REFERENCE

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Application of genome-scale metabolic models to the optimization of recombinant protein production in *Escherichia coli*

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Escherichia coli has been the organism of choice for the production of many recombinant proteins with high therapeutic value. However, while the research on molecular biology has allowed the development of very strong promoters, there are still some phenomena associated with this process that hamper the full use of those technologies: aerobic acetate production associated with high specific growth rates, and the so-called stringent response that usually occurs when very high levels of heterologous protein production takes place. In both cases, productivity is affected due to a decrease in the specific growth and production rates. In this work, a systems biology approach for modelling recombinant protein production processes was used aiming its optimization. The existing genome-scale metabolic model of *Escherichia coli* was modified by including an equation for protein production (the model protein GFP – Green Florescent Protein), based on its amino acids content. For the validation of the genome-scale model in high-cell density processes, highly reproducible fed-batch fermentations are run with constant specific growth rate. The developed data acquisition and control system allows to control the substrate addition rate, and to acquire on-line the fermenter's weight, to calculate oxygen and carbon dioxide transfer rates, as well as to obtain glucose and acetate concentrations using a developed Flow Injection Analysis system.