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Artificial Neural Networks for On-line Optimisation of Biotechnological Processes

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Abstract. Since artificial neural networks represent a commercially attractive tool for process modelling and optimisation, some examples of their use in biotechnology are briefly reviewed. Models based on neural networks can be successfully applied for the optimisation of industrial fermentation processes, as long as the reliability of the network outputs is taken into account. Special network types provide a statistical measure that indicates the particular reliability of the estimation.

1. Introduction

Commercial requirements for the development of biotechnological processes include lower cost, higher output, better quality, and rapid response to changing markets. Although the benefits of the scientific way that utilises process models to achieve the commercial demands have been accepted, the cost and time spent on model development often outweigh the perceived benefits and, thus, conventional model-based approaches have been rarely applied to the control of biotechnological production plants. In daily industrial practice, most of the process improvements have been accomplished in a pragmatic way by development of the strains and culture media, or by scaling-up.

In different industrial fields, artificial neural networks (ANNs) are firmly established as a valuable tool for both rapid and reliable description of extremely complex non-linear systems, (see, *e.g.*, [1]). Since such features are also intrinsic to biotechnological processes, ANNs became a commercially attractive means of data-driven process modelling and optimisation (discussed in [2–6]). The above statement is proven by the fact that more than ten biotechnological companies have published on the use of advanced supervisory control of fermentations with neural networks (*Table*).

Table. Overview of Data Published on Application of Artificial Neural Networks to Industrial Fermentation Processes[a])

	Fermentation process *(strain)*	Company	Reference
Estimation, (Prediction) & Feedback-control	Penicillin	*Harbin Pharmaceutical factory* (China)	[14]
	Penicillin G (*P.chrysogenum*)	*SmithKline Beecham* (Irvine, UK)	[3] [25] [26]
	Penicillin	*Gist-brocades* (Delft, NL)	[8]
	Antibiotics	*Eli Lilly* (Lafayette, USA)	[27] [28]
	Oxytetracycline	*Pfizer Ltd.* (Sandwich, UK)	[29] [30]
	Rekombinant protein (*E. coli*)	*Zeneca Pharmaceuticals* (Billingham, UK)	[25] [31]
	Glucoamylase (*A.niger*)	'Industry'	[15]
	Baker's yeast	'Industry'	[32]
	Lysin (*Brevibacterium flavum*)	'Industry'	[33]
	'Bioprocessing'	*Novo Nordisk, Merck, Life Sciences International, etc.*	[2] [27]
On-line optimisation (model-predictive control)	Riboflavin (*B. subtilis*)	*F. Hoffmann-La Roche Ltd.* (CH)	[13]
	Phytase (*H. polymorpha*)	*F. Hoffmann-La Roche Ltd.* (CH)	[12]

[a]) Manuscripts of academic nature as well as further applications of artificial neural networks in biotechnology [5], *i.e.*, image analysis for taxonomy and biomass determination, analysis of DNA and proteins, *etc.*, are not listed.

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2. Modelling Techniques

Process knowledge is available from different sources simultaneously: from huge databases of on-line and off-line data, from mathematical (conventional) models, and from heuristic knowledge of specialists and operators (*i.e.*, rule-based knowledge). To avoid any loss of information, hybrid modelling techniques are preferable because they allow a quick implementation of all accessible knowledge into one process description [6–10].

ANNs are one key component of hybrid models and are used to describe the parts of the process that are difficult to elucidate using mathematical models or where it is difficult to compensate for errors in mathematical models, (see, *e.g.*, [8][11]). Artificial neural models rely on data from former cultivations and are capable of extracting input-output dependencies from these data. Such models are readapted with fresh data in order to incorporate new information continuously. In general, the re-adaptation (= training) of the ANN may proceed in two different modes:

i) prior to each subsequent cultivation, *i.e.*, the ANN model is readapted with data from the previous runs, and this model is used to control the subsequent cultivations [12][13]. In contrast to *(ii)*, such an approach allows process validation.

ii) on-line after each sampling interval (for an attempt referred to as rolling learning prediction, see [14]).

3. Control Strategy

Generally, control applications of ANNs include estimation, prediction, and optimisation of process variables.

