BioX^{++} – NEW RESULTS AND CONCEPTIONS CONCERNING THE INTELLIGENT CONTROL OF BIOTECHNOLOGICAL PROCESSES

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Abstract. The article at hand presents new results and conceptions concerning the intelligent and autonomous control of biotechnological processes by integrating conventional, knowledge-based and learning methods. The extended system *BioX*$^{++}$ facilitates the transparent generation of process control strategies and sequences based on automatically self-organized structured process models. Experimental results showing the increased product yield and the discussion of approach-specific problems are part of this paper as well as the new approaches actually examined.

Key Words. Expert systems; neural networks; fuzzy systems; learning control; fermentation processes; biotechnology; genetic algorithms.

1. INTRODUCTION

In contrast to fermentation control strategies based on mathematical process models in recent time a lot of research work focusses on new methods, e.g. expert systems, fuzzy logic and neural networks. Even if improvements in bioprocess control using only one of these techniques have been reported by several authors it becomes obvious, that in future intelligent control concepts must flexibly cope with several of the design methods mentioned before.

The concept of such a control system – called BioX – using a flexible integration of expert system techniques and learning control based on neural networks as well as first results in fermentation control using this system were presented in (Gehlen *et al.*, 1992). New results using BioX for optimization of a fermentation process and a demonstration of the achievable improvements will be reported in the first part of this paper. The second part of this paper will show the actual structure of the extended system *BioX*$^{++}$ and discuss the new features including

- automatic generation of fuzzy rules for a transparent process optimization and
- automatic generation of non-linear structured process models

in detail. A short summary and a preview of future practical and theoretical work will be given in the last section.

2. PROCESS OPTIMIZATION USING BioX

The first stage of this intelligent and integrating approach for the control of biotechnological processes called BioX is explained in detail in (Gehlen *et al.*, 1992) and (Gehlen, 1993). In order to avoid any kind of confusion this section will present the gained experimental results using this first implementation before the actual stage of development is described in the next section.

BioX was applicated to the control of an α-amylase production with *Bacillus subtilis* . The process was performed in a 19 l fermenter. Temperature, pH, stirrer speed, pO_2, air-flow and CO_2-fraction in the outlet were measured with a sampling time of 1 minute, the amylase concentration was monitored every 30 minutes using a flow-injection analyzer (FIA) in a bypass of the fermenter. The complex medium used leads to multiple growth phases. Based on the data of 17 process runs with constant setpoints of underlying conventional temperature and pH controllers predictive process models were learned using AMS – explained in detail in (Tolle and Ersü, 1992) – as an effective software implementation of an interpolating storage device of the CMAC type (Albus, 1975). The whole process was divided into two physiological states, the first state describes the lag and main growth phases (ca. 0 - 10 hours processing time), the second state all following growth phases and the main amylase production (ca. 10 - 50 h). It has been shown in (Konstatinov and

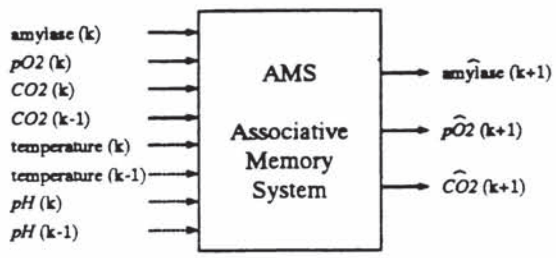

Fig. 1. Associative memory mapping for process prediction during first classified process phase (k means $k \cdot T_0$, $T_0 = 30min$).

Yoshida, 1989) that a separation of characteristic process phases is helpful. The active model is selected by a knowledge-based phase classification. In both states appropriate models predict amylase, pO_2 and CO_2 with a forecast of 30 minutes based on the actual and past values of amylase, pO_2, CO_2, temperature and pH as shown in fig. 1. With this approach an accurate process prediction was achieved (Gehlen *et al.*, 1992). For process optimization these predictive models were used for process planning. The optimization procedures implemented (Hooke-Jeeves and/or evolution strategy) determines in each cycle the best setpoints for the underlying temperature and pH controllers minimizing the performance criterion $I(k) = r_{CO_2} \cdot [\hat{CO_2} - w_{CO_2}]^2 + r_{amy} \cdot [\hat{\alpha}_{amy} - w_{amy}]^2$. $\hat{CO_2}$ and $\hat{\alpha}_{amy}$ are the predicted values of CO_2 and amylase concentration, r_{CO_2}, w_{CO_2}, r_{amy} and w_{amy} are free parameters. For the first physiological state r_{amy} was set to zero, so the optimization was concentrated on the cell growth only, afterwards growth and amylase production were balanced appropriately. The aims were set to $w_{CO_2} = 5$ and $w_{amy} = 500$ in order to maximize the CO_2 and amylase concentration by minimizing the differences in the criterion.

