

CELL-tainer® single-use bioreactor 200L

Microbial and cell culture application



The CELL-tainer® single-use bioreactor is developed to optimally support bioprocesses in the biotech industry and the bio-pharma industry. In a bioprocesses mixing and mass transfer are critical parameters in combination with the control of pH, DO and Temperature.

The CELL-tainer® bioreactor ensures excellent mixing properties and offers superior mass transfer, due to the patented 2-dimensional movement of the system. Therefore the CELL-tainer® is applicable in a wide variety of applications under strict sterile conditions, like for mammalian cells and also microbial cultures.

The optimal working volume for cell cultures is 10 – 180 L and for microbial fermentation processes 10 – 120 L.

Such, this bioreactor can be applied as production system for small batches, but also as seeding system for larger reactors.

Why single use:

- Assurance of sterility
- Reduction time to start
- Shorter validation times
- Reduce risk of cross contamination
- Lower utilities
- Less labor
- Flexibility

CELL-tainer® System

The patented 2D-movement of the CELL-tainer proved to outperform the simple rocking or wave-type bioreactors as well as the single-use stirred systems.

The mass transfer in the CELL-tainer® can be influenced by the speed of shaking and the angle.

CELL-tainer® Bioreactor Bag

The key feature: bottom mounted sensors for pH and DO (patent pending). The sensors are an integrated part of the bag which is sterilized by gamma irradiation as a whole. There's no need to manipulate the pH sensor to install into the bioreactor bag. Calibration is done with a one-point calibration (off-set) based on a sample before inoculation.

The DO sensor exists of two parts, one part – the membrane in a polycarbonate (Makrolon) housing – is making part of the bag and sterilized as integrated part of the bag. Before use, the other part (making part of delivery of the equipment), is screwed into the membrane-part. Such, no sterile handling is needed, as the membrane is the sterile barrier. Calibration is done at saturation with air.

CELL-tainer® GMP aspects

The CELL-tainer® is applied at several customers under GMP conditions both for cell-culture as for microbial application. For this purpose at delivery of the CELL-tainer® a FAT is included and IQ/OQ support can be provided. Documents may be adapted to the customer's requirements.

CELL-tainer® Controller

The CELL-tainer system consists of a cabinet in which the 2D rocker, the actuators and the controller are installed. The cabinet contains the transmitters, power supplies, and I/O hardware required to connect to pumps and flowmeters/solenoid valves to the controller (PLC).

The cabinet contains 2x peristaltic pumps used for pH control (alkaline/acid). The gas manifold contains up to four mass flow controllers for the DO control: Air, O₂, CO₂ and N₂.

Data export: Ethernet UTP interface (xml.file) to be approached from web browser (via LAN cable)

Control parameters

Temperature

Direct heating and cooling of the culture liquid, using a heat exchanger directly underneath the bag, perform temperature control. This heat exchanger is connected to an internal heating/cooling device (electrical) which is integrated into the system. This thermo-circulator is placed on a drawer for easy access (service).

The temperature sensor is a pT100 contact sensor which measures the temperature of the medium/culture and is placed directly underneath the bag.



pH

The pH is controlled using two (2) peristaltic pumps (alkaline and acid) or by alkaline (pump) and CO₂ (mass-flow controller). Control strategy can be chosen by the user.

Note:

The pH sensor is a disposable low-drift electrochemical electrode, already integrated in the bioreactor bag and gamma irradiated before use. The supplier calibrates the pH sensor prior to sterilization and only offset needs to be checked at start of the culture (one-point calibration). The electrode has a linear behavior in between pH 2 – 10.

DO

The DO control is by using mass flow controllers for the addition of gasses Air, N₂ and O₂. Only the gasses required for the particular experiment need to be connected (and used).

Note:

The membrane of the DO sensor, is already integrated in the bioreactor bag and gamma irradiated before use. The DO, a polarographic type sensor, simply is inserted in the non-sterile side of the membrane and can be calibrated before use. Polarization of the electrode takes place in less than 30 minutes.

There is an option to control feed of nutrients on basis of DO in case a feed pump is installed.

Movement and speed

The 2D movement can be adjusted (simultaneously = diameter of the circle) by a manual positioning. Rocking speed can be accurately controlled in the range 1 – 30 rpm.

