CFD FOR PROCESS OPTIMIZATION AND SCALE UP: A CASE STUDY

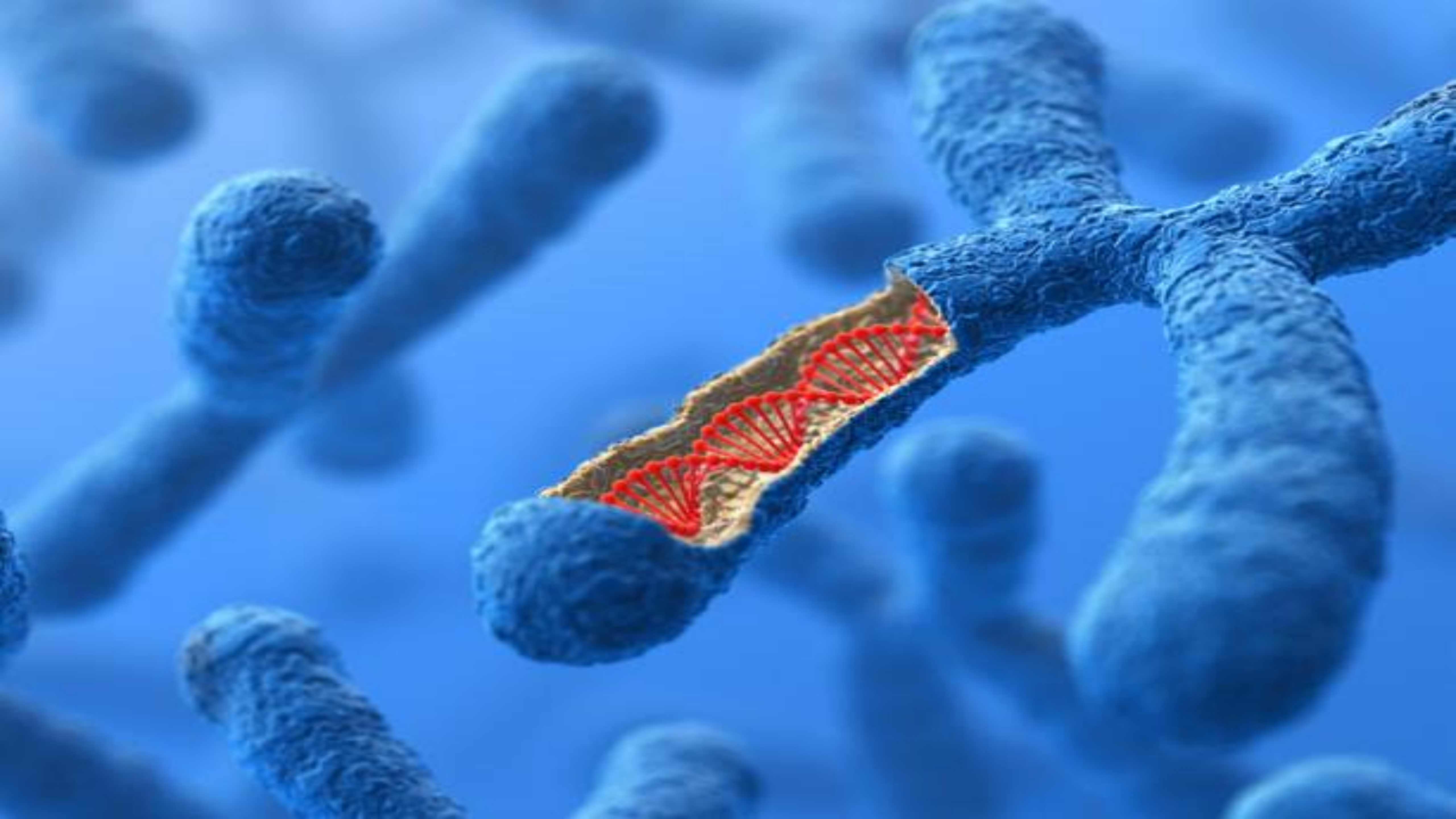
APRIL 2020

BiOENGiNEERiNG

dcvmn

Developing Countries Vaccine
Manufacturers Network

BIOENGINEERING

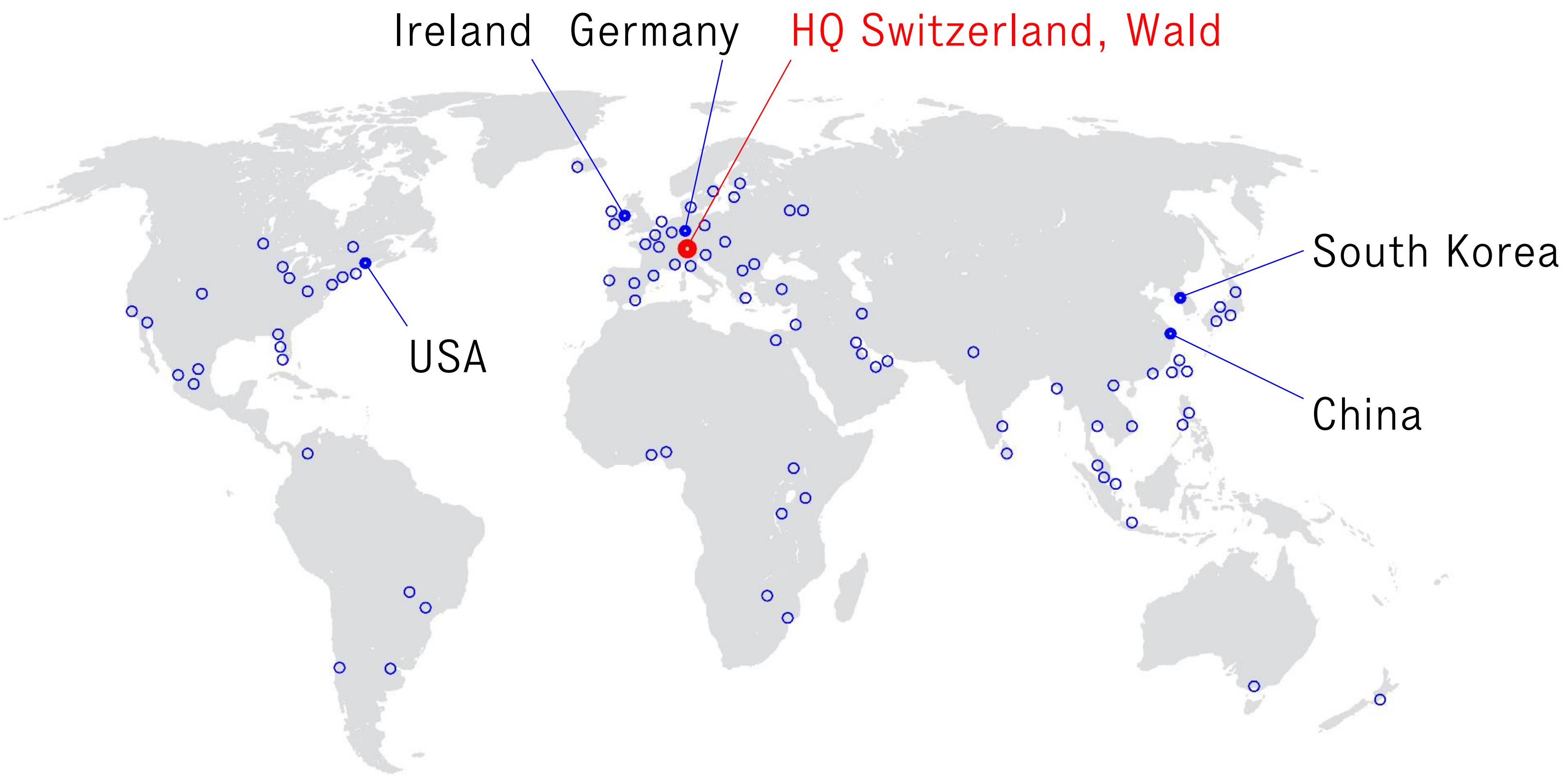


