

Single-Use for up-stream

Scalable platforms for
cultivation and fermentation

5 easy steps to simplified use

1. Remove STR/SUF from dual foil bags
2. Mount sensors, ad media to the STR/ SUF and condition the temperature
3. Connect with gas in/out
4. Calibrate the pH and DO sensors
5. Inoculate and start the process



CellVessel 21 series

The advanced CellVessel 21 series STR out-perform the conventional glass/steel STR for batch and fed-batch cultivation



CellVessel 21 series general specifications are

- Conical PMP (Polymethylpentene), cylindrical PC (Polycarbonate) or PMMA (Polymethylmethacrylate) vessel
- Polyamide cover integrating three ports for classical PG13.5 sensors
- Advanced aircraft style helical screw impeller for low shear force contribution
- Impeller fixed to an axel rotating hanging in low-friction polyamide bearing secured in the polyamide cover (from 21-2000 and up)
- Clockwise rotation impeller for up-flow integrates sealed-in permanent magnets
- Impeller integrates in its centre one or more 15 µm pore size sparger disc (from 21-2000 and up)
- Baffled stator for axial vortex mixing, donut shape flow pattern and high mass transfer for increased productivity (from 21-1000)
- All materials in media contact is FDA approved
- High precision E-beam irradiated (4x8 kGy) and supplied in dual PET foil bags

CellVessel variations, p/n	21-0250	21-1000	21-2000	21-3000	21-5000
Vessel volume/size, ml	250	1,000	2,000	3,500	5,500
Working volume, ml	>50	>350	>600	>1,250	>1,250
Required rpm span	40-250	40-150	20-150	20-150	20-150
Rotating power requirement, Watt	1	1	2	3	5
Vessel OD for heating blanket, mm	HSF	HSF	132	151	179
Height, without sensors, mm	140	190	230	250	280
Diameter cover, mm	75	120	155	175	215
Weight, grams	150	300	450	550	700
Sensor length, PG13.5, mm	120	120	160	160	220



CellVessel 21 single-use platform scalable 1:80

From screening to research or even small scale production the CellVessel STR family offers freedom and ease of use in cultivation

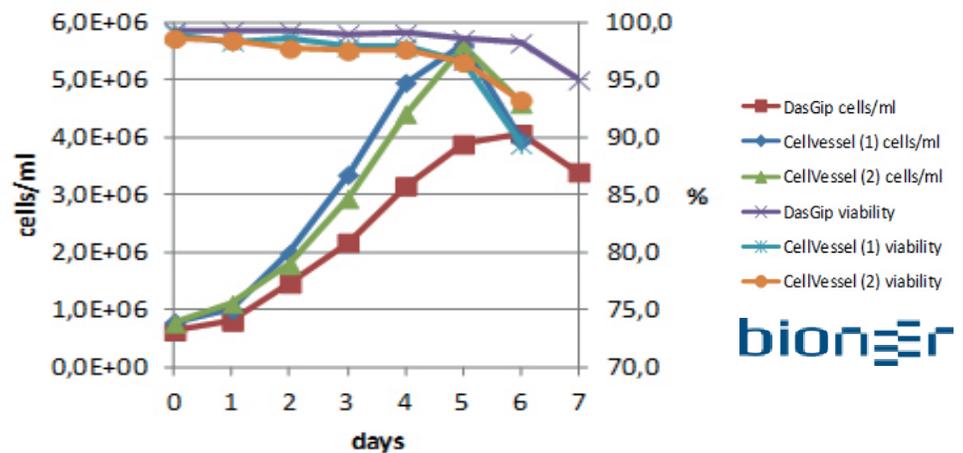
CellVessel 21 series of advanced single-use Stirred-Tank-Reactors (STR) for batch and fed-batch cultivating of shear sensitive mammalian, stem cell or insect cell lines in suspension are unique as to their agitation system, compact design and 1:80 scalable platform.

All CellVessel is designed for Magnetic-Stirrer-Table (MST) operation handled by most Process-Control-Systems (PCS) and replaces any traditional glass/metal STR. CerCell offer a MST kit for Kollmorgen (Biostat and T300), SEM (BJ), Applikon and other PCS servo motors.

The range from as little as 50 ml to 4,000 ml working volume in just one radical platform satisfies most needs for cultivation in research or small scale production, etc.

CellVessel 21 series products:

- operate better than traditional and autoclaved glass/steel bench-top STR
- fits easily in between your preferred cell lines and your existing Process-Control-System (PCS)
- operate with a variety of turntables or servo motor drives
- facilitate classical format and signal sensors with PG13.5 thread – Re-Use-Sensors and SUS as you wish
- are precision E-beam irradiated and ready to use right out of the bag



CellVessel 21-2000 vs classical STR

CellVessel is a fully functional STR (cells survive, multiply, and produce antibodies) and it performs identical or better than DasGip STR (for this specific cell line).

Antibody produced amounts to 76 µg/ml for the CellVessel STR as compared to 76 µg/ml for the DasGip STR. Furthermore, the figure above clearly demonstrates, that cell viability during exponential growth is the same for the two reactors

(well above 97 %) and that the maximal cell densities achieved are the same for the two different reactors.

