Online-Controlling of Glucose in Cultivations and Fermentations

TRACE Analytics

INTRODUCTION

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Glucose is used as substrate for many microbial and eukaryotic cells. In cell cultivations and microbial fermentations the glucose concentration has to be monitored. Furthermore it is beneficial to control the glucose concentration on a certain level to reduce the formation of by-products. In most of the processes low glucose concentrations in the medium will be preferred (substrate limitation).

A new device that simultaneously measures and controls the substrate concentration is presented.

TRACE C2 Control

TRACE C2 Control is a new online analyzer for controlling the glucose concentration (figure 1).

Figure 1. TRACE C2 Control

The integrated PID controller is able to keep the glucose concentration on a low and constant level in cell cultivations and microbial fermentations. The installed feeding pump is suitable for bioreactors with a working volume up to 5 L. Feeding in large bioreactors is also possible by direct connection of an external pump (e.g. Watson-Marlow 505DU) via the serial port of the instrument.

Glucose can be controlled in a range between 0.1 g/L and 40 g/L. The parameter lactate can be additionally measured in a range between 0.05 g/L and 10 g/L.

Depending on the application the maximum measurement frequency is 60 measurements per hour. The ambient temperature range can be between 15°C and 25°C due to the internal temperature correction.

Advantages

- Controlling of the substrate concentration without the need of SCADA
- Safe and economic operations
- Low installation size
- Less maintenance effort
- Disposable consumables
- Connection to different fermenter types

Sampling

For connecting the device to the process, the patented dialysis probe, the filtration probe, or the single-use dialysis probe are optional available (figure 2). Therefore the TRACE C2 Control can be connected to common glass and stainless steel fermenters as well as to novel single use bioreactors.

Figure 2. Single-use dialysis probe

PID Controller

Feeding in a cell culture cultivation can be reliably controlled with the integrated PID controller.

The PID controller consists of three interacting single controller. This are the proportional controller (P), the integral controller (I), and the derivative controller (D). The control action of the controller is described by a differential equation (figure 3).

$$u(t) = K_P \times e(t) + \frac{K_P}{T_N} \times \int_0^t e(\tau)d\tau + K_P \times T_V \frac{d}{dt} e(t)$$

Figure 3. Differential equation of the PID Controller

The persistent control deviation of the proportional part of the controller can be balanced with the integral part. With the derivative part of the controller it is possible to react to fast changings of concentrations inside the reactor. The PID controller is better suited for feeding processes than a simple two-level controller.

Adjusting the PID-Controller

The principle of the PID controller is known since 1922 (Minorsky[1]), but useful rules for adjustment were not available since 1942 (Ziegler and Nicols[2]). Today most of the controller will be adjusted by empirical design. This design can also be used in the field of biotechnology.

Disturbance reaction (Step response)

Disturbance reactions were performed in a glass fermenter with a filling volume of 1.5 L. The set point was adjusted to 5 g/L glucose and a glucose consumption rate of 1 g/(L*h) was applied. A feed solution containing 200 g/L glucose was automatically fed with the internal pump. The system was disturbed by addition of water and the glucose concentration of 5 g/L was dropped to 3 g/L. With the step response the parameters of the PID controller was optimized using empirical design (figure 4). The control range (±10%) can be reached in 15 minutes instead of 50 minutes (green line).

