Optimising Bioreactor Yields with Smart Sensors

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Smart sensors for accurate condition control in bioreactors create new opportunities in healthcare and the pharmaceutical industry. By integrating connected systems, pharmaceutical instruments manufacturers can offer higher yields at reasonable cost as well as key additional features.

Bioreactors are used, among other things, to grow organisms such as enzymes, plant and animal cells, and microorganisms. Such active ingredients are used for medical drug research, treatment development, clinical trials and the production of high-value pharmaceuticals. Besides the latest example of mRNA vaccines, monoclonal antibodies for treating cancer, rheumatoid arthritis and other diseases are produced in these vessels. Life science innovators assume they will likely be able to grow organ and other muscle tissue in the future.

Whether in pharmaceutical R&D, large-scale manufacturing or medical treatment, bioreactors must provide a perfect environment under which sensitive microorganisms can change and grow by interacting with one another and under the influence of the apparatus' environmental conditions. For ideal cell growth in terms of quality and output, the environment of biotic populations needs to be controlled precisely. Fundamentally, that means maintaining pH value and temperature, ensuring the supply of air, nitrogen and other gases as well as nutrients.

This is not new, but today's increased requirements can make the growing of organic materials so complex that the physiochemical dependencies of the individual parameters have to be carefully synchronised with each other. In addition, the more and more versatile deployment of bioreactors, the aim to reduce contamination risks for operators and avoid disrupting ongoing processes by conventional "measuring by sampling" are complicating the matter, too.

Versatility, repeatability and efficiency

Bioreactors must be able to accommodate different cell types. If we take a look at the influenza vaccine, for example, its production processes vary from year to year, as different viruses with slightly different characteristics develop in each cold season. Moreover, as the pandemic has shown us, large quantities of cultivated cells were needed from one day to the next, resulting in a high demand of maximum yields. Producing huge amounts of mRNA vaccines not only required reactors with high efficiency, but also a high process reliability and repeatability. These requirements also apply to any other application of bioreactors, which are deployed for all kinds of high-volume drug manufacturing.

With the rise of biotechnology and recent experiences, pharmaceutical manufacturing and healthcare needs also require a higher robustness in order to increase yields. The key to meeting the new needs lies not only in the development of novel bioreactor designs, but also in new process control concepts using smart sensors that are biocompatible, fast, stable, accurate and easy to clean (if they are not disposable).

Parameters for optimum cell growth

Creating physiochemical conditions and enabling fast adjustments for specific cell cultures require the measurement of the following parameters inside a bioreactor:

- pH-value
- Temperature
- Humidity
- Gas and liquid concentration
- Gas and liquid flow
- Headspace pressure

In most cases the temperature is kept at 37°C and the CO2 concentration at 5% during cell growth. However, in some cases these parameters must be finely adjusted to reach the target pH range, to which priority is given.

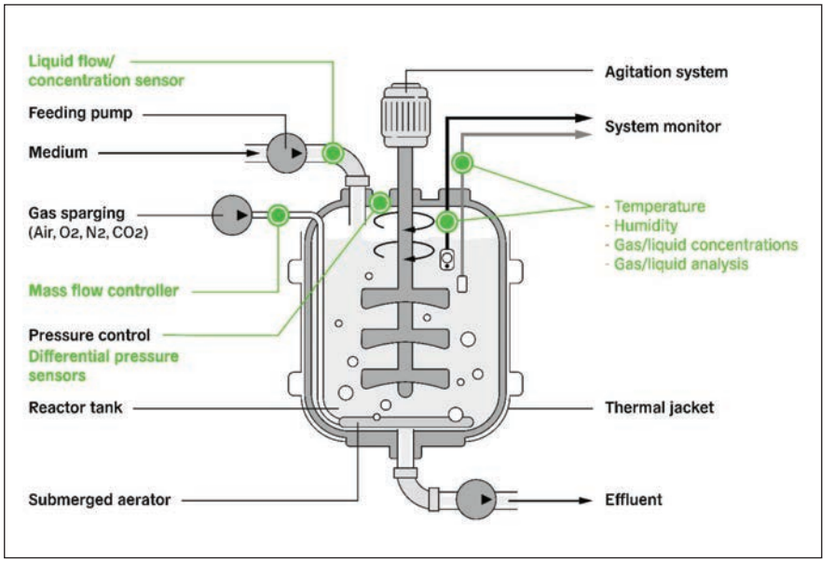
Often, the pH value must be kept in between 7.0 and 7.4. Keeping it stable in this narrow range can be challenging, insofar as there are several other parameters that have to be balanced in parallel, such as temperature, cell growth, lactic acid and the CO2 level. This can be done by so-called buffers, which neutralise any additional acid (H+ ions) or base (OH ions) to keep the pH value stable.

