Continuous monitoring irrespective of time and location

by Martin Grolms

The more complex a biotechnology process is, the more difficult it is to predict how the process will proceed. The amounts of data generated are also increasing, driven both by the number of clones being analysed and the process parameters being monitored and controlled. Mobile monitoring of critical process parameters, together with an intelligent information management system, provide an efficient solution.

The economic success of biopharmaceutical manufacturing is heavily dependent on the development cycle of the relevant production processes. Acceleration of the development processes offers the potential for enormous savings, but places high demands on the efficiency and reliability of the methods used.

Biotechnology processes in particular are characterised by frequently costly materials and by run times of up to several weeks. In addition, the nature of the process is not always predictable, leading to the occurrence of key events at unexpected times.

In order to optimise the processes involved, the parameters used are varied and the thresholds of the system are ascertained. Parallel processing offers a time- and cost-saving solution, particularly in the biopharmaceutical production process. Because, unlike with production, reasearch and development does not normally involve shift work, continuous monitoring of the processes cannot be adequately ensured. Mobile technologies, however, can enable the monitoring of critical process parameters at any time and from any location, and if required, can allow direct intervention in order to modify the processes.

Another challenge for laboratories involved in process development is the increasing amounts of data generated. Developing new medications not only requires the monitoring of numerous parameters, but there must also be detailed recording and systematic analysis. The parameters that are recorded when cultivating bacterial, animal and human cells in a bioreactor include temperature, pH, amount of dissolved oxygen and the actual value of key components such as pumps, stirrers and gassing systems. Furthermore, data such as viable cell density and nutrient or metabolite concentrations are determined using external analysers.

Permanent overview of continuous processes

Bioprocesses can be accessed at any time and from any location using the DASGIP Remote Control system. The web browser-based application enables access from a PC, Mac or laptop computer without the need to install software. Users can not only monitor the current processes online, but directly intervene in order to change reference values or deactivate pumps, for example. The alarm option triggers immediate warnings, which can even be sent via e-mail or text message, when critical situations occur. The remote control system thus gives the user complete control of the bioprocesses from any networked location in the world.

As with all other user interventions, changes carried out remotely are also logged in the events archive. The integrated access rights management and mandatory authentication control ensures that user access is in accordance with the company-specific security guidelines.

This well-established remote control system has been enhanced with the company's innovative iApp, the first application for monitoring and controlling parallel biotechnology cultivation processes using an iPhone, iPod Touch and iPad. This allows users to monitor and control all relevant process parameters online in up to 16 parallel reactors at different locations around the world.

The iApp takes advantage of the innovative features of these mobile devices, such as their multi-touch capability and position-dependent visualisation [Figure 1]. The universal DASGIP application automatically adapts to the device on which it is installed. This provides unsurpassed simplicity in the operation and layout of the application.

Users can enjoy a wide range of display options using different windows, zoom and rotation functions, all of which can be intuitively managed. In the trend chart, for instance, users can glance at the reference and process values as well as the control profile. They can also use the graphic timeline to browse between past and real-time process-variable data in a stepless manner. An overview allows users to track the current values of critical process parameters. Any warning or alarm thresholds that are exceeded are highlighted.

The user device, iPhone or iPad, can be connected to the remote control system via Wi-Fi or GSM. Data security is ensured by utilising virtual private network (VPN) connectivity [Figure 2]. As with all official applications of the iPhone and iPad, the iApp can be purchased through Apple's iTunes store. This also ensures a user-friendly distribution process for new versions of the application.

All research data in a central database

The remote control system is enabled via an OPC link. This open network standard is used to connect the individual devices to the central control software. The OPC connection can be used to integrate not only external control platforms to the bioreactor system, but also other equipment such as sampling and analysis devices, provided that the bioreactor system has an OPC interface.

The DASGIP control software collects the incoming data and visualises and stores it, together with the process data, in a central database. Using the data mining tool, the process data can be merged with process-relevant information, such as feeding strategy, cell and media composition, live cell counts or product yields. The information in these databases can be stored and retrieved based on user-defined keywords. Integration in long-term archive and process control systems enables the uniform

Figure 1. For mobile remote monitoring, the DASGIP iApp typically runs on an iPhone. If the iPhone is turned round, the display adjusts automatically. The upright position is the best for displaying numerical data. The landscape format is ideal for graphic analyses.

