

METABOLITE-BASED MODEL PREDICTIVE CONTROL OF CELL GROWTH

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Batch-to-batch variation causes significant challenges in the production of cell and gene therapies in terms of manufacturing planning and process comparability. Since the processes deal with living systems that are complex and time-varying, remediating process variability requires dynamic control over the Critical Process Parameters.

In this work, the aim was to control the length of the culture time while optimizing medium consumption by applying Model Predictive Control (MPC) to the medium feed-rate for a cell culture vessel (Figure 1). First, a dynamic predictive model was created, that links nutrient consumption or waste production (lactate production in this specific case) to the growth kinetics of the cells ($Y(k)$). With the aid of this model, MPC is then used to optimize, based on measurement data from the batch under consideration, the amount of nutrients that should be provided to the cells ($C_2(k+1)$) (i.e. controlling the medium refreshment frequency and volume $U(k)$) in order for the cells to follow an *a priori* determined reference growth trajectory ($Y_R(k)$). Adjustable constraints are applied to the controller in a way that the maximum and minimum refreshable volume and frequency can be tuned to the culture system in use. Furthermore, the MPC cost function can be defined to include economical optimization of the process by optimizing not only the cell growth rate, but also minimizing the cost of goods via active controlling of the medium refreshment volume.

Simulated results of the MPC optimizer has shown that by using a predictive controlling of the cell growth we were able to save up to 49.5% of media in comparison to conventional methodology (i.e., 6.1 ml instead of 12 ml in a small scale experiment).

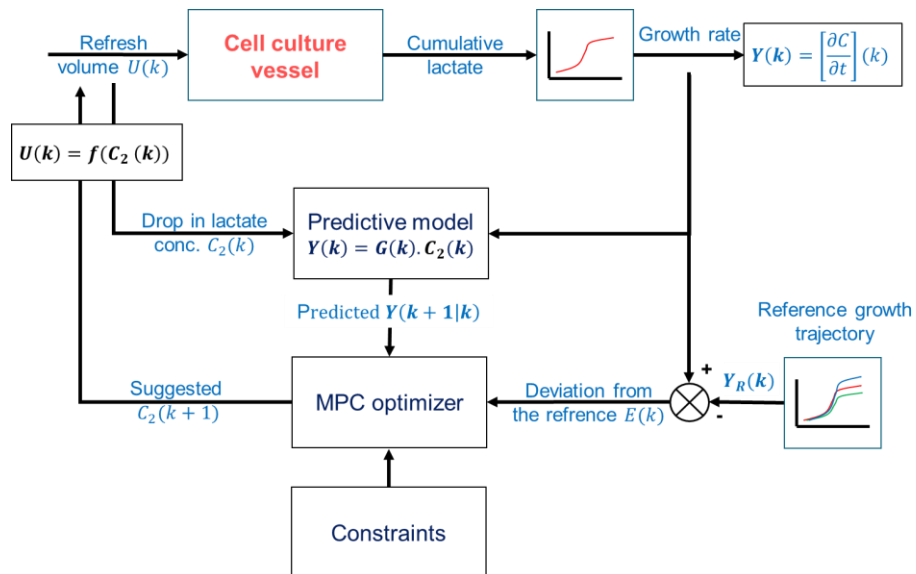


Figure 1 – Schematic process control scheme