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# Multi-omics data integration in constraint-based modeling of metabolic networks to study the metabolism of adipose-derived stem cells



Maximilian STINGL<sup>1</sup>, Juliette COOKE<sup>1</sup>, Julie GERING<sup>2</sup>, Yannick JEANSON<sup>3</sup>, Agnès EMANS<sup>3</sup>, Emmanuelle ARNAUD<sup>3</sup>, Jean-Charles PORTAIS<sup>3,4,5</sup>, Valérie PLANAT<sup>3</sup>, Fabien JOURDAN<sup>1,4</sup>, and Nathalie POUPIN<sup>1</sup>

<sup>1</sup> Toxalim, Université de Toulouse, INRAE, ENVT, El-Purpan, Toulouse, France.

<sup>2</sup> Cell-Easy, Centre Pierre Potier, Toulouse, France

<sup>3</sup> RESTORE Research Center, Université de Toulouse, INSERM 1301, CNRS 5070, EFS, ENVT, Toulouse, France

<sup>4</sup> MetaboHUB-Metatoul, National Infrastructure of Metabolomics and Fluxomics, Toulouse, France

<sup>5</sup> Toulouse Biotechnology Institute - INSA de Toulouse INSA/CNRS 5504 - UMR INSA/INRA 792, 135 avenue de Rangueil 31077 Toulouse CEDEX 04

## Context

**ASCending – Scaling-up the production, quality and safety of Adipose-derived Mesenchymal Stromal Cells (ASCs) for therapeutic applications**

**Background:** Cell-easy develops a 4-step culture process to produce cell therapy out of donor-derived ASCs

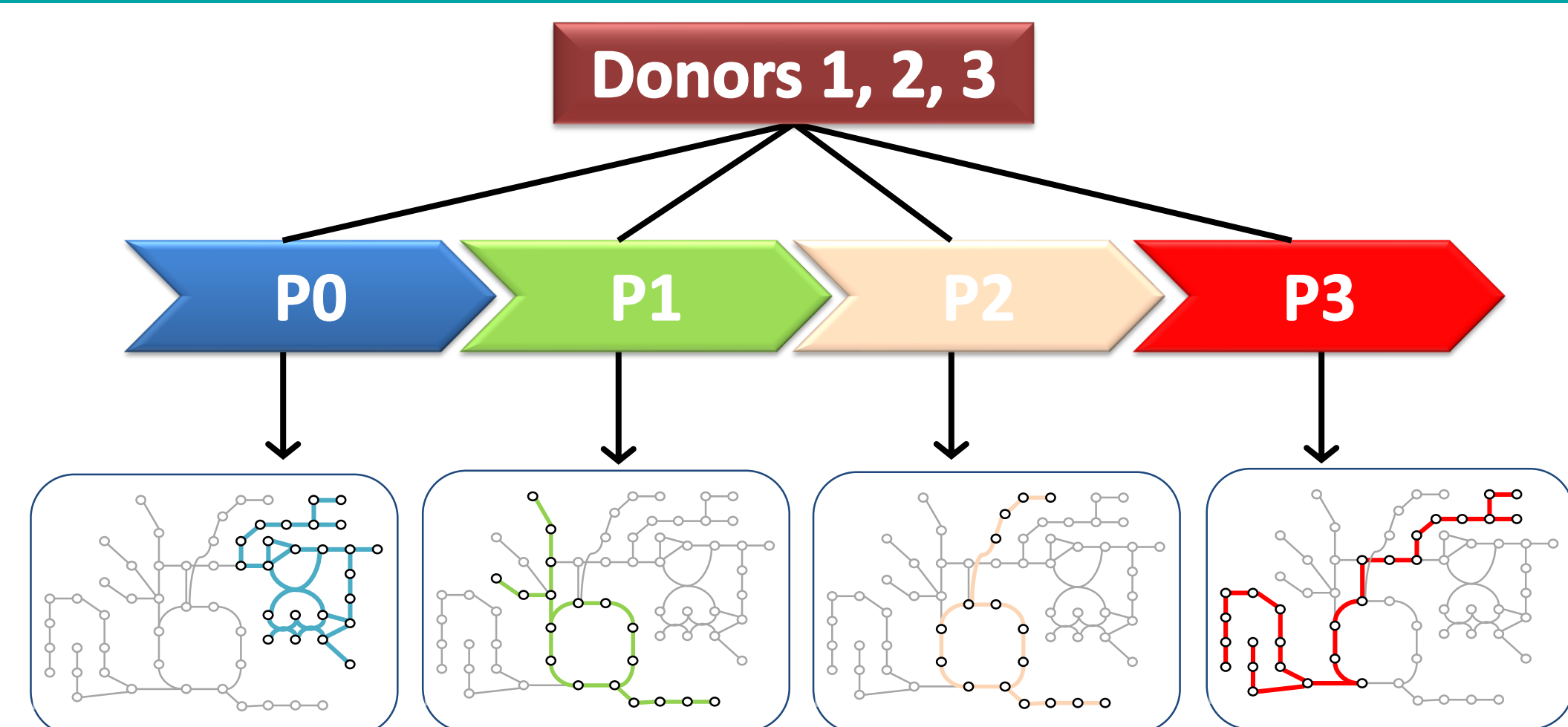
**Final objective:** Optimize and control the culture process

