Simplifying Progress

Shedding Light On the Dark Art Of Bioprocess Scaling

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Establish a Successful Transition Between Manufacturing Scales

A unique feature of the bioprocessing industry is that process development is carried out on a significantly smaller scale than during clinical or commercial manufacturing. The resources used to manufacture biologics (facilities, trained personnel, cells, media components, consumables, and instrumentation) are expensive and require significant expertise to handle. In order to limit development costs, increase design space understanding, and maximize efficiency, upstream bioprocesses are typically developed and optimized at the smallest scale possible.

This introduces a hurdle for bioprocessing scientists: keeping conditions consistent across scales to retain critical quality attributes. In this white paper, Sartorius outlines the challenges of scaling a bioprocess before discussing how predictive software in the process analytical technology (PAT) toolbox can shine a light on previously concealed data to help improve the chances of success between scales.

Scaling Up Production

Bioreactor scaling involves the transfer of a bioprocess from one production volume to another. The properties of the cellular microenvironment must be recapitulated between different vessel volumes to retain the critical quality attributes (CQAs) of intermediate and final products. Scaling between bioreactors is not simple; it requires detailed insights into how the properties of each scale influence the physical, chemical, and biological attributes of the process and their interactions.

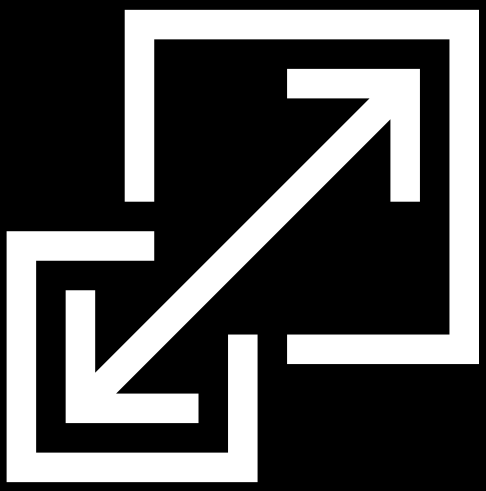
Keeping the process parameters as consistent as possible between scales is challenging. To reduce process variability across different scales, the environment in which the cells and/or biologic is produced must be carefully replicated. Bioprocess scientists must make predictions using the principles of process engineering, modeling, and complex calculations to minimize variability and support risk mitigation strategies. However, the physical differences between vessels of different scales and complexity of these systems means compromises might have to be made when making predictions and establishing process parameters.

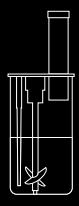
How is Scaling Traditionally Performed?

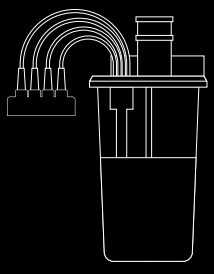
Scaling is often carried out as a simple estimation without considering all potential variability. Typically, one parameter – such as specific power input (PPV), volumetric mass-transfer coefficient (KLa), or tip speed – is taken in isolation and matched across all scales.

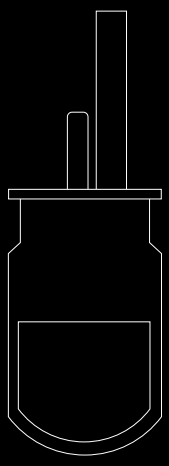
Alternatively, scaling is carried out by a few experts in the team, or consultants, using advanced, often custom-built tools. These tools contain models based on numerous in-house physical characterization experiments or calculated based on bioreactor data supplied by manufacturers. Those with the means to do so may employ a team of data scientists who use advanced analytical software to assess similarities in the process data across various scales. However, the need for specialized knowledge restricts access within the wider team and limits knowledge transfer.

