

Automation Increases Productivity in Bioprocess Development

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Abstract

The design space of bioprocesses strongly depends on the technological limits of a system. Digitization helps us to push these boundaries and reach new optimization. A vivid example of this technical extension is the use of additional PAT tools to monitor and control bioprocesses. Biosyntia uses additional offgas analysis to control feed rates in the production of vitamins.

Biosyntia

Biosyntia is an innovative start-up located in Copenhagen. In a smart lab, they develop the processes of tomorrow. The products range from natural and eco-friendly B-vitamins to selected nutraceuticals with applications in personal care, dietary supplements, and animal feed products.

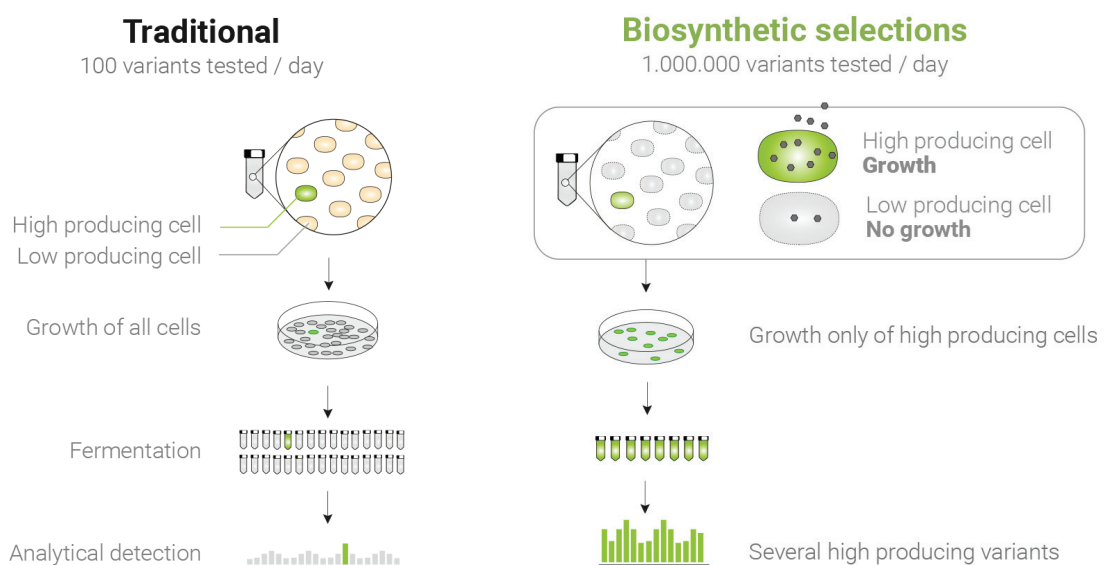


Fig. 1 Traditional approach vs the Biosyntia approach

Bioprocess development at Biosyntia

The aim of process development at Biosyntia is the design of a robust vitamin production process at a competitive price. Process development is faster thanks to six identical parallel bioreactor set-ups. Each set-up consists of a bioreactor (Applikon Biotechnology, my-Control) and an off-gas analyzer (BlueSens, BlueVaris). The applied software for data recording, visualization, and process control is Lucullus® PIMS, which is installed on a single computer used as a workstation.

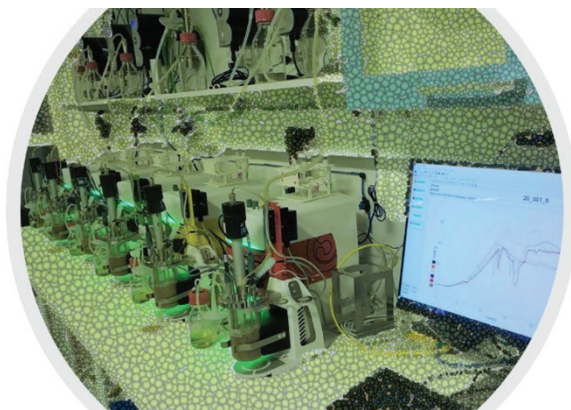


Fig. 2 Reactor farm with six Applikon my.Control, six BlueSens off-gas analyzers, and a Lucullus® control.

