Heterogeneity in recombinant protein production

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A crucial step in biotechnology is the scale-up process. Normally, lab scale verification and optimization of production processes and strains are performed in small reactors with perfect mixing and hence the cells experience a homogenous environment. The gradients that occur in industrial scale bioreactors are often not taken into consideration in these experiments. Gradients occur due to insufficient mixing in the reactor, and affect the process in a variety of ways. When cells travel through the reactor and encounter different substrate concentrations, oxygen availability, pH, temperature, etc. the cell physiology is affected. Cells are stressed, and this may severely affect growth, by-product accumulation, biomass yield and recombinant product yield. The stress caused by exposure to divergent microenvironments, genetic differences of individual cells, differing cell cycle stage and cell age, all contribute to make a population in a fermenter heterogeneous, resulting in cell-to-cell variation in physiological parameters of the microbial culture. Our study aims at investigating how population heterogeneity and recombinant protein production is affected by environmental gradients in bioreactors. For this purpose, a Saccharomyces cerevisiae strain, that functions as a protein production reporter, has been developed. A heterologous protein has been tagged with a fluorescent protein providing a way to measure the amount of heterologous protein produced by the cells on single cell level. Gradients are simulated in small bioreactors and the population heterogeneity can be visualised by analysing single cells with flow cytometry. This can give new insights to cell physiology and recombinant protein production at the industrial scale.

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