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$BioX^{++}$-EXTENDED LEARNING CONTROL OF BIOTECHNOLOGICAL PROCESSES

K.D. Bettenhausen and H. Tolle

Section Control Systems Theory and Robotics, Institute of Control Engineering, Technical University of Darmstadt, Darmstadt, Germany

Abstract. The technical use of biological or biochemical processes requires additionally to the biological preparation and process engineering an intelligent automatic control engineering whose performance characteristics excel the classical approaches. Most fermentations are operated in a phase-building batch mode, which does not allow a linearization of the not or only inexact known process model and the operation near one or several different working points. With $BioX^{++}$ an intelligent control system was successfully designed, whose fundamentals and extensions will be the contents of the article at hand.

Key Words. Biotechnology; batch fermentations; learning systems; associative memories; expert systems; fuzzy systems.

1. INTRODUCTION

A lot of severe problems of our modern society, like the always increasing waste, the feeding of an exponentially growing number of people living on this planet and the production of new and effective medicines require the technological use of natural biological or biochemical processes. The difficulty in practical use is found in the complexity of these processes and their dependencies on a lot of different partially unknown or not measurable environmental conditions. So normally in the laboratory scale first experiences and qualitative models are extracted, whose small number of input and output variables in the form of measured data sets are the available informations for the optimization of a given criterion, for example achieving maximum efficiency in minimum time. During the following experiments in the technical school a so-called scale-up process is used to transfer the scale onto always increasing production units. Furthermore, the tests take a lot of time and therefore hardly permit a time-dependent optimization of manipulated values. In short the optimal manipulated values of the laboratory scale which in general are stationary applied do not have to be the valid ones for the larger production scale. Because of this the intelligent control system $BioX^{++}$ was designed as a new approach for the successful automation of biotechnological processes. It allows, on the base of technical school experiments, a time-dependent off-line optimization. Furthermore it can be used to operate the real process and to execute an automatic on-line actualized optimization therein, in order to improve the production and to achieve higher autonomy in automation.

2. $BioX^{++}$

Based on the learning control loop LERNAS [Ersü and Tolle, 1984], the intelligent control system $BioX^{++}$, which is shown in fig.1, was developed [Gehlen *et al.*, 1988] [Gehlen *et al.*, 1992]. This system consists of the following three layers:

- Lower Level: Subordinate control loops in classical architecture.
- Medium Level: Modelling using interpolating associative memories and numerical optimization.
- Upper Level: Knowledge-based coordination and management layer including fault diagnosis, phase classification, choice of phase-specific model memories and definition of phase-specific optimization criterions.

2.1 *Subordinate Control Loops*

The subordinate control loops are classical control loops, using P-, PI- or PID-controllers, for

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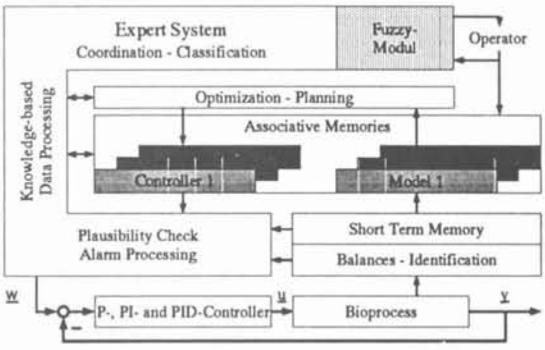

Fig. 1: Architecture of $BioX^{++}$

physical environmental conditions like temperature or pH-value in order to guarantee the maintainance of applied setpoints for the actual fermentation received from the two higher-level control layers. We examined as a pilot process the fermentation of *bacillus subtilis* producing α-amylase in a batch process.

