133b Stoichiometric Modeling of Complex Pharmaceutical Reactions

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A systematic stoichiometry identification methodology is developed to help optimize the reaction section of the process design of complex reaction systems in the pharmaceutical industry. Currently, the most common design in reaction sections of the production plant resembles lab scale steps that synthesize the desired compounds using a number of reactors in sequence that mimic the synthesis steps in the development laboratory. Over the years, the operational process evolves into one that performs several reaction synthesis steps in a single batch reactor. The proposed methodology aims to achieve the optimal design of the production reactors during the initial design, thus minimizing the need for process retrofits. In such a design, each reactor carries out a certain number of reaction steps providing sufficient control over both conversion and selectivity. To achieve this, one needs a model of the stoichiometric and kinetic characteristics of the related synthesis reactions. This modeling task should utilize the available reaction data from highly instrumented high-throughput experimental systems. The present paper describes a methodology for enumerating all stoichiometries that do not contradict the available data.

Some initial efforts inferring stoichiometry information from concentration data are reviewed. This includes works by Waller and Makila (1981) and primarily Filippi et al. (1989). Hamer (1989) used Singular Value Decomposition (SVD) to calculate the minimum number of linear independent reactions needed to represent the data at hand. Bonvin and Rippin (1990) reviewed this method and applied it to a complex reaction system. Fotopoulos (1996) first proposed Structured Target Factor Analysis (STFA), making the discovery of the plausible reactions more systematic.

However, for complex reactions, the identification of all the adequate stoichiometric models under a limited understanding has not been reported, which motivated the work reported here. The concentration versus time data used here are simulated from the complex reaction system proposed by Bonvin and Rippin (1990). SVD and STFA are used to decide the number of independent reactions and to construct all possible stoichiometric targets. These targets are also restricted by the desire to have only stoichiometric coefficients that are integers less than 10. The additional constraint of atom balances is imposed on each reaction to reduce the many choices of acceptable targets that appear to exist. Even after the application of the well known constraint of monotonically changing extents of reaction, the number of possible stoichiometries is quite large for a high dimensional problem such as the present one. To attempt to order the accuracy of representing the available concentration data, a cross validation methodology has been developed that rank orders the predictive ability of each plausible stoichiometric model.

The overall assumption of this stoichio-kinetic modeling approach is that the stoichiometric model can be found first and is independent of the kinetic model that follows. We will call this the Modeling Separation Principle (MSP). However, in the case where two reactions have substantial similarities in the stoichiometric coefficients and the kinetic forms of their reaction rates, the Modeling Separation Principle might not be possible.

Keywords: Batch Reactors, Stoichio-Kinetic Model, Singular Value Decomposition, Structured Target Factor Analysis, Pharmaceutical Reactions

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