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The paper is submitted to the IFAC symposium on Adaptive Control of Chemical Processes, ADCHEM' 88, Copenhagen, August 17-19, 1988.

Key words
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On the role of adaptive controllers in fed-batch yeast production

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Abstract. The substrate control problem of fed-batch yeast production is analysed. It is based on broth ethanol measurement as indicator of over- or under-feeding. The main reason for control is to track the drastic growth in feed demand during a cultivation. Uncertainity in this growth is considered the main disturbance, and variation in process dynamics is regarded of minor importance. The discussion focuses on the low-frequency aspects of the control design. The limitation of conventional PID control is analysed. It is found that the integral part, while maintaining stability, cannot be made strong enough to compensate for the exponential increase in the feed demand. Introduction of a basic dosage scheme may result in a smaller disturbance and smaller ethanol errors, while an observer of the exponential load gives a further improvement of the ethanol control. An error in the initial estimate of the feed demand is eliminated, and influence from variation in the growth rate parameter is reduced. The strength of the disturbance rejection increases with the closed loop bandwidth. A longer sensor response time would call for a lower bandwidth. A moderate phase advance can be obtained by derivative action. However, tuning of the derivative part of the regulators is found difficult and quite sensitive to the process parameters. The limited time for tuning during a cultivation makes straight forward application of auto-tuners or self-tuners of minor value. A self-tuner would require some added excitation and need special care for the load disturbance. The analysis of simple regulators suggests adaptivity of the internal disturbance model.

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Introduction

Feedback control of the substrate feed in baker's yeast production processes is slowly winning industrial application. Production is traditionally done in fed-batch using precalculated schemes for substrate pumping. Such schemes are the secrete behind good yeast making, and they are based on long industrial experience. Even if the environment conditions are held as constant as possible it is very difficult to get reproducible batches. The amount and quality of the yeast inocculum varies, and some manual adjustments of the feeding is quite normal. The yeast needs a certain feeding to grow optimally, while too much substrate starts ethanol production and causes the yield to go down. The yeast quality is also affected by the substrate dosage profile.

Different sensors have been used to estimate the metabolic state of the yeast culture and thus the demand for substrate. Exhaust gas analysis and the calculation of the respiratory quotient has been a popular laboratory method to monitor whether the yeast is consuming or producing ethanol. Actually controllers are deviced using such a signal (Aiba et al, 1976) (Wang et al, 1977) and some adaptive variants have also been proposed (Dekkers and Voetter, 1985) (Verbruggen et al, 1985) (Montgomery et al, 1985). Another popular method is to let the volatile compounds of the broth diffuse over a semipermeable membrane and use a carrier gas transport them to an analyzer (Dairaku et al, 1981). Gas chromatography can be done using commercial equipment, but it is an expensive method although several different gases can be analyzed at the same time. Here we use a less specific semiconducter sensor (Mandenius and Mattiasson, 1983), to get a quite fast and reliable value for the ethanol concentration.

The main reason for control is to track the drastic increase in the substrate demand. The control performance is limited by the measurement delay, and the limited time for a batch makes tuning time critical. In these respects the feedback design problem are similar irrespective of measurement technique. One difference is that the respiratory quotient reflects the ethanol production rate and thus approximately the derivative of the ethanol signal (Dairaku et al, 1981). However, the complexity of the growth process makes it difficult to guarantee such a simple correspondence. The signals may show differences in the time scale of hours as well as in the response to transients in the substrate feed rate.

We have previously described (Axelsson et al, 1988), how we use the ethanol sensor for PID-control of the substrate feed rate, and in an accompanying paper (Axelsson, 1988b) it is used to evaluate a dynamical model for the system using identification in closed loop. Other papers report substantial difficulties with achieving good control (Dairaku el al, 1983).

In this paper we discuss the need for adaptive controllers of the process. Insight into the control difficulties are obtained by studying simple regulators with fixed parameters and using a simple process model. Experience from the identification experiments is incorporated. The importance of low frequency disturbance rejection is emphasized and the role of the varying process dynamics is played down. Arguments are given for introducing an internal model of the exponential feed demand. Since the tuning of regulators at a plant is a nontrivial task, the possibility for autotuning using the relay method is also discussed (Åström and Hägglund, 1984).

