \nu_i(M, b) b_i \\ \partial_t M_j &= \sum_{i \in C} \nu_{i,j}(M, b) b_i \end{aligned}$$

$$\nu_i = \arg \max B \nu_i$$

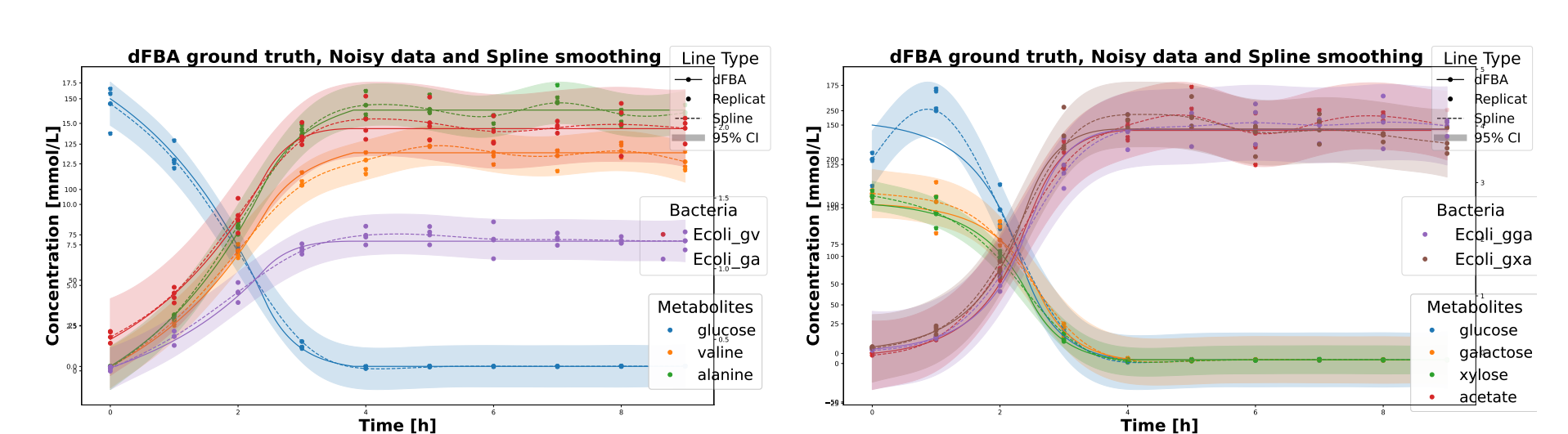
$$S.T \begin{cases} S_i \nu_i = 0 \\ C_M \leq \nu_i^s \leq 0 \\ 0 \leq \nu_i^p \leq C_{max} \\ -C_{max} \leq \nu_i^{in} \leq C_{max} \end{cases} \quad S = \begin{pmatrix} m_1 & r_1 & r_2 & r_3 \\ m_2 & -1 & 0 & 0 \\ m_3 & -1 & 0 & 0 \\ m_4 & 1 & -1 & 0 \\ m_5 & 1 & 0 & -1 \\ m_6 & 0 & 1 & 0 \\ m_7 & 0 & 0 & 1 \\ m_7 & 0 & 0 & 0 \end{pmatrix}$$

