541c Application of State Space Modeling Techniques to Biological Systems

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The state space framework has been put forward as a synthesis tool for the design of optimal process networks. This technique of decomposing a given network into two domains, a distribution network that controls the flow of material and an operator network that controls the transformation of material, has been successfully implemented in many chemical process applications as well documented in the literature [1-6]. This and other optimization based modeling techniques have revolutionized the field of chemical process design [7-12]. Thus far the state space methodology has yet to be applied to the modeling of a biological system. We propose that by viewing the operation of a biological system as a set of chemical processes one can decompose the operation of such a system utilizing a state space approach.

To demonstrate this we shall present the results of case study analyses on the production of protein (mAb) from mammalian cell systems (hybridomas / CHO cells). Monoclonal antibodies (mAb) represent one of the largest growing markets of therapeutic proteins and are plagued by low yield and relatively high production costs. Preliminary analysis has indicated that these problems may be addressed via the application of systematic, data-driven, optimization based synthesis tools which can identify optimal cellular networks which lead to maximum antibody production rates. Results from these optimal networks can then be used to developing the appropriate system conditions and cellular modifications required to achieve these higher production rates.

This work has two major focuses: the experimental component and the numerical component. The experimental component involves the acquisition of data for analysis in the numerical component. It is also being used to test the results of the numerical studies to determine how feasible/reliable they are. In the numerical component, data from the experimental studies (and literature reviews) has been used to characterize the behavior of the cell as a network of reaction systems with quantifiable intake and release rates. From this data, models that describe the reaction network that leads to protein production (mAb) have been identified. From this, we have formulated a constrained mathematical program that is capable of determining the cellular reaction network that maximizes protein production (mAb).

Also included will be a discussion of the models reliability and limitations. This work is not intended to replace or substitute for the multitude of biological simulation techniques currently available [13-20] but rather to present a novel simulation alternative used almost exclusively in chemical process systems. This methodology is robust and allows for more complex interactions (as they become available) to be incorporated into the model to greater capture the action of a cellular system.

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