Characterization of the control problem

The discussion here is based on the accompanying paper (Axelsson, 1988b) where a process model was developed and the main control difficulties were described. The experimental set-up is shown in Figure 1.

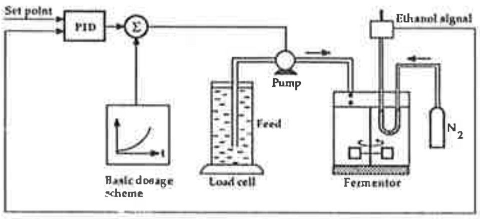

Figure 1. The experimental set-up.

Process model

In (Axelsson, 1988b) it was discussed how the cell density X and the volume V slowly increase. Actually it takes about 3-4 hours for the cell density to double. The ethanol concentration on the other hand reacts to changes in the substrate feedrate in the time scale of a couple of minutes.

The feed rate demand $F^{\circ}(t)$ is proportional to the cell mass. It can be approximated with an exponential function

$$F^{\circ}(t) = (F_0 + \delta F_0)e^{(\mu+\delta\mu)t} \tag{1}$$

where the parameter deviations δF_0 and $\delta\mu$ represents process uncertainty.

To describe the ethanol dynamics around the critical feed rate $F^{\circ}(t)$ it was found useful to introduce a second order linear time-varying model containing a pure integrator. Cell density X and volume V enter the model through the parameter variations of the gain K and the time constant T. The broth ethanol measurement system is well described by a time delay T_d and a time constant T_s. The total process transfer function G_p is given below. Note that it can be structured into one fix and one time-varying part.

$$G_p(s) = G_{var}(s) \cdot G_{fix}(s) = \frac{K}{Ts+1} \cdot \frac{e^{-sT_d}}{s(T_s s+1)} \tag{2}$$

where the parameters vary as

$$K \sim \frac{1}{V}, \quad T \sim \frac{1}{X}, \quad F^{\circ} \sim VX \tag{3}$$

There are some factors in the reactor conditions that are not modeled in (3). Results from identification experiments showed actually that the process gain K increased slightly with time rather than decreased. One factor that is not modeled is that the oxygen transfer may become a limiting factor at high cell concentrations. Further, unmetabolizable products of the feed and certain byproducts of the cell metabolism, may accumulate and reduce growth. Such changed conditions would also influence the process dynamics. However, the most immediate stoichiometric analysis shows that the gain would remain constant despite a decreased oxygen supply (Axelsson, 1988a).

A first try with adaptive control

Based on the given process description it is natural to attempt a straight forward self-tuning regulator. The process parameters are only approximately known and the process time constant changes slowly during one cultivation by a factor of 25. This is however no good idea. In Figure 2. is shown a first simulation of a pole placement self-tuner with four free parameters. Integral action is built in in the regulator design (Åström, 1979). Control is done around a basic dosage scheme that matches the actual feed demand $F^{\circ}(t)$. Reasonable process parameters were chosen as initial values for the estimator states and the control system was excited through periodic changes in the set-point value. Note the time for adaptation. To get the self-tuner to work properly use must be made of the process knowledge, and it is worthwhile to first analyse the properties of fixed parameter regulators.

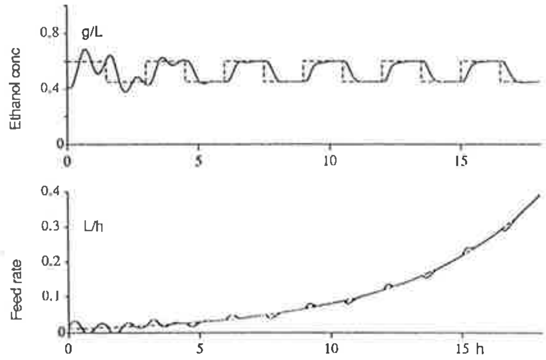

Figure 2. Simulation of an adaptive pole placement regulator for ethanol control. The upper diagram shows the ethanol concentration (solid line) and the set-point (dashed), and the lower diagram shows the feed rate (solid) and the basic dosage scheme (dashed).