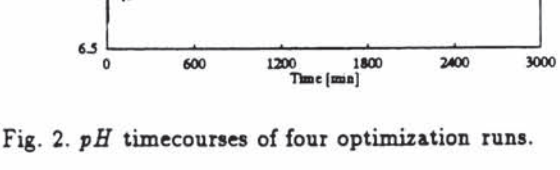

Fig. 2. pH timecourses of four optimization runs.

Fig. 2 shows stepwise the development of pH timecourses in case of four fermentations with optimized setpoints for temperature and pH controllers. Corresponding timecourses for α-amylase are given in fig. 3. During the first optimization run (32) the pH was driven to high values ($pH > 8$) leading to a saturation in amylase production. This behaviour is a consequence of modeling errors due to extrapolation problems outside of trained process points.

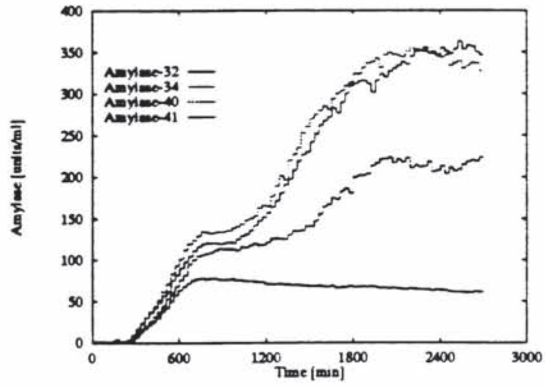

Fig. 3. Resulting amylase timecourses.

After model adaptation with the data of each optimization run during the following four fermentations the process productivity was increased step by step. In contrast to our best fermentations with constant setpoints ($T = 37°C$, $pH = 7.0$) the final amylase concentration was increased by more than 100%. In addition, the production time was shortened. These practical results demonstrate the achievable improvement in performance by using knowledge-based and learning methods. But there still remain a couple of problems:

- As mentioned before, the modelling errors can lead the optimization procedure into previously unknown regions of the memory input space.
- A long-term prediction is not possible due to propagation errors during recursive model predictions.
- The input-output mapping of the interpolating memories does not directly allow to take inner states of the fermentation process or existing operator or expert knowledge into account.
- Well known conscious strategies that can a priori be integrated in the process managements knowledge-based level cannot be improved during automatic optimization.
- The distinction between the knowledge-based upper and the medium learning level in BioX which can also be found in the software implementation – the programming language Lisp is used in the knowledge-based, C in the learning layer – does not bring the positive characteristics together.

Thus the extended system *BioX*$^{++}$ was developed in order make a higher autonomy of the process management system accessible to the user.

3. THE EXTENDED SYSTEM

BioX^{++}– shown in fig. 4 and first described in (Bettenhausen and Tolle, 1993) – does not distinguish in its implementation explicitely between a knowledge-based and a learning layer but it performs related tasks. This can be achieved by a

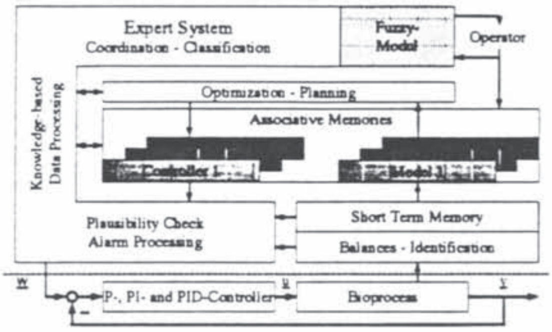

Fig. 4. Structure of *BioX*$^{++}$

methodical and a conceptional change.

- First, the upper level generating the setpoints for the underlying conventional control loops is implemented in the object oriented programming language C^{++} – still on a SUN-Workstation .
- Second, a fuzzy approach for rule representation instead of an interpolating memory extensively uses the similarities between nonlinear mappings generated by neural or fuzzy conceptions, see for example (Brown and Harris, 1994).