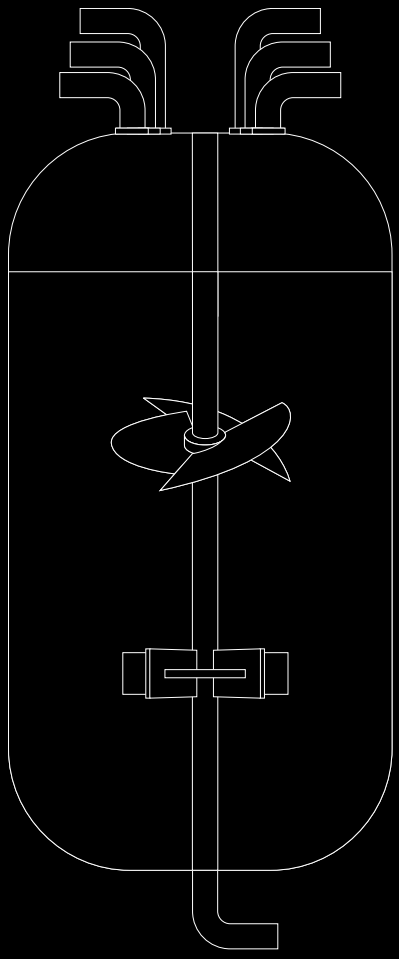
The methods employed often provide acceptable results for product titer and time course matching. Still, lack of resources for further investigation and incomplete datasets mean outcomes are not always optimal.

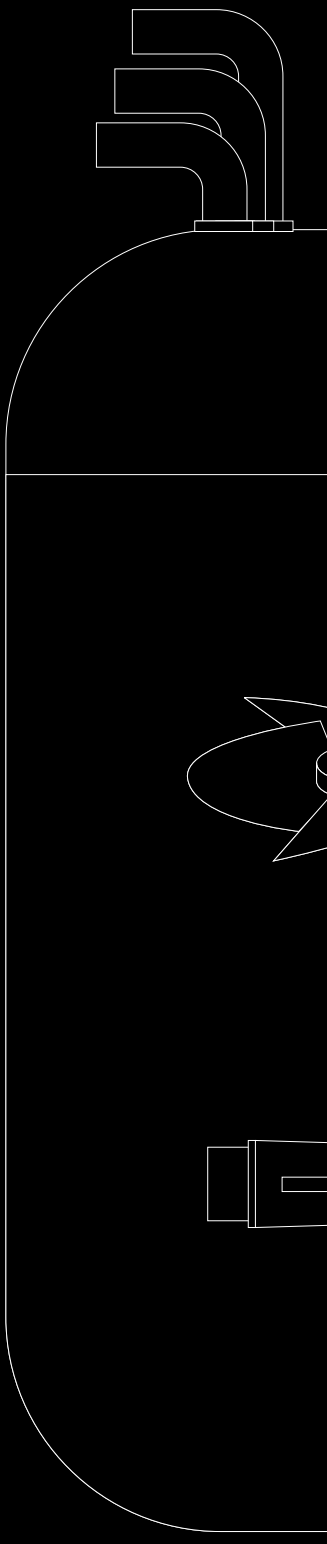










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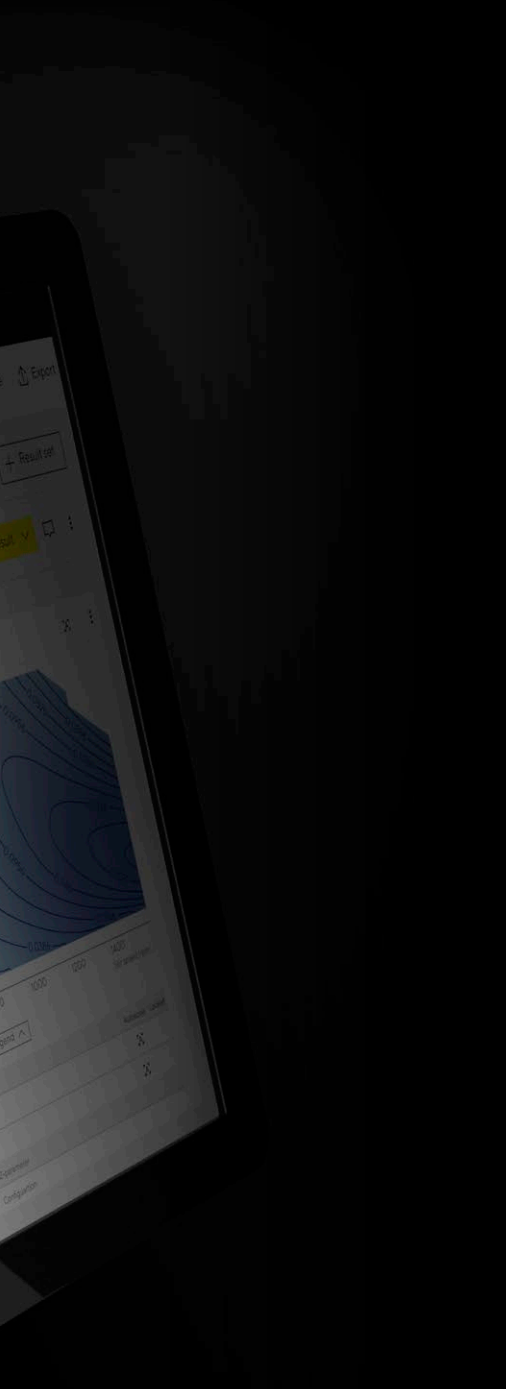
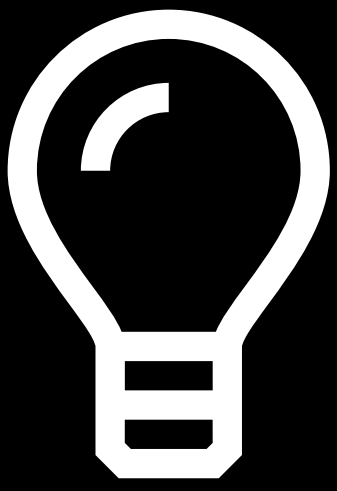


