

Parallel Systems for Unparalleled Results



Increasing development complexity and tightening regulation of therapeutic drugs drive up development costs while slowing down drug launch timelines. In 2004, development costs in Germany rose from €3.55 billion to €4 billion, a nearly 9% upsurge; meanwhile, the number of product launches and patent grants remained unchanged.

Companies race against each other to have the next new drug on the market and continuously seek improved efficiency to take products through the pipeline to market. Optimal use of human resources as well as an improved productivity of processes are key to shortening development timelines. Regulatory requirements also contribute to this demanding environment. With each launched drug, the regulatory agencies become more knowledgeable about appropriate laboratory and manufacturing practices. So all aspects of biotechnology-based drug development and manufacturing are becoming more stringent, requiring high levels of consistency and monitoring at each scale.

To overcome those obstacles, scientists seek ways to develop new processes with higher productivity in both products and labor, reproducibility to minimize experimental variation, and scalability to simplify scale-up in manufacturing. DASGIP parallel bioreactor systems are the ideal tool for achieving these challenging goals.

DASGIP PARALLEL BIOREACTOR SYSTEMS

DASGIP cellferm-pro® and fedbatch-pro® are parallel and modular cultivation systems designed for mammalian cell culture and microbial fermentation. Both are capable of running a variety of vessel types and sizes from as small as 50 mL to more than 15 L. With DASGIP control modules, users can independently operate four to 16 vessels with precise control of parameters such as pH,

temperature, dissolved oxygen, agitation speed, gassing, and feeding. The new GA4 off-gas analyzer provides continuous reading of oxygen and carbon dioxide in the culture's off-gas without multiplexing. It features four independent analyzers to provide real-time reading and calculation of respiratory quotient, oxygen transfer rate, and carbon dioxide transfer rate. Those easy read-outs enable productivity to be optimized based on the metabolic state of a culture (Figure 1).

User-friendly DASGIP control software also provides sophisticated features such as time-based parameter profiling for parameter shifting, triggering automation for automated triggered feeding, metabolic activity monitoring for insights into each culture's needs, and perfusion operating mode to suit different development platforms. Using this high level of software intelligence, scientists can design and execute their experiments with confidence.

HIGH PRODUCTIVITY

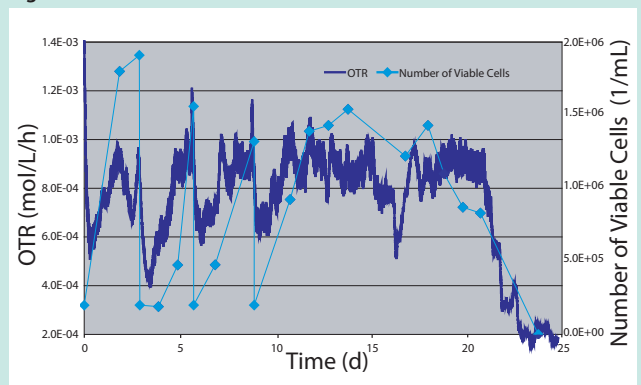
Increased productivity is one of many benefits in using a parallel bioreactor system. The compact size of DASGIP systems allows users to maximize their laboratory space. A typical four-vessel DASGIP system occupies the same footprint as a single-vessel system. With its ease of set-up and centralized control, the DASGIP system improves experimental throughput. Current users of DASGIP systems such as the Massachusetts Biological Laboratory at the University of Massachusetts (UMass) are able to perform the same amount of cell culture work in half the time compared with using other cultivation systems.

"We are able to achieve significantly higher cell productivity with selected cell line using the DASGIP system. Acquiring the DASGIP system was a valuable investment to increase and improve cell culture capability."—John Que, PhD, UMass

REPRODUCIBILITY

Reproducible results in cell growth and product yield have long resulted from tightly controlled culture parameters and precision engineering in DASGIP systems. Process parameters are controlled in a tight range using the mass-flow-controlled gassing module MX4/4 to supply a precise mix of gases and the peristaltic pump module MP8 with variable speed drive to deliver true continuous feeding, and the same results are reproduced in every vessel and every run. When culture conditions are kept unchanged, individual parameters can be isolated and optimized easily. Companies like CuraGen Corporation have taken advantage of the DASGIP system's reproducibility to successfully optimize monoclonal antibody production in a CHO fed-batch culture. They optimized process parameters pH, dissolved oxygen, and temperature, the shift values each, and the time of shift using a response surface model. By using two eight-vessel DASGIP systems, they completed 47 experiments of more than 12 days runtime each in six weeks.

Fig 1: Data GA4





Four-fold DASGIP bioreactor system

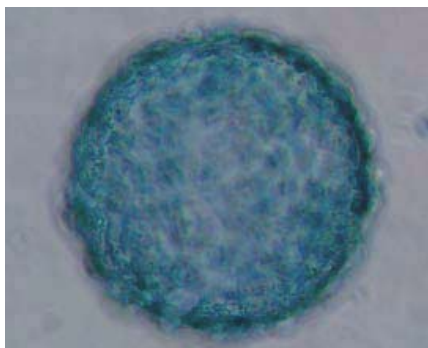
SCALABILITY

Having the capability and flexibility to operate at volumes ranging from 50 mL to more than 15 L, DASGIP is a useful tool for process scale-up from development to pilot manufacturing. The Dow Chemical Company has demonstrated the power of combining factorial design with the DASGIP system in performing fermentation development in eight 400-mL DASGIP bioreactors and 16 20-L bioreactors to scale up. This advanced infrastructure provides speed and flexibility in their process development projects. Their protein or peptide expression was optimized to produce rates of up to 1 g/L per hour, and the process was sustainable for extended periods.

BROADENING APPLICATIONS

For more than 15 years DASGIP systems have been proven as effective research, development, and scale-up tools for microorganisms such as *E. coli*, *Pichia pastoris*, yeasts, fungi, and mammalian cell lines including CHO, NS0, and hybridomas. In recent years, this advanced technology was transferred to the stem cells research arena.

Human embryonic stem cells (hESC) have been extensively studied for



Stem cell

applications in cell-based therapies. Medical relevance relies critically on the cells' ability to proliferate without changes to their pluripotency. Professor Oliver Brüstle, a German stem cell pioneer and chief executive officer of Life and Brain GmbH, has developed a scalable microcarrier-based process for the suspension culture of hESCs in the DASGIP system. Equipped with a 50-mL miniature spinner, this system is ideally suited to assay a variety of culture parameters and media conditions without the need for large amounts of precious cells and expensive media. Professor Peter W. Zandstra, from the Institute of Biomaterials and Biomedical Engineering at the University of Toronto in Canada, demonstrated that differentiating embryonic stem cells can be grown in DASGIP bioreactors — and that this growth is much more efficient when agglomeration of cells is inhibited by microencapsulation.

DASGIP continues to support groups such as Brüstle's and Zandstra's to optimize cultivation strategies for growth of primary cell lines. Parallel experiments using the DASGIP system did confirm that subtle changes in parameters such as pH, dissolved oxygen, and shear forces greatly affect the growth and differentiation of hESCs.

CONCLUSION

DASGIP technologies focus on precision in equipment engineering, flexibility in culturing mode and scale, and unmatched intelligence in software engineering. These parallel bioreactor systems provide scientists and companies with a perfect tool to help them achieve their goals: high productivity, reliable reproducibility, and easy scalability.

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