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How scalable and suitable are single-use bioreactors?

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Although the scalability of stainless steel bioreactors has been investigated for more than 50 years, and many methods for the characterization of these bioreactors have been evolved, the investigation of scalability of single-use bioreactors (SUBs) contains several new challenges. SUBs permit a versatile design that is not necessarily oriented towards classical geometric conditions and allows a wide variety of mixing principles. Among the various principles might be some advantageous for the cultivation of particular types of shear-sensitive cells, such as mycelium-forming organisms and stem cells. In addition, these systems must be applicable in emerging fields like continuous perfusion processes.In this paper, we will discuss the current state of disposable bioreactors in terms of cultivation performances, with a special emphasis on the impact of physiological properties of cells across several scales and cultivation modes beyond classical engineering parameters.

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Introduction

The era of disposable bioreactors (SUBs) began about 20 years ago with the commercialization of the first wave bioreactor system. The initial SUBs were simple shaking systems with bags and did not follow the design principles of stainless steel bioreactors. In the following years, many new single-use systems have been developed based on various principles of mass transfer and mixing. At the same time, the increased efficiency of cellular production systems enables industrial cultivation in smaller volumes. The need for faster implementation and cost reduction has paved the way for the use of parallel single-use systems already in the early stages of process development down to the μL-scale, but also as flexible, modular systems in later stages of development and in production [1]. With the development of automation platforms for parallel and controlled cultivation, the working range of SUBs has been extended to include mL and even μL scales in recent years. The lower working volume is a challenge for size reduction, while practical considerations often lead to a change from small-scale shaken systems to large-scale stirred systems. Other principles apply in shaken systems: for example, volumetric power consumption and the Reynolds number could be of minor importance, whereas the gas mass transfer of such systems is more dependent on other parameters such as the surface area, wall adhesion, water film formation, and so on.

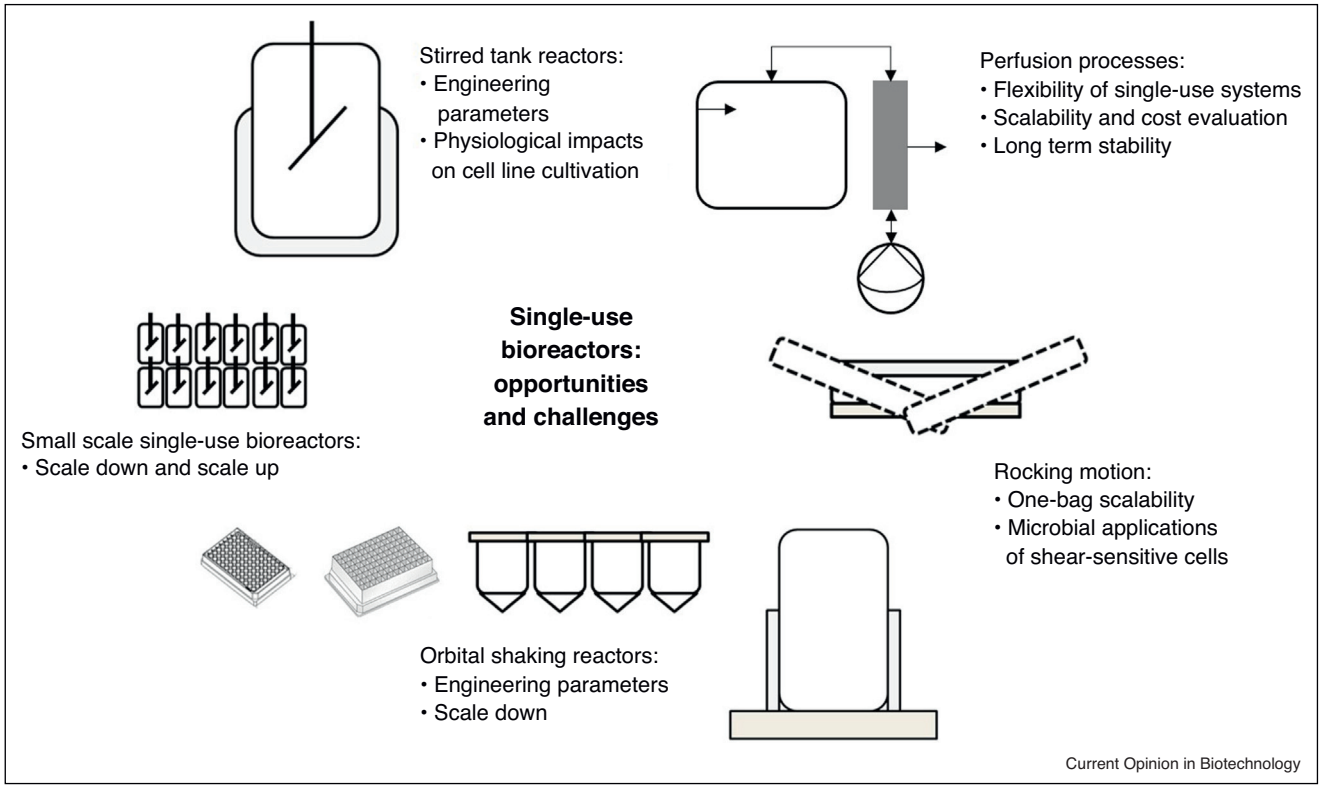
The current commercially available SUBs cover a range of up to several m^3 and allow small-scale parallelization. As a result, investments in disposable infrastructure are steadily increasing. Although the traditional stirring vessel design has also become dominant in the field of SUBs, there are a number of designs based on other principles. They are suitable for a wide range of applications where power consumption, shear stress, gas transfer and mixing have not been studied in detail yet. The question of how to increase efficiency and reduce volume through the application of continuous cultures or hybrid processes [2], for example, perfusion technology, raises new challenges in connection with the reliability and robustness of disposable systems [3].

