Optimization of Fed-batch Culture of Hybridoma Cells using Genetic Algorithms

Optimizing a fed-batch fermentation of hybridoma cells using a GA is described in this chapter. Optimal single- and multi-feed rate trajectories are determined via the GA to maximize the final production of MAb. The results show that the optimal, varying, feed rate trajectories can significantly improve the final MAb concentration as compared to the optimal constant feed rate trajectory. Moreover, in comparison with DP, the GA-calculated feed trajectories yield a much higher level of MAb concentrations.

2.1 Introduction

Fed-batch processes are of great importance to biochemical industries. Although they typically produce low-volume, high-value products, however, the associated cost is very high. Optimal operation is thus extremely important, since every improvement in the process may result in a significant increase in production yield and saving in production cost. The major objective of the research that is described in this chapter is not to keep the system at a constant set point but to find an optimal control profile to maximize the product of interest at the end of the fed-batch culture. In this work, real-valued GAs are chosen to optimize the high order, dynamic and nonlinear system.

GAs are stochastic global search methods that imitates the principles of natural biological evolution [65, 64, 67, 60]. It evaluates many points in parallel in the parameter space. Hence, it is more likely to converge towards a global solution. It does not assume that the search space is differentiable or continuous and can be also iterated many times on each data received. GAs are a promising and often superior alternative for solving modelling and optimal control problems when conventional search techniques are difficult to use because of severe nonlinearities and discontinuities [79, 76]. Some researches on bioprocess optimization using GAs are found in the literature [80, 81, 76].

GAs operate on populations of strings, which are coded to represent some underlying parameter set. Three operators, selection, crossover and mutation,
are applied to the strings to produce new successive strings, which represent a better solution to the problem. These operators are simple, involving nothing more complex than string copying, partial string exchange and random number generation. GA realize an innovative notion exchange among strings and thus connect to our own ideas of human search or discovery.

The remaining sections of this chapter proceed as follows: in Section 2.2, a seventh order model is introduced and the related practical problems are formulated; Section 2.3 explains the basics of GAs; in Section 2.4, the simulation results are given; conclusions are drawn in Section 2.5.

2.2 Proposed Model and Problem Formulation

A seventh order nonlinear kinetic model for a fed-batch culture of hybridoma cells [24] is used in this work. The mass balance equations of a fed-batch fermentation for a single-feed case are:

\[
\begin{align*}
\frac{dX_v}{dt} &= (\mu - k_d)X_v - \frac{F}{V} X_v \\
\frac{dGlc}{dt} &= (Glc_{in} - Glc)\frac{F}{V} - q_{glc}X_v \\
\frac{dGln}{dt} &= (Gln_{in} - Gln)\frac{F}{V} - q_{gln}X_v \\
\frac{dLac}{dt} &= q_{lac}X_v - \frac{F}{V} Lac \\
\frac{dAmm}{dt} &= q_{amn}X_v - \frac{F}{V} Amn \\
\frac{dMAb}{dt} &= q_{MAb}X_v - \frac{F}{V} MAb \\
\frac{dV}{dt} &= F
\end{align*}
\]  

(2.1)

where, \(X_v, Glc, Gln, Lac, Amn\) and MAb are respectively the concentrations in viable cells, glucose, glutamine, lactate, ammonia and MAb; \(V\) is the fermentor volume and \(F\) the volumetric feed rate; \(Glc_{in}\) and \(Gln_{in}\) are the concentrations of glucose and glutamine in the feed stream, respectively; Both glucose and glutamine concentrations are used to describe the specific growth rate, \(\mu\). The cell death rate, \(k_d\), is governed by lactate, ammonia and glutamine concentrations. The specific MAb production rate, \(q_{MAb}\), is estimated using a variable yield coefficient model related to the physiological state of the culture through the specific growth rate. The parameter values and detailed kinetic expressions for the specific rates, \(q_{glc}, q_{gln}, q_{lac}, q_{amn}\) and \(q_{MAb}\) are presented in Appendix A.

The multi-feed case which involves two separate feeds \(F_1\) and \(F_2\) for glucose and glutamine respectively is reformulated as follows:

\[
\begin{align*}
\frac{dX_v}{dt} &= (\mu - k_d)X_v - \frac{F_1+F_2}{V} X_v \\
\frac{dGlc}{dt} &= \frac{F_1}{V} Glc_{in} - \frac{F_1+F_2}{V} Glc - q_{glc}X_v \\
\frac{dGln}{dt} &= \frac{F_2}{V} Gln_{in} - \frac{F_1+F_2}{V} Gln - q_{gln}X_v \\
\frac{dLac}{dt} &= q_{lac}X_v - \frac{F_1+F_2}{V} Lac \\
\frac{dAmm}{dt} &= q_{amn}X_v - \frac{F_1+F_2}{V} Amn \\
\frac{dMAb}{dt} &= q_{MAb}X_v - \frac{F_1+F_2}{V} MAb \\
\frac{dV}{dt} &= F_1 + F_2
\end{align*}
\]  

(2.2)