By means of ANNs, variables that are difficult to measure on-line, *e.g.*, biomass and product concentration, can be estimated in quasi-real-time (*e.g.*, software sensors [15][16]). Furthermore, using readily available on-line signals, the process performance can be predicted for some hours in advance. The length of the prediction horizon is a compromise between the accuracy of the prediction (small horizon) and the ideally required prediction up to the harvest point.

Applying model-predictive control concepts [17–19], the ANN-models can be used by an on-line optimiser to determine the optimum control signals (*Fig. 1*). The control signals are updated during each sampling interval. It should be noted that the control signals are optimised on-line, however, the model is most commonly readapted off-line prior to each subsequent fermentation (see the section on Modelling Techniques).

ANNs possess satisfactory extrapolation properties in a small range that surrounds the process data already known. Thus, the optimiser must be restricted to operate only in this area. This can be achieved using networks that indicate the reliability of the prediction, *e.g.*, the CMAC adaptive memory [18][20] or the local linear maps (LLM; [21]).

4. Results and Conclusions

The combination of neural models with a predictive control scheme described above (*Fig. 1*) has been developed to optimise the fed-batch process for the commercial production of riboflavin [13]. The optimisation goal was to find an optimum operating mode while at the same time maintaining the medium composition, the applied strain, and the facility design [22]. The optimisation goal of achieving the highest possible product concentration and product yield at the time of harvesting was realised by a continuous on-line search for an optimum substrate feed. The results presented for the riboflavin process (*Fig. 2*) clearly show that ANNs can be used to improve the process performance, *i.e.*, the substrate to product yield ($Y_{P/S}$) increases by more than 10%, and the reproducibility of subsequent cultivations is enhanced. The optimisation approach has been adapted and verified for the fed-batch production of a recombinant protein (*e.g.*, phytase, see [12]). Finally, it appears that the opti-