### IMPLEMENTATION

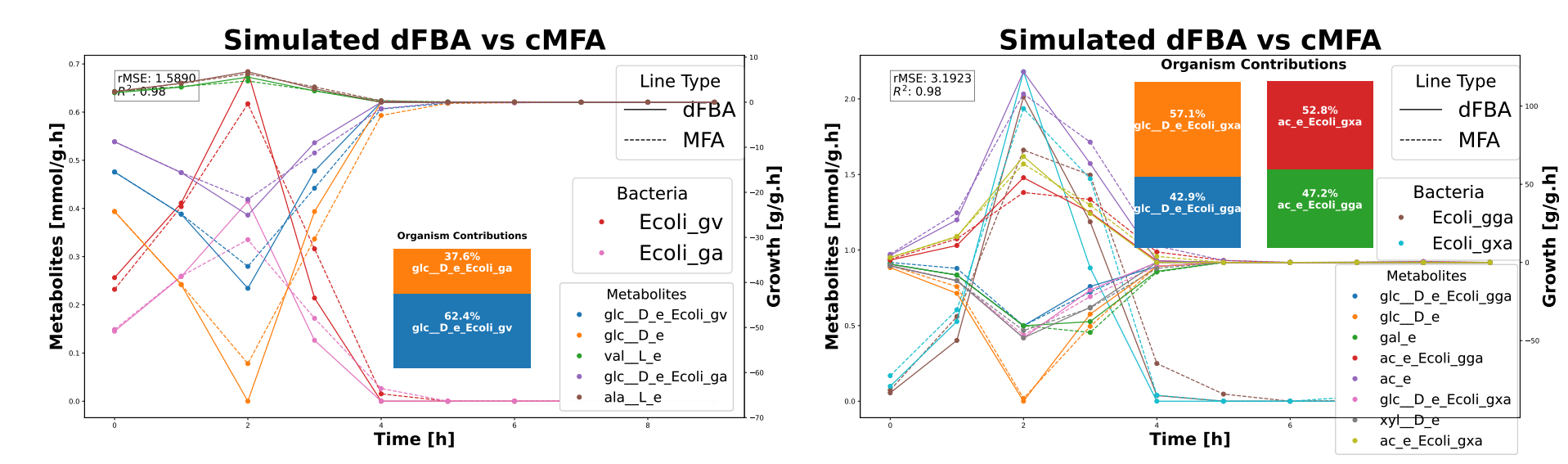
- NumPy and Pandas for data handling and structure.
- PyGAM for spline smoothing.
- Matplotlib for visual representations.
- COBRApy for constraint-based modeling (dFBA).
- OSQP for quadratic programming problems.

