



Mechanistic, Cybernetic and Neural based Modeling Approaches for Levan Production Optimization in Non-Ideal Reactors

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The improvement of large-scale productivity and biochemical/genetic properties of producing strains requires mathematical modeling and process/strain optimization procedures. Unfortunately, there is no single type of mathematical model that express exactly all the characteristics of producer strains and/or features of industrial-scale plants. A qualitative model can be formulated when course of culture process is not amenable to mathematical modeling. 'Fuzzy logic' models are intended to rectify the demerits of pure rule-based models by invoking some form of algebra to enhance accuracy. Mechanistic models developed by using a set of ordinary differential equations (ODEs) and/or partial differential equations (PDEs) with related algebraic equations which can simulate the real systems. Neural based models are particularly suited to model the complex non-linear processes, in which problem being tackled along with input data representation and the form of the required output. Other proposed advanced network architectures include dynamic, fuzzy, and stacked neural networks. In addition, statistical approaches take care of uncertainties surrounding process variables, and they play important role in data mining, data compression, principal component analysis (PCA), statistical process control (SPC).

In many bioprocesses, the cellular behavior and bioreactor performance attracts the two exciting research areas. Firstly, visualizing living entities (cells) with least rudimentary intelligence and secondly, functional mimicking of natural intelligence of living organisms. Cellular intelligence attributes that cells' ability to 'learn' from their training under stimulating conditions and responding 'intelligently' to further situations. This feature of the cell to 'think and act' distinguishes the microorganisms from chemical species and allows the cellular processes to be reproducible in nature. Such a tailoring method of conditions that gives the responses which suit our requirements for large (industrial scale) bioprocesses needs judicious and flexible mathematical modeling and control. Industrial bioreactors are operated in more 'real' situations than in 'ideal', where these large bioreactors prone to have spatial variations

within vessel, noise influx from environment. Culture behavior in such 'non-ideal' conditions is quite different from that in 'ideal' reactors, and the mechanistic mathematical models developed on the basis of lab-scale observations becomes inapplicable.

Mechanistic models, generally, have a chemical reaction framework that imparts simplicity but neglects the regulatory processes within the cells and confines their flexibility to adapt to the dynamic environment, where disturbances and non-homogeneity may be variable and significant events. Therefore, cybernetic approach was proposed as an alternative, which has basic tenet was that living cells possessed an innate 'intelligence', whereby they could adjust their internal metabolism and results maximization of responses under varying conditions. The non-ideal features of industrial reactors, equipped with expensive sensors for variables of interest, provide the data in the form of derived models in complicated ways. These lead to the use of artificial intelligence (AI) methods which include artificial neural networks (ANNs) fuzzy logic, genetic algorithms (GAs) and expert systems. These methods allow the rapid on-line estimations of variables that were difficult to measure and optimally filter the noise inflow.

On a macroscopic level, noise enters through inlet streams and noise is linked with stochasticity in gene expression due to cells' phenotypic variations in molecular level. Controlled noise inflow via feed streams has been shown to enhance the product formation in variety of fermentations. Likewise, a controlled genetic noise favors the resistance to diseases and induces the cooperative intra-cellular dynamics with increase in dominance of favorable phenotypes in adverse conditions. At the cellular vicinity, three types of noise i.e., extrinsic (inter-cellular), intrinsic (intra-cellular) and external (environmental) influence the bioproduct synthesis. Fermentations, therefore, require accurate and rapid on-line data acquisition, mathematical modeling and control. However, the understanding of mechanisms involved in biological noise generation and its effects have started recently.

Like cybernetic models, neural networks have cognitive approach. Cellular intelligence is ingrained in the neural network architecture and these networks differ in the manner in which the neurons are laid out, their processing functions, and the directions of the information flow streams. Recent work has shown that different neural network designs were developed as better ones than standard algorithmic filters such as extended Kalman filter, Butterworth filter and moving average filter. It is also not possible to generally state which model type is the best for mathematical modeling of different problems connected with Levan synthesis. Combinations of some of these models in hybrid-type models by implementation of necessary degree of structuring could be the right way to obtain a model capable of reflecting the broad spectrum of biological and physical diversities. Multi objective optimization is a natural extension of single-objective function, which can be converted into a minimax problem and with the help of hybrid differential evolution inferred minimax problem gets the global solution. The mathematical estimation of model parameters is based on minimization of some quantity which can be calculated and is a function of parameters to be estimated. Despite all those difficulties, process modeling has gained enormous popularity due to effects of an array of production characteristics such as increasing product quality, reducing manufacturing cost, risk, and time.

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