Main control objective

The main reason for control is to track the exponential increase in the feed rate demand $F^{\circ}(t)$. It can be considered as a load disturbance at the process input. In the control system it is natural to incorporate knowledge of the growth characteristic of the culture, for instance in terms of a basic dosage scheme $F_b(t)$. The difference between the critical feed rate and the basic dosage scheme remains as a load disturbance. The control system is shown in Figure 3.

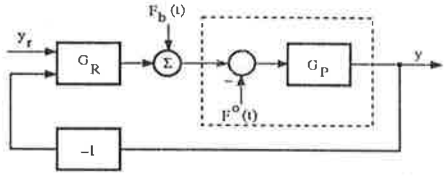

Figure 3. Block diagram of the substrate control system.

The time delay and dynamics of the sensor set a constraint on the magnitude of the control gain that can be used with maintained stability. The fact that the process dynamics change as the cell culture grows actually poses only minor difficulties. At start-up there is a considerable phase lag. During the first few hours the phase increases for all frequencies. The gain variation of the model is more complicated. In a mid frequency band, around a typical bandwidth, the parameter variations in K and in T interact and make the gain first increase and then decrease.

The fed-batch process is finished after a finite time and that fact has consequences for control design. The exponentially growing disturbance is a difficult problem but it must be considered only over a given time interval. Discussions about asymptotic behaviour are not relevant. Another consequence is that there is a limited time for tuning of the regulator to the actual process. Automatic tuning procedures are only interesting if they are rapid.

Possibilities with PID control

It is natural to first explore the possibilities with conventional PID control. Tuning of the PID regulator and understanding of its limitations can give valuable insight into the control problem and the role of adaptivity. Modification of the regulator structure is also discussed.

In fact, PID control have been used for dozens of cultivations with a reasonable performance (Axelsson et al, 1988). Different ways to change the regulator parameters during the cultivation have been discussed in the literature (Dairaku et al, 1983) and (Axelsson et al, 1984). Here, the characteristics of the disturbance is emphasized and the role of the varying process dynamics is played down.

Integral action and basic dosage scheme

To study what disturbance rejection that is possible to obtain, the process is first approximated as an integrator and the derivative part of the PID-regulator is neglected. In the next section it is then discussed how the stability is augmented using the D-part and the more detailed model (2). The low frequency behaviour is thus described by the approximate transfer functions

$$G_p(s) = \frac{K}{s} \tag{4a}$$

$$G_{PI}(s) = K_R(1 + \frac{1}{T_I s}) \tag{4b}$$

giving the closed loop transfer from the load disturbance d to the output ΔE as

$$G_d(s) = \frac{Ks}{s^2 + KK_R s + KK_R/T_I} \tag{5}$$

The critical feed demand can be approximated by an exponential function (1), and $\mu \approx 0.2\ h^{-1}$ and $F_0 \approx 0.01\ L/h$ are typical parameters. Closed loop time constants in the order of 10 min are achievable, so initial transients die out within an hour. The response to this load disturbance would thus be

$$\Delta E \approx -G_d(\mu) \cdot F_0 e^{\mu t} \approx -\frac{T_I \mu}{K_R} \cdot F_0 e^{\mu t} \tag{6}$$

With reasonable parameters, $T_I/K_R \approx 3$, the deviation $|\Delta E(t)|$ may grow from 0.004 g/L to about 0.10 g/L in about 15 hours. Despite the integral part in the controller it is impossible to keep the desired ethanol concentration.

