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CONTROLLER DESIGN FOR EFFECTIVE GLYCOSYLATION CONTROL IN MABS

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Key Words: Glycosylation, monoclonal antibodies, controller design, controllability analysis, design of experiments

Monoclonal antibodies (mAbs), a class of commercially viable biotherapeutics, undergo post-translational modifications when expressed in mammalian cell lines, resulting in structural and pharmacological changes in the protein. One such post translational modification is N-linked glycosylation, where the non-template driven enzymatic attachment of different sugar moieties (glycans) to the mAb can alter the product quality of the mAb, compromising the efficacy and safety of the drug product. While significant research effort has been devoted to developing techniques for characterizing and monitoring the glycosylation pattern in mAbs, a robust technique for controlling the glycan distribution and ensuring consistent glycosylation does not currently exist. In this work, we present a framework for designing and implementing controllers for effective control of glycosylation in mAbs. The two-step procedure requires first performing output controllability analysis [1, 2] to identify specific inputs that can be manipulated to control particular glycan species (outputs) along with a quantitative relationship between inputs and outputs. Next, this structural information is used to design appropriate proportional integral (PI) controllers. The effectiveness of the controller design technique to track a specified glycan distribution trajectory has been evaluated via simulation for two cases of practical importance: (a) where glycosyltransferase enzyme concentrations are used as manipulated variables (inputs) to control glycan distribution (output) and the input output relationship is represented by a dynamic glycosylation model [3]; and (b) where amino acids are used as manipulated variables (inputs) but the quantitative relationship between the inputs and the outputs is established experimentally. In each case, we design appropriate controllers and then test the controller performance under nominal conditions (i.e., when the process model accurately represents the process in question) and under more realistic model-plant mismatch conditions. The results indicate how effective glycosylation control is possible with appropriate controller design using our proposed technique.

1. St. Amand MM, Tran K, Radhakrishnan D, Robinson AS, Ogunnaike BA: **Controllability Analysis of Protein Glycosylation in CHO Cells.** *PLoS ONE* 2014, **9**:e87973.
2. St. Amand MM, Radhakrishnan D, Robinson AS, Ogunnaike BA: **Identification of manipulated variables for a glycosylation control strategy.** *Biotechnology and Bioengineering* 2014, **111**:1957-1970.
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