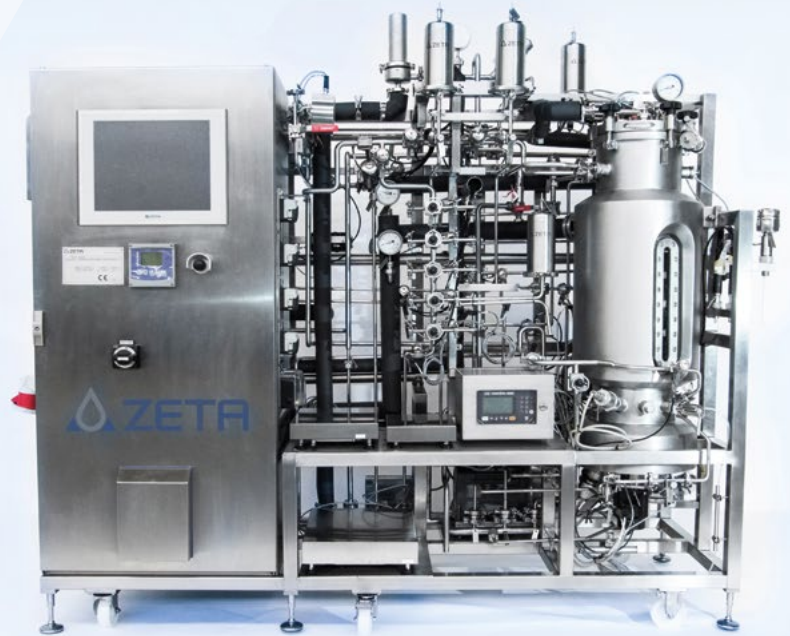


# ZETA BIRE SYSTEM

Best-in-class bioreactor  
by highly developed  
scale down from  
industry process  
to small scale



ZETA BIRE System is a compact designed bioprocess system for microbial and cell culture applications and operates with one vessel a 2:1 and 3:1 ratio from 10 to 60L.

The ZETA BIRE Bioreactor System is a compact, pilot-scale bioprocess system for microbial fermentation and cell culture. It is based around a single bioreactor vessel that can be operated with volumes from 10 l to 60 l and is suitable for cultures at 2:1 or 3:1 H/D ratios. Proven ZETA quality, industry-standard controls and automation and expert support make the system an excellent platform for process development.

The ZETA BIRE bioreactor is a pilot-scale platform designed to support the best possible approximation of production-scale processes. It is constructed and equipped to GMP-compliant industry standards and is versatile enough to accommodate both microbial cultures and cell cultures.

With its process measuring system, the quantification of exhaust gas concentrations in combination with mass balancing and OPC interface for control data flow, the BIRE provides a PAT equipped and QbD compliant bioreactor system.

## The ZETA BIRE Bioreactor System is organized in three sections:

- Automation Unit
- Supply Unit
- Bioreactor Unit

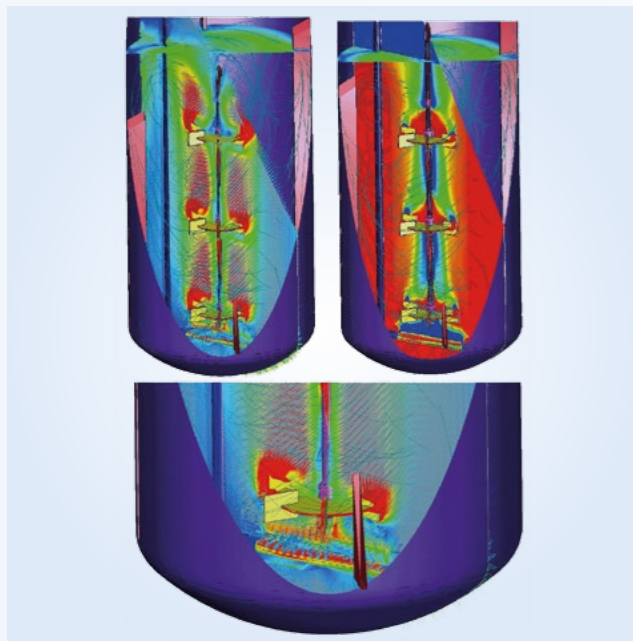
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- Automatic Sterilization in Place (SIP)
  - Cleaning in Place (CIP)
  - Individual feed, harvest and sample lines
  - Dual pH and DO measurement capability
  - WIT-Ready filter housings
  - Dual exhaust Filter housing line
  - Tube exhaust cooler
  - Exhaust heater
  - Automatic or manual addition arrays
  - Storage glass container for media addition
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#### Automation Unit

The control and automation unit is based on state-of-the-art industrial hardware running a SCADA system. The user interface is based on a 19" touch screen and is highly intuitive and easy to learn. User authorizations, signatures and records are implemented to GMP standards. Graphics, trends and process parameters can be retrieved easily.