## RESULTS

### DATA SMOOTHING WITH SPLINE

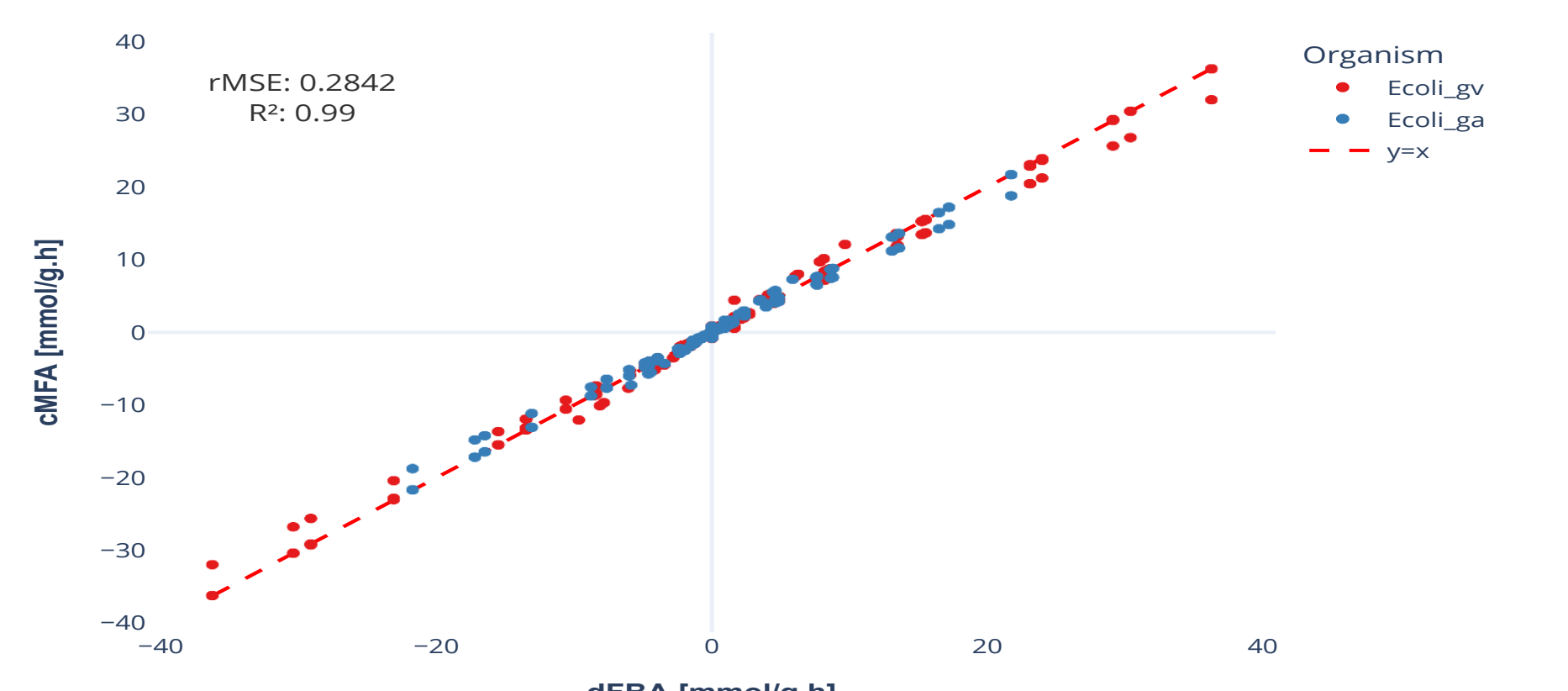


### INFERRING EXCHANGE FLUXES: dFBA vs cMFA

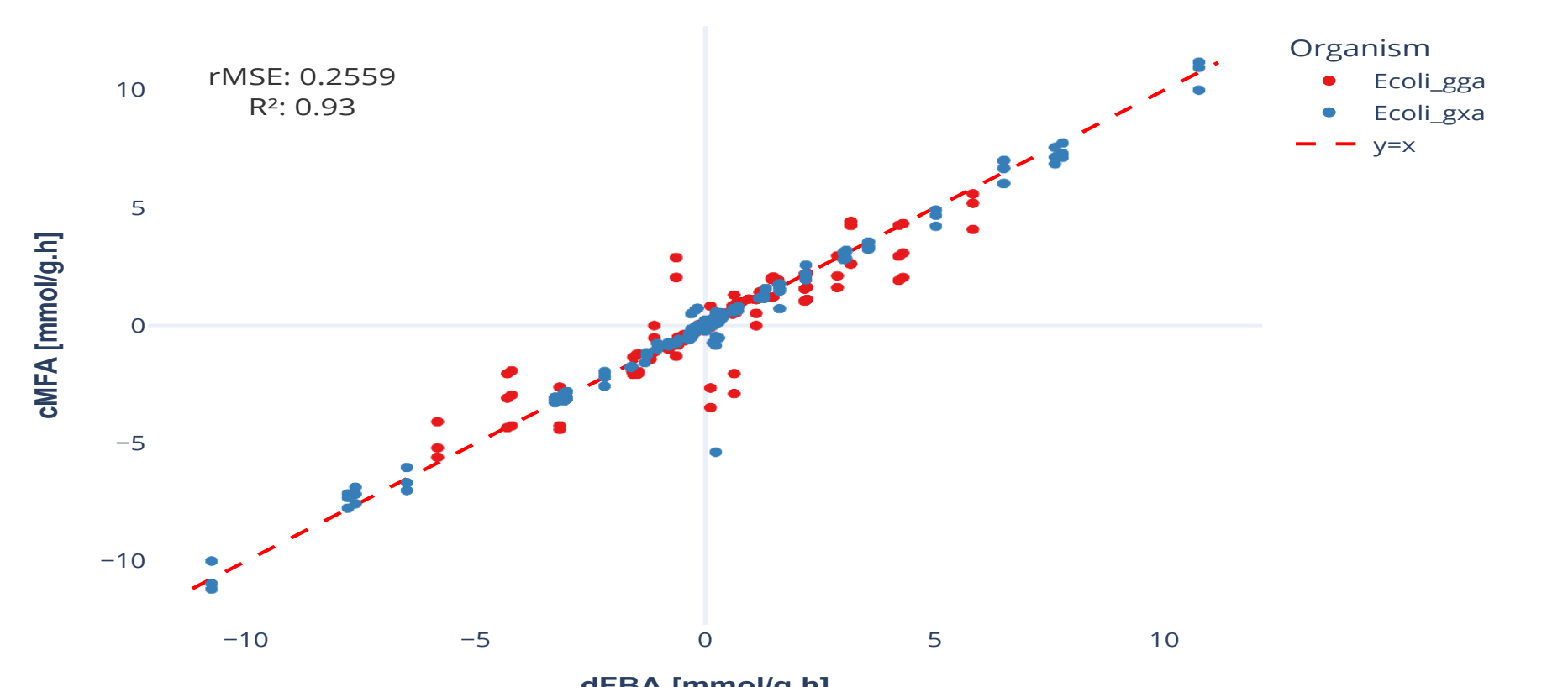


### INFERRING INTERNAL FLUXES

#### Comparison of simulated dFBA vs cMFA for Multiple Organisms



#### Comparison of simulated dFBA vs cMFA for Multiple Organisms



## PERSPECTIVES

- Benchmark on real data.
- Expand the community model to incorporate a diverse set of more than 10 to 20 microorganisms.
- The extension of MFA and the inclusion of metatranscriptomic data

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