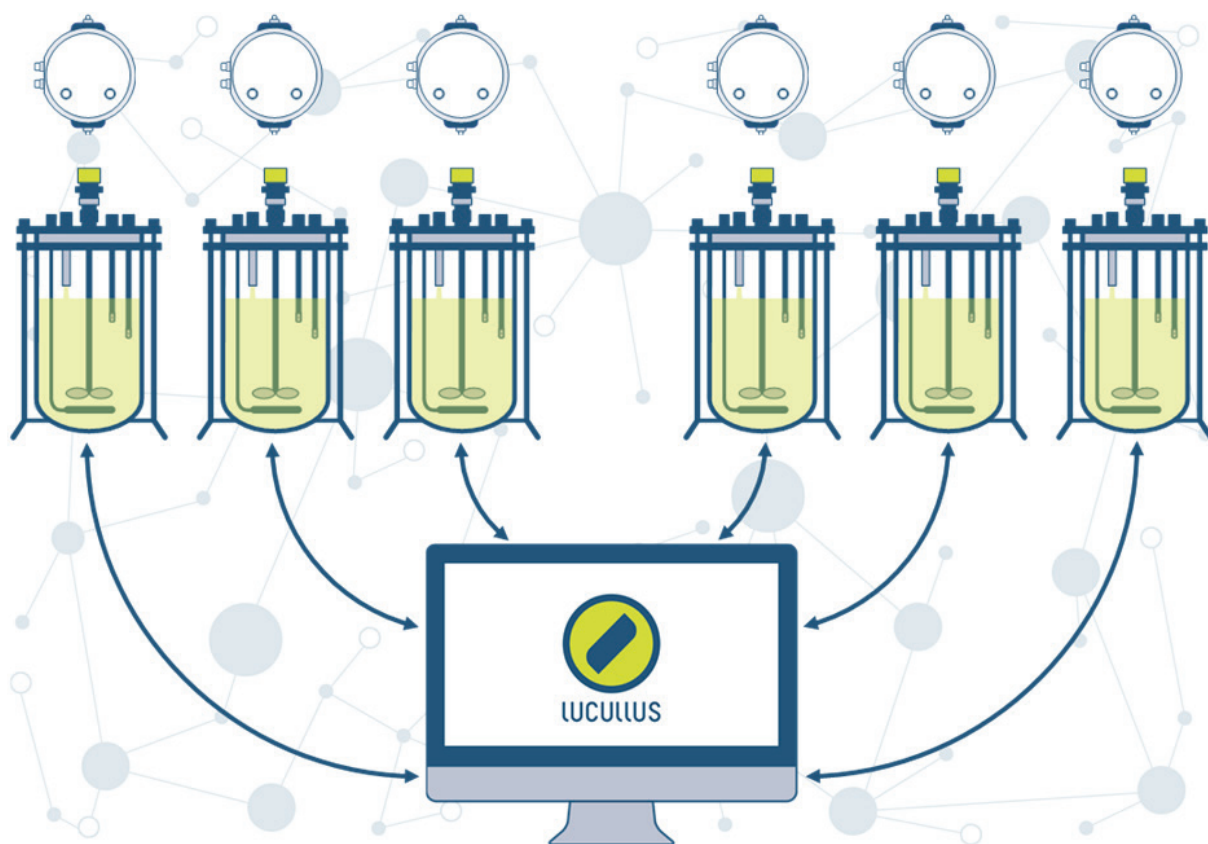


Fig. 3 Schematic representation of the laboratory infrastructure at Biosyntia, which includes six reactor set-ups, each one expanded with an off-gas analyzer. Lucullus® is used as the central bioprocess software.

The Process

To optimize the time-space yield, an improved feeding profile can be set as a key process parameter (KPP).

The process is designed as an induced fed-batch and allows direct control of the carbon evolution rate (CER).