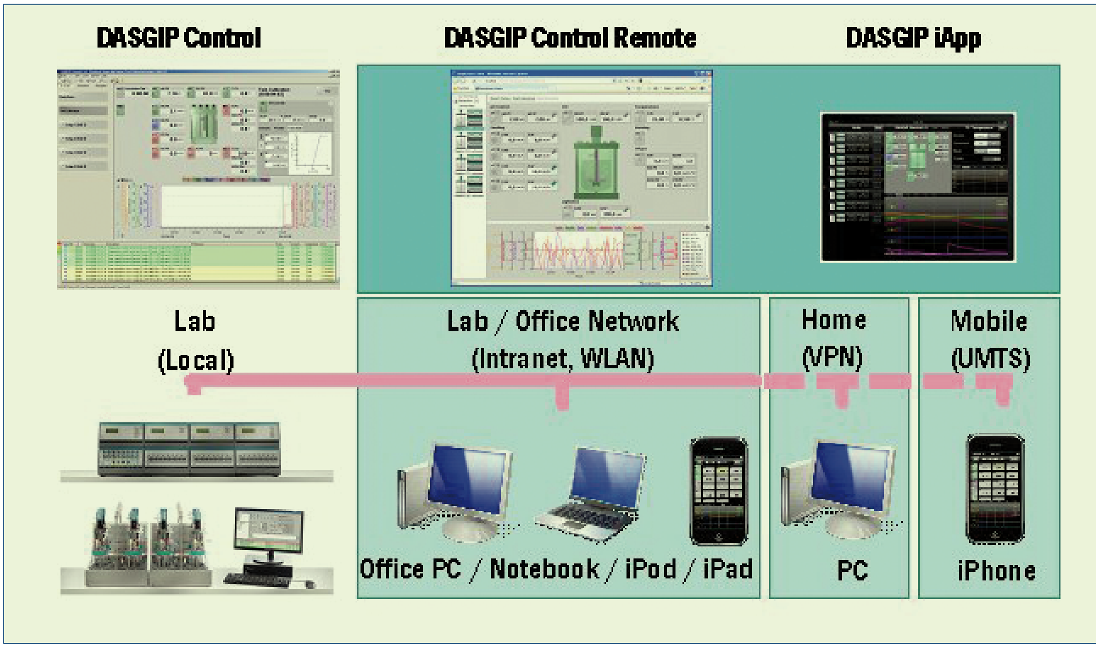

Figure 2. The connection to the control system can occur via a local network, Wi-Fi or a mobile phone network.

archiving of process and analysis data from different systems. Scientists can access this research data from any company location.

Users thus benefit from technologies that make it possible to utilise the research data in a holistic fashion, from the bioreactor system to the individual laboratory. The research data are seamlessly integrated into the information infrastructure of the company, and simplify targeted access to the information, which is provided to the user in a timely way.

Parallel processing

In combination with the tried-and-tested parallel processing, the intelligent information and integration management system offers enormous potential for saving time and money during the process development phase. The system can operate between four and 16 reactors in parallel, with working volumes ranging from 35 mL to 4.5 L. The system offers diverse functions such as monitoring and control of pH, amount of dissolved oxygen and optical density, as well as exhaust gas analysis and determination of redox potential.

Because large volumes of data are generated during parallel processing, with the data mining tool or via integration in external long-term archive and process control systems, the intelligent information management adds great value. Users can access these data in online mode at any time and from anywhere via the remote control software, and can directly intervene in running processes.

From its inception around 20 years ago, DASGIP has always focused on parallel planning, execution, monitoring and analysis of bioprocesses using centralised control software, including extended control functions. With the introduction of the iApp, the company is once again demonstrating, with its technology and innovation, that it is a world leader in the field of parallel cultivation systems for biotechnology processes.

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Erythromycin A produced in *E. coli* for first time

Researchers at Tufts University School of Engineering, USA have reported the first successful production of the antibiotic erythromycin A, and two variations, using *E. coli* as the production host. The method offers a more cost-effective way to make both erythromycin A and new drugs that will combat the growing incidence of antibiotic-resistant pathogens. Equally important, the *E. coli* production platform offers numerous next-generation engineering opportunities for other natural products with complex biosynthetic pathways. Previous research had reported manufacture of erythromycin A intermediates in *E. coli* but not the final product. The Tufts team focused on reconstituting and ultimately manipulating the compound's original biosynthetic pathway rather than using analogous enzymes extracted from analogous pathways.

http://www.tufts.edu/