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The Use of Hybrid Modelling for the Optimization of the Penicillin Fermentation Process

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1. Introduction

In industry, improvement of existing production processes is a key activity. For complex biological processes, such as large-scale fermentations, this is not an easy task. Because of its complexity, process optimization is often accomplished by means of trial and error. The scientific way of using process models is less com-

mon. The main reason is limited knowledge about the process under consideration. Moreover, many processes suffer from a complex nonlinear dynamics, which cannot easily be translated into mathematical equations without undesirable model simplifications.

Model-based optimization is attractive since it can significantly reduce the number of experiments necessary to obtain pro-

cess improvements as compared to the experimental trial-and-error approach. Process models can be improved by incorporating more relevant knowledge about the process. Hybrid modelling is a relatively new approach to quickly implement all available knowledge into a well-performing software [1]. Hybrid models combine mathematical models, rule-based knowledge as well as information hidden in process data via artificial neural networks (ANNs). After learning from process data, ANNs are particularly powerful in describing the nonlinear relationships between process parameters. Thus, ANNs are taken as a key component in hybrid models in order to describe parts of the process which are difficult to account for by mathematical models. Also, they can be used to compensate for the errors in the mathematical model.

In this study, we discuss the application of hybrid modelling to improve the penicillin fermentation process.

2. Results

The hybrid modelling technique was implemented in the HYBNET software [2], which is organized in highly modular network. HYBNET allows to process the data and information fluxes in different ways and to tune the process model to the real process behavior. HYBNET is running on a workstation (DEC Alpha). To obtain a well-performing implementation, experts with process knowledge and modelling skills incorporated information from different sources, such as process data, mathematical equations, and heuristic rules into the software.

The general procedure was first applied to a lab-scale penicillin fermentation process in order to improve the feed control of precursor (phenyl acetate) and ammonia. Fig. 1 shows a schematic representation of the HYBNET model used to improve state estimation of the penicillin fermentation. As input variables on-line data of the different feeds (carbon source, precursor, ammonia) as well as OUR and

