Experimental and in-silico investigation of population heterogeneity in continuous Sachharomyces cerevisiae scale-down fermentation in a novel two-compartment setup.

BACKGROUND: In large-scale bioreactors, microbes often encounter fluctuating conditions of nutrient and oxygen supply, resulting in different microbial behavior at the different scales. The underlying reason is spatial heterogeneity, caused by limited mixing capabilities at production scale. Consequently, scale-up of processes is challenging and there is a need for laboratory-scale reactor setups that can mimic large-scale conditions to enhance the understanding of how fluctuating environmental conditions affect microbial physiology.

RESULTS: A two-compartment, scale-down setup, consisting of two interconnected stirred tank reactors was used in combination with mathematical modeling, to mimic large-scale continuous cultivations. One reactor represents the feeding zone with high glucose concentration and low oxygen, whereas the other one represents the remaining reactor volume. An earlier developed population balance model coupled to an unstructured model was used to describe the development of bulk concentrations and cell size distributions at varying dilution rate, glucose feed concentration as well as recirculation times between the two compartments. The concentration profiles of biomass and glucose were successfully validated experimentally. Single cell properties of two fluorescent reporter strains that were applied for deeper investigation of cell robustness characteristics and ethanol growth distributions were quantified compartment-wise revealing differences in cell population distributions related to environmental conditions and also compared with the one-compartment, conventional chemostat.

CONCLUSION: Results underline the utility for the proposed combined approach as well as the use of continuous scale-down reactors for process investigations as insights concerning single-cell characteristics of the process are revealed, which are normally hidden.

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