The following article shall provide an overview of recent progress in applying the most common SUBs in different cultures. In the scope of the article are scaling effects on physiological properties and potential applications for certain cultures (Figure 1), but only a few technical parameters that were already described in other reviews and textbooks (e.g. [4]).

Single-use stirred tank bioreactors

Stirred SUBs are available from the mL to the m^3-scale. An overview of established, commercially available systems is provided in Table 1. Advantages of stirred SUBs are the flexible choice of agitators, various geometries can be easily achieved, for example, by 3-D printing. An early consideration of agitated systems can be advantageous if parameters that cannot be kept constant over the entire scale anyway, such as shear forces, are less important. In this case, compliance with certain values of gas mass transfer and mixing times is sufficient. However, a scale reduction of such systems shall consider the transfer of the population's physiological features. Methods to assess such data are naturally established for bench-scale stirred

Figure 1



Schematic presentation of applications of single-use bioreactors.

Table 1

Overview of several commercial single-use bioreactors (only systems available together with control instrumentation were considered).

Reactor brand name	Working volume [L]	Mixing principle	Distributor	Characterization in peer-reviewed publications
Allegro™ STR200	20–200	Stirred	Pall	
BioBLU®	0.07–40	Stirred	Eppendorf	
bioReactor	0.01	Stirred	2mag	
BIOSTAT® Cultibag STR200	50–2000	Stirred	Sartorius Stedim Biotech	[47]
CerCell	0.5–30	Stirred	CerCell	
iCELLis® fixed-bed bioreactor	0.004–25	Stirred	Pall	
Mobius® CellReady	3–2000	Stirred	Merck Millipore	[48]
Sartorius ambr®	0.01–0.25	Stirred	Sartorius	[7]
SmartVessel™/HyPerforma™	3–2000	Stirred	Finesse/ThermoFischer	
Xcellerex XDR™	10–2000	Stirred	GE Healthcare Life Sciences	[49]
Air-Wheel® bioreactor	0.1–500	Rotating wheel	PBS Biotech	[49]
Nucleo™ Single-use bioreactor	20–1000	Paddle	ATMI/Pierre Guerin	
Micro-24 MicroReactor Cassettes	3–7 $\times 10^{-3}$	Orbital-shaking	Pall	[13]
BioLector	8–24 $\times 10^{-4}$	Orbital-shaking	m2p-labs	[22,50]
SBX reactor	2–1000	Orbital-shaking	Kuhner	[51]
Allegro™ XRS bioreactor	2–20	Bi-axial rocking	Pall	
Appliflex	1–25	Rocking	Applikon Biotechnology	[49,52]
BIOSTAT® CultiBag RM	0.1–100	Rocking	Sartorius Stedim Biotech	[53]
CELL-tainer®	0.1–200	2D rocking	Celltainer Biotech	[23]
CellMaker PLUS	8 and 50	Bubbling	Celexus	

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