Gas addition

Gasses applied: Air, O₂ CO₂ and N₂. The gas addition typically is into the headspace (no sparger needed). The gas manifold of the CELL-tainer cabinet is configured to control four (4) mass-flow meters offering the option of gas mixing, pH and DO control.

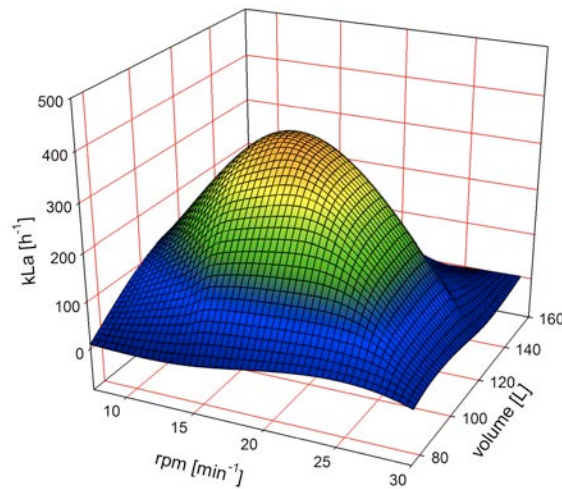
Pressure

The pressure of the gas to be connected to the CELL-tainer should be reduced to 2 barg. In the CELL-tainer the gasses are reduced to 0.1 barg. A pressure safety valve prevents increasing of the pressure inside the bioreactor bag above the set pressure (on inlet).

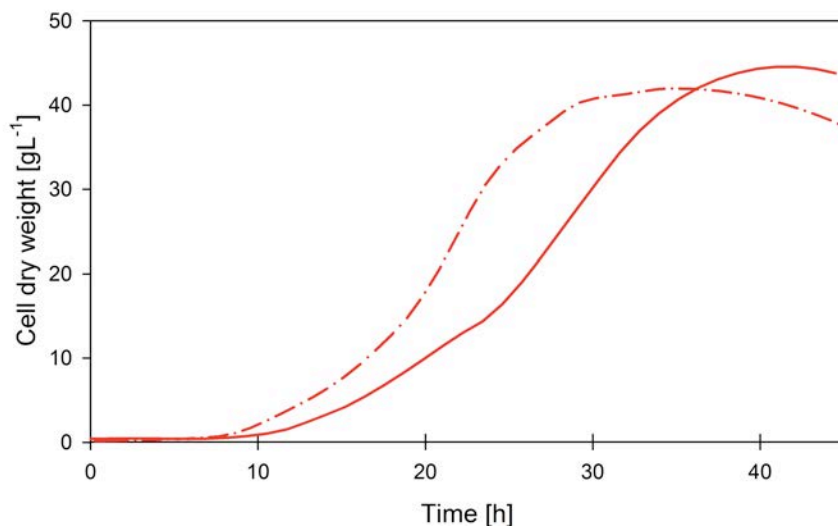


Process performance

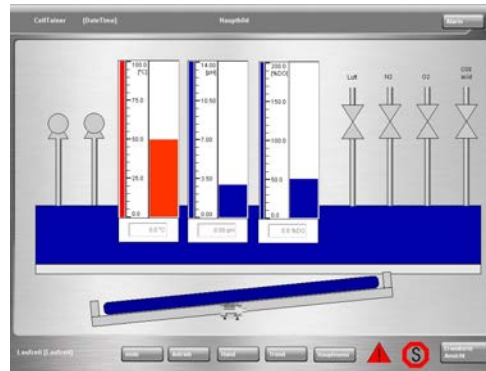
Mass transfer data (Junne, et al., CIT, 2013), the oxygen mass transfer depends on volume and rocking speed. Optimal mass transfer for microbial application is achieved at a working volume of 110 – 130 L at 20 rpm.



Data *E. coli* cultivation (Junne et al, CIT, 2013), comparison between 12L (dotted line) and 120L (straight line); typical OD600 > 130 (cell dry weight > 40 g/L) can be achieved in less than 25 – 30 hrs (depending on medium, temperature and seeding concentration).