A substantial improvement is obtained if an approximation of the feed demand F° (1) is included in the regulator as a basic dosage scheme

$$F_b(t) = F_0 e^{\mu t} \tag{7}$$

Now the ethanol response would be

$$\begin{aligned} \Delta E(t) &\approx G_d(\mu)F_b(t) - G_d(\mu + \delta\mu)F^\circ(t) \\ &\approx \frac{T_I}{K_R} \cdot \mu F_0 \left(e^{\mu t} - (1 + \frac{\delta\mu}{\mu})(1 + \frac{\delta F_0}{F_0})e^{(\mu+\delta\mu)t}\right) \end{aligned} \tag{8}$$

which for good estimates means almost total elimination of the ethanol error. On the other hand it could be worse if the estimates were off by a factor of two. Actually if $(\mu + \delta\mu)$ were as little as 25 % larger than μ the term $e^{(\mu+\delta\mu)t}$ would be twice as large as $e^{\mu t}$ after 15 hours, giving an $|\Delta E|$ of the same size as without the basic dosage scheme. If $F_b(t)$ is kept smaller than the demand $F^\circ(t)$ it follows that $|\Delta E|$ is always smaller than for $F_b(t) = 0$ but it leads to a decreased ethanol concentration. A too low ethanol concentrations may result in bad growth conditions, and an overestimated basic dosage scheme is the therefore often prefered.

It should also be mentioned that feedback control is really needed to keep small ethanol deviations even if $F_b(t)$ were a good approximation of the demand. Any deviation between F_b and F° would be integrated, and in the later part of a cultivation substantial ethanol errors would result within a couple of minutes.

Derivative part

The closed loop system (5) with $KK_R/T_I \approx 25\ h^{-2}$ and $KK_R \approx 8\ h^{-1}$ would have a damping of $\zeta = 0.8$, which indicates a well damped system. However, if you include the neglected high frequency dynamics of (2), the phase margin drops from about 70° to as little as 5° for $T \approx 6\ min$. The stability has to be improved. A moderate derivative part with derivative time 6 min and high frequency gain $N = 4$ adds phase advance at the crossover frequency giving a phase margin of about 40°. The resulting PID-regulator preserves stability also for a process time constant of about 15 min, a doubled time delay, or a factor two in process gain. No excessive noise magnification is introduced.

It should be noted that although the regulator is fairly robust, this parameter setting requires quite a bit of knowledge of the process and some skill in the use of a Bode diagram. A computational tool like PC-Matlab is certainly of great advantage. Similarly it would require a lot of experience to tune the regulator at the process.

Adaptation of PID-regulators, alternatives

The tuning of the PID-regulators was found to be quite tricky. The low frequency requirements are strict and the process variation makes it difficult to match the phase advance to the crossover frequency. As discussed in the accompanying paper (Axelsson, 1988b), the process variation is partly known. The process time constant T in (2) decreases by a factor of about 25 in a well-known way during a batch. Parameter scheduling of especially the derivation time T_D of the regulator would enhance the stability robustness. Another parameter to adjust would be the integral time T_I. At the start of the batch there is very little disturbance load and the strong integral action of the regulator is really not called for. A much larger T_I, like 1-2 h, would be sufficient and greatly enhance the stability robustness. A similar reduction would certainly be necessary in order to maintain stability, if the sensor were slower.

The regulator design makes use of a lot of process knowledge. It would have been nice to go to the process with an auto-tuning regulator, and let it adjust to the specific batch. This is not so easy. The length of the batch is limited and the process is quite slow, at least in the beginning. A simulation of a relay auto-tuner (Åström and Hägglund, 1984) shows that about two hours are required for three periods, and this is much to long. It does not give enough information either for the fine tuning of the derivative part.

One could decrease the relay period by introducing phase advance in the loop and that would give better estimates of the behaviour at the desired crossover frequency. However, it still requires about an hour of relay experiments. Another complication is the load disturbance. The simulations were done around a correct basic dosage scheme, and although the initial feed estimates are quite good it is known (Hang and Åström, 1987) that a changing load disturbance might influence the estimate of the process dynamics.

What is promising is to close the loop including a nominal PID-regulator around a low amplitude relay and then adjust especially the D-part according to the resulting relay-period. How this should be done and what performance that could be achieved is so far an open question. It requires much work both using simulation and analysis and experiments at the real process. In fact relay oscillations might excite more dynamics of the cell culture. The cells have different metabolism in different phases of cell cycle, and if oscillations in the substrate flow cause the cell population to synchronize, it may induce sustained oscillations (Parulekar et al, 1986). Such a behaviour was actually found in early cultivations using glucose as substrate instead of molasess (Axelsson, 1985).

