Integration of protein dynamics in batch bioprocess optimization

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1 Introduction

The production of products of interest in batch bioreactors is becoming a real opportunity for more and more industries. In batch operating mode, the culture medium is defined at the beginning of the experiment and cannot be changed over time. As a consequence, in order to optimize the process, it is necessary to focus on cell modification and strain design. To do so, it is important to develop a model with more information than Monod model or other macroscopic models.
Constraint based models are good candidates for modelling intracellular processes. In fact, the predictability of these methods relies on mass conservation and optimal resource allocation principle in cell in general. As an example, Resource Balance Analysis (RBA) method developed in [1] is an intracellular process description relying on: (i) mass conservation, (ii) ribosome capacity limitation to produce proteins, (iii) constant total protein concentration, (iv) maximization of growth rate. The constraints are centred on proteins as it is know to be the main cell's resources allocation. Coupling constraint-based models to production optimization has already been done, notably in [2]. The optimal strategy is divided into two steps. In the first phase, the goal is that the cells grow as much as possible without producing. In a second stage, growth is minimal and production is at its maximum. The main contribution of our work compared to [2] is the consideration of protein dynamics in the calculation of the optimum. As it is the largest spending pole of the cell, it is relevant to take it into account.

2 Approach

In this work, an aggregated model is developed: the bioreactor dynamics (substrate concentration, product of interest quantity and biomass dynamics) is coupled to the intracellular species dynamics which are gathered in representatives pools of components. The intracellular processes are described with the same approach as in [1]. As an example, in this model, the growth rate formulation comes from the constant total protein concentration assumption and not form empirical observations. The model is the same as in [3].
The problem at stake is to maximize the product quantity by time, that is to say the yield of the process: $P(t_f)/t_f$.
The nonlinear optimization problem is discretized and solved by the collocation approach [4].

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3 Results & Interpretation

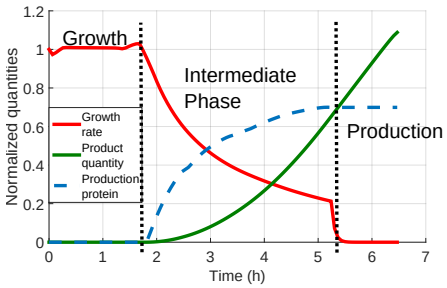


Figure 1: Optimal time evolution of three main variables

Optimal strategy is presented in Figure 1.
As in [2] and fed-batch classical strategies, the optimization result is first to grow and then to produce the product of interest. But, the great difference is the intermediate phase during which the growth rate gradually decreases while the concentration of production proteins increases as well as product quantity produced in the bioreactor. In fact, there is a need for this intermittent phase during which the behaviour of the cells changes: the proteins catalyzing the production flux have to be produced and it takes time.

4 Perspectives

As an ongoing work, the methodology could be extended to fedbatch bioreactors. In fact, the impact of protein dynamics on the global control strategy must be taken into account and would certainly change the optimal feeding profile.

References

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