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Nonlinear model predictive control of fed-batch fermentations using dynamic flux balance models

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ABSTRACT

Fed-batch fermentation is an important production technology in the biochemical industry. Using fed-batch *Saccharomyces cerevisiae* fermentation as a prototypical example, we developed a general methodology for nonlinear model predictive control of fed-batch bioreactors described by dynamic flux balance models. The control objective was to maximize ethanol production at a fixed final batch time by adjusting the glucose feeding rate and the aerobic–anaerobic switching time. Effectiveness of the closed-loop implementation was evaluated by comparing the relative performance of NMPC and the open-loop optimal controller. NMPC was able to compensate for structural errors in the intracellular model and parametric errors in the substrate uptake kinetics and cellular energetics by increasing ethanol production between 8.0% and 14.7% compared with the open-loop operating policy. Minimal degradation in NMPC performance was observed when the biomass, glucose, and ethanol concentration and liquid volume measurements were corrupted with Gaussian white noise. NMPC based on the dynamic flux balance model was shown to improve ethanol production compared to the same NMPC formulation based on a simpler unstructured model. To our knowledge, this study represents the first attempt to utilize a dynamic flux balance model within a nonlinear model-based control scheme.

1. Introduction

The biochemical industry continues to expand due to high demand for manufactured products and improved understanding and engineering of cellular systems [1–3]. Many biochemical reactors, including those used to manufacture ethanol, human interferon, and insulin [4–6], are operated in fed-batch mode where the substrate is gradually fed to the bioreactor and the product is only removed when the fermentation has been completed (Fig. 1). Most operating strategies developed for fed-batch bioreactors have focused on open-loop optimization owing to the highly nonlinear dynamic process behavior [7,8]. Open-loop control involves the determination of a substrate feeding policy that maximizes the product concentration predicted by a suitable model. Open-loop optimal fed-batch operating strategies developed for immobilized enzyme synthesis [9], penicillin production [10] and ethanol manufacturing [11–13] have resulted in improved performance over previously reported methods. However, many investigators have noted that open-loop policies need to be periodically recomputed [10,14] or replaced with closed-loop implementations [12,15] in the presence of large disturbances and/or substantial plant-model mismatch.

In practice, improved performance can be obtained by introducing measurement feedback into the open-loop operating strategy [8,16–19]. Because of its economic and industrial relevance, the fed-batch bioreactor control problem has received considerable attention [3,20–27]. However, most methods have been based on unstructured models which provide overly simplified, lumped descriptions of intracellular metabolism in terms of a specific growth rate and yield coefficients [6,15,23,28–31]. While relatively simple to construct, such unstructured models are inherently incapable of generating accurate predictions over the wide range of transient conditions observed in fed-batch fermentations. Dynamic flux balance models (DFBMs) [32–35] represent a suitable compromise between unstructured models and the detailed mechanistic descriptions of kinetic models. A DFBM is constructed by combining a flux balance model of intracellular metabolism with substrate uptake kinetics and extracellular mass balances on substrates and secreted products.

The use of DFBMs for bioreactor operation and control is relatively unexplored. We previously developed an open-loop optimal

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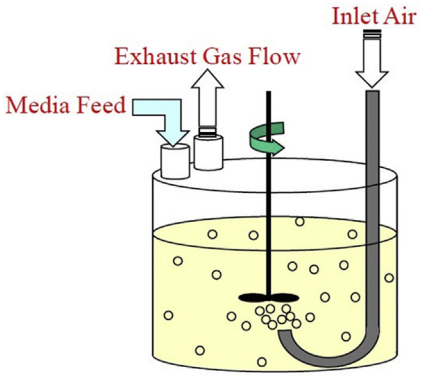

Fig. 1. A fed-batch biochemical reactor.

control strategy for fed-batch *Saccharomyces cerevisiae* fermentation of glucose to ethanol using a small-scale DFBM [12,36]. However, the proposed strategy did not include measurement feedback and therefore could not be expected to compensate for disturbances and modeling errors. In this paper, we develop and evaluate a closed-loop implementation of this open-loop optimal controller based on nonlinear model predictive control (NMPC) over a shrinking time horizon. In addition to solving this specific yeast fermentation control problem, the proposed methodology is widely applicable to other fed-batch bioreactors for which DFBMs are available or can be developed.