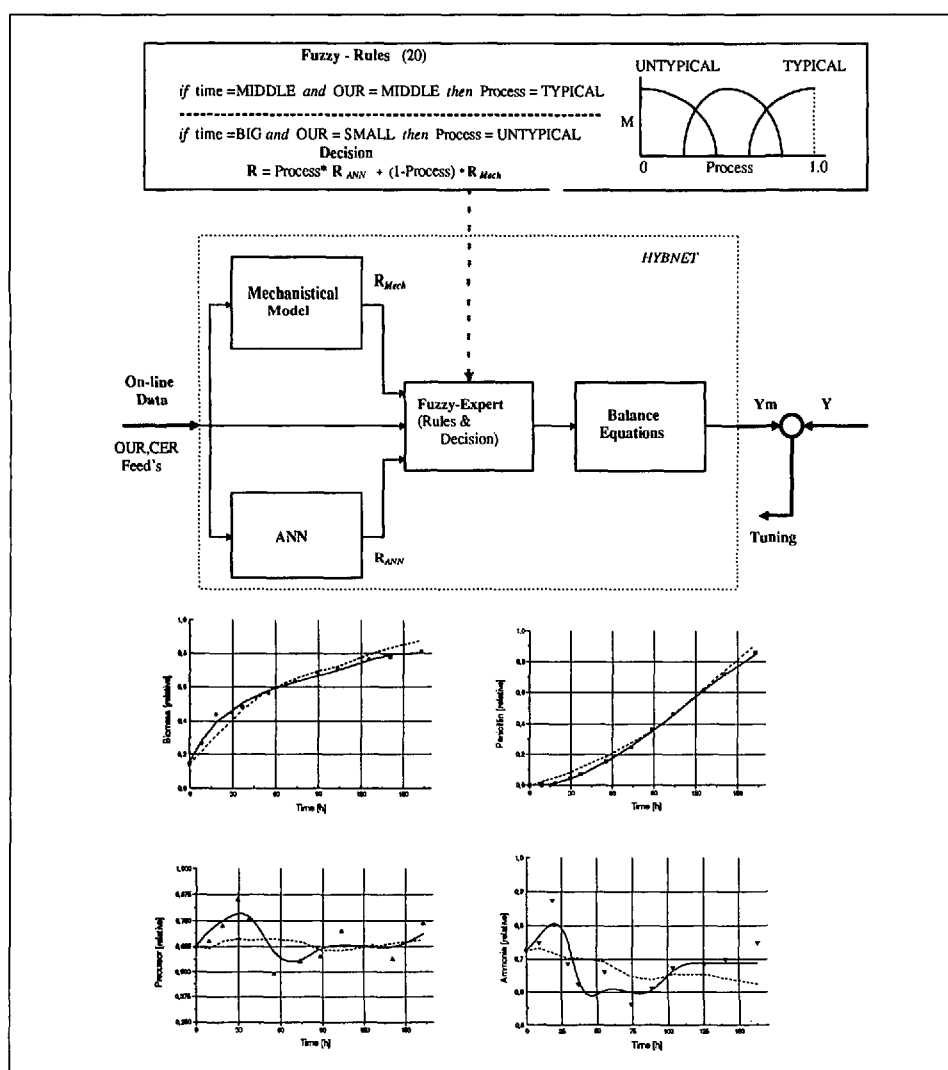


Fig. 1. Hybrid modelling approach for lab-scale penicillin-process state estimation (--- mechanical model, — hybrid model, symbols: measurements)

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CPR were taken. Output variables are biomass concentration, penicillin titre, precursor and ammonia concentration. The HYBNET model consists of a mechanistic model, developed at *Gist-brocades* for process kinetics, an ANN-based model for detailed process kinetics, and a fuzzy expert block to decide whether or not the process behaves typical. For typical processes situations, obviously, much data are available, hence, ANNs can be trained sufficiently well, so that they can describe much more details than mechanistic models. In exceptional situations, which we have not experienced often, it might be better to use classical models since they usually depict more generality. The output of the different blocks are considered as different votes and are weighted in a fuzzy decision block to yield the output of the model. The real process data are taken to tune the models using optimization techniques like back-propagation and random search techniques. Typical results for state estimation are shown in *Fig. 1* and compared to those of a pure mechanistic model. State estimation with hybrid models can be seen to be much better in cultivations, that do not deviate significantly from their normal behavior. With this model, the control of precursor and ammonia concentration could be improved, resulting in improved quality of the data obtained from the bench-scale system.

Hybrid modelling was also used for optimization of the production-scale process. *Fig. 2* shows the two-step procedure used. In the first step, the hybrid model was designed. The model already discussed was complemented by an additional module describing the oxygen transfer, which is a very important issue in large-scale cultivations. In the second step, the optimization, the HYBNET model was combined with an open-loop fuzzy controller, which determines the sugar feed rate as a function of time using a profit function considering several constraints. Some results obtained with the optimized feed strategy are shown in *Fig. 2*. For obvious reasons, only the course of the penicillin and biomass concentration are shown. The results confirm that it was possible to improve the productivity of the fermentation process by means of the hybrid modelling technique.

3. Conclusion

Besides general requirements to a process model as to be accurate and predictive, modelling of industrial processes must also be economically attractive. In other