2.2 *Modelling and Optimization*

In the medium layer the modules for the predictive self-learning modelling of the process and the numerical optimization are arranged. The short term memory – connecting the lower and the medium level – supplies the whole system with the values of the process input variables u_i and the from that resulting measurable output variables y_j, including a pre-defined history. As interpolating associative memories modelling the process, the neuronally inspired system called AMS or the mathematically inspired memory called MIAS are in use, see e.g. [Tolle and Ersü, 1992]. In this system it is their task to realize the following mapping

$$\begin{bmatrix} \underline{U}(k) \\ \underline{Y}(k) \end{bmatrix} \mapsto \underline{y}(k+1)$$

where $\underline{U}(k)$ is a vector representing the sequences $\underline{u}_i(k) = [u_i(k), u_i(k-1), ..., u_i(k-m)]^T$ and $\underline{Y}(k)$ combines all $\underline{y}_j(k) = [y_j(k), y_j(k-1), ..., y_j(k-m)]^T$. As an example see fig.3. This predictive behaviour can be achieved by either utilizing off-line training using archived measured data or by artificial time delay in on-line operation making use of the short term memory. As the up to now examinations have shown [Gehlen and Bettenhausen, 1990] [Gehlen and Kreuzig, 1991], this procedure is well suited to any non-linear process modelling without depending on structural conditions. Only the knowledge of the input and output variables contributing to the process behaviour is necessary. For the prediction properties one has to distinguish between short time prediction and long time prediction. With short time prediction we mean the prediction of the output variables for the next sampling period $(k+1) \cdot \Delta T$, with long time prediction we want to forecast the values for a later point of time $(k+n) \cdot \Delta T$. This can be achieved learning the predictions for later points of time or recursively re-applying the short time prediction. Making use of these predictive models, numerical optimization can be done to find out the effects of the manipulated variables on the process and to minimize or maximize a pre-defined optimization criterion. The adequate manipulated variables can also be stored situation-dependent, by what, corresponding to a learned non-linear process model, learned favourable non-linear controllers arise, so that in the long run the optimization layer will only be needed in exceptional situations. The corresponding structure diagram, the learning control loop LERNAS, is shown in fig.2. This learning control loop supplies in the considered case the setpoints for the conventional lowest layer of $BioX^{++}$.

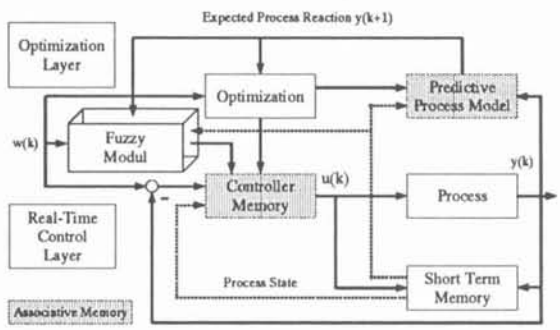

Fig. 2: Structure of the learning control loop LERNAS including heuristic knowledge

2.3 *Knowledge-based Coordination*

A detailed examination of fermentation processes shows that phases with more or less activity can be distinguished which reasonably are stored in various models and also should meet different optimization criterions [Gehlen *et al.*, 1992]. But the general profile of the phase shapes is known and can be described heuristically. Therefore the first task of the upper knowledge-based level is the phase classification for detection of physiological states, for example the single or several times appearing characteristic process phases for a batch fermentation: lag phase, exponentially growing phase, intermediate phase, stationary phase and death phase. A faultless classification of the process phases assumed, phase-specific model memories and phase-specific optimization criterions can be chosen. One possible mapping for the exponentially growing phase for α-amylase production with *bacillus subtilis* – our pilot process – is shown in fig.3. Additional to these features the upper level will perform fault diagnosis, which recognizes dangerous operating states like non-working pumps, blocked membran filters or broken tubes, it will display alarm signals and demand the operator to correct failures.