This fuzzy approach is based on a pre-defined complete rule space and allows the automatic correction and extension of rulebases. This process can be called learning of rules and is transparent for the operator because of the linguistic man-machine interface. It was first examined concerning the rule based classification of characteristic process phases of the α-amylase fermentation. These results were part of the oral presentation related to (Bettenhausen and Tolle, 1993) and published in German (Bettenhausen *et al.*, 1993). This mechanism of rule learning was also applied to a multivariable continuous working stirred tank reactor – a benchmark problem for the design of nonlinear controllers (Klatt and Engell, 1992) – generating high-level signal range controller outputs superpositioned to a classical diagonal PID controller. The conception called *Fuzzy-Lernas* is explained in detail in (Bettenhausen, 1994). Genetic algorithms and the search algorithm of Hooke and Jeeves (Hooke and Jeeves, 1961) were used in order to optimize the rulebase, applied to continuous processes and supporting transitions between several working or equilibrium points. This behaviour can also be achieved by a pure neural approch (Suykens *et al.*, 1994). In the meantime several implementation and representation specific optimization strategies with increased performance were developed and examined. These results will be published separately.

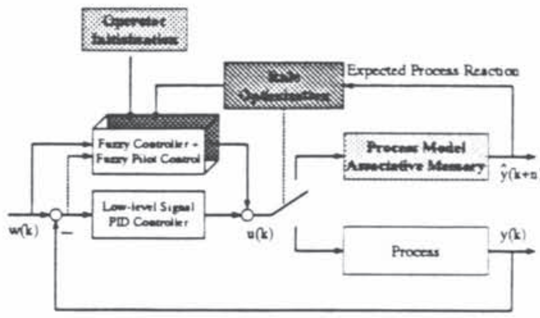

Fig. 5. Structure of *Fuzzy-Lernas* for the transparent and autonomous control of continuous processes.

The autonomous production of process management strategies is based on long-term predictions using structured process models. A system supporting modelling simply by preparing dynamic simulations and parameter estimations in predefined structures was presented in (Schumann, 1991). However, before such an enhanced sequence generation can experimentally be verified some conception for the data-driven automatic self-organizing generation of structured process models is essential. Due to this fact the actual work is concentrated on a methodology inspired by Koza's ideas of genetic programming (Koza, 1992).

3.1. *Self-organizing structured modelling*

The design of structured mathematical models of biological processes in a certain level of abstraction defined by the given task appears to be difficult and time consuming even to experienced experts. The methods of so called process identification mentioned above usually have strong limitations since the models structure has to be known a priori. However in practice an overall structure is not known in general.

Using the new methodology structured mathematical models can be generated automatically in a self-organizing way. Fig. 6 shows the underlaying concept of self-organizing model generation. Starting with some elementary transfer elements like time-delay or Monod kinetics placed in a so called "model construction set" a number of models are more or less randomly created. Using well known optimization methodes – e.g. the algorithm of Hooke and Jeeves (Hooke and Jeeves, 1961) – the parameters of the models are adapted to measured process response. For each model a fitness value is evaluated by assessing its accuracy and complexity. By imitating the principles of natural selection and reproduction (Holland, 1975) a process of evolutionary improvement of the models structure is achieved. This finally leads to models that combine high accuracy and low complexity, which are needed for most kinds of control purposes. A priori knowledge on structural properties can be taken into account in this process by constraining the elements in the model construction set and by influencing their selection frequency.

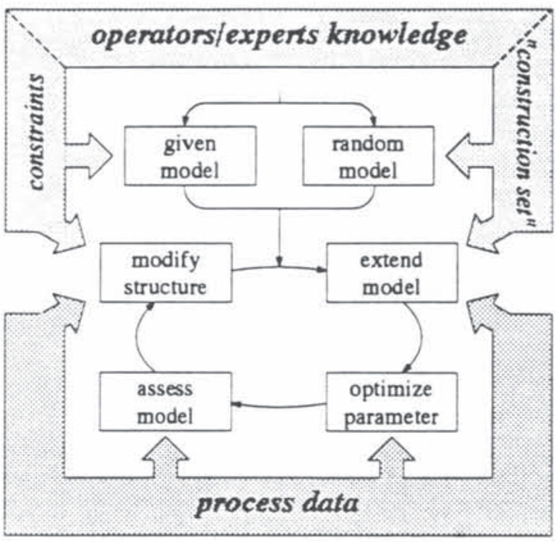

Fig. 6. Structure of automatic self-organizing structured modelling.

4. CONCLUSIONS

In the previous sections first experimental results using an intelligent system integrating conventional, knowledge-based and learnig methods for the control of biotechnological processes as well as new conceptions increasing the autonomy of the system and the transparency of automatically generated and learned process models and sequences of control strategies were presented.

The actual pratical work is concentrated on the extension of the fermentation system adding nutrients in order to allow a fed-batch mode for future fermentations which gives the possibilities of direct metabolism manipulation.

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