If anything, cell density achieved for the CellVessel STR (5.6x10E+06 cells/ml) is clearly higher than for the DasGip counterpart (4.1x10E+06 cells/ml). The work was performed Q1/2012 by senior scientist Holger K. Riemann at www.bioneer.dk

CellVessel 23 series

CellVessel 23 single-use platform scalable 1:250



From screening to research or even small scale production the CellVessel STR family offers freedom and ease of use in cultivation

The simple and low-cost CellVessel 23 series present a range of STR that replaces the conventional glass/ steel STR for batch and fed-batch cultivation

CellVessel 23 series general specifications are

- Conical PMP (Polymethylpentene), cylindrical PC (Polycarbonate) or PMMA (Polymethylmethacrylate) vessel
- Polyamide cover integrating three ports for classical PG13.5 sensors
- Twin blade pitch polyamide impeller suspended on a shaft with polyamide bearing
- Impeller integrates silicone sealed permanent magnets for clockwise rotation and up-flow media motion
- Impeller integrates in its centre one or more 15 µm pore size sparger disc from size 23-2000 and up
- Impeller creates the traditional STR radial vortex flow, mixing pattern
- All materials in media contact is FDA approved
- High precision E-beam irradiated (4x8 kGy) and supplied in dual PET foil bags

CellVessel variations, p/n	23-0250	23-1000	23-2000	23-3000	23-5000	23-7000	23-15000
Vessel volume, ml	250	1,100	2,400	3,500	5,500	7,500	15,000
Working volume, minimum, ml	>50	>350	>600	>1,250	1,250	1,500	1,500
Required and max MST, rpm	0-350	0-250	0-250	0-250	0-200	0-200	0-150
Required power at 300 rpm, watt	1	1	2	3	4	12	20
Sparging method	direct	direct	porous				
Height, mm	140	190	230	250	280	250	500
Diameter cover, mm	75	120	155	175	215	210	210
Diameter for heating blanket, mm	HSF	HSF	132	151	179	200	200
Vessel design	conical	conical	conical	conical	conical	cylindrical	cylindrical
Weight, grams	150	300	450	550	700	900	1,200
4 Sensor length, PG13.5, mm	120	120	160	160	220	220	425

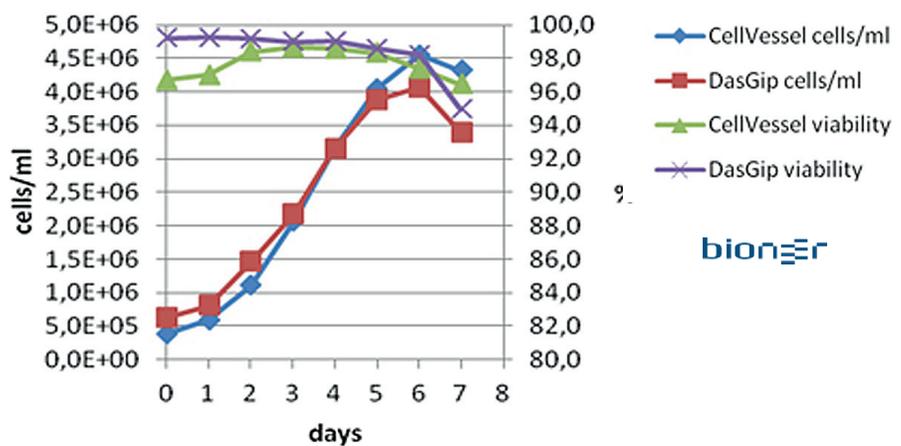


CellVessel 23 series of low-cost single-use Stirred-Tank-Reactors (STR) for batch and fed-batch cultivation of mammalian cell lines are unique as to their compact design and ability to accept classical sensors in 1:250 size scalable platform.

The range from as little as 50 ml to 12,000 ml working volume in just one platform satisfies most need for cultivation in research or small scale production, etc.

CellVessel 23 series products:

- operate identical or better than traditional and autoclaved glass/ steel bench-top STR
- fits easily in between your preferred cell line and your existing Process-Control-System (PCS)
- operate with a variety of turntables or servo motor drives
- facilitate classical format and signal sensors with PG13.5 thread – RUS and SUS as you wish
- are precision E-beam irradiated and ready to use right out of the bag



CellVessel 23-0250 vs classical STR

CellVessel STR is fully functional (cells grow, multiply, and produce antibodies) and it performs almost exactly as the DasGip STR (this specific cell line).

Antibody produced amounts to 77 µg/ml for the CellVessel STR as compared to 76 µg/ml for the DasGip STR. Furthermore, the figure above clearly demonstrates, that cell viability during exponential growth is the same for the two reactors (well above 98 %) and

that the maximal cell densities achieved are the same for the two reactors.

If anything, cell density achieved for the CellVessel STR (4.6x10E+06 cells/ml) is somewhat higher than for the DasGip counterpart (4.1x10E+06 cells/ml).

The work was performed Q1/2012 by senior scientist Holger K. Riemann at www.bioneer.dk

BactoVessel 25 series

**BactoVessel platform
for microbial use**



From screening to research or even small scale production the BactoVessel SUF family offers freedom and ease of use in fermentation

BactoVessel 25 series Single-Use-Fermenter (SUF) products represents many new features

- Replaces and is operation compatible with traditional steel, glass/metal STR
- Operates combined with your existing Process-Control-System (PCS) such as Biostat, Applikon, Finesse, Fogale and many others
- Bearing assembly designed for +5 days operation at 1,000 rpm in liquid media
- Optimised mass flow with combined stator / baffles / internal temperature controlling devices via liquid
- Combined 95% radially and 5% axially flow operating turbine integrating power transferring magnets
- Penetration ports via barbs / hoses in top cover for external connection to gas and liquids
- Ports for three classical Re-Usable-Sensors (RUS) and one non-invasive well for 6 mm thermocouple
- Integrated heating/cooling heat exchanger with two GL18 threaded connections on cover (fit Biostat vessel hoses)
- Entire SUF working pressure 10 kPa, bursting pressure 30 kPa
- Designed for bottom drive on powerful Magnetic-Stirrer-Table (MST) such as the MST (p/n 2250) from CerCell
- Designed for Newtonian fluids with max viscosity of 50,000 cP (similar to yogurt)
- Sparging gas supplied through four 30 µm micro porous PP discs in the polyamide turbine core
- High precision E-beam irradiated (4x8 kGy) and supplied in dual PET foil bags
- p/n 25-5000 accepts treatment, exposure with ethanol

World first Single-Use-Fermenter presents a range of SUF that replaces the conventional glass/ steel STR for microbial applications

BactoVessel variations, p/n	25-5000	25-7000	25-15000
Vessel volume, ml	5,500	7,500	15,000
Working volume, minimum, ml	1,500	2,000	2,000
Max MST, rpm	1,000	1,000	1,000
Required power at 800 rpm, watt	100	150	200
Height, mm	300	250	500
Diameter cover, mm	210	210	210
Weight, grams	900	900	1,200
Sensor length, PG13.5, mm	220	220	425



Single-use exhaust gas cooler for use on bioreactors and fermenters. Gas cooler mounting is simplified as to the PG13.5 thread in one end.