Furthermore, the oxygen concentration requires precise control. For most cell cultures it must be kept at 20%; occasionally, some cultures grow better under different conditions. Therefore, it is fundamental that the oxygen efficiently transfers from the gaseous to the liquid state in the cell culture medium so that the cell metabolism functions as quickly as possible. The efficiency of the oxygen transfer is affected by the temperature, the pH value and the gassing rate.

Finally, humidity should be stable and monitored in real-time to detect evaporation system failures. The same applies for the headspace pressure, particularly in single-use bioreactors since their flexible plastic bags cannot withstand overpressure of a few hundred millibars over a long period of time.

Condition monitoring, failure detection and data logging

When it comes to keeping conditions under control, connected sensors play a key role in bioreactors. Multiple smart sensor systems for highly precise physiochemical process control and accurate monitoring can take the performance of such an apparatus to the next level.



Due to the already addressed mutual dependencies of the different parameters, successful cell growth can turn out to be a complex undertaking. The easiest and most cost-efficient way to optimise the growth of organic materials is to consistently monitor and control the cultivation condition with a closed-loop system. Stable environments are particularly relevant for any high-volume drugs or during the R&D phase of drug design. In such cases, only small deviations occurring for a short time can affect the desired output of organic material.

State-of-the-art sensors enabling real-time feedback loops not only allow bioreactors to change conditions immediately and with high precision, but also to detect failures. In case of deviating set points, a system automatically triggers an alarm and blocks the vat before any damages occur and expensive materials are wasted (as in the case of overpressure in single-use devices).

Accordingly, different sensor types might be used to detect different failure modes. For example, sensors that monitor liquid concentration may also be deployed to verify that the right liquid is injected into the device. The same applies to liquid flow sensors, which might be implemented to measure total dispensed volumes (especially for expensive liquids) as well as to precisely dose multiple liquids in order to obtain the right concentration. This also applies to gas flow sensors. In short, feedback loops help to optimise process safety and reliability.

Furthermore, in some bioreactors it can be helpful to implement multiple sensors of the same type – for example, one at the inlet and one at the outlet of the bioreactor. Obtaining spatial information of different locations allows for a better understanding of the physiochemical processes in the cell culture.

An additional benefit of a smart control system is the ability to log sensor data and store it in a database. Should the growth results not be satisfying, an easily accessible logbook of all measured parameters provides clarification. Especially for safety reasons and research purposes, it can be extremely valuable to have access to the data history of a cultivation process. Thanks to a tracking system, operators can quickly identify root causes for failures, and thus modify processes.

The solution: reliable, fast and robust sensors

Recent advances in MEMS-based sensors have led to compact, low-power and high-performance solutions that are also suitable for single-use bioreactors (which, compared to conventional bioreactors, require lower volumes of water and detergents and no cleaning or maintenance procedures). Besides environmental reasons, such applications also stand out due to reduced costs and better turnover rates.

Sensirion offers a wide portfolio of compact, high-performance sensors - including single-use sensors - for precise process control and accurate process monitoring in various types of bioreactors, from pilot to commercial manufacturing. Sensirion's biocompatible new-generation sensors can easily be integrated in existing bioreactors, allowing users to upgrade their apparatus instead of acquiring a new one. The digital sensors of the Swiss manufacturer cover wide measurement ranges without losing their high accuracy, even down to the lowest limits. No wonder that they have become an in-demand component for next-level bioreactors in various pharmaceutical fields.

Sensirion's bioreactor portfolio

Liquid flow sensors
Liquid flow concentration sensors
Mass flow controllers
Mass flow sensors
Differential pressure sensors
Humidity and temperature sensors
CO2 sensors
Gas analysers/gas chromatography