ZETA
INNOVATION
PARTNER

ZETA
EVOLUTION OF TECHNOLOGY

BIOREACTOR CHARACTERIZATION – FOCUS ON k_La MEASUREMENT

Adding value
to bioprocesses

The bioreactor should create a biosphere that provides the ideal environment for optimum growth conditions for microorganisms to meet the main target of production: maximum product formation.

The design of a bioreactor for the optimal process is a challenge for bio-engineers. In this context special focus is set on the oxygen transfer rate (OTR), and the k_La value in particular, which is among the most critical parameters for the design. In biotechnological processes, the k_La (volumetric mass transfer coefficient) indicates the efficiency of oxygen supply. Possible measures taken to increase the k_La include: increased power input and gassing rate, optimization of fermenter design and agitator geometry and optimization of the media composition, thus overall improving the performance of the biological process. Since the k_La value depends on numerous hydrodynamic conditions, it cannot be precisely predicted. Therefore empirical investigation by means of k_La measurements is imperative to the success and stability of the process.

Highly sophisticated oxygen probes

WHY MEASURING k_La?

- ensure adequate supply of oxygen
- optimize control variables
- for a better process understanding
- optimize scale-up and scale-down models
- for an improved bioreactor design

KEY VALUES OF k_La OPTIMIZATIONS:

- higher product yield and quality
- better product purity and safety
- optimized processing time
- lower power consumption

THE IMPORTANCE OF THE OXYGEN TRANSFER RATE IN BIOREACTORS

- Cells in aerobic cell culture, but also bacteria and yeast, take up oxygen from the liquid phase. The rate of oxygen transfer from gas to liquid is therefore of prime importance, where the demand for dissolved oxygen is high.
- To eliminate oxygen limitations and allow cell metabolism to function at its fastest, the dissolved oxygen concentration has to be above a critical level at any point of the bioreactor.
- An increasing oxygen-depleted (anaerob) environment in a bio-reactor causes both: a lower productivity and undesired metabolites.
- The whole upstream process is improved in terms of product quantity, quality, purity and safety.
- The scale-up and scale-down of the process has to be guaranteed.
- The bioreactor design and operation can highly affect the OTR .

FDA: GENERAL GUIDANCE FOR PROCESS VALIDATION

- Laboratory or pilot-scale models to be representative of the industrial process
- Laboratory or pilot-scale assist in prediction of the industrial process
- Laboratory and pilot studies provide additional assurance that the commercial manufacturing process performs
- To understand the industrial process sufficiently, the manufacturer will need to consider the effects of scale

IT NEEDS TO BE DEMONSTRATED THAT SMALL & INDUSTRIAL BIOREACTOR SCALES ARE COMPARABLE.

FLEXIBLE AND EASY TARGET ACHIEVEMENT

1. **Project kick-off** with assessment of status quo
2. **Data screening** of design and process
3. **Team building** of customer experts & ZETA
4. **Specification of project objectives**
5. **Project roadmap**
6. **Experiments & analysis**
7. **Regular time-based project workshops**
8. **Final project report and presentation**

For further information on k_La measurement services please contact:

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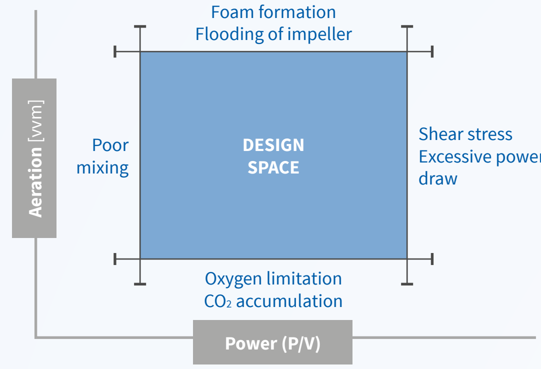
STARTER-SERVICE: **BIOREACTOR DESIGN AND SCALE-UP**



Optimized reactor design & process scale-up

STARTING POINT:

- The bioreactor design is not fixed
- Concept phase under development

STRATEGY:

- The services offer testing of different stirrer and sparger design combinations to find the most suitable system for the biological system.
- They include test runs with VE water under defined process conditions.
- Performance indicators k_La, mixing time and shear stress are determined

BENEFITS OF THE k_La SERVICES:

- Optimized control variables on the basis of the characterization of the bioreactor system (k_La, mixing time, shear stress)
- Deep understanding of process conditions on bioreactor performance indicators
- Optimization of process parameters and process control
- Scaleable process information
- Development of scaleable models and design spaces

SERVICES AT A GLANCE

Study on prior data
Output:
- Combination of customer's knowledge and ZETA experience
- Establish prior knowledge as a starting point

Study on bioreactor design
Output: Select most promising design combinations of agitator and sparger

Determination of experimental setup, numbering of experiments
Output:
- Experimental plan
- Design of Experiment (DoE)

ZETA Performance of test runs
Output: k_La and mixing time profile under various designs and process conditions

Data Analysis
Output: Dependencies of designs and process parameters on k_La and mixing time

Model development for k_La prediction
Output: Scaleable process information – basis for design space

Fermenter Design
Output: Optimization of bioreactor design based on biological needs

Scale-up
Output: Scaleable bioreactor modelling

ADVANCED-SERVICE: **BIOREACTOR CHARACTERIZATION**

k_La-Measuring

Knowledge based optimization on production scale bioreactors

STARTING POINT:

The existing lab-, pilot or production scale bioreactors are installed/under operation at customer‘s site

STRATEGY:

- The service includes test runs with VE water under defined process conditions.
- Performance indicators k_La and mixing time are determined.