Predictive Scaling Software – A Beacon of Light?

PAT is increasingly used in the biopharmaceutical industry to support innovation and improve efficiency. Most people think of traditional PAT as sensors that measure on-line or at-line for process control. However, PATs include a much broader set of tools, including analytical, chemical, physical, microbiological, and risk analysis solutions that serve to improve the quality and efficiency of biopharmaceutical processes[1].

Such innovative solutions can bridge gaps in current scaling approaches and unlock new insights into what is occurring inside the bioreactor. Consequently, PATs offer broader access to a new dimension of process characterization.

In the following, we review the challenges associated with bioprocess scaling and how predictive software can help simplify scaling calculations and improve outcomes.



Challenges of Scaling a Bioprocess

Scaling is Complex and Often Poorly Understood

Bioprocessing is a multidisciplinary field, and scientists that require scaling expertise exist in all shapes and forms, from microbiologists to biomedical scientists and biochemists to chemical engineers. Effective scaling typically requires specialist knowledge, and the perception is that it is only truly mastered by a few experts.

Scaling the production process of a biologic could be described as both a scientific and artistic venture. Intuition and experience with repeated scaling campaigns might give some insights into how systems are likely to behave at different scales. Traditionally, it is an exercise in trial and error, which can be expensive and time-consuming. Many variables affect environmental conditions throughout the process. It is only now that we have probes and mechanisms to monitor and control many of these parameters. PAT can help you determine how differences in scale affect your process and how to manipulate the equipment to maintain closely matched environments at different scales.

Performing Experiments to Test Scaling is Expensive and Time-Consuming

Successful scaling relies on an accurate understanding of the characteristics of the bioreactor(s), understanding of the process, and understanding of the biology. Multiple experiments generating a significant amount of bioreactor characterization data are often needed to accurately test scaling performance. Sensitive and reliable tools facilitate proper monitoring and control of parameters to ensure the data used for modelling is reliable. Intuitive analysis software is required to evaluate this data and provide meaningful insights.

Scaling between relatively similar volumes does not guarantee success at larger scales, especially if performed without reliable monitoring of conditions and modeling based on historical experiments. Repeated experiments (especially at a larger scale) waste expensive facility time, documentation, support staff, reagents, and product. Importantly, they also take a significant amount of time, as large-scale experiments frequently require seed trains, need to be carried out in the production facility and cannot typically be run in parallel.

For most projects, time-to-market is a critical business driver. This means scientists might not have the luxury of carrying out comprehensive bioreactor characterization, intermediate scaling, equipment shakedown, and engineering experiments. They may lack the resources to conduct experiments to test performance and variability at different scales. Bioprocess scientists need to understand how the operational parameters of their equipment translate to the microenvironment in which their product is produced.

From Cells to Spreadsheet – Getting Lost in Translation

Cells and other biologics do not operate under the conditions that we "see" and can directly control. They sense the concentration of nutrients and the physical stresses they are subject to inside the bioreactor, but these parameters can be difficult to measure and correlate to optimal agitation speed, gassing rates, pressure, pH, and oxygen levels set points.

