Bioreactor scaling made easy: navigating the design space

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Abstract

The scaling of upstream processes requires a good understanding of the bioreactor. This includes the shear regime induced by the agitator and the oxygen and carbon dioxide mass transfer capacity by the spargers at different gas flow rates. The process needs to operate in a design space where the oxygen and carbon dioxide stripping requirements of the culture are fulfilled. In addition, prohibitive high shear stress and high gas flow rates that can create bubble damage or foaming issues should be avoided. To identify this design space, where the process can be operated, is difficult.

We show that *in silico* models can be used to determine ranges in the design space for agitation, and gas flow rates using the configured spargers, fulfilling the boundary condition of maintained oxygen transfer and carbon dioxide stripping.

Furthermore, the models allow navigation in the design by locking one or two of the parameters within the determined ranges and calculating the remaining ones.

With this methodology, it is possible to navigate within the design, understand correlations of the operating parameters *in silico*, and build understanding about the limits for all operating parameters.

Introduction

Process development at a small scale is the essential starting point of all bioprocesses that are then scaled up to pilot and production scales (Fig 1). This scale-up process is often a scientific and time-bound challenge where different bioreactors with different working volumes and potentially different sparger and agitation configurations are used. The operating parameters must be adjusted at each scale.

On the other hand, it is pivotal to develop a process in small scale that can run with the mass transfer in the pilot or production scale bioreactor in mind. In other words, it is equally important to establish good scale-up and scale-down models (Fig 2).

The scaling of upstream processes requires thoroughly characterized bioreactors. This includes the shear regime induced by the agitator and the oxygen and carbon dioxide mass transfer capacity by the spargers at different gas flow rates.

The process needs to operate in a design space where the oxygen and carbon dioxide stripping requirements of the culture are fulfilled. In addition, prohibitively high shear stress and high gas flow rates that can create bubble damage or foaming issues should be avoided. To identify this design space, where the process can be operated, is difficult. However, Cytiva has developed a tool to guide users.

Fig 1. Illustration of the scaling journey during the development of a product.

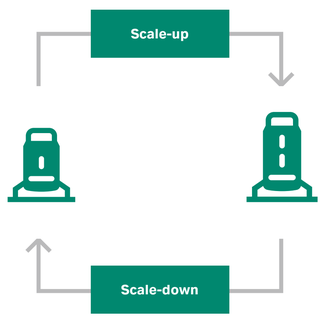


Fig 2. Illustration of the importance to have valid scale-up and scale-down models.

Bioreactor Scaler

Cytiva has developed a tool that helps upstream scientists to scale bioreactors. The tool uses *in silico* models that were developed using extensive physical and CFD-based characterization of bioreactor mass transfer, shear regime, power input, mixing time, and tip speed.

The tool guides the user to scalable and suitable operating parameters for the agitation and aeration regime. The two steps outlined in Figure 3 are followed.

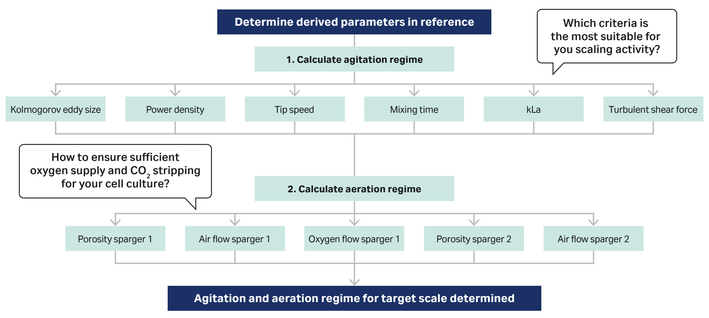


Fig 3. Steps in bioreactor scaling.

The challenge in bioreactor scaling is that targets for oxygen transfer and carbon dioxide removal can be match with infinite combinations of operating parameters. The ranges for operating parameters meeting oxygen supply and CO_2 stripping requirements span a design space.

It is important to ensure that the design space for ALL planned bioreactor runs is overlapping.

An example for a design space is shown below:

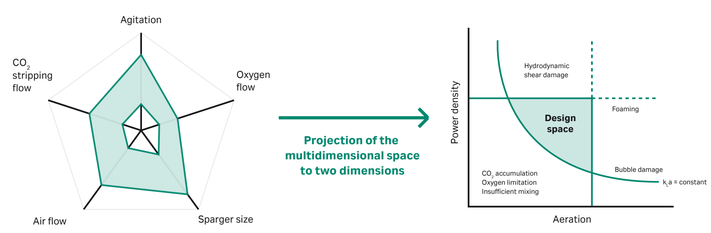


Fig 4. Illustration of a design space in two different projections.

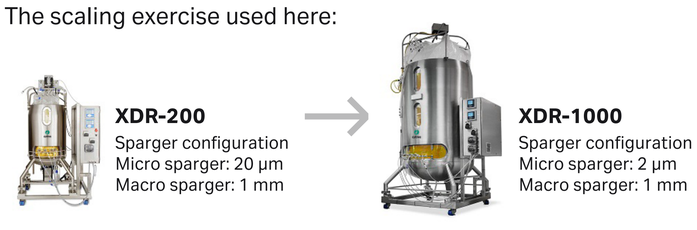
To illustrate the power of the scaling tool to navigate in the design space, a case study of a CHO process is used.

