

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 bioreactor 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.

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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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.



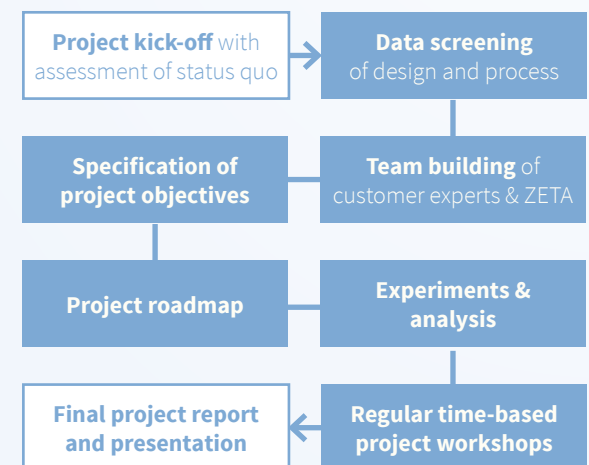
WHY MEASURING k_La ?

- 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

FLEXIBLE AND EASY TARGET ACHIEVEMENT



For further information on k_La measurement services please contact:

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www.zeta.com

STARTER-SERVICE: BIOREACTOR DESIGN AND SCALE-UP

Optimized reactor design & process scale-up

STARTING POINT:

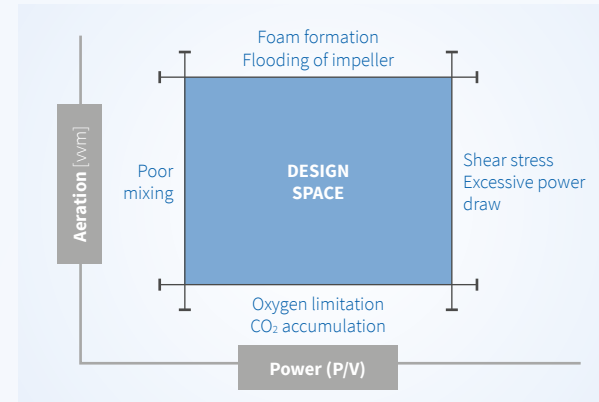
- The bioreactor design is not fixed
- Concept phase under development

STRATEGY:

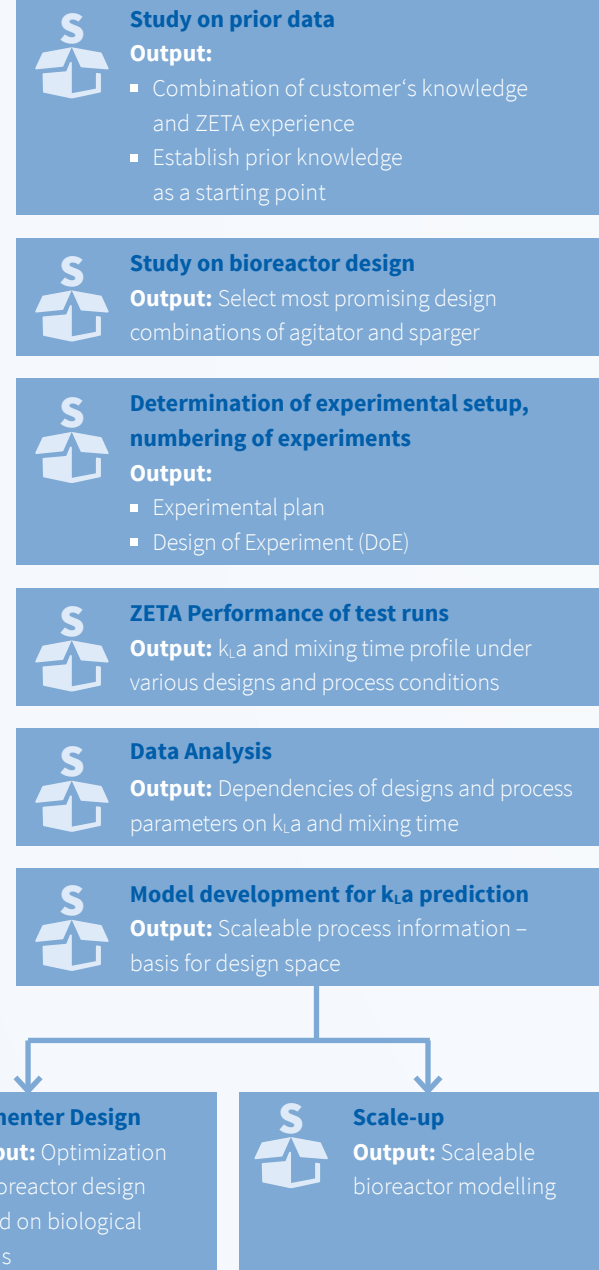
- The services offer testing of different stirrer and sparger design combinations to find the most suitable system for the biological system.
- They include test runs with VE water under defined process conditions.
- Performance indicators $k_L a$, mixing time and shear stress are determined