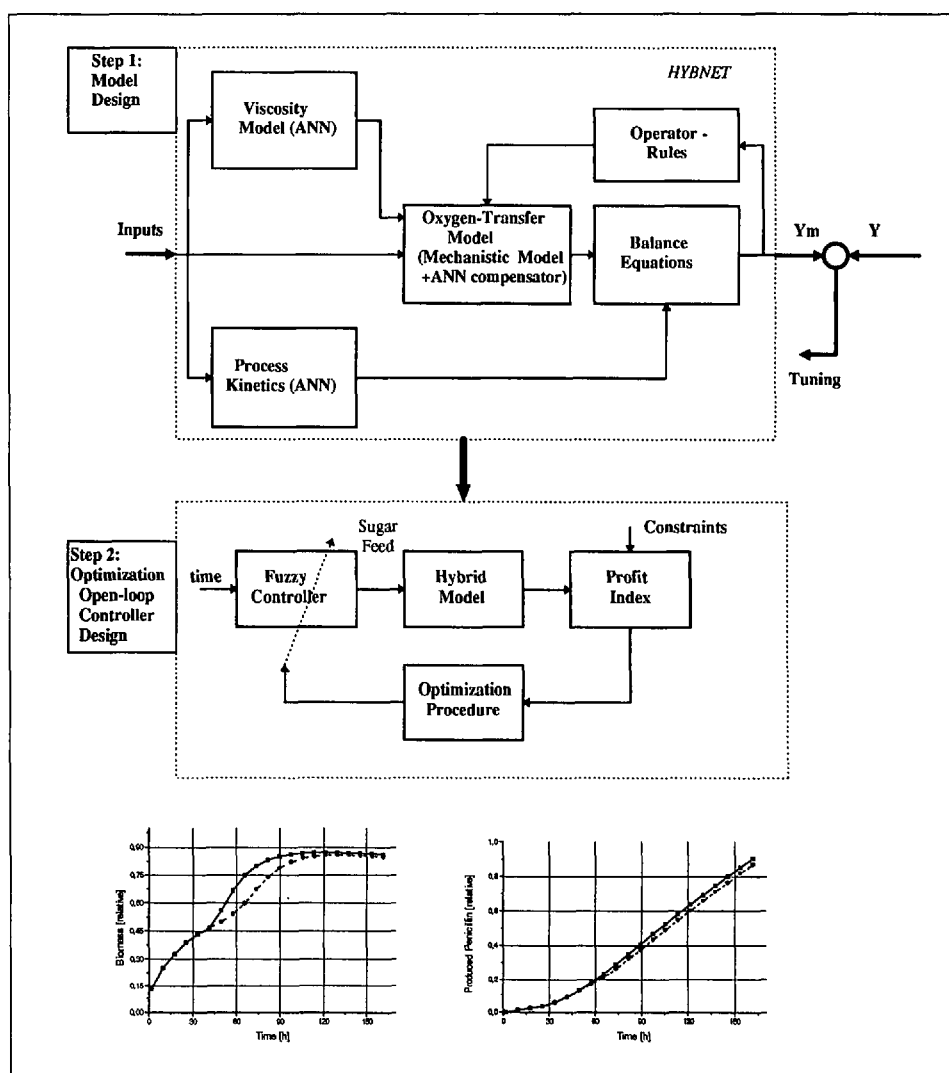


Fig. 2. Hybrid modelling approach for optimization of the penicillin production process (100-m³ fermenter, --- conventional feeding, — optimized feeding)

words, the modelling must not take much development time. The models are required to be flexible enough to be adaptable to changing conditions in the production plant without considerable efforts. To meet these demands, hybrid modelling turned out to be a promising new method. This could be shown by applications to control and optimization of the penicillin production process. The key advantage resulted from the possibility of hybrid models to activate a larger part of the available knowledge. The use of on-line process data *via* ANNs, in addition to the routinely used mechanistic model, improved the state estimation of the penicillin lab-scale process. Combinations of process data, knowledge of process operators, and mechanistic models also resulted in an improvement of the large-scale production process. Thus, information, which on first sight is not useful in process modelling, can be very valuable (both scientifically and economically) providing the right tools are used to process the information.

- [1] J. Schubert, R. Simutis, M. Dors, I. Havlik, A. Lübbert, *J. Biotechnol.* **1994**, *35*, 51.
- [2] R. Oliveira, R. Simutis, S. Azevedo, A. Lübbert, *Bioprocess Eng.* **1996**, submitted.