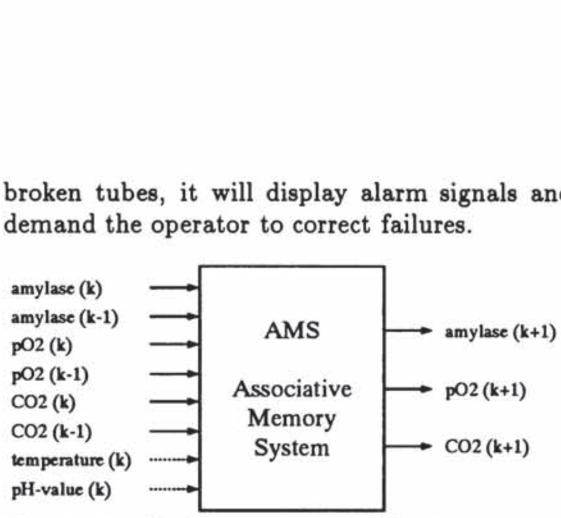

Fig. 3: Predictive process model using an associative memory mapping

2.4 *System Status*

The whole system is implemented on a SUN-4 workstation using the operating system UNIX and is connected via serial interfaces to personal computers. Till now the activities were concentrated on the construction of the medium level, using heuristic control strategies of the upper layer but not specifying them in detail. Thus the future attention will be put on the flexible realization of the upper coordination layer in order to offer the operator a much more efficient and intelligent man-machine-interface and to integrate heuristics more extensively. In order to integrate learning components in the upper knowledge-based layer it is sensible to use the same programming language for medium and upper level. Because of this the concept is realized using the programming language C^{++} which supports classical numerical and algorithmic programming as well as object-oriented programming. Keeping in mind that the operator in general has problems to express his knowledge in crisp formulations, the extended knowledge-based system was designed to deal with fuzzy knowledge. But according to subsection 2.3 also tasks of fault diagnosis shall be handled, which partly require exact models with crisp rules. This feature could be realized using an approach which can transform, only depending on the choice of some simple parameters, the fuzzy estimate into a crisp estimate.

3. EXPERIMENTS

As in the previous section has been put forward the phase-specific modelling and optimization is a basis for further improvement of the whole system for the operation of batch fermentations. A necessary presupposition for the successful execution of this strategy is the faultless automatic classification of the process phases. For detecting the different phases one has to take into account, however, that due to the living substrate seemingly identical substances may behave differently. Fig.4 demonstrates this by showing the shapes of carbon dioxide concentration and oxygen partial pressure for three fermentations with identical initial and environmental conditions.

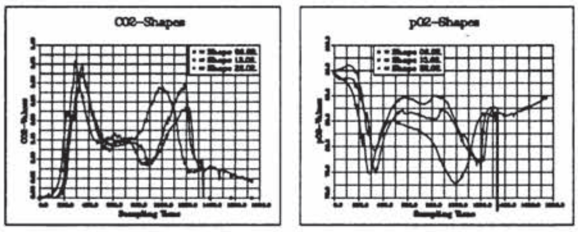

Fig. 4: CO_2- and pO_2-Shapes

3.1 *Phase Classification*

In order to assess the activity and therewith the actual physiological state one needs the information about the trend of the measured variables CO_2 and pO_2. The gradient is calculated using the first order difference quotient followed by a short time average filter $\Delta X(k) = (1-\alpha)\cdot\Delta X(k-1) + \alpha\cdot\frac{X(k)-X(k-1)}{T}$ where X is either CO_2 or pO_2 and the memory factor $\alpha = 0.01$. Fuzzy rules can reduce the number of rules in phase classification and allow some more tests like detection of rule inconsistencies. For the evaluation the following five simple rules were constructed:

- **IF** (CO_2 is constant) **and** ((PO_2 decreases) **or** (PO_2 is constant)) **and** (lastphase == lag phase) **THEN** (newphase = lag phase)
- **IF** (CO_2 increases) **and** ((PO_2 decreases) **or** (PO_2 is constant)) **and** ((lastphase == lag phase) **or** (lastphase == exponential phase) **or** (lastphase == intermediate phase) **or** (lastphase == stationary phase))
  THEN (newphase = exponential phase)
- **IF** (CO_2 decreases) **and** (PO_2 increases) **and** ((lastphase == exponential phase) **or** (lastphase == intermediate phase))
  THEN (newphase = interphase)
- **IF** (CO_2 is constant) **and** (PO_2 is constant) **and** ((lastphase == intermediate phase) **or** (lastphase == stationary phase))
  THEN (newphase = stationary phase)
- **IF** (newphase is not classified)
  THEN (newphase = lastphase)