Controls & software



Parameter	Specifications
Process monitoring and control	Single Board panel PC (B&R) with I/O cards PP500
	DISPLAY 15" XGA display touchscreen
Data storage and operation	-Measuring rpm, T, DO, pH (adjustable sampling time) -Data storage / batch -Alarm logs: door open, change set-points, not reaching set-point, sensor failure -Dose monitoring: show total sec/ml or percent in the Process View screen -Manual operation of valves and pumps -Manual position of tray (jog, sample, drain)
Data export	USB interface (csv.file)
Safety	Door opening / safety switch (stop) on all functions
Protection	CE/IP54
Manuals	Operation & Installation

B&R electronics for CELL-tainer® 200L description:

Power Panel 500 (PP500): Power Panel 500

Panels with the performance of an industrial PC
The new Power Panel 500 series with Intel® Atom™ architecture advances into areas that were previously only handled by industrial PCs.

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The new Power Panel 500 series with Intel® Atom™ architecture advances into areas that were previously only handled by industrial PCs. The Intel® Atom™ Z510/Z520/Z530 processors used in the Power Panel 500 have plenty of power, even for demanding applications. There is also plenty of RAM – up to 2 GB.



Screen

The extensive product range includes panels ranging from 5.7" VGA to 15" XGA displays with intuitive touch screen and function keys. Gigabit Ethernet ensures high-speed communication over the plant network. Additional fieldbus interfaces or another gigabit Ethernet interface can also be added if needed. When designing the Power Panel 500, a great deal of attention was given to minimizing installation depth so that it can also be used in tight spaces.

Flexibility

As a centralized operating and control unit, Power Panel devices combine control, visualization and motion control technology into a single package. From embedded processors to full PC power, this product range always provides an optimal system architecture, enabling cost-effective solutions for machine manufacturing.

If expansions are necessary, remote I/O modules and drives can be easily connected using modular fieldbus interfaces. If needed, Power Panel devices can also be expanded with POWERLINK, CAN, PROFIBUS DP or other fieldbus interfaces. This allows additional topologies to be implemented at a later date without problems. Several distributed operating stations are often used in order to guarantee that complex machines are operated reliably. This provides easy access for operating personnel and ensures that process information is available on the machine where it is needed.

Open system platform

In addition to providing complete automation solutions, Power Panel devices are also an optimal platform for open operating systems. This provides users with the highest degree of flexibility because it allows different software architectures to be implemented on the same system platform.

Regardless of whether they are used to automate complete systems, as intelligent visualization terminals or together with open PC operating systems, the Power Panel series offers the right tool for any situation.

X20 System

Slice-based I/O and control system

There are many different I/O slice systems. With the X20 System, B&R is setting new standards according to the motto "Perfection in Automation". Born from experience gained from applications all over the world, numerous conversations with customers, and with the aim for more simple, economical and secure usage, the X20 System is the new universal solution for any automation task in machine and system manufacturing.



With its well thought-out details and a sophisticated ergonomic design, the X20 System is more than a remote I/O system, it is a complete control solution. Depending on the user's demands and individual application requirements, the X20 System family makes it possible to combine the exact components necessary.

The X20 System is the ideal addition to a standard fieldbus and expands the possibilities of standard control systems. Simply connect it, configure it, and you're done.

Teamed up with other B&R components, the X20 System achieves its full potential and allows the implementation of applications with unimagined performance and flexibility.

Seamless integration is a major advantage.

Components and modules X20 configuration:

Bus receivers and transmitters	BR9300
Temperature modules	AT4244
Analog input modules	AI4622 (1)
Analog input modules	AI4622 (2)
Digital input modules	DI9371
Digital input modules	DI4371
Analog output modules	AO4622
Analog output modules	AO2622
Digital output modules	DO9322
Digital output modules	DO6322

Software description:

The CELL-tainer® software consists of:

- Process Parameters:
 - PID factors, dead zone for pH, %DO (including rpm cascade with O₂) and temperature control
 - PID set points and motor speed
 - Constant outputs actuators
- Measurements and control of pH, %DO and temperature
- Activation of valves and pumps: O₂, N₂, Base and Acid/CO₂ and Feed
- Feed control: a.) auto-feed, on timer basis b.) on basis of DO% (feed reduction, to prevent anaerobic conditions in the culture).
- Alarms and Events: Stop, Start, Emergency stop, Opening door, Sensor failure, Motor failure, Parameters too Low / High
- Safety: when the motor is running the covers (sliding left and right) are secured (locked).
When released, covers can be opened and the bag can be positioned.
- System settings: IP address, Screensaver, log interval, volume factors

The CELL-tainer® Life cycle is according Laboratory equipment Category D/E.

