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Pichia process optimization by methanol/sorbitol co-feeding

Recombinant protein production driven by AOX1 promoter is challenged by a high oxygen demand and heat production, especially in large-scale bioreactor. A promising solution relies on a methanol/sorbitol co-feeding strategy during the induction phase. In this work, transient continuous cultures were first performed to quantitatively assess the benefits of a methanol/sorbitol co-feeding process with a *P. pastoris* Mut+ strain bearing a pAOX1-lacZ construct served as a reporter gene. Our results demonstrated that cell-specific oxygen consumption (qO_2) could be reduced by decreasing the methanol fraction in the feeding media. Optimal pAOX1 induction was achieved and maintained in the range of 0.45~0.75 C-mol/C-mol of methanol fraction. In addition, the qO_2 was reduced by 30% at most in those conditions. Based on a simplified metabolic network, metabolic flux analysis (MFA) was performed to quantify intracellular metabolic flux distributions during the transient continuous cultures, which further shed light on the advantages of methanol/sorbitol co-feeding process. Secondly, chemostat cultures were performed to investigate the cell growth, metabolism and regulation of the AOX1 promoter (pAOX1) regarding co-feeding rate of optimized methanol/sorbitol mixture. Our results highlight that methanol/sorbitol co-feeding allowed cells to adapt to oxygen transient limitation that often occur at industrial scale with reduced effect on pAOX1 induction and cell viability. The optimal feeding rate tested here was 6.6 mmolC.(DCW.h)-1 at an oxygen transfer rate (OTR) of 8.28 gO_2 (l.h)-1 with over five-fold pAOX1 induction (probably directly associated with target protein productivity) compared with previous work.

Biography

Patrick Fickers has obtained his PhD from University of Liege, Belgium in 2004. He has worked as Post-doctorate at Polytech Lille, France and as a FNRS Fellow at the Centre of Protein Engineering, Liege, Belgium. He was an Associated Professor at Unversité libre de Bruxelles and the Head of the Biotechnology and Bioprocess Unit (2009-014). In January 2015, he has joined as a Professor the Microbial Processes and Interactions Research Unit (MiPI) at Gembloux AgroBiotech, Univerity of Liege. He has published 37 research papers in peer-reviewed journals and 6 book chapters. His researches focus on the development of yeast and bacterial strains by metabolic engineering and on process development in bioreactor for the production of valuable compounds.

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