The rule base does not include a rule to classify the death phase, because this phase does not appear in our fermentation data. The variables CO_2 and pO_2 are defined as fuzzy variables, while the last phase is treated with a 'winner takes it all' - strategy, which means that the grade of membership is one for the phase classified in the last step while all other grades of membership are set to zero. The defuzzyfication ensues from the determination of the maximum grade of membership according to one of the terms. Fig.5 shows the impressing results, especially since similar results apply to all other fermentations of fig.4 (not shown).

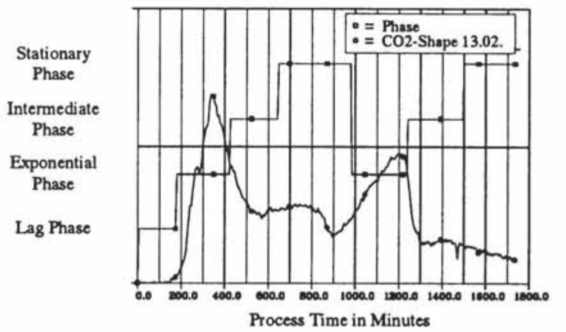

Fig. 5: Classified Physiological States

3.2 *Outlook*

The capability of learning in the upper knowledge-based level can be achieved in two different ways: manipulation of membership functions and modification of the rule base. Membership functions represent a $R^1 \mapsto R^1$ mapping for each term of any linguistic variable. The already performed tests use linear membership functions. Only the interpolation points are stored and allow to approximate any desired membership function with polylines. The initial startup parameters of these linear membership functions could also be stored in one of the already mentioned associative memories AMS or MIAS. The contents of these memories can be modified on-line or during an off-line pre-training using the optimization structure of LERNAS. For the modification of the rule base another procedure is envisaged which is shown in fig.6 for a single rule:

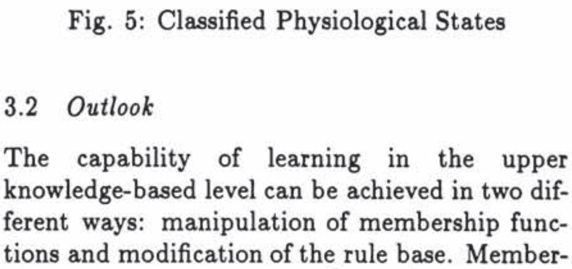

Fig. 6: Learning rule connection

In our example *and* and *or* operators are realized as minimum and maximum operators. The result of any elementary block will be weighted with a factor a_{ij}. The indices describe the number of the actual input and the depth from the goal. Combinations of such blocks, each consisting of elementary blocks will build a network of rules. In this network it is not possible to supplement new rules because of the existing structure, but a deletion of unnecessary rules can be achieved using a weighting factor zero. The weighting factors will be optimized using numerical optimization criterions as it is already explained. The on-line learning will be performed in a parallel process and actualize the parameters and weighting factors during the initialization step.

4. CONCLUSIONS

The article at hand describes and explains the development of an intelligent system for learning control of biotechnological processes. Based on earlier results with the learning control loop LERNAS and the intelligent system *BioX*, using integrated learning capabilities in a medium layer including modelling and optimization modules, $BioX^{++}$extends the learning features into the upper knowledge-based layer. This reduces the extensive and time-expensive work for the scale-up process. Additionally optimal phase-specific operation of batch and fed-batch fermentations can be guaranteed based on a maximum faultless phase classification. The chosen fuzzy estimate increases the already available features and also includes the classical crisp knowledge representation. Based on the impressing results of a phase classification using static rules and static membership functions one of the next steps will be the self-learning phase classification stored in locally interpolating associative memory systems and the use of the sketched weighted learning rule connection.

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