The automation unit is in a compact stainless steel housing that rests on the system frame with minimal floor contact, facilitating cleaning.



#### Supply Unit

The supply unit includes all the features and functions that would be expected in a production-scale plant. Five independent feed lines and a glass nutrient media reservoir with gravimetric feed control are standard.

The exhaust line can be either cooled, to return condensate to the reactor, or heated so that vapor passes through the filter without problems. There are also separate harvest and sampling lines.

An integrated and fully automated temperature control unit allows heating and cooling control without additional supply media. The system has sensors for pO<sub>2</sub>, pH, temperature, pressure and optical density. Exhaust air analysis can be used for balancing the culture conditions.

Special care has been taken to configure valves and accessories with zero dead volume, to ensure good cleaning and low maintenance. The system runs automated internal self CIP and automated SIP cycles.

CFD Simulation with different stirring set-up (left)



#### Bioreactor Unit

Due to different operation ranges, the system provides two different types of stirrers. Rotation elements are either Rushton or elephant ear elements which may be adjusted in height infinitely variable.

Thanks to a step motor stirring speed covers a very wide range and therefore the agitation drive ideally serves the demands of bacterial and cell cultures as well.

Free adjustment of agitation elements allows the operation at any filling level and at operation ranges 3:1 or 2:1.

The longitudinal sight glass and 2 opposite sight glasses provide an extraordinary option for optical measuring methods through the vessel.

The longitudinal sight glass can be substituted with the PROBE port with 4 spare nozzles for instrumentation.



## ZETA BIRE Bioreactor SYSTEM AT A GLANCE

**Culture Vessel:** Operated in 2:1 or 3:1 modes  
Sterilization in Place: fully automated for culture vessel, gas inlet, exhaust gas, feed lines, filter, drain line and sampling

**Cleaning in Place:** internal cleaning cycle, CIP pump, dual pH control, automated CIP receipt, feed lines, gas lines, drain line, filter housing, spray ball

**Agitation:** bottom-driven magnetic agitator; step motor is highly adjustable from gentle, low-shear agitation up to high-speed mixing. Choice of different mixing elements, adjustable height.

**Control system:** SCADA system, intuitive touch screen, easy to operate HMI, large normalized symbols. Password protection, user authorizations, batch recording and reports in accordance with 21 CFR part 11. FDA-approved.

**Weighing System:** with balancing function. Five independent inlet lines: two feed lines, acid, base, antifoam. Media can be supplied from glass bottles or cans. Peristaltic pumps, gravimetric feed control.

**Gassing System:** submersed-ring sparger and head volume gassing, 4 separate gas media lines with mass flow control.

**Dosing Pumps:** 5 peristaltic pumps for feed and support media, balancing and probe control.

**OPC Interface:** for data transmission to an external data analysis tool, creation of soft sensors and potential replay of a new control parameter.

**CFD Simulation:** CFD Simulation available providing dimensionless key numbers for modelling homogeneity under different conditions.

## BIRE IN PRACTICE!

### Industrial Knowledge meets Scientific Partner!

The ZETA BIRE Bioreactor System is an ideal platform for research and development work on bioreactor performance. The special achievement of this system is a new approach to scaling down from a large-volume bioreactor to the small scale, which improves on existing hydrodynamic scaling methods.

In order to scale down an industrial process to BIRE scale, ZETA has developed a dimensionless key number describing the homogeneity status. A mixing scenario that is reliably comparable to the larger scale is achieved using the freely adjustable mixing elements and a wide range of stirring speed.

ZETA BIRE bioreactors have been used successfully in important scientific projects. In collaboration with University of Technology, the ZETA research team has completed studies on Effects of Homogeneity and their Effects on Productivity.



### Please find below an excerpt from important hypothesis:

#### Hypothesis 1:

*[Lorantfy, B. et al.: Inhomogeneities in production-scale bioreactors influence microbial growth and product quality due to insufficient mixing and mass transfer. A two-component bioreactor system mimicked problems that might occur with scale-up.]*

Microbial cultures yielded significant amounts of a side-product when exposed to critical low dissolved oxygen (DO) concentrations. Even brief exposures to low DO levels, for 1–1.5 min, triggered a metabolic shift.