Exploring the design space: finding operating parameters and understanding ranges

To explore the design space, we want to investigate a CHO process at peak VCD to be transferred from Xcellerex™ XDR-200 to XDR-1000.

Case study set-up

The scaling exercise used here:



XDR-200
Sparger configuration
Micro sparger: 20 µm
Macro sparger: 1 mm

XDR-1000
Sparger configuration
Micro sparger: 2 µm
Macro sparger: 1 mm

Table 1. Parameters used in the case studies

Operating parameter	XDR-200	XDR-1000
Volume (L)	160	800
Agitation (rpm)	110	Tbd, see Fig 5–8
Air micro sparger (slpm)	1.5	
O_2 micro sparger (slpm)	1	
Air macro sparger (slpm)	1	
Cell density (10^6 cells/mL)	18	18

Use case 1: Best guess results from Bioreactor Scaler, scaling by constant P/V, OTR and total vvm

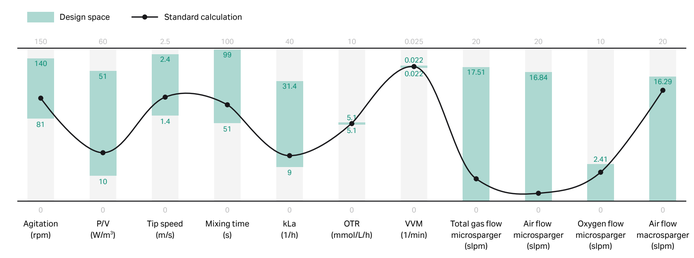


Fig 5. Visualization of operating parameters for XDR-1000 in the design space. The operating parameters for the XDR-1000 at this time point were calculated to: 101 rpm, 2 µm air 0.34 slpm, 2 µm oxygen 1.81 slpm, 1 mm air 12.84 slpm.

Use case 2: What is the impact of maximized agitation, reaching a tip speed of 2 m/s on the gassing regime?

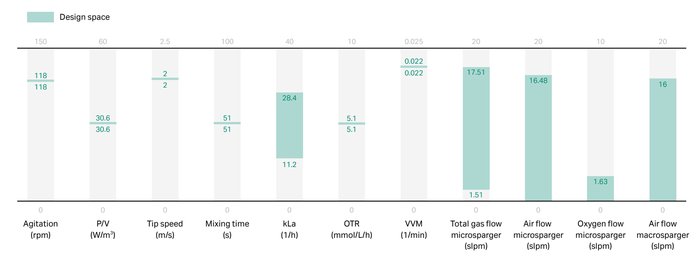


Fig 6. Visualization of the design space when the agitation is locked to 118 rpm, which corresponds to a tip speed of 2 m/s.

Use case 3: How can we reduce the micro sparger gas flow by sparging with pure oxygen?

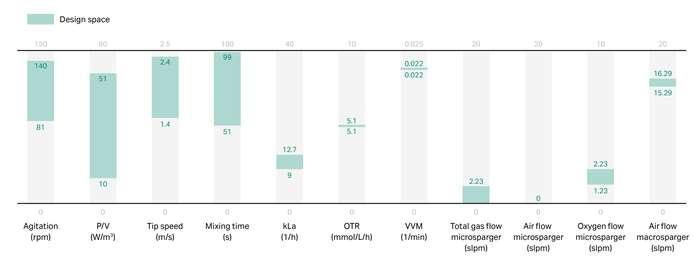


Fig 7. Visualization of the design space when the air flow through the micro sparger is set to 0 slpm. Limiting the micro sparger gas flow is expected to improve the viability and longevity of culture.

Use case 4: What is the design space for this process with cell densities between 10 and 30 x 10^6 cells/mL?

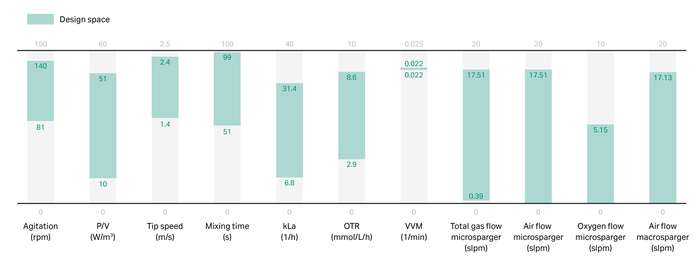


Fig 8. Visualization of the design space assuming viable cell densities between 10 and 30 × 10^6 cells/mL. This is achieved by defining a range for the OTR between 2.85 and 8.55 mmol/L/h.

Conclusions

The Bioreactor Scaler:

- Reduces the time needed to optimize bioreactor scaling and makes scaling more accurate
- Makes scaling accessible for non-engineers, builds process understanding and reduces risks during tech transfer
- Translates setpoints between different scales of operation
- Gives guidance to navigate in the design space between scales
- Creates a common language around scaling and standard ways of working

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