ENCODED IN OUR DNA

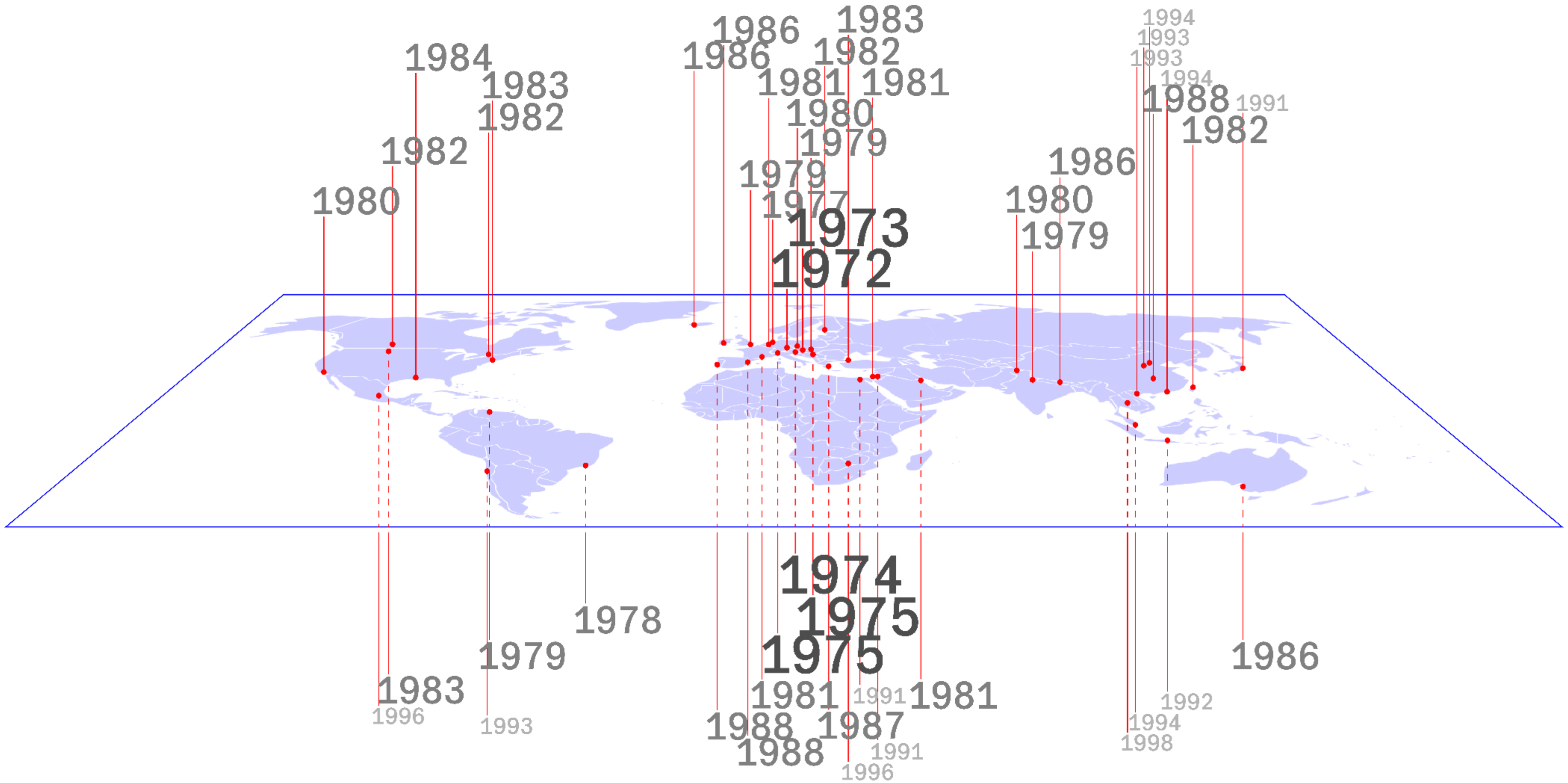
Inspiring

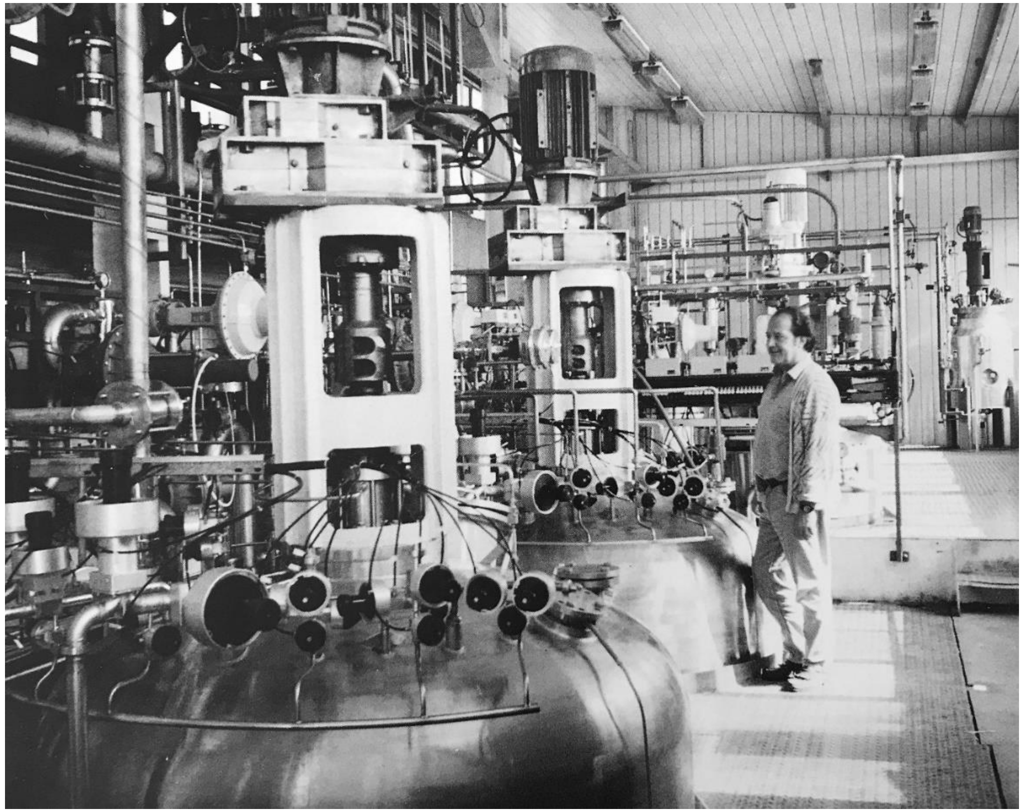
Excellence

HEADQUARTERS, SUBSIDIARIES AND REPRESENTATIVES

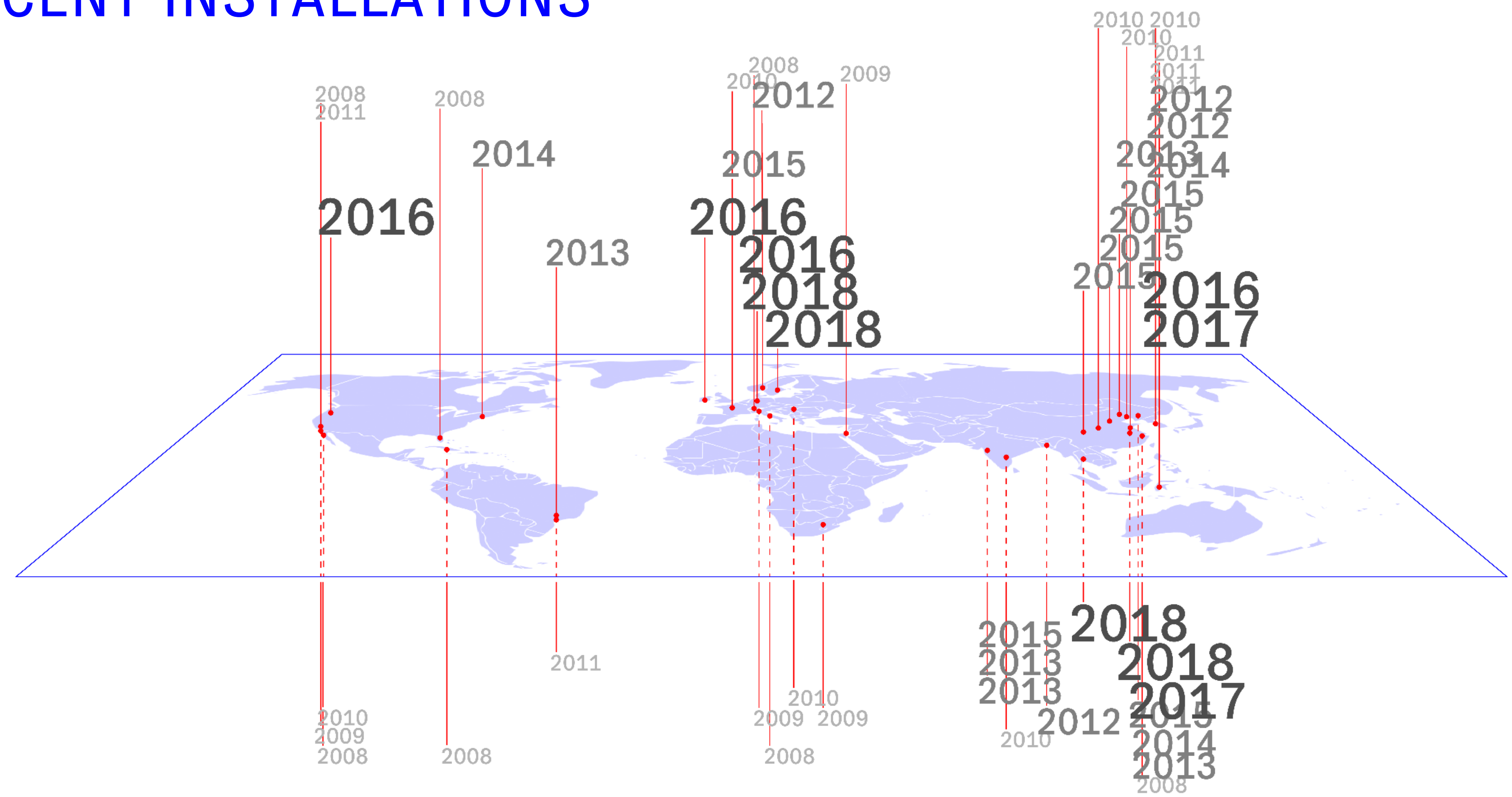