#### Hypothesis 2:

Inhomogeneities in the bioreactor can be improved by using

- fluctuating feeding profiles, yielding an increased YX/S in lower advantageous bioreactor setups

*[S. Bhargava et al.: Substrate feed was given pulse-wise during fed-batch in a 20 L Aspergillus oryzae fermentation. Changes were only visible in the growth of fungal mycelia, leading to a lower viscosity and therefore a better oxygen transfer rate, compared to a continuous fed-batch fermentation.]*

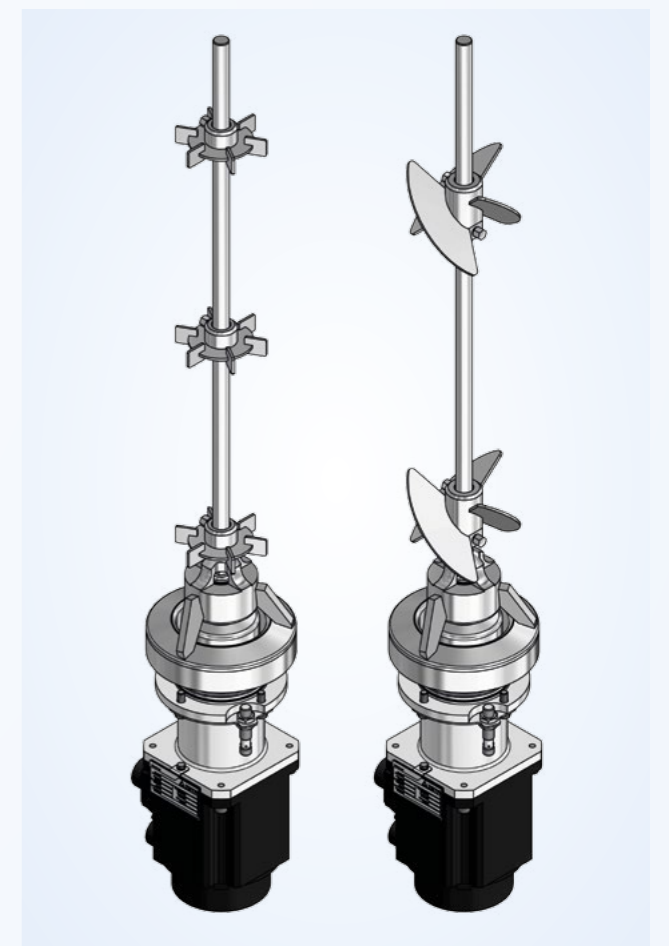
Strong feed pulses during the fed-batch mode might increase the quality of the substrate dispersion. A submersed pulse at a location close to the stirrer might increase the dissipation.

#### Hypothesis 3:

*[Fricke, J. et al.: local inhomogeneities resist easier during uninterrupted addition of feed, especially in large bioreactors. A feed pulse might help to dissipate these local inhomogeneities leading to a partly removal or more homogeneous distribution of these inhomogeneous areas.]*

## WHY BIRE BIOREACTOR?

- Small compact design
- GMP compliant
- Ready for use - qualified system
- Top-quality for inner surface
- Best-in-class welding
- Various spare ports and nozzles available
- Fully automated processes
- Free user-defined process steps
- Free parameter setting
- OPC Interface
- Free access for calibration and maintenance
- Proven cleanability
- Process improvement and scaling
- Investigation on process characteristics



### For any further Details please contact ZETA Customised Systems under the following contact:

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## ZETA BIRE SYSTEM FACTS

Bioreactor Main System Equipment	Mobile Package (Rack), integrated drip pan and plates for scale and feed cans 1 Reactor with 2 types of agitator 1 can 40L for Feed 1 1 can 2L for Feed 2 2 cans 1,5L for acid and base 2 cans 400 mL for Antifoam and other media 3 peristaltic pumps digital controlled 2 peristaltic pumps continuously controlled
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### Functional and Hardware Description

General	Cultivation of microbial and cell cultures Sterile Feeding, inoculation and addition of acid, base and antifoam while process operation in a closed system.  Sterile sampling anytime, thermal Inactivation
CIP	Integrated CIP-System with pump, cleaning of bioreactor system incl. connected pipework. Cleaning media prepared in bioreactor.
SIP	Fully automated SIP bioreactor full, empty, feed lines (parallel / single) harvest line, CIP line
Prozesses	Standby (pressure controlled), pO2 cascade control, tightness testing, fed-batch, batch processing, tempering 4°C to 40°C, transfer of Media /inoculum /additives /harvest

