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## Targeting population heterogeneity for optimal cell factories

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### Abstract:

To achieve an efficient production process, it is essential to optimize both the strain and the cultivation conditions. Traditionally, a microbial population has been considered homogeneous in optimization studies of fermentation processes. However, research has shown that a typical microbial population in a fermentor is heterogeneous. There are indications that such heterogeneity may be both beneficial (facilitates quick adaptation to new conditions) and harmful (reduces yields and productivities) for the robustness of the fermentation process. Significant gradients of e.g. dissolved oxygen, substrates, and pH are typically observed in many industrial scale fermentation processes. Consequently, the microbial cells experience rapid changes in environmental conditions as they circulate throughout the reactor, which might pose stress on the cells and affect their metabolism and consequently affect the heterogeneity level of the population. To further investigate these phenomena and gain a deeper understanding of population heterogeneity, *Saccharomyces cerevisiae* growth reporter strains based on the expression of green fluorescent protein (GFP) were constructed which enabled us to perform single cell level analysis, and thereby created the possibility to map population heterogeneity. A factorial design with pH, glucose concentration and oxygen level was performed in batch cultivations using the growth reporter strains to evaluate the effect of those environmental factors on heterogeneity level and amount of living cells. A highly dynamic behavior with regard to subpopulation distribution during the different growth stages was seen for the batch cultivations. Moreover, it could be demonstrated that the glucose concentration had a clear influence on the heterogeneity. The results from the factorial design experiments will be further discussed.