MARKET PRESENCE SINCE...





MORE RECENT INSTALLATIONS



OUR CORE COMPETENCE

- Engineering & Design

  Nearly 50 years of experience designing customer specific solutions with plants by Bioengineering having won Facility of the Year
- Plants

  Complete systems for upstream and downstream including bioreactors, media & buffer preparation vessels, CIP and distribution systems, mobile tanks and formulation vessels.
- Lab & Pilot

  From <1L modular and expandable benchtop devices to scalable 1000+L plants for the manufacturing industry
- Service

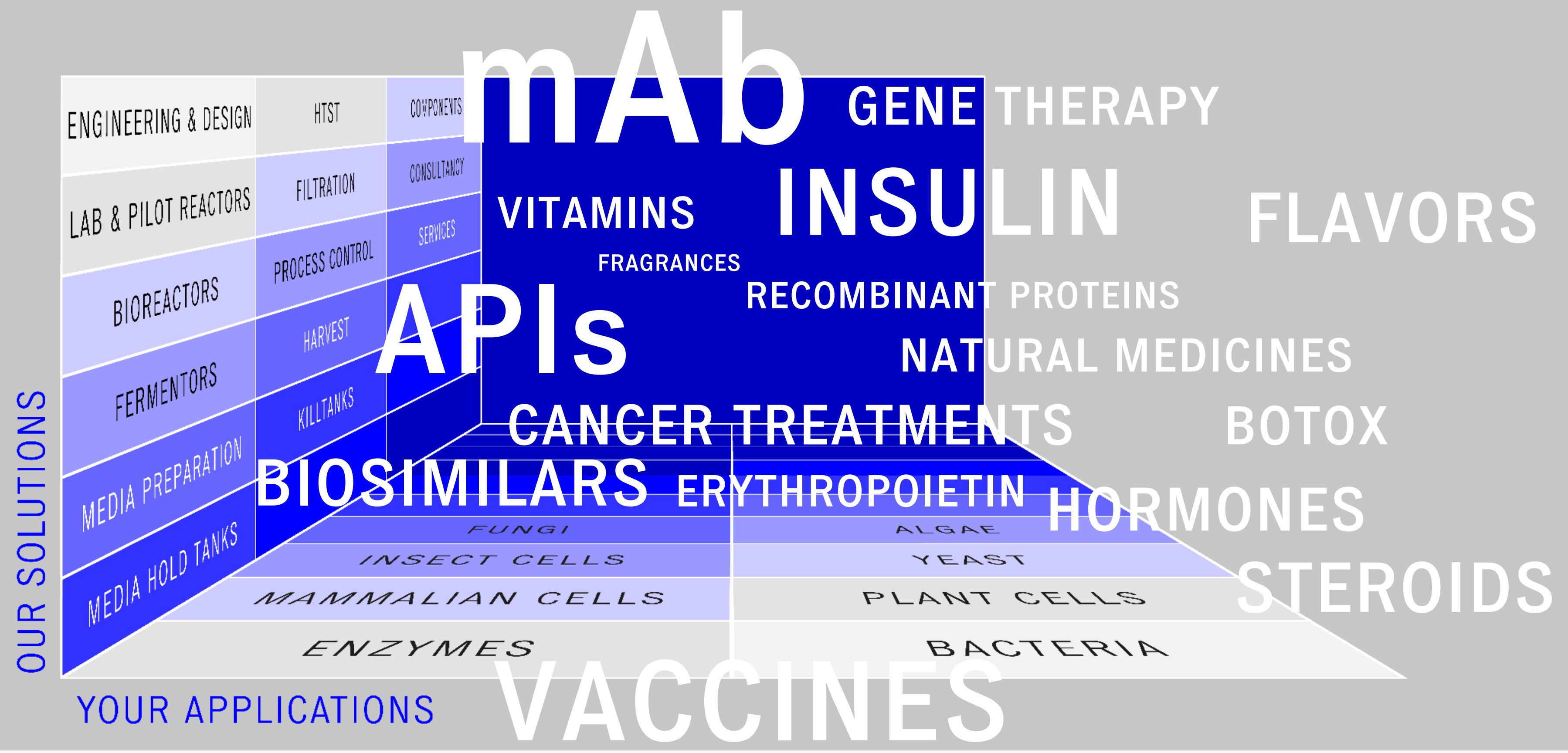
  Expert knowledge, servicing, inspection and documentation to assist with the operation of your plants
- Bioprocess control

