Performance Limits and Feedback Control of Biomass in Continuous Fermentation

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Abstract: Industrial biotechnology increasingly relies on continuous and fed-batch cultivation, where maintaining the cell population close to a prescribed trajectory improves yield and run-to-run consistency. In practice, however, most installations regulate only the feed and leave biomass essentially uncontrolled, particularly under low residual-substrate conditions. In this work, we compare the control performance of different feedback strategies for steering biomass toward a setpoint in a low-substrate regime. We first derive an analytic ceiling on achievable biomass tracking performance, bounded by the maximum specific growth rate, and use it as a comparable benchmark. Against this reference, we evaluate three controllers for a *Corynebacterium glutamicum* continuous culture: a cascaded PID controller employing manipulated-variable switching, a linear-quadratic regulator (LQR), and a nonlinear model predictive controller (NMPC). Every controller settled at the target population within 4% of the derived bound. The LQR tracked biomass accurately with minimal variation in the control action but incurred up to 40% error in volume tracking; the PID approached the analytic limit, though with pronounced switching activity in the feed streams; and the NMPC reduced manipulated-variable movement by roughly 60% relative to the PID while preserving comparable tracking performance. A bioreactor experiment confirmed the simulated NMPC behaviour, with closed-loop performance close to the theoretical ceiling.

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