The main reason for feedback control is the exponentially growing feed demand and the variation in this demand. A well-known principle is, that regulators should contain an internal model of the disturbance they are supposed to eliminate (Bengtsson, 1977). The I-part of the PID-regulator could be viewed as a model for a constant load disturbance. It is intuitively reasonable to try to include a model of the exponential load-increase in the regulator. This is done in the next section.

Observer for the exponential feed demand

In the previous section it was found that a regulator with integral action was not sufficient to reject the exponential load disturbance. A regulator with an internal model of the disturbance has a potential to eliminate its influence. Actually one could regard the basic dosage as a model of the load. If that model is supplemented with feedback, i. e. an observer is used, the requirement of good estimates of the initial feed demand could be relaxed.

Derivation of a reduced order observer

The feed demand, $F^\circ(t) = F_0 e^{\mu t}$, grows slowly, and a simple observer can be based on $G_p(s) = \frac{K}{s}$ as the process model. Introduce the state variables $x_1 = \Delta E$ and $x_2 = F^\circ$ and μ as an estimate of the true growth rate $\mu + \delta\mu$. The observer and the corresponding simplified model are then

$$\begin{cases} \dot{x}_1 = -Kx_2 + Ku \\ \dot{x}_2 = (\mu + \delta\mu)x_2 \end{cases}$$
$$y = x_1 \tag{9}$$
$$\begin{cases} \dot{\hat{x}}_1 = -K\hat{x}_2 + Ku + K_1(y - \hat{x}_1) \\ \dot{\hat{x}}_2 = \mu\hat{x}_2 - K_2(y - \hat{x}_1) \end{cases}$$

where K_1 and K_2 are the observer gains. The ethanol measurement signal has a low noise level, and it is natural to use a reduced order Luenberger observer instead of the full state observer (Kailath, 1980). The estimate $\hat{x}_2$ of the feed demand could then be obtained as

$$\frac{d\hat{x}_2}{dt} = \mu\hat{x}_2 - K_O\Big(\frac{dy}{dt} - K(u - \hat{x}_2)\Big) \tag{10}$$

A Luenberger observer is implemented without any measurement signal derivatives by using a direct feed through from y to $\hat{x}_2$ as seen from the Laplace transformation of (10). Let $\hat{x}_{20}$ denote the initial state of the observer.

$$\begin{aligned} L\{\hat{x}_2\} = &\frac{1}{s - \mu + KK_O}\hat{x}_{20} \\ &- \frac{k}{s - \mu + KK_O}\big(sL\{y\} - KL\{u\}\big) \end{aligned} \tag{11}$$

A state feedback

$$u = -K_R y + \hat{x}_2 \tag{12}$$

would then give perfect disturbance elimination, when $\hat{x}_2$ is equal to the feed demand x_2.

The two input form (11) and (12) of the regulator is valuable for the design of features for anti-windup and manual/automatic mode changes. Neglecting such nonlinear effects the internal regulator feedback would give the observer based compensator as

$$L\{u\} = -\Big(K_R + \frac{K_O(s + KK_R)}{s - \mu}\Big)L\{y\} + \frac{1}{s - \mu}\hat{x}_{20} \tag{13}$$

The regulator thus consists of three parts, a proportional feedback gain, an unstable dynamical part, and one part that could be interpreted as an exponential basic dosage scheme.

Load disturbance rejection

Similarly to the analysis of the PI-regulator it follows from the process model (4a) and the regulator (13) that the low frequency transfer from a load disturbance d to the output ΔE could be described by

$$G_d(s) = \frac{K(s - \mu)}{s^2 + (KK_R + KK_O - \mu)s + KK_R(KK_O - \mu)} \tag{14}$$

The disturbance d is the difference between the approximation $\hat{x}_{20}e^{\mu t} = F_0 e^{\mu t} = F_b(t)$ of the feed demand and the actual demand $F^\circ(t) = (F_0 + \delta F_0)e^{(\mu + \delta\mu)t}$.