BENEFITS OF THE k_La SERVICES:

- Higher product yield and quality due to optimized process design
- Insights on process criteria as crucial adjustment parameters on the basis of full characterization of the bioreactor system (k_La, mixing time)
- Better understanding of process conditions on bioreactor performance indicators
- Optimization of process parameters and process control
- Scaleable process information
- Development of scaleable models and design spaces
- Design optimization by retrofitting

SERVICES AT A GLANCE

Study on prior data
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Determination of experimental setup, Numbering of experiments
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ZETA Performance of test runs
Output: k_La and mixing time profile under various process conditions

Data Analysis
Output: Dependencies of process parameters on k_La and mixing time

Model development for k_La prediction
Output: Scaleable process information – basis for design space

Parameter optimization
Output: Definition of new parameter setpoints for various process phases (batch, fed-batch, induction, harvest)

Design optimization – Retrofitting
Output: Optimized bioreactor design for higher productivity, quality and safety

Scale-down for pilot equipment or scale-up for larger commercial scale
Output: Scaleable bioreactor modelling

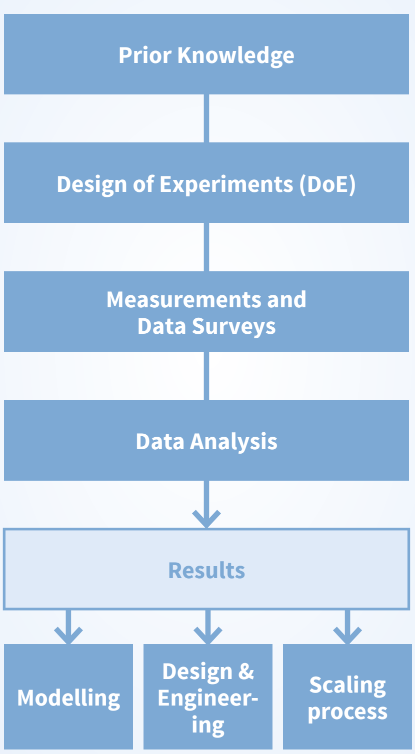
SUBSTANTIAL ADVANTAGES

- Accurate k_La measurements at any defined position in the bioreactor
- Comparison of different process conditions and parameters
- Revolutionary impact on QbD approach
- Comparison of bioreactor geometries, agitator design and sparger design
- Highest flexibility: k_LA measurements adaptable to different cultivation systems
- Comparison with a wide range of different analyzed systems due to ZETA´s long-term experience as an engineering specialist and equipment manufacturer

MEASUREMENT METHOD

- Fast detection system using high speed oxygen probes
- Measurement points all over the bioreactor for an comprehensive vessel characterization
- No structural changes of the fermenter needed
- Bubble separation prior to measurement for optimum measurement results
- Accurate data analysis by using proven calculation models

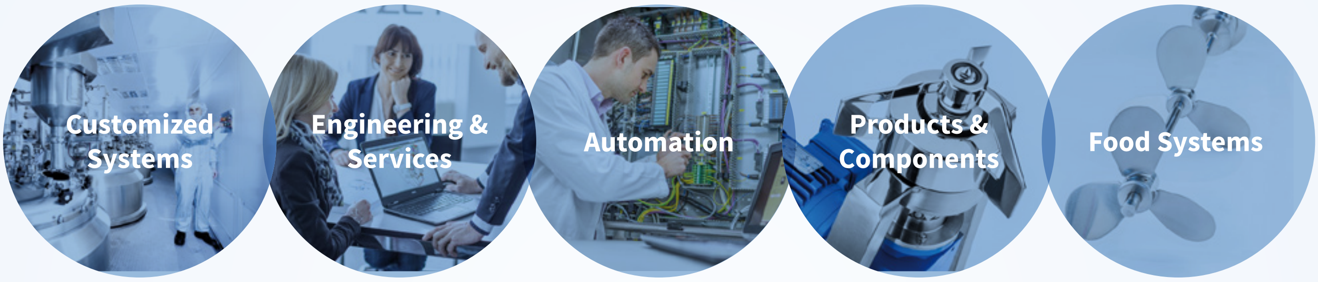
TYPICAL APPROACH OF k_La MEASUREMENT



ZETA k_La measurement test stand

INNOVATIVE SOLUTIONS FOR OUR CUSTOMERS

EVOLUTION OF TECHNOLOGY



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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