BENEFITS OF THE $k_L a$ SERVICES:

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



SERVICES AT A GLANCE



ADVANCED-SERVICE: BIOREACTOR CHARACTERIZATION

Knowledge based optimization on production scale bioreactors

STARTING POINT:

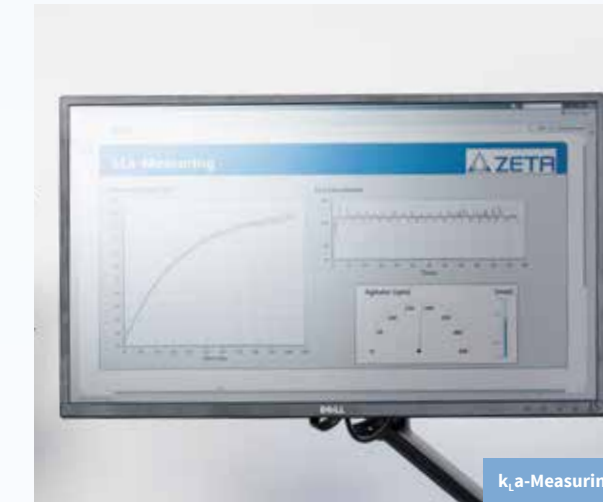
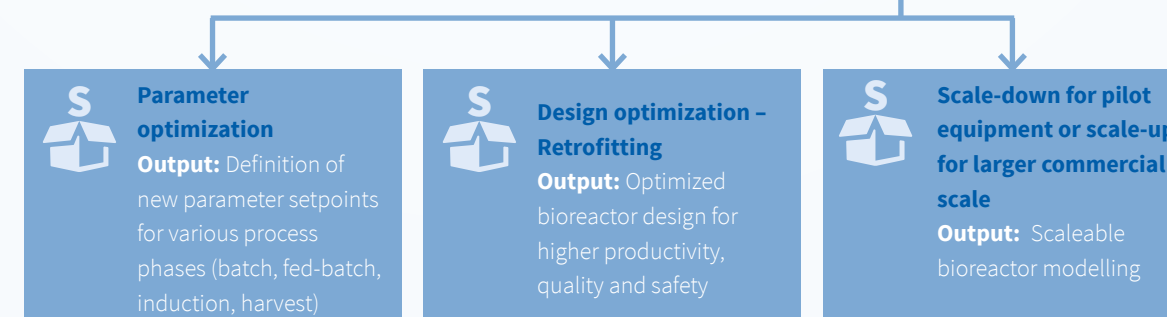
The existing lab-, pilot or production scale bioreactors are installed/under operation at customer's site

STRATEGY:

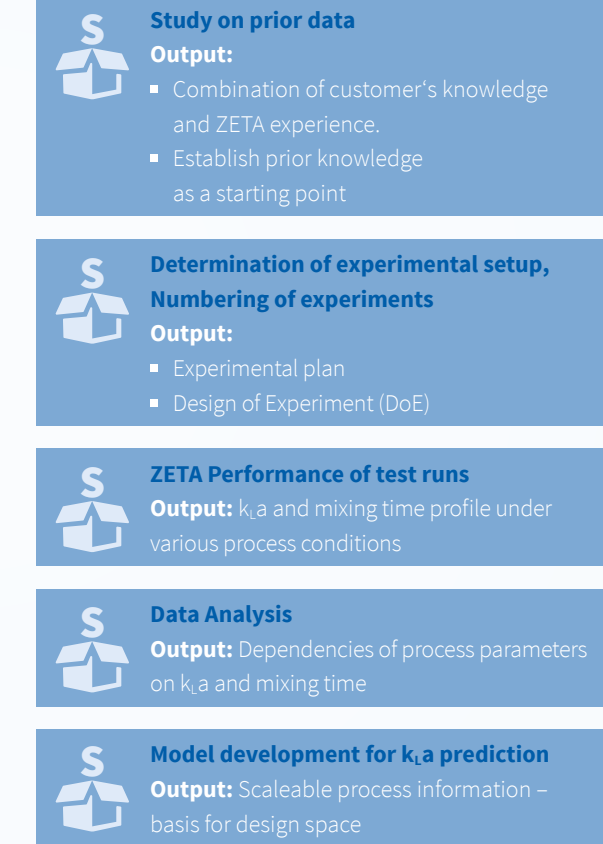
- The service includes test runs with VE water under defined process conditions.
- Performance indicators $k_L a$ and mixing time are determined.

BENEFITS OF THE $k_L a$ 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 ($k_L a$, mixing time)
- Better understanding of process conditions on bioreactor performance indicators
- Optimization of process parameters and process control
- Scalable process information
- Development of scaleable models and design spaces
- Design optimization by retrofitting



SERVICES AT A GLANCE



SUBSTANTIAL ADVANTAGES

- Accurate $k_L a$ 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: $k_L a$ 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 $k_L a$ MEASUREMENT