Calibration of all parameters is possible.

Type number of the controller and version number of the installed software can be recorded in an IQ document for each instrument.

Testing of all critical functions as physical and logical security of data can be verified in the IQ. As well as the verification of the accuracy and reproducibility of the measurements.

We offer optional IQ and OQ testing which is always performed and documented, according Factory Acceptance Test (FAT) documents. Filed on paper and digital (pdf file).

Specifications CM200EU CELL-tainer®

Parameter	Specifications
Dimensions unit	W x H x D = 2100 x 1530 x 1750 mm (approx.) (Height excl. signal light); display at 1500 mm height Weight (empty) 800 kg (approx.) Floorload < 180 kg/m ² , under operation
Dimensions bag / shaker platform	W x H x D = 1400 x 1000 x 200 mm (approx.)
Light protection	Closed cabinet. The top sections of the cabinet can be shift to side in order to load the bag. Internal view is possible with camera mounted inside. Camera connected to control screen.
Movement profile	2D movement: horizontal displacement combined with vertical displacement. Tilt is manually adjustable. Tilt angle: 6.0° – 14.5°; positioning in 8 steps of 0.85°
	Rotational speed 1- 30 rpm Microbial Rotational speed 1- 20 rpm Cell-culture resolution 1 rpm; accuracy 0.5 rpm
Temperature control	Sensor on platform, directly under the bag; accuracy ± 0.2°C Control range: 20-40°C (under ambient temperature conditions) Resolution: 0.5 °C
Heating / cooling capacity	Temperature control by heat-exchanger (water-filled) underneath the bag, connected to a thermo-circulator (electrical heater / chiller, integrated in the CELL-tainer-system) Heating capacity : 6.9 KW Cooling capacity : approx. 2.4 KW
DO measurement	Dissolved Oxygen amplifier with polarographic electrode to be positioned into a separate - pre-mounted and gamma irradiated membrane plug (integrated part of the bag) in the bottom of the bag. 5 – 150 % air saturation (+/- 5% air saturation) Air flow control by mass flow controller (Burkert MFC 8626,) 0 - 200 Ln/min (accuracy)±1.5% o.R. ±0.3% F.S

DO control (PID)	Mass flow controllers (Burkert MFC 8626), (accuracy $\pm 1.5\%$ o.R. $\pm 0.3\%$ F.S) 0 – 50 Ln/min O ₂ 0 – 50 Ln /min N ₂
pH measurement	pH- amplifier with disposable electrochemical sensor fixed mounted in the bottom of the bag. with disposable electrochemical sensor - pre-mounted and gamma irradiated - fixed in the bottom of the bag pH = 2.00 – 10.00 (+/- 0.03 unit)
pH control (PID)	Alkaline: Peristaltic pump Watson Marlow 313, 24VDC, 45 rpm. Pumphead 313: applicable with 1.6mm wall tube. Complete with adjustable tube clamps for 0.5 mm to 8.0mm ID tubing
	Acid: Peristaltic pump Watson Marlow 313, 24VDC, 45 rpm. Pumphead 313: applicable with 1.6mm wall tubing. Complete with adjustable tube clamps for 0.5 mm to 8.0mm ID tubing Or (dependent on application) Mass flow controller (Burkert MFC 8626), CO ₂ 0 – 50 Ln/min (accuracy $\pm 1.5\%$ o.R. $\pm 0.3\%$ F.S) (CO ₂) 0 – 50 Ln/min
Air supply	1-6 barg.
	Additional gasses (microbial: O ₂ , N ₂) or (cell-culture: O ₂ , CO ₂): Input 1-2 barg Gasses internally reduced to 0.1 barg max. Pressure safety-switch at 0.1 barg
	Maximum bag pressure (operating) 0.12 barg
Exhaust gas	Easy-Load filter heater for exhaust gas filter. maximum setpoint 15oC above culture temperature; cut-off at 500C
Power	400 Vac/50Hz (3 phase, 0, ground) 6 kW

Working volume

Advised working volume for cell culture application : 10L – 180L

Advised working volume for microbial application : 10L – 120L

For cell culture application, it is advised to minimize the rocking angle. For microbial, maximum rocking angle should be applied.

Preliminary drawing 200L bioreactor-bag:

TBD