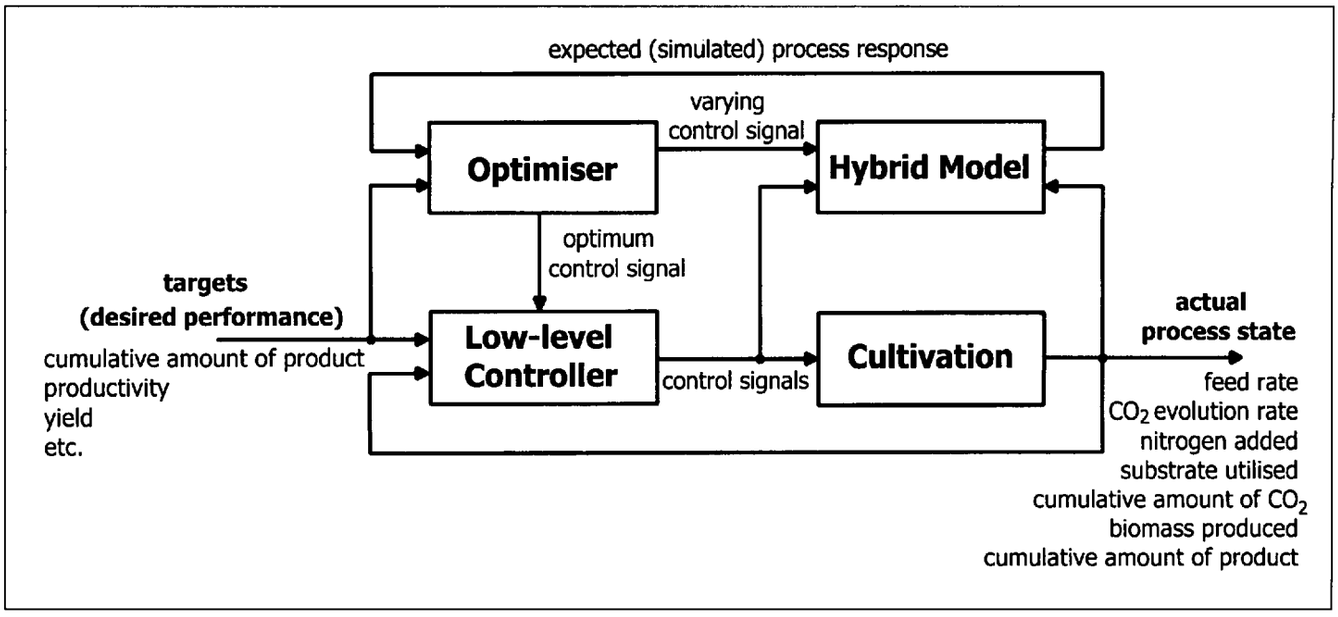

Fig. 1. *Structure of model-predictive control scheme.* An optimiser simulates variations in the control signal, *e.g.*, feed rate, and sends them to the neural process model that forecasts the development of all important process parameters on-line for some hours in advance. The optimiser assesses the predicted model outputs according to the desired process performance that is described by an objective function. The optimum control signal is then applied to the process *via* a low-level controller. At each sampling interval, changes in the process state are monitored and used to update the control signal on-line.

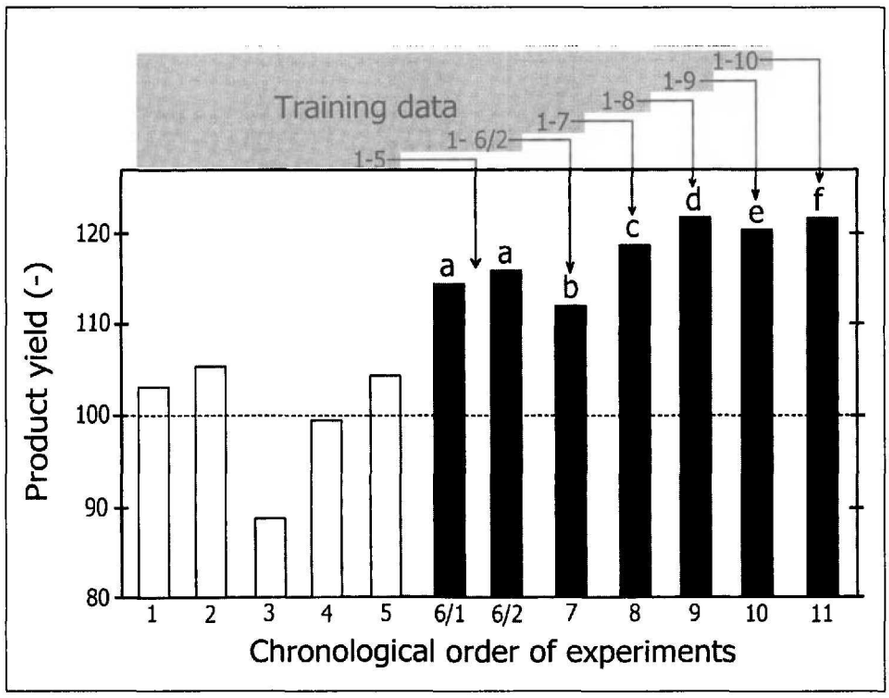

Fig. 2. *Yield ($Y_{P/S}$) optimisation during the fed-batch process for the production of riboflavin by recombinant* Bacillus subtilis *strain* (adopted from [13]). White columns: batches controlled by set-point profiles; black columns: batches controlled by means of ANNs. The value of the average yield of the batches controlled by set-point profiles is arbitrarily set to 100%; a change of 2.5% is statistically significant. The shaded area indicates the data used to adapt (= train) different networks. The letters *a, b, c, d* indicate different neural networks used as process models, *i.e.*, the network *a* was trained with data from experiments controlled by set-point profiles, the training data-set for network *b* included data from experiments controlled by set-point profiles and additionally the data from all experiments *a, etc.*

misation approach is quite general and can also be applied to other biotechnological processes [23][24].

Critical factors for the successful implementation of advanced control systems are both the quality and on-line availability of experimental data. However, an improvement of the equipment will cause additional costs. On the other hand, it should be taken into account that compared to mathematical modelling,

i) the hybrid-modelling method activates a larger part of available knowledge,

ii) the model-development times can be drastically shortened, and

iii) the models can be readily readapted to both new processes and new data. Thus, even from the industrial point of view, the novel techniques of process optimisation are economically attractive (*Table*).

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