BactoVessel 25 series of Single-Use-Fermenter (SUF) for microbial fermentation facilitates a range of accessories such as single-use exhaust gas cooler, filter heater, bubble traps, etc. Here a used p/n 25-5000 is shown including gas cooler and dual exhaust filters.

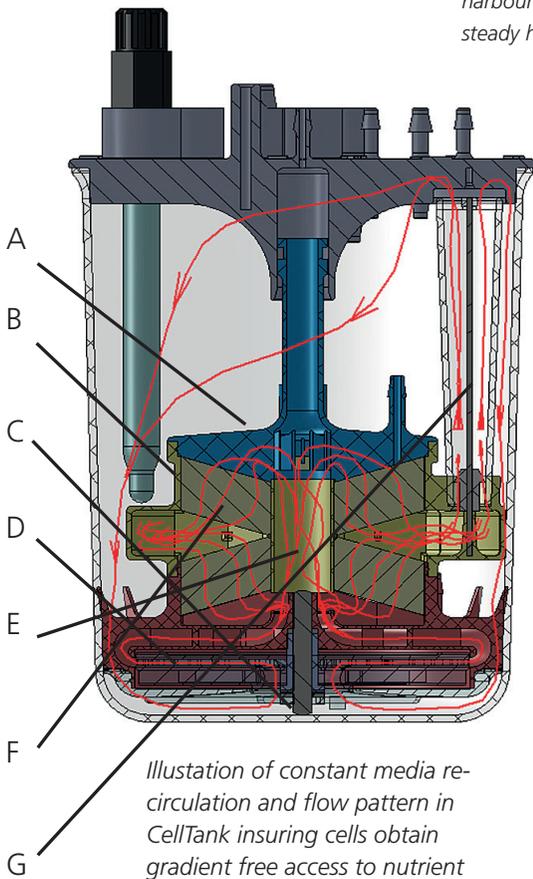


CellCore 30 series

**Perfusion platform
scalable 1:1000**



Perfusion is a method of the future for continuous cultivation, where cells are harboured inside a matrix and a steady flow of nutrients fed to the cells, giving a steady harvest for an extended period in an expression process.

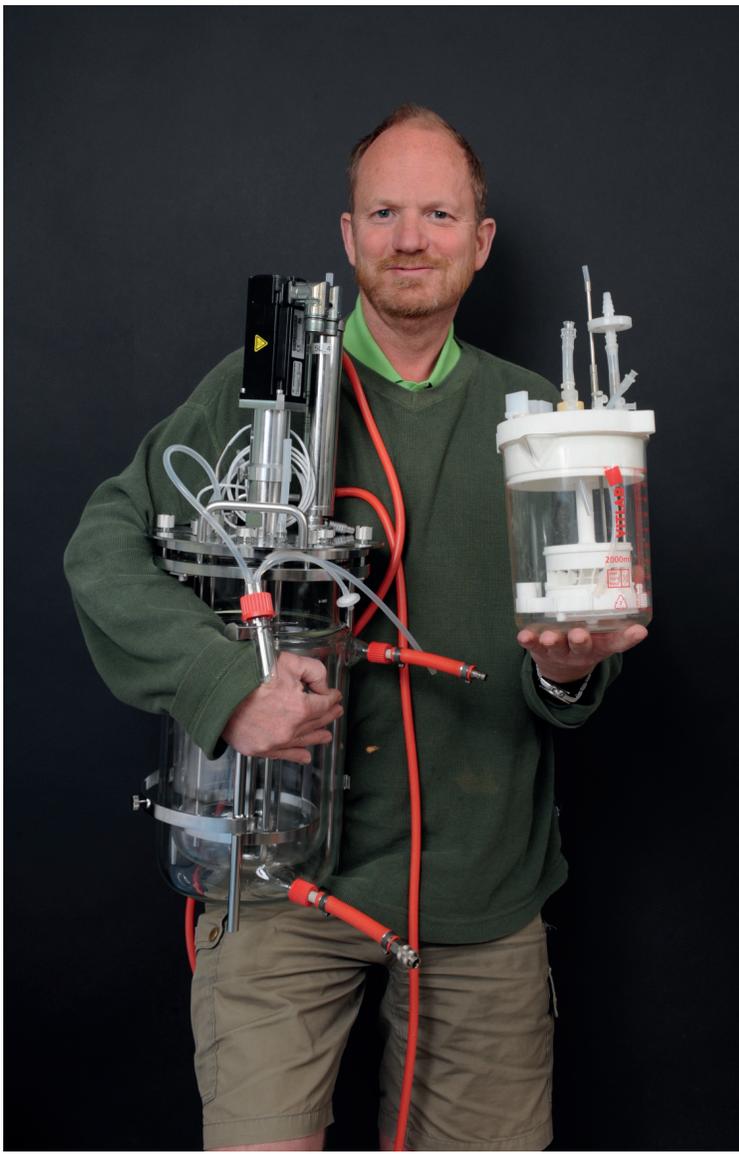


Single-use perfusion bioreactor for fast set-up, extended cultivation time, easily adaptable to any Process-Control-System

CellCompact 15 ml, CellTank 150 ml and future CellReactor 1,500 ml and CellDream range 15,000 ml matrix volume in just one platform. Radically new and satisfies all cultivation needs from lab to small scale production.