2. Nonlinear model predictive controller

2.1. Bioreactor model

The main objective of this paper is to develop a general NMPC strategy that utilizes DFBMs to compute closed-loop fed-batch operating strategies. The industrially relevant problem of glucose conversion to ethanol with the yeast *S. cerevisiae* was used to illustrate our computational framework. The DFBM consisted of a steady-state stoichiometric description of intracellular metabolism combined with substrate uptake kinetics and dynamic mass balances on the extracellular environment. In previous publications [35,43,44], we have shown that DFBMs can provide excellent agreement with batch fermentation data. Due to the complexity of the fed-batch optimization problem with DFBMs, a small-scale model of *S. cerevisiae* primary metabolism [12,36] was used for control calculations. However a genome-scale metabolic reconstruction [37] was used in the bioreactor model, thereby generating mismatch between the control and plant models.

Regardless of the scope, stoichiometric models invariably contain more unknown reaction rates (termed fluxes) than balanced metabolites. Therefore, the small-scale and genome-scale models

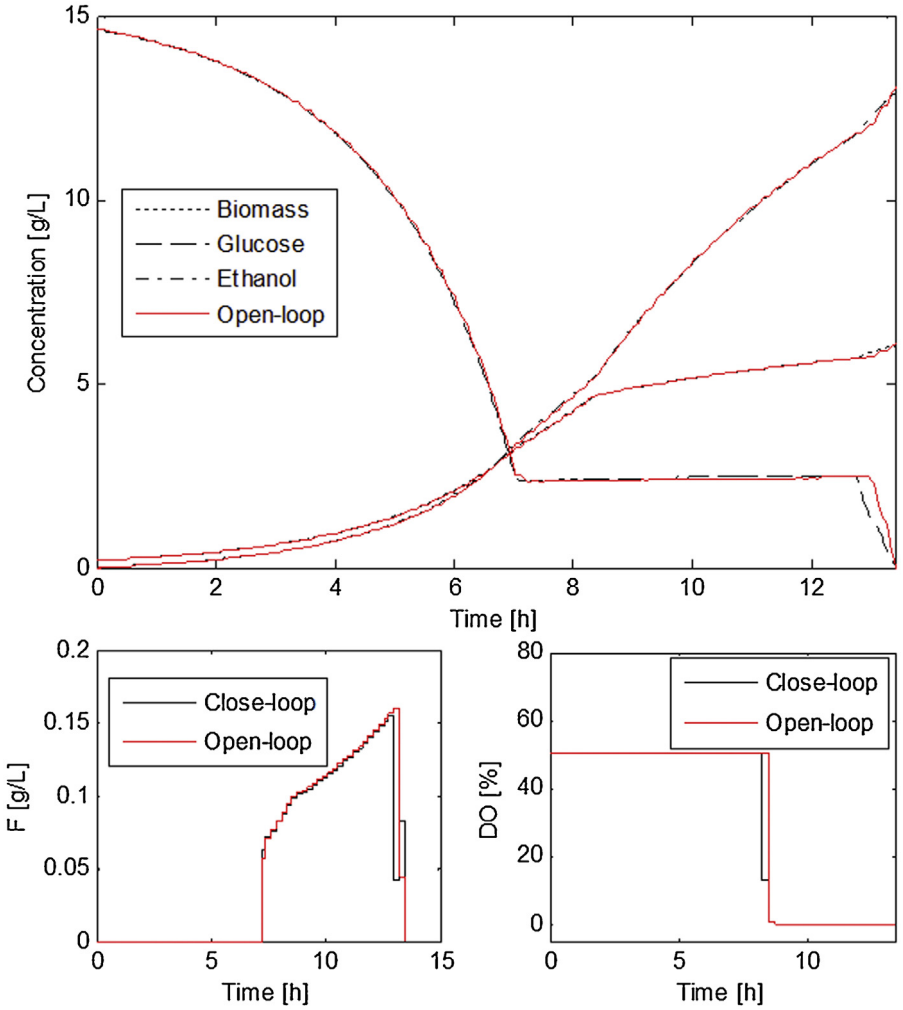

Fig. 2. Comparison of optimal solutions obtained for open-loop and NMPC closed-loop control implementations.