In the batch phase and the first part of the fed-batch phase, the focus lies on biomass growth. Afterwards, the vitamin production is induced. Lucullus® automatically performs the whole bioprocessing control set-up in its control recipe. The basic structure of the recipe is illustrated in figure 3.

To enable feed control, two steps must be executed:

1. Real-time calculation of CER
2. Control of the feed pump

The calculation of the CER is easily performed with the Lucullus® Calculator (LCALC). The calculator uses the data from the mass flow controllers and the off-gas analyzer and applies the following equation:

$$CER = \frac{\dot{V}_{in}}{V_R} \cdot \frac{p}{RT} (y_{CO_2,out} - y_{CO_2,in})$$

Equation 1

The step controller, a system device available in Lucullus®, allows the complete bioprocess control to be performed: If the CER is too low, the feed rate is increased; if the CER is too high, the feed rate is reduced. The whole feeding is performed in a continuous mode.

In addition to the actual feed control, the event-based start of the fed-batch and the end of the fed-batch are detected and controlled by Lucullus®. The criteria for the fed-batch start were set up in a robust manner using two starting conditions: the maximum of the reached CER must be bigger than 45 and the current CER below the actual setpoint. This ensures that the feed will not start at the beginning of the process when the biomass is low, but it will start when the CER is lower than 40. The process is finished and harvested after 72h.

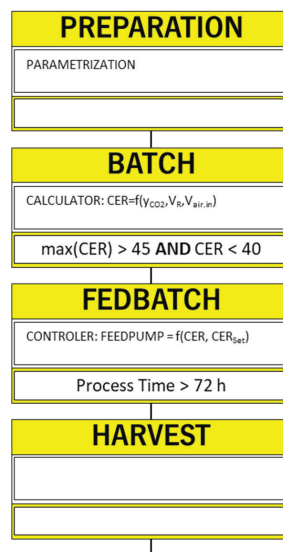


Fig. 4 schematic illustration of the applied control recipe.

Conclusion

The CER was efficiently controlled over the whole fed-batch phase (Fig. 5). Lucillus® enables Biosyntia to perform its processes as designed and empowers their production.

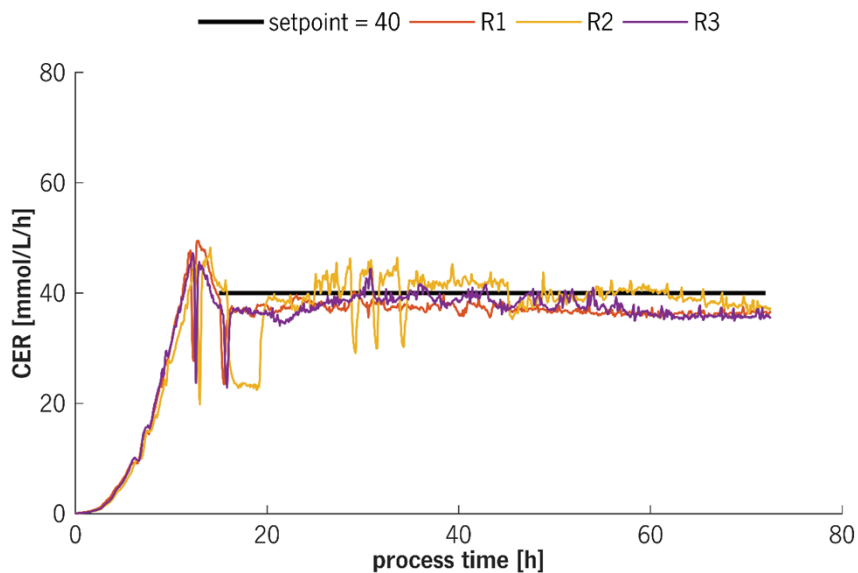



Fig. 5 CER for three different fed-batch processes

 **Biosyntia** “Lucillus® is an irreplaceable tool for process development. It enables Biosyntia to monitor and control novel processes for vitamin production”.

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