How is the design?

1. The reactor core A design is a cylinder with stacked even number of circular envelopes B. They are arranged parallel with radial inlet and axial outlet. As the envelope diameter and pair number are variable an incredible scalability is created. The span is from few ml to 15,000 ml!
2. Internal re-circulation of media inside the SUB insures constant, gradient free access to nutrient and gasses for constant expression of product.
3. Media pump inlet C is at the very bottom. The media passes the impeller D driven by external magnetic forces (not shown) and exits the pump into the reactor core centre E into the triangular volumes and flows further perpendicularly through the matrix F. Having passed the matrix, media is collected in the hollow circumference collection volume in direct correspondence with the media flow instrument G.



Mammalian cells lines are harboured inside a 3D matrix / scaffolding and a steady flow of nutrients are fed to the cells, giving a continuous harvest for an extended period. A benefit of using rigid plastics without softeners is further the vastly reduced weight! Here CellTank is shown compared with 5 litre jacketed glass/steel STR for equal total cell density in the light weight CellTank offer 4-8 times the cultivation time.

The CellCore perfusion platform is engineered to

- Increase volumetric productivity by 10-50 times compared to STR
- Cultivate 100-150 mio adherent or suspension cells per ml
- Allow perfusion cultivation for months with constant harvest
- Use conventional Process-Control-Systems (PCS)
- Eliminate gradients where cells are located
- Retain cells in the matrix and hereby avoid external arranged cell retention membranes
- Accept a variety of scaffoldings / porous matrix materials harbored inside each envelope supporting adherent as well as suspension mammalian cell lines for expression or proliferation
- Integrate classical signal Single-Use-Sensor (SUS) pH sensors, DO non-invasive well and bio mass sensors
- Be precision E-beam sterilized and ready to use right out of the bag
- Operate with a variety of turntables or servo motors
- Avoid contact between aeration bubbles and cells
- Offer selectable cell bleeding depending on model

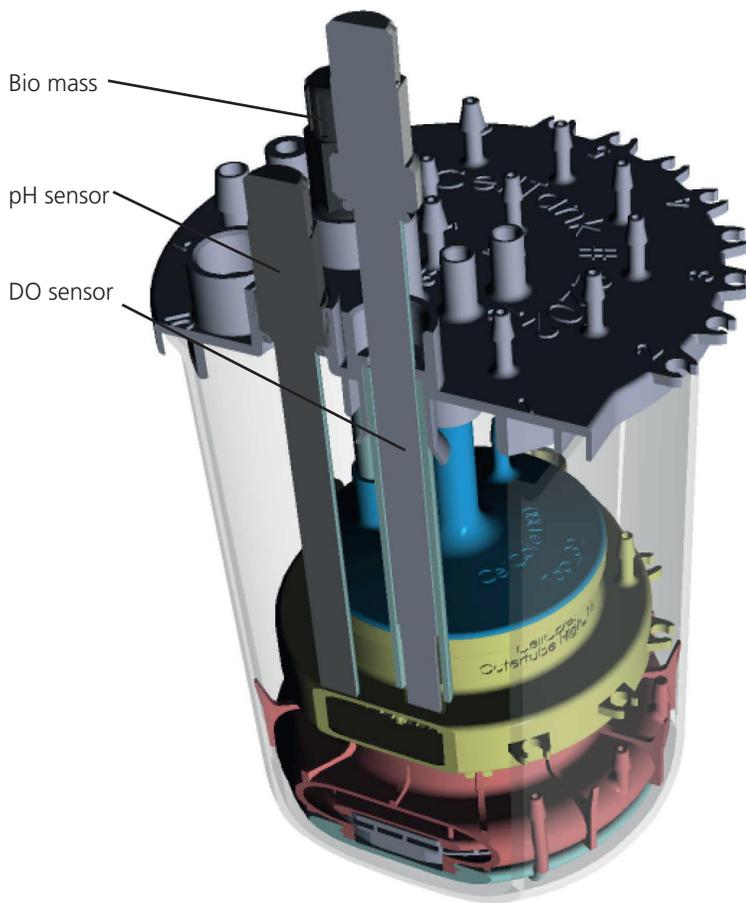
The CellCore platform

Four different SUB sizes take advantage of the CellCore platform

- CellCompact 15 ml (33 series - 1 discs)
- CellTank 150 ml (34 and 35 series - 2 discs)
- CellReactor 1,500 ml (36 series - 4 discs)
- CellDream 15,000 ml (38 series - 8 discs)

How does CellTank work?

1. The CellCore platform is a reactor core A designed as a cylinder with stacked two slightly angled and circular envelopes B. The envelopes are arranged parallel with radial / axial inlet / outlet. As the envelope diameter and pair number are variable the incredible scalability is created. The volume span is from few ml to 15,000 ml.
2. The shown CellTank 34-38 series use non-woven polyester fiber scaffolding / porous matrix F materials to create the millions of cavities to harbour both suspension and adherent cells. Other scaffolding materials may be introduced into the envelopes for specific needs.
3. Internal re-circulation of media inside the SUB insures constant, gradient free access to nutrient and gasses for constant expression of product.
4. Media pump on CellTank inlet C is at the very bottom. The media passes the impeller D driven by external magnetic forces (not shown) and exits the pump into the reactor core centre E into the triangular volumes and flows further perpendicularly through each of the envelopes / matrix discs F. Having passed the matrix, media is collected in the hollow circumference collection volume in direct correspondence with the built-in media mass flow instrument G capable of 0.4 - 2.4 liter/min.
5. The centrifugal pump D flows 0-3 liter/min at 250-600 rpm depending on cell density ranging up to max practical 1.5×10^8 cells/ml matrix. Up to 25 Watt of power is required to overcome the 0-50 mBar pressure difference accros the cell packed matrix.
6. Each of the two envelopes B has 50 cm² inlet surface area and close to 80 ml volume. This is also how CerCore creates the 4 - 24 cm/min flux / media velocity accros the 18 mm thick envelopes B in order to avoid gradients.