**Intermediary steps:**

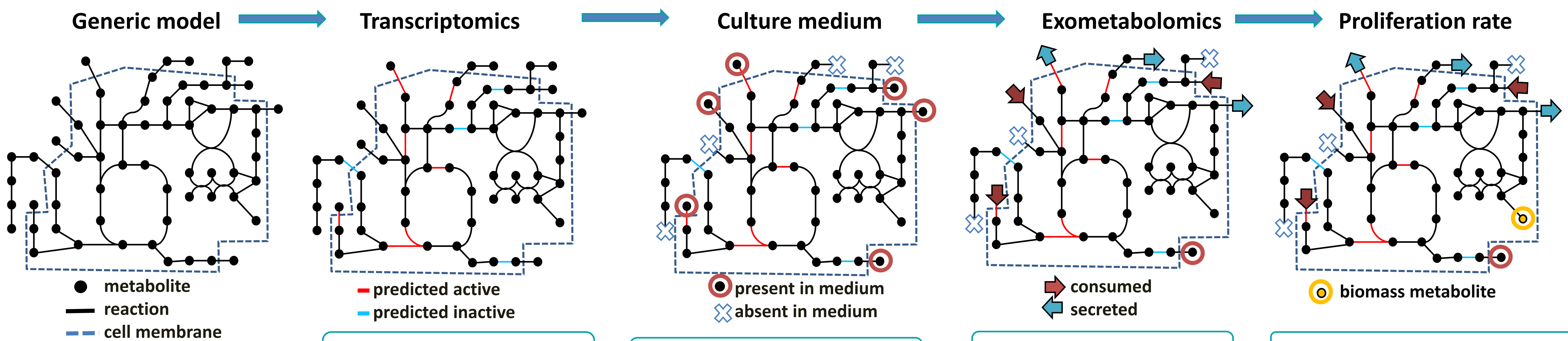
- Decipher ASC metabolism using **experimental approaches** combined with **metabolic modelling**
- Design **optimal culture medium** with mainly plant-derived ingredients
- Create and test assays for **quality control**

**Metabolic modelling strategy & objectives**

- Explore metabolic adaptations during cell culture process
- Use systems biology strategy, based on **constraint-based modelling (CBM)**
- Integrate various **experimental & OMICS data** into **genome-scale metabolic networks (GSMNs)** to obtain **condition-specific metabolic networks**
- Assist in culture medium design through simulations of metabolic states



## Materials and Methods



**Human1 GSMN[1]:** metabolic capacity of all human cells  
12971 reactions, 8455 metabolites,  
2887 enzyme-coding genes

With RNA-seq data and **Gene-Protein-Reaction** rules, we infer reactions associated with **high** or **low** gene expression

