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Stochastic modelling of fermentation processes: State estimation of perfusion cultivations using the Extended Kalman filter

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Mammalian cells, particularly Chinese Hamster Ovary (CHO) cells, used for the production of recombinant proteins has gained widespread popularity in recent years due to their capability to produce proteins that are more similar to those found in humans [1], an essential feature in the development of therapeutics. CHO cells are recognized as one of the most reliable mammalian cell lines due to their high growth rate, ability to grow in suspension culture, and substantial protein production capacity [2]. Despite their advantages, the metabolic processes and production involved with CHO cells are complex, requiring optimization in order to enhance efficiency, productivity, and product quality.

Production of therapeutic proteins is frequently achieved through the use of continuous cultivations. This process involves the growth of a cell culture in a bioreactor, where a continuous supply of nutrients is maintained, and the product is continuously harvested. Fermentation processes of this nature on lab scale has been cultivated using a specific CHO cell line for the production of monoclonal therapeutic antibodies (mAb). A total of five batches were run to completion – between 36 and 42 days – reporting various measurements during the entire period.

The present master's thesis explores the mathematical modelling of continuous cultivations using CHO cells. It aims to develop a system of differential equations that describes the dynamics of the CHO cell metabolism in a perfusion cultivation, including the evolution of biomass, glucose, lactate, and product titre. The developed system will be solved using the Extended Kalman filter; an algorithm used to estimate parameters related to nonlinear systems including statistical noise. The equations are based on previous definitions [3] and models various metabolic pathways of the CHO cell line, as well as the in- and outlet of nutrients and components involved in the perfusion process. The challenge lies in creating a model that is both mechanistically meaningful and that is not too intricate in order to be estimated using Kalman filtering.

Two models with increasing complexity have been implemented, showing promising results in estimating rates related to cell consumption and production of various metabolites and cell growth, despite facing various challenges; some of which including the sensitivity of the algorithm used for parameter estimation when the system of equations increase in complexity, and a loss of observability when measurement values reach zero, challenging the rate estimation for certain metabolites. Although at an early stage, this study has the potential to contribute to the field of mathematical modelling of biochemical phenomena and provide a foundation for future research in the area of cultivation monitoring and/or design of experiments.

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