  License-free hardware and software automation solution designed for the bioreactor environment
- Components

  Patented components for cleaning, mixing and dosing with a focus on hygienic design, efficiency and ease of use
- Case studies

  Available at www.bioengineering.ch

OUR STRENGTHS

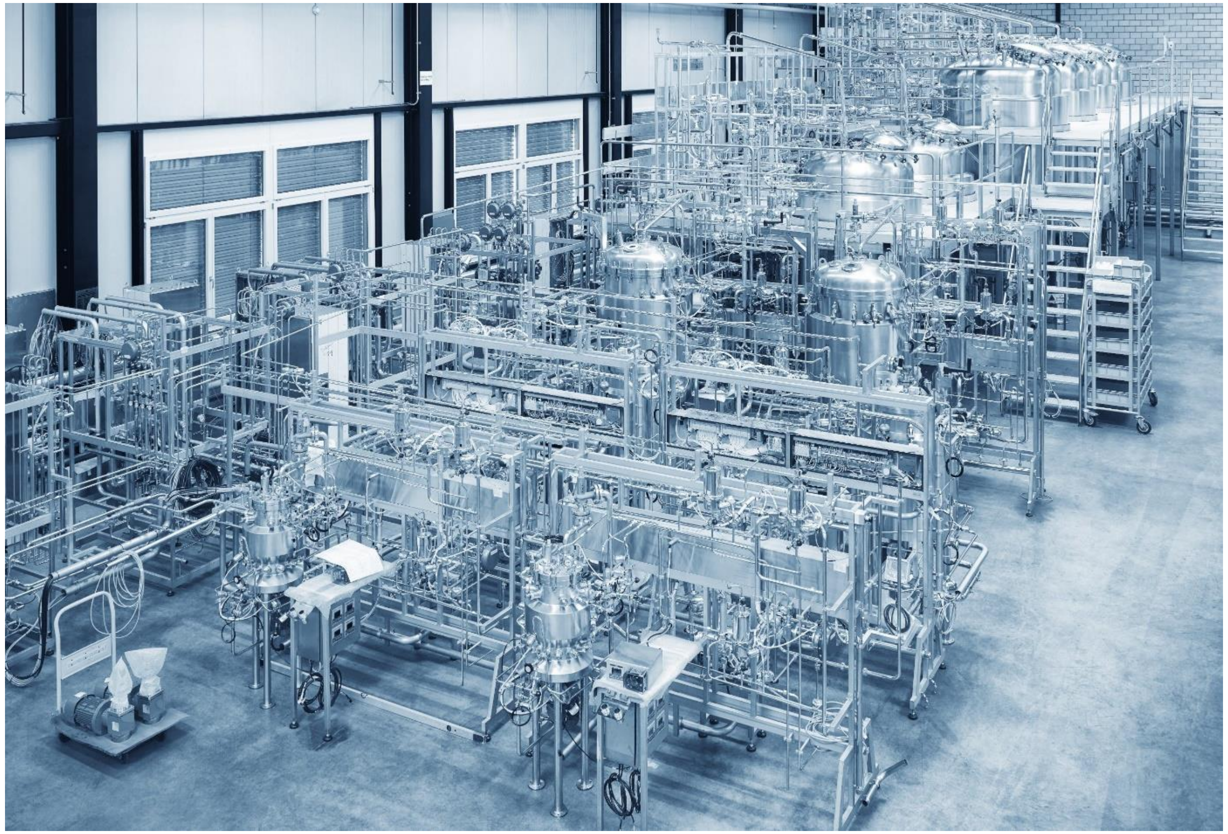


VACCINES PRODUCED IN OUR SYSTEMS

Diphtheria
Foot & Mouth
Hepatitis
HPV
Influenza
Malaria adjuvant (plant cell-based)
Meningococcal
Acellular & whole-cell Pertussis
Pneumococcus

Polio
Porcine cirovirus 2
Rabies
Rotavirus
Tetanus
Tuberculosis
Various unknown

Multivalent vaccines
Multipurpose R&D and formulation



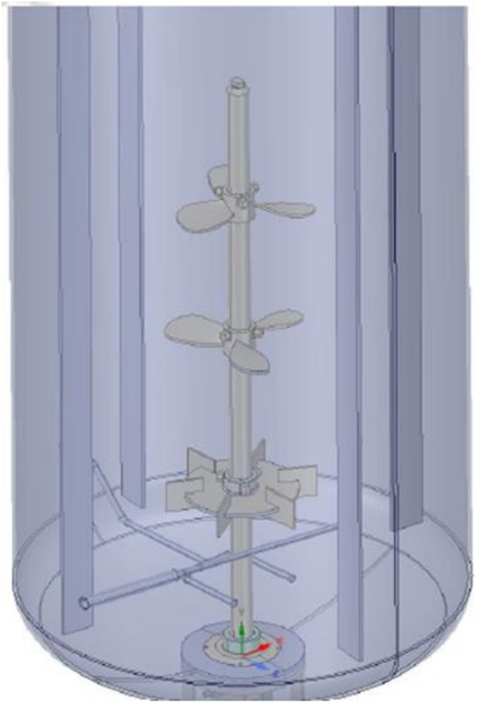
CIM Centro de Inmunología Molecular
Firmenich for good, naturally
SANOFI
biofarma
MSD
novo nordisk®
AMGEN
BAYER
通化東宝 Tong Hua Dong Bao Group
MERCK
SERUM INSTITUTE OF INDIA LTD.
POONAWALLA GROUP
GE
Roche
Givaudan
NOVARTIS
Phyton Biotech®
Acambis
金宇生物技术股份有限公司 JINYU BIO-TECHNOLOGY CO., LTD.
GEDEON RICHTER
CELLTRION
Biocon
ESTĒE LAUDER COMPANIES
SAMSUNG
celonic
Crucell
RAUCH
Pfizer
SACCO
Schering-Plough

3000L BIOREACTOR SCALING

GOAL AND MOTIVATION

- Characterize an operational 3000L bioreactor to allow a comparative assessment of a new 1500L design prior to construction.
- The fluid flow behavior and interaction with air bubbles in the aerated and stirred vessel was investigated by means of Computational Fluid Dynamics (CFD).
- The analysis includes an assessment of the general flow field, wall shear stress in the impeller zone of influence and an evaluation of the overall oxygen mass transfer coefficient averaged over the total volume, as well as mixing time profile (homogeneity 60s after introducing 0.1% volume of fresh fluid).

EVALUATING PROCESS EQUIVALENCE OF EXISTING 3000L BIOREACTOR