Metabolites **absent** from medium **cannot be consumed** by the model  
→ only **57/1660** imports allowed

**Time-series NMR spectrometry** data provides **flux estimations** for **13 metabolites**

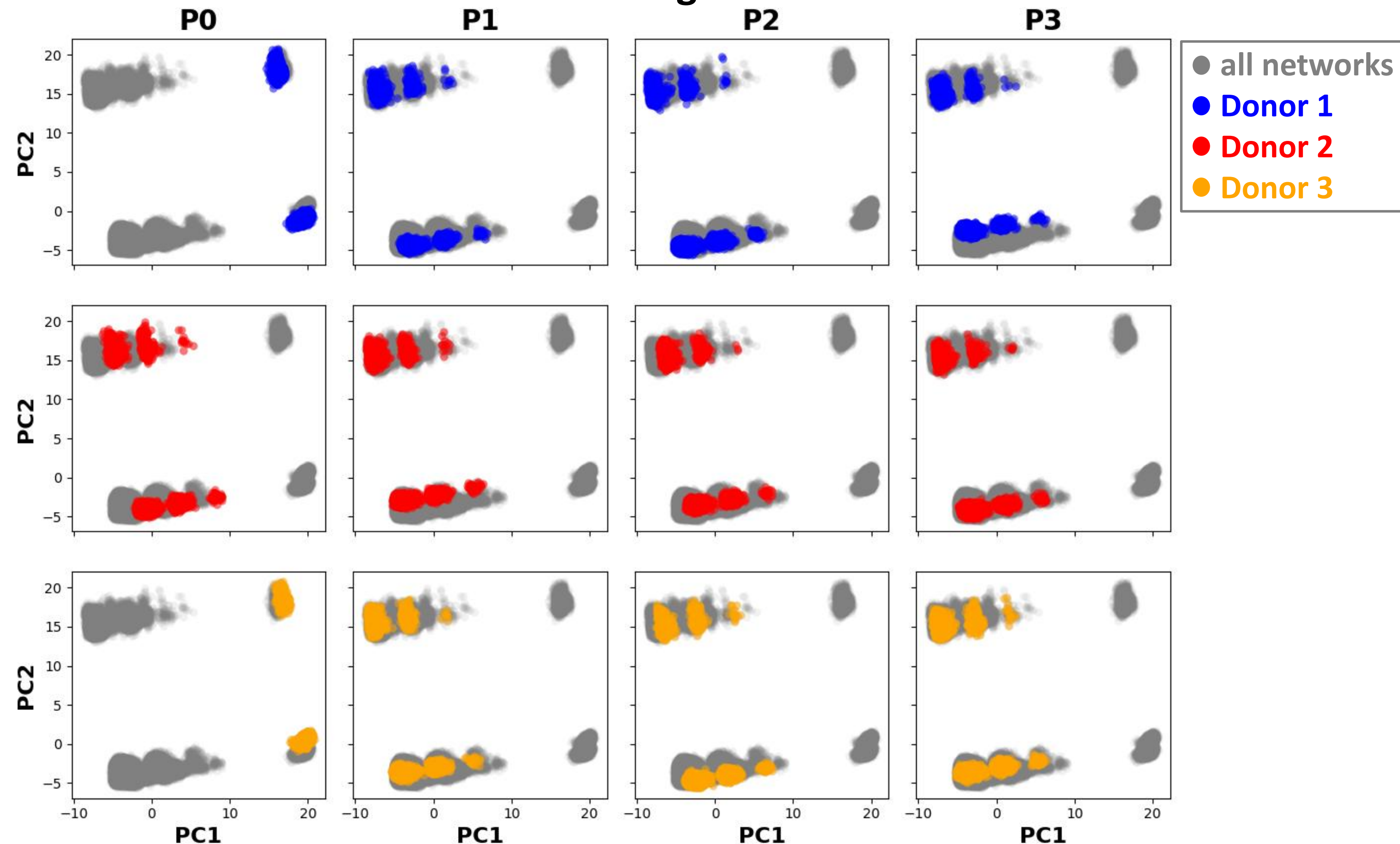
Cell population **doubling time** is converted into **biomass flux**



The **OCMMED workflow** uses a CBM approach [2] to produce up to **10.000 networks** which fulfill all constraints.