CellTank series 34-35

Integrated Single-Use-Sensors

3D cut through the CellTank illustrates a 120 mm pH SUS on the left and the re-usable VisiFerm DO sensor on the right fitted to the non-invasive well with the SUS optical membrane in the front. The 120 mm SUS bio mass sensor is seen behind the pH sensor.

Photo of CellTank below shows

- Non-invasive well with inserted DO sensor
- Non-invasive well for temperature, (empty)
- Single-use pH sensor installed
- Single-use bio mass sensor installed
- Single-use mass flow rotameter installed

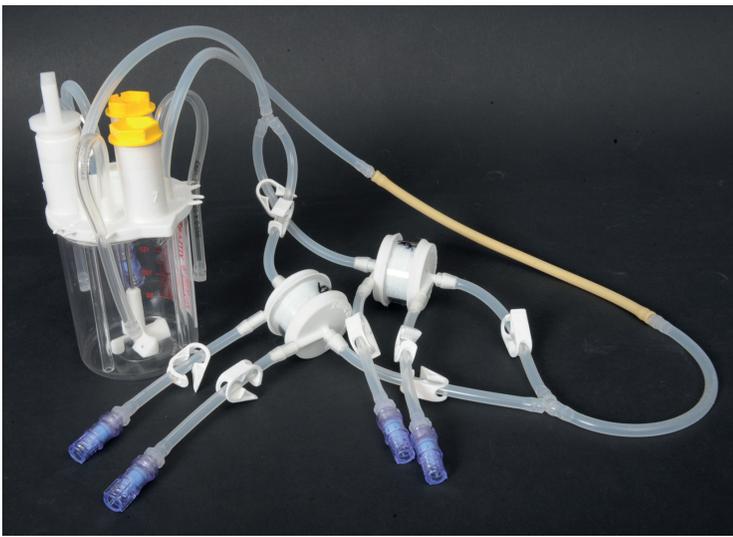
Hamilton Single-Use-Sensors (SUS) for DO and pH offer the following advantages

- Integrated SUS eliminates contamination risk
- Saves hours of prep time and labor, as no autoclaving or cleaning is needed
- Enables SUS setup right on the bench – no biosafety cabinet / hood needed for operation
- Optical membrane in non-invasive well for re-usable VisiFerm classical DO sensor
- Extends DO sensor life, as it is never autoclaved
- Classical pH sensor for extended lifetime needed for months of perfusion cultivation
- Classical pH and DO sensor signal fit any PCS



CellTank's integration of Fogale's single-use capacitive sensing technology allows precise on-line monitoring of the cell mass, viable cell density as well as cell physiological state. Users can also track cell cycle changes, model apoptosis, and predict protein titer all in real time, and this from inside the scaffolding matrix.





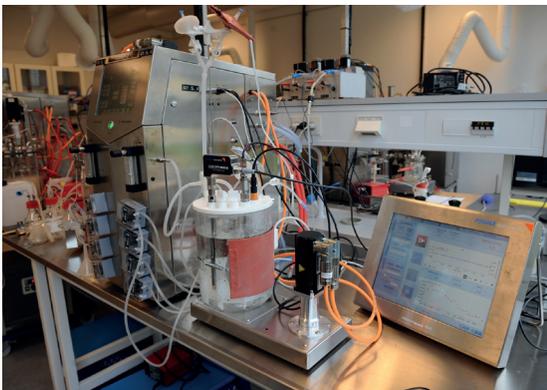
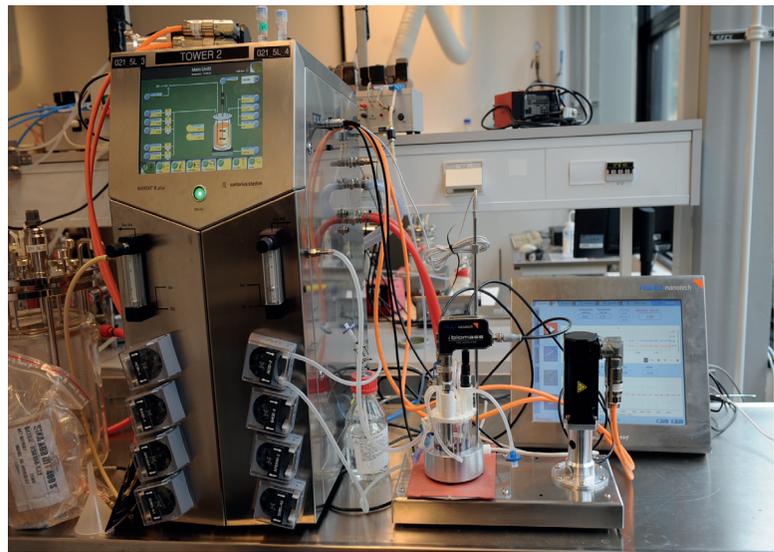
CellCompact series 33

Mini perfusion

A 2x15 ml volume perfusion CellCompact kit based on two CellCompact 33-0015 combined with one CellVessel 23-0250 STR and a durable peristaltic pump hose.

Drive methods

CellVessel 21-0250 in photo to the right and CellVessel 21-7000 below on the CerCell 2250 MST in these examples are driven by the Kollmorgen servo motor. The angled blue display is coupled to a capacitance bio mass sensor.



