MIMO control for recombinant protein production in a 2-feed microbial cultivation

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Abstract: *Escherichia coli* is a common bacterial host organism for the production of recombinant protein for pharmaceuticals, enzymes and other proteins. The information to express the target product is usually carried on a plasmid that includes an induction mechanism. The T7-promoter system activated through the addition of isopropyl β-d-1-thiogalactopyranosid (IPTG) is a frequent choice. This irreversible trigger causes a strong transcription with high productivity but also elevated metabolic stress. The presented 2-feed cultivation process for the production of Green Fluorescent Protein (GFP) utilizes lactose as the induction agent instead, which is digestible by the cells. In combination with a glucose feed as the main carbon source, this enables the control of the induction level as an additional degree of freedom for improved cultivation conditions and process performance. Previous efforts yielded a state-space model based on mechanistic equations and kinetic expressions, which was used to design optimal feeding profiles for highest productivity and space-time yield. The results were verified in laboratory-scale experiments and showed potential for model-based control strategies. This contribution suggests a controller setup that includes the obtained model as a soft-sensor combined with limited online signals such as the off-gas composition. The two independent feed-rates are manipulated to best balance productivity and microbial growth for stable and optimal processes. The model-based advanced control algorithm is tested in a simulation study alongside traditional feed-forward control. Experimental verification of the results is planned including comparison to the conventional IPTG induction strategy.

Keywords: Modelling, parameter identification and state estimation in biosystems, Biological and pharmaceutical systems, Batch and semi-batch process control, Model-predictive and optimization-based control in chemical processes, Advanced process control

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