### Technical Details Bioreactor

Working volume	20 - 40 L cell culture 20 - 60L microbial culture
Fermentation temperature	15 - 40°C (± 0,2°C)
Operation Pressure	-1 / 6 bar
Operation temperature	0 - 135 °C
Sterilisation temperature	122 - 135°C (± 1°C)
Fermentation pressure	0 - 2 bar (± 0,1 bar)
Agitator for cell culture	Segmental stirrer, (d/D = 0,4; Dip-speed app. 2 m/s, 3-blades) 2 elements, variable movable on shaft
Agitator for cell microbials	Rushton Impeller (power input 10 W/L; d/D = 0,3-0,33; Dip-speed < 10 m/s, 6-blades) 3 elements, variable movable on shaft
Gasification Process Air Head space	0,1 - 2 vvm
Gasification Process Air Sparger	0,1 - 2 vvm
Gasification Oxygen Head space	0,1 - 1 vvm
Gasification Oxygen Sparger	0,1 vvm
Gasification Nitrogen Sparger	0,1 vvm
Gasification CO2 Sparger	2 - 12 (± 0,05)
pH value control	0 - 100 % (± 1%)
P O2 control	10 L - 50 L (100 L/h), incl. Filtration, weigh controlled
Feed 1/ Media addition	200 - 6.000 mL/h, weigh controlled
Feed 2/ Inokulum addition	Each 1,5 L (5 L/h) , weigh for base
Acid / Base addition	400 mL (1,5 L/h)
Antifoam addition	

### Bioreactor Vessel Data

Vessel Material	1.4435
Double Jacket	316L
Insulation cover	1.4301
Screws	A4-Qualität
Sealings / O-rings	EPDM (FDA zugelassen)
Surface Quality	inner: Ra ≤ 0,6 µm, e- polished, outer: Ra ≤ 1,6 µm

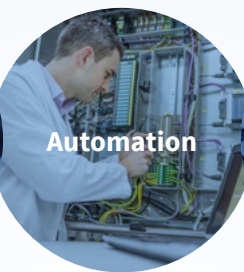
## ZETA BIRE SYSTEM FACTS

### Ports

Vessel Lid	1 Nozzle for rupture disc 1 Nozzle for exhaust air 1 Nozzle for pressure gauge 1 Nozzle for pressure transmitter (in exhaust air line) 1 Nozzle for light 1 Nozzle for Foam detection 1 Nozzle NA-Connect spare 1 Nozzle Ingold spare
Vessel Collar	5 Nozzles Media addition 2 NA-Connect with sight glasses, opposite 1 longitudinal sight glass, 1 Nozzle for pH- Probe 1 Nozzle for pO2- Probe 1 Nozzle for OD- Probe 1 Nozzle for dry run protection 1 Nozzle for sampling valve, steamed 1 Nozzle Ingold spare, 1 Nozzle NA-Connect spare
Lateral Low Nozzle Belt	1 welded nozzle for temperature probe
Vessel bottom	1 welded nozzle for temperature probe
Sparger	Ring-Sparger, dismountable
Heating / Cooling Cycle	Sanitizing empty and full. Heating from 20°C to 122°C in 60 min. Cooling from 20°C to 4°C in 25 min.
Gasmodule	Pressure reducing, self degassing each for CO2, N2, O2, Process Air for Sparger and O2 for head space
Submerge and Head space	
Submerge and Head space	1xMFC; control valve and non-return valve for process air and O2
Submerge	1xMFC; control valve and non-return valve for N2 and CO2 for Sparger
Gas Filter	2 x sterile filter, WIT ready 0,2 µm
Exhaust Air	1 Exhaust air cooler (chilled water 6/12°C). 1 sight glass Gas analyser (CO2 and O2) 1 Sterile filter, WIT ready
Automation	1SCADA control with longterm data storage, FDA 21 CFR Part 11 compliant, OPC interface, Integration control relevant parameter from external data sources, data transfer to external devices
HMI	PID scheme visualization Color display, TFT, 19" Password protection in 4 levels (free configuration), Admission acc. FDA 21 CFR Part 11
Essential control loops	pO2-control, freely combined with gas module; rotation speed; pressure; Feed: as ramps, exponential, time controlled, set-point controlled, feed profiles; incl. weigh data, pO2 Signal and off-gas analyzer

# INNOVATIVE SOLUTIONS FOR OUR CUSTOMERS

## EVOLUTION OF TECHNOLOGY



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### ZETA Business Activities

Bioreactors & Fermentation Systems  
Downstream Systems  
Preparation Systems  
CIP/SIP Systems  
Magnetic Agitators  
Freeze & Thaw Systems  
Engineering  
Automation

### Customer Benefits

Deep process understanding  
GMP FDA Compliance  
Super-Skid Design  
Focus on Sterility  
High Process Reliability  
Scale-up capabilities  
Experience in complex biologics  
Customized Process Systems

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