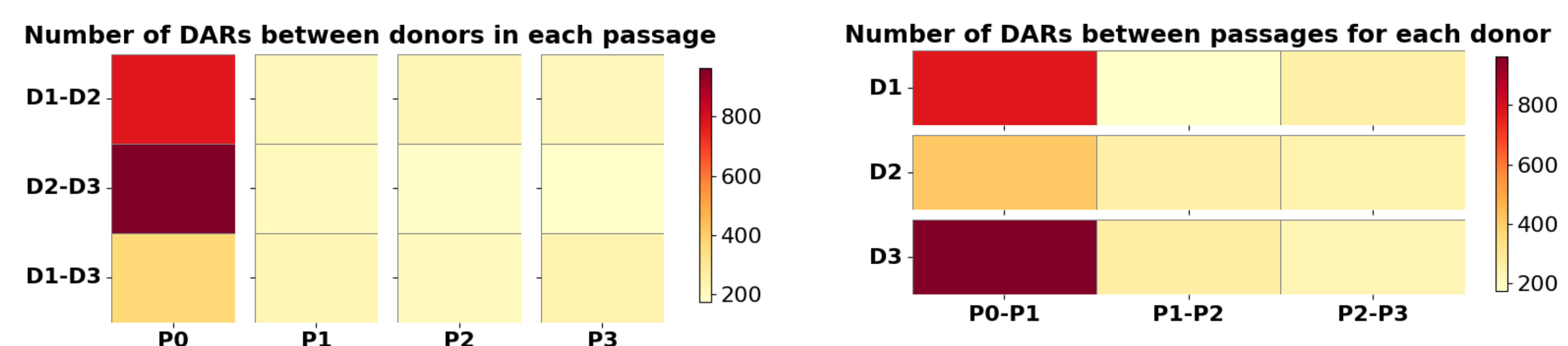
## Results

**PCA of 98.167 metabolic networks generated across 12 conditions**



**PC1 separates P0 samples of D1 & D3, D2 contains less variability**  
**PC2 separates all conditions into 2 clusters** → artefact of network topology

- **Differentially Activated Reactions (DARs)** are computed based on the difference in reaction activation frequencies between 2 conditions.
- DARs represent metabolic reactions with **significant differences** between two conditions, and allow for more **precise insight** into **modulated metabolic functions** [3].
- The **number of DARs** can serve as a **distance metric**, and produces an overview of the pairwise comparisons between conditions.



A strong metabolic adaptation occurs **during culture step P0** with a gradual **homogenisation** of cellular metabolism. The cell population extracted from **Donor 2** is already more **homogeneous** from the beginning.

**Conclusions:**

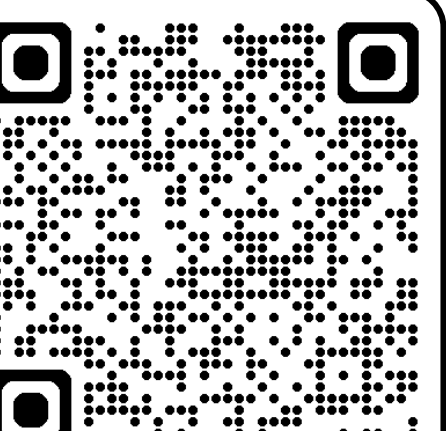
- Simultaneous integration of **multiple types of experimental data** is possible using constraint-based approaches.
- This metabolic modelling approach allows us to identify **when and where** metabolic adaptations occur.
- With further analysis, we can identify the **specific metabolic pathways** and functions which are modulated in each experimental condition.

Source code for the OCMMED workflow can be found here:

<https://forge.inrae.fr/metexplore/cbm/ocmmmed>

Do you have any questions about this poster?

Contact: [maximilian.stingl@inrae.fr](mailto:maximilian.stingl@inrae.fr)



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