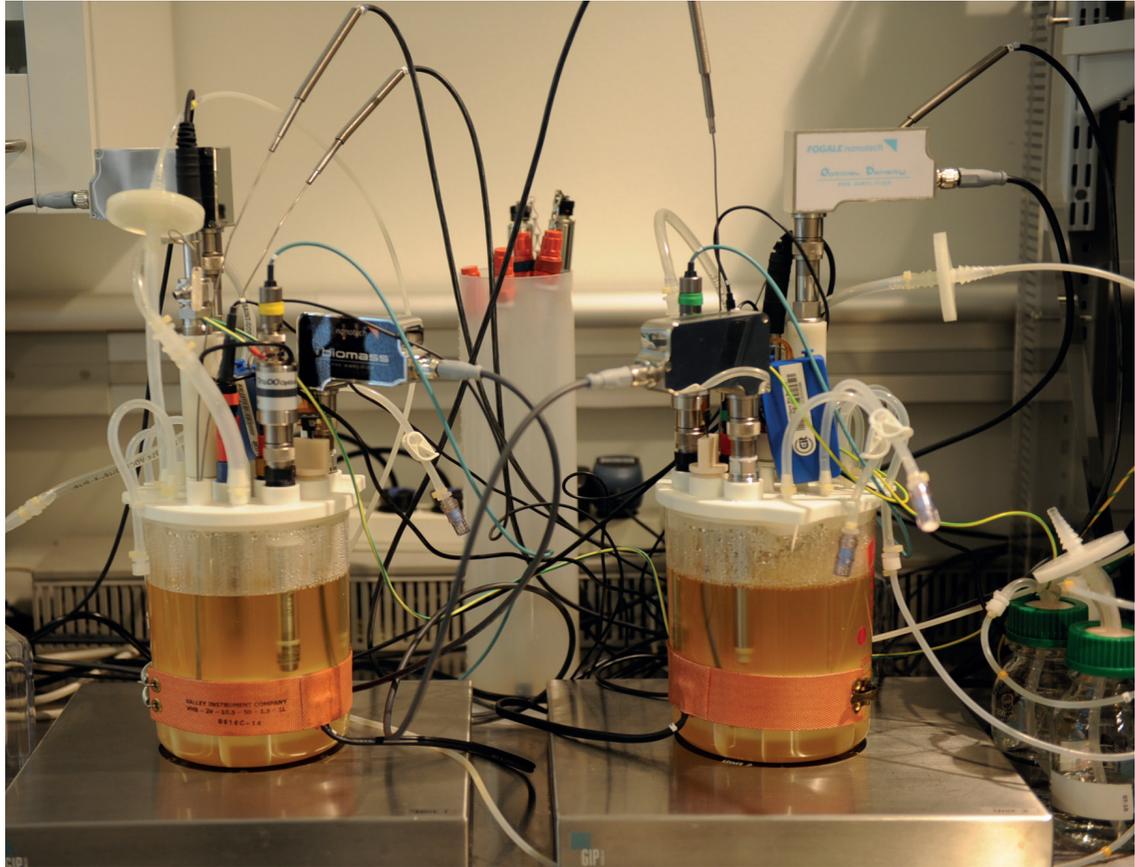
For Biostat or the like a series of water conveying Heating-Cooling-Coils (HCC) is simple to hook-up with the MST. Easy connection to the water heating / cooling system as found on Biostat.



The MST

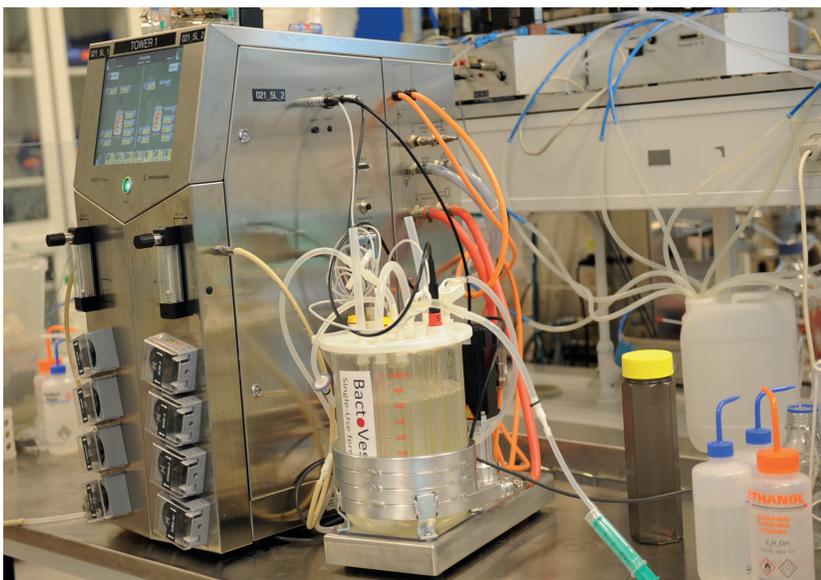
- Is a solid stainless steel construction featuring long life and silent running toothed polyurethane belt, two sealed double-row ball bearings and aluminum sprockets.
- Rotor is equipped with 12 permanent magnets and able to transfer 150 watt of power depending on the particular servo motor capacity.
- RPM span depends on the servo motor amplifier and range mostly from zero and to 1,250.
- Required power to overcome internal friction is 2 watt at 250 rpm and 10 watt at 750 rpm.
- Dim: 390x180x50 mm, weight is 5,7 kilo.





