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Optimization of high-cell density cultivation to produce monoclonal antibody in glycoengineered *Pichia pastoris* by real-time monitoring of glycerol and methanol

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Monoclonal antibodies with humanized N-glycosylation have been successfully and highly expressed in glycoengineered *Pichia pastoris* using high-cell density fed-batch fermentations. High titer and production consistency require tight control of glycerol and methanol as primary carbon source and inducer, respectively, in fed-batch culture of *P. pastoris*. In this study, glycerol, methanol, and cell density were monitored in real-time for multiple fermentations using a new on-line NIR (near infrared) monitoring system. The real-time measurements provided accurate concentration profiles and kinetic data for process characterization and optimization throughout the entire 52-week study, with no recalibration or user expertise required. Critical operation variables available in real-time include the time of methanol dose, peak methanol concentration, time of methanol depletion, and volumetric methanol consumption rate. Under oxygen-limited fed-batch conditions, the methanol dosage level for these high cell density cultures was optimized at 10 gL^{-1}, with a 30 $mmol.L^{-1}h^{-1}$ Oxygen Uptake Rate (OUR) controlled by adjustment of agitation speed (rpm) and aeration rate (vvm). The real-time kinetic data, including volumetric consumption rates ($mmol.L^{-1}h^{-1}$) of glycerol and methanol, allowed monitoring and control of cell metabolism at various phases of cell growth and induction, thereby improving quality control and culture consistency of industrial bioprocesses for both developmental and scale-up purposes.

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