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Abstracts

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Observer based estimation in heterologous protein production by *Pichia pastoris*

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The methylotrophic yeast *Pichia pastoris* has been widely reported as a suitable expression system for both basic research and industrial use. In order to achieve high productivity, constant product quality, as well as to allow optimization and control of biotechnological processes, real-time monitoring of the key fermentation variables (biomass, substrate and products) is of major academic and industrial relevance.

In this work, asymptotic observers (AO) have been designed for the estimation of state variables in the heterologous production of *Rhizopus oryzae* lipase (ROL) by *P. pastoris* in fed-batch bioprocess. AO allow reconstructing the missing state variables even if the process is not exponentially observable and the kinetics are unknown. Thus, from biomass estimation and by using a second order tuning procedure, the estimation of the specific growth rate (μ) was obtained. Effects of different parameters on state and μ estimation have been studied, considering their overall performance.

Simulations results have been analyzed taking into account implementation simplicity, rate of convergence, initialization and model error effects, tuning parameters selection, and requirements of system model. Finally, experimental validation has been conducted, showing satisfactory results although slight deviations in substrate and biomass being detected. The estimation procedure will allow the implementation of a "true" specific growth rate controller. This would represent an improvement regarding those based either on pre-programmed exponential feeding or an indirect μ -control keeping constant the substrate concentration. The overall methodology can be used to improve the global performance of the process in terms of productivity, yields and reproducibility in the heterologous protein production by *P. pastoris*.