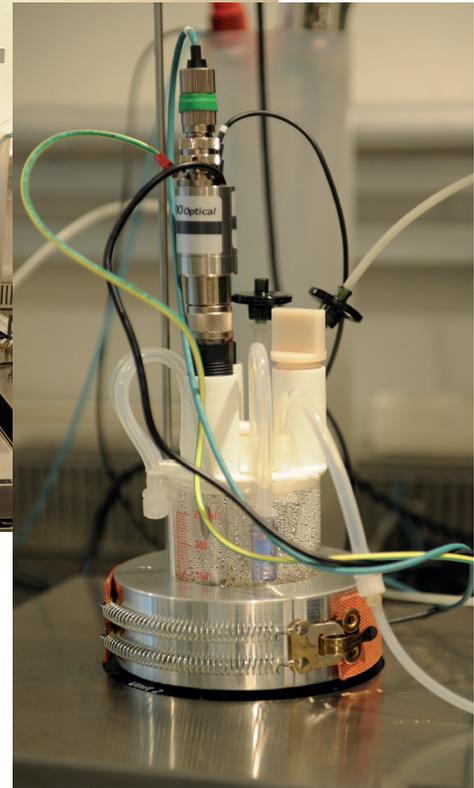
Operation practise

The series of single-use CellVessel's fits also the DasGip Process-Control-System (PCS) with Magnetic-Stirrer-Table able to supply more than 15 watt of rotation energy. The shown two CellVessel 21 series is designed for shear sensitive suspension mammalian as well as stem cell line cultivation and operate similar to traditional re-usable STR. Both SUB's further equipped with OD and pH SUS from Hamilton.



Biostat with water heating in perfusion setup controlling a CellTank for one month cultivation of CHO suspension cell line. Bio mass sensor amplifier is visible.

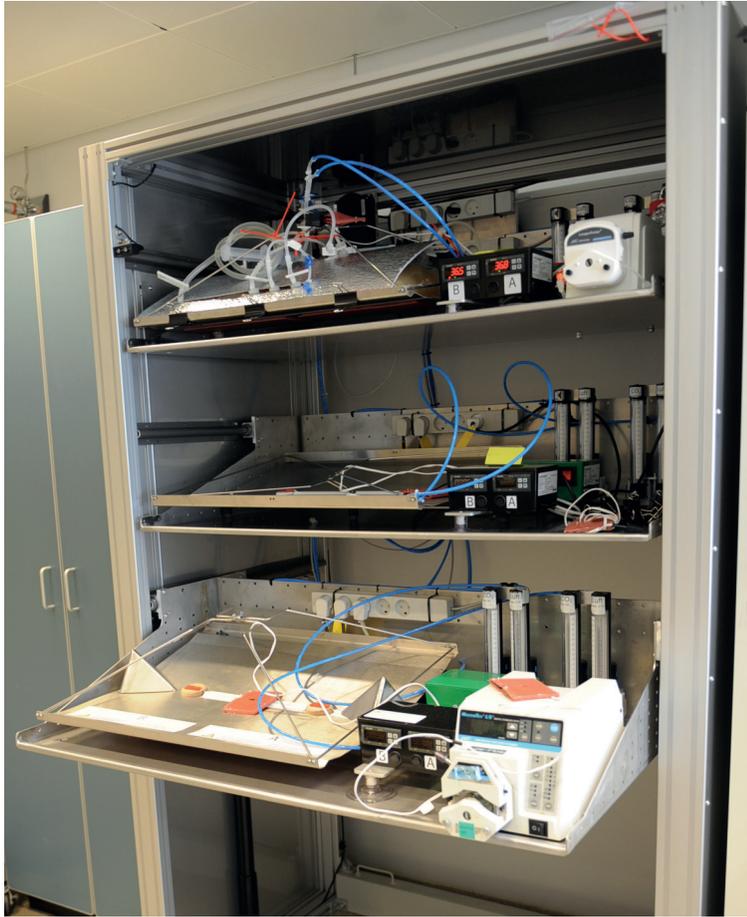
BactoVessel for microbial fermentation such as yeast or bacteria mounted on MST with (or without and use of integrated heat exchanger) HCC all controlled by the standard PCS connections for sensors, heating/cooling water and servo motor on the Biostat.



Smallest CellVessel 23-0250 on well known DasGip MP8 PCS and M10 MST (60-1500 rpm) for mammalian and stem cell cultivation. The aluminum Heating-Support-Foot (HSF) insure mechanical support of the tiny and low thermal mass CellVessel 23-0250 STR and facilitates stable thermal control by the PID of the PCS.



Work at Bioneer in Denmark on CellTank in perfusion on DasGip MP8 with identical suspension CHO cell lines compared to autoclaved 8 litre glass STR. Both STR and SUB hold 1.5×10^{10} cells. The SUB operates for weeks or month in perfusion setup. The traditional STR with 6 litre wv was cultivated for 6 days before termination due to extensive lactate levels.



CellTumbler 50 series

**Stack CellTumbler
on three extractable
and up&down
movable shelves**

Ergonomic handling is important and requires traditional wave bag systems arranged horizontal on desktops next to each other. Not really efficient use of space! CerCell offer a cabinet with 3 shelf's each for one CellTumbler arranged vertical and operated vertically with servo motor actuators. Each shelf on horizontal sliding bearings is easy to extract in the desired height for ergonomic handling.





Application Note from Symphogen, Denmark

Aim

Batch experiment – growth of CHO cells in shakers, and two wave bag systems: 1) A commercially available widely used Wave system and 2) CerCell CellTumbler in order to do:

- Comparison between two wave bag systems
- Comparison between wave bag systems and shaker culture

Cultivation of CHO cells

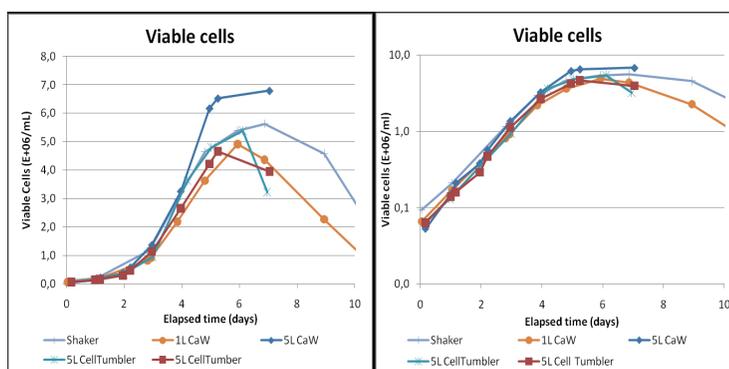


Figure 1. Viable cell density. Maximum viable cell densities are similar (left). Logarithmic curve (right) show similar growth rate.