A closed loop bandwidth of about 10 min is achievable, as discussed below, so the initial transients die out within an hour giving the remaining ethanol response as

$$\begin{aligned} \Delta E &= G_d(\mu)F_b(t) - G_d(\mu + \delta\mu)F^\circ(t) \\ &\approx -\frac{\delta\mu}{K_R(KK_O - \mu)}F^\circ(t) \end{aligned} \tag{15}$$

Comparison to the corresponding expression (8) for the PI-controller it is seen that errors δF_0 in the estimate of the initial feed demand $F_0 = \hat{x}_{20}$ are totally eliminated, while the improvement achieved for errors $\delta\mu$ in the growth rate μ is less obvious. The regulator (13) closely resembles the PI-regulator (4b) with $K_R^{(PI)} = (K_R + K_O)$ and $T_I \approx 1/KK_R + 1/KK_O$. Comparable parameters give

$$\frac{\Delta E_{PI}}{\Delta E_{obs}} = 1 + t\mu \cdot \frac{1 - e^{-t\delta\mu}}{t\delta\mu} > 1 \tag{16}$$

Typical values are $\mu = 0.20\ h^{-1}$ and $\delta\mu = -0.05\ h^{-1}$ and this gives after 15 *hours* a factor 5 in stronger load rejection for the observer based regulator.

Stability margins and phase advance

The substantial improvement in load rejection (16) was obtained with comparable parameters and it is reasonable to slightly reduce the "integral action". Just as in the PID-case some phase advance is required for "integration times" T_I as short as 20 min. A straight forward modification is an added D-part, the tuning of which exactly parallels that of the PID-regulator. The same parameters $N = 4$ and $T_d = 6$ *min* give almost identical behaviour and robustness, around the crossover frequency, and the tuning of the D-part similarly would benefit from a scheduling with respect to the process time constant T. The main difference as compared to the PID-regulator is that the system is only conditionally stable.

Safety nets have to be included to ensure a minimal gain through the process. The form (11)-(12) for the regulator is preferred and the phase-lead derivative term should be interpreted as an observer with one more state corresponding to an approximate process time constant T. The safety net, the anti-windup features, and the mode change mechanisms are then more easily designed.

Drawbacks of simple self-tuners

There is limited time for tuning during a fed-batch cultivation. The excitation level is low and precaution against estimator wind-up should be done. Laboratory experience of estimator wind-up has been reported in (Dekkers and Voetter, 1985) where an adaptive regulator based on the respiratory quotient was used for substrate control. Simulation studies with ethanol as measurement signal show a similar behaviour. Further, small deviations in basic dosage from actual feed demand gave a large bias in the estimated process parameters and in some cases caused unstable control actions.

Conclusion

Substrate control of baker's yeast fed-batch production has been investigated. The control is based on a broth ethanol signal. The process dynamics was studied in the accompanying paper (Axelsson, 1988b). However, most of the results here are based on the low frequency aspects of the model only, and it is thus approximated with a pure integrator.

The main reason for control is to track the exponential increase in the feed demand during a cultivation. The variation in process dynamics is considered to be of minor importance. Analysis show that introduction of a basic dosage scheme may result in a smaller disturbance and smaller ethanol errors. An observer of the exponential load gives a further improvement of the ethanol control. An error in the initial estimate of the feed demand is eliminated, and influence from variation in the growth rate parameter is reduced. An internal model of the approximate exponential feed demand thus facilitates the low frequency disturbance rejection without altering the properties around the bandwidth.

The sensor response time sets a limit to the strength of the disturbance rejection. A moderate phase advance can be obtained by derivative action. However, tuning of the derivative part of the regulators is found difficult and quite sensitive to the process parameters. From dynamical studies (Axelsson, 1988b) dead time compensation seems feasible and it would provide more phase advance, but probably require more parameter scheduling. The robustness may thus be sacrificed.

The emphasis of low frequency disturbance rejection and the lack of excitation around the bandwidth suggests that adaptivity should be applied to the internal disturbance model.

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