M2 SFB 2021-2022

COCA-COLI: Gly**co**lytic **c**ontrol of **a**cetate overflow in *Escherichia **coli*.**

Project description

During growth on glucose and other glycolytic carbon sources, the bacterium *Escherichia coli* produces acetate, a toxic compound which inhibits microbial growth [1,2]. This phenomenon has been extensively investigated because of its fundamental and applied importance in biotechnology (see e.g. [2]). However, the origin and regulation of the production of this toxic by-product remain to be clarified.

We have developed a systems biology strategy combining ^{13}C-isotope labelling experiments with modelling to investigate acetate production in *E. coli*. Using this strategy, we have shown that i) the Pta-AckA pathway responsible for acetate production is reversible *in vivo*, ii) *E. coli* can co-consume glucose and acetate, iii) the shift between acetate production and consumption is determined by the thermodynamic control of the Pta-AckA pathway [3]. We then found that acetate should not be considered a wasteful by-product since it is both a co-substrate of glucose and a global regulator of the physiology and metabolism of *E. coli*, thus providing a rationale for the established "toxicity" of acetate [4].

This knowledge was obtained during growth of *E. coli* on excess glucose, a condition that is not fully representative of the environment of this bacterium in its natural and industrial environments. New hypotheses have been generated by the model under glycolytic limitations. Simulations indicate a strong control of the acetate flux by glycolysis [4], and suggest that, despite its established "toxicity", acetate may in fact enhance growth of *E. coli* under glycolytic limitations by compensating the reduced glycolytic flux. Preliminary results support these predictions. In the COCA-COLI project, the student will test extensively these predictions. She/he will quantifying the response of *Escherichia coli* to modulations of both the glycolytic flux (using inhibitor & alternative glycolytic carbon sources) and acetate concentration. She/he will quantify metabolic fluxes by combining growth experiments, metabolomics and isotopic analyses by NMR, and metabolic flux calculations.

The internship will take place in the MetaSys team at the Toulouse Biotechnology Institute (http://www.toulouse-biotechnology-institute.fr/en/research/molecular-physiology-and-metabolism/metasys.html).

References

1. Harden. The chemical action of *Bacillus coli communis* and similar organisms on carbohydrates and allied compounds. J. Chem. Soc., 1901, Trans. 79:610–628.
2. Pinhal, Ropers, Geiselmann, de Jong. Acetate metabolism and the inhibition of bacterial growth by acetate. J. Bact., 2019, doi: 10.1128/JB.00147-19
3. Enjalbert, Millard, Dinclaux, Portais, Létisse. Acetate fluxes in *Escherichia coli* are determined by the thermodynamic control of the Pta-AckA pathway. Scientific Reports, 2017, 7:42135.
4. Millard, Enjalbert, Uttenweiler-Joseph, Portais, Létisse. Control and regulation of acetate overflow in *Escherichia coli*. Elife, 2021, doi: 10.7554/eLife.63661

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