Understanding how these parameters interact is critical to performing scaling optimally. Accessible tools that make predictions based on relatively small datasets can limit the need for costly and time-consuming engineering runs.

Illuminate Your Process With Predictive Scaling Software

The challenges of scaling up production primarily surround a lack of reliable insights into the bioreactor environment and how this affects CPPs and CQAs at different scales. This information is typically used to populate custom-built tools or inform some decisionmaking strategies in relation to scaling.

Even when employing advanced analytical instruments designed to measure chemical, physical, and biological variables in a bioprocess, handling and analyzing large datasets and using them reliably to perform scaling requires significant expertise and effort.

BioPAT® Process Insights is a new type of PAT designed specifically for bioreactor scaling. The software application eliminates the need for complex formulae and statistics to scale production. Instead, the tool can leverage small amounts of information into successful scaling. It can be combined with techniques like design of experiments (DoE) and multivariate data analysis (MVDA) to generate large datasets and improve overall scaling outcomes.

The culmination of extensive experiments measuring Sartorius bioreactors and modeling thousands of process conditions, BioPAT® Process Insights leverages large volumes of empirically gathered data to make predictive calculations and model process scale-ups. The predictive modeling capabilities empower users to conduct advanced scaling calculations without deep knowledge of bioreactor design or scaling algorithms.

Scientists can simply extract the information they need from the tool; characterization experiments have already been performed and the data built into the platform. This limits the need for significant data collection using analytical tools.

The calculation engine has a user-friendly interface that helps users select their equipment, preferences, process conditions and level of risk, and characterization data to deliver the ideal conditions for scaling. This helps bioprocess scientists take a balanced approach to scaling different parameters and across different scales simultaneously, saving time and the need for expertise. Its simple interface and streamlined workflow accommodate a range of operators, from inexperienced users to advanced scaling experts.

Scaling Risk Mitigation With Process Insights

Process analytical technologies, such as the BioPAT® range from Sartorius, enlighten users with a vast amount of data, as well as the tools to assimilate, evaluate, and respond to their findings. When combined with process intensification strategies and single-use technologies, the introduction of robust sensors and complementary process analytics strengthens the benefits of single-use processing principles, likely to become essential in next-generation facilities.

Moving from pilot to production scale with minimal deviations to the CPPs and CQAs requires significant process understanding and expertise. Bioprocess scientists want to simplify scaling, make it more accessible to the broader team, and achieve it quickly and with confidence.

This requires better access to intuitive and predictive, reliable scaling calculations supported by robust models based on extensive characterization data. These findings can be implemented into an effective strategy using risk evaluations for conventional bioreactor scaling and design space exploration.

BioPAT® Process Insights provides a platform for users to simulate process outcomes and adapt to different scaling scenarios without performing multiple experiments at a significant time and financial cost. These advances promote speed, agility, and quality, helping facilities to remain competitive in the dynamic biopharmaceutical market.

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Kevin McHugh joined Sartorius through the TAP Biosystems acquisition in 2013. Today, he is today a Global Technology Expert for Cell Culture Technologies. He earned his BS in Bioengineering from Lehigh University in 2007.

In 2013, he joined TAP Biosystems as a Product Specialist. Previously, he worked in the biopharmaceutical and vaccine industry where he focused microbial process development, evaluating and implementing new technologies, developing and optimize scaling models. In his current role he shapes the development and direction of the Bioreactor product lines.
He explores technology integrations, investigates developments, and examines new application areas for Cell Culture Technologies.

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Sinyee Yau-Rose joined Sartorius with the TAP Biosystems acquisition in 2013, where today she is Global Product Manager for Ambr® Software Applications. She earned her PhD and a MEng degree in Biochemical Engineering from University College London, UK.

In 2010, she joined as a Bioprocess Product Specialist for Ambr® at TAP Biosystems before becoming a Product Manager in 2018. In her current role, she manages the Ambr® Clone Selection and the BioPAT® Process Insights software products.

Katy McLaughlin
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Katy is part of the Marketing Communications team at Sartorius, where she supports the creation of a variety of written pieces, from published articles to web content.

Before joining Sartorius in 2021, Katy was employed as a Post-Doctoral Research Associate at the University of Edinburgh, where she also completed her doctoral studies. Here, she carried out research in genetics and cellular biology and began taking on writing projects, eventually entering into a career as a freelance writer for various biotech companies and agencies.

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