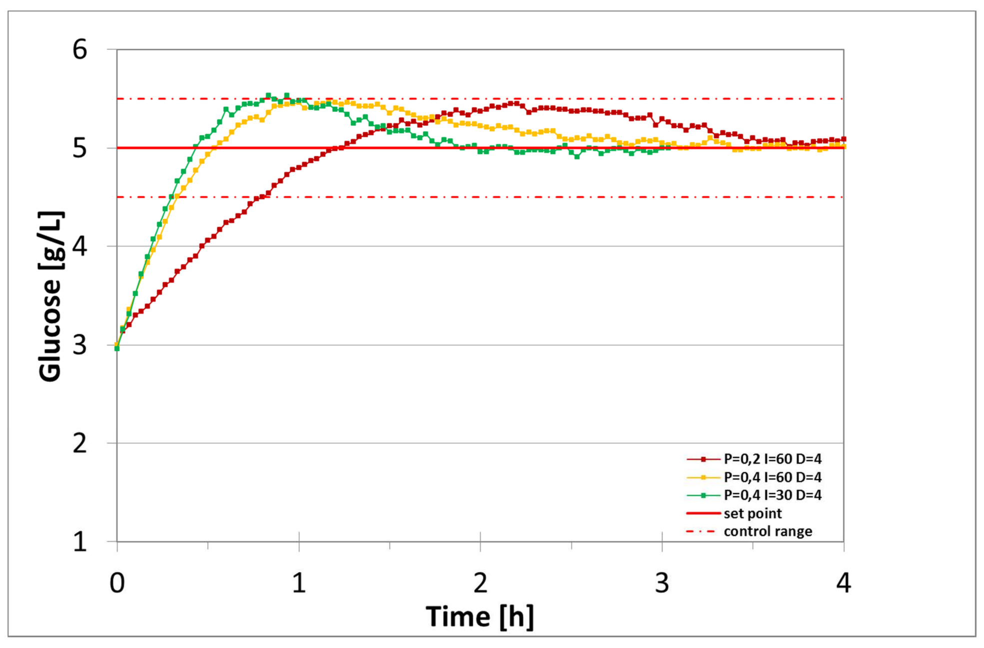

Figure 4. Different adjustments of the PID controller and the influence on the step response .

Simulated cultivations

With the optimal setting of the controller a simulated cultivation was performed. Starting with a glucose concentration of 5 g/L. By adding water to the reactor the consumption of substrate was simulated. The filling volume of the reactor was kept constant on 1.5 L. The set point was adjusted on 1 g/L glucose.
The control range was immediately maintained (figure 5). With this settings a reliable control of the process is possible.

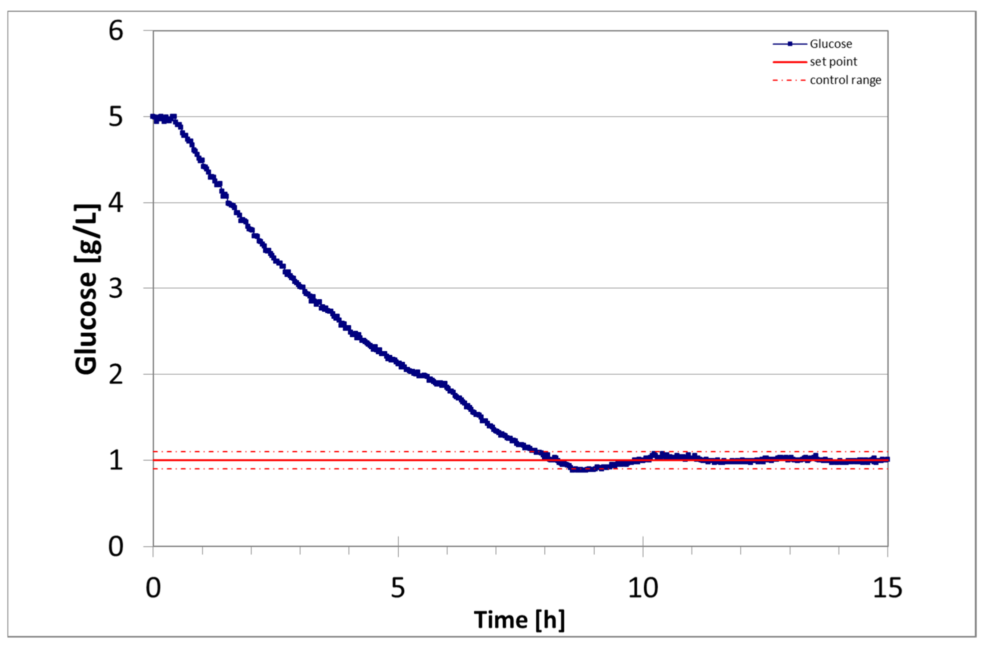

Figure 5. Simulated cultivation.

CONCLUSION

TRACE C2 Control is a new online analyzer for monitoring and controlling of glucose concentrations in bioprocesses.

In disturbance reaction experiments and in simulated cultivations it can be successfully shown that a reliable control is possible.

Literature

[1] Minorsky, Nicolas: Directional stability of automatically steered bodies; J. Amer. Soc of Naval Engineers 34 (1922), pp. 280–309.
[2] Ziegler,J.G. and Nicols, N.B.: Optimum settings for automatic controllers; Trans. ASME, 64 (1942), pp.759-768