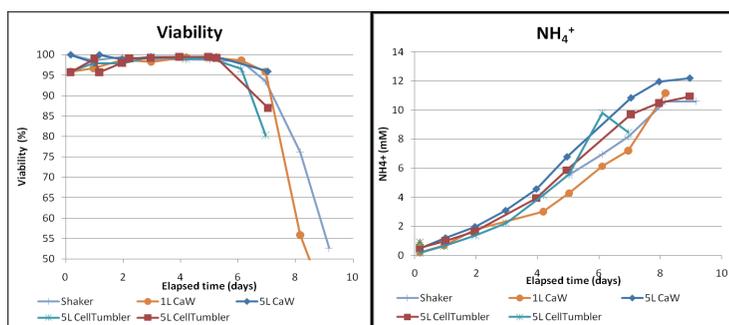


Figure 2. Viability and ammonium. Viability curves are very similar in all systems (left). NH_4^+ (right) measured by BioProfile.

Results

Batch cultivations using CHO cells were carried out in:

- Shaker (90 ml working volume)
- 1L bag using a Commercially available cell culture Wave system (1L CaW)
- 5L bag using a Commercially available cell culture Wave system (5L CaW)
- Two 5L bags using CerCell's Cell Tumbler platform

All cultivations in wave systems were done using GE Cell bags.

The results of the viable cell density measurements from the experiments (Figure 1) show that the cells grow quite similarly in the different systems with respect to growth rate, peak viable cell density and cultivation length. This shows that the growth properties are very similar in the different systems. The high cell density measured in 5L CaW from day 5 and forward was not observed in other runs and most likely represents an analysis outlier. Viability curves (Figure 2, left) are very similar in all systems showing that the systems have similar effect on the cells. The increase in NH_4^+ in the cultures with time is also similar (Figure 2, right) as well as other parameters (glucose, L-glutamine, lactate and osmolarity profiles; data not shown).

List of products

CellVessel 21-23 series batch or fedbatch STR

Part No.	Vessel, ml	wv, ml	Drive system	Usage
21-1000	1,000	>350	Turn table	Cultivation mammalian, insect
21-2000	2,000	>500	Turn table	Cultivation mammalian, insect
21-5000	5,500	>1,500	Turn table	Cultivation mammalian, insect
23-0250	250	>60	Turn table	Cultivation mammalian, insect
23-1000	1,000	>350	Turn table	Cultivation mammalian, insect
23-2000	2,000	>500	Turn table	Cultivation mammalian, insect
23-5000	5,000	>1,500	Turn table	Cultivation mammalian, insect
23-7000	7,500	>1,500	Turn table	Cultivation mammalian, insect
23-15000	15,000	>2,000	Turn table	Cultivation mammalian, insect

BactoVessel 25 series batch or fedbatch SUF

Part No.	Vessel, ml	wv, ml	Drive system	Usage
25-5000	5,500	>1,500	Turn table	Fermentation microbial
25-7000	7,000	>2,000	Turn table	Fermentation microbial
25-15000	15,000	>2,000	Turn table	Fermentation microbial

CellCompact 33 series perfusion SUB kit

Part No.	Vessel, ml	Matrix, ml	Drive system	Cultivation of adherent, suspension cell lines
33-0015	50	15	peristaltic pump	For expression or proliferation

CellTank 34-35 series perfusion SUB

Part No.	Vessel, ml	Matrix, ml	Drive system	Cultivation of adherent, suspension cell lines
34-0150	2,000	150	Turn table	For expression of a product
35-0150	2,000	150	Turn table	For proliferation of cells

CellReactor 36 series perfusion SUB

Part No.	Vessel, ml	Matrix, ml	Drive system	Cultivation of adherent, suspension cell lines
36-1500	5,500	1,500	Turn table	For expression of a product

Accessories

Part No.	Description
2250	Magnetic-Stirrer-Table (MS) for CellTank, CellReactor, BactoVessel and all CellVessel, servo motor adaptor for Kollmorgen, Applikon and others
2261	Heating-Cooling-Coils (HCC) for CellTank and CellVessel combined with Biostat water heating
2190	Heating-Support-Foot for CellVessel 21-0250
210	Off-gas filter heater 4 x 3 watt /230 VAC
211	Off-gas filter heater 3 watt /230 VAC EU plug and 110 VAC US plug

CellTumbler 50 series

System No.	Description of systems
5011	Operates four GE 0.5/1 or two 1/2 bags on the same platform. Or mix the bags such as two GE 0.5/1 and one 1/2 bag.
5013	Two identical sized GE 5/10 bags on individual platforms rocking mutually.
5014	System for two identical sized SS 5/10 bags on the same tray.
5015	System for two identical sized GE 5/10 bags on one tray.
5016	One 10/20 either GE or SS bag on one platform connected to the blue Drive+Heat+Unit.

Accessories for CellTumbler

5022	Gasunit with 2 rotameters. Gasunit flow block 150 mm long precision rotameter 0-50, 0-150 or 0-300 ccm Air or CO2 assembled each with one inlet pressure control.
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Malmlosevej 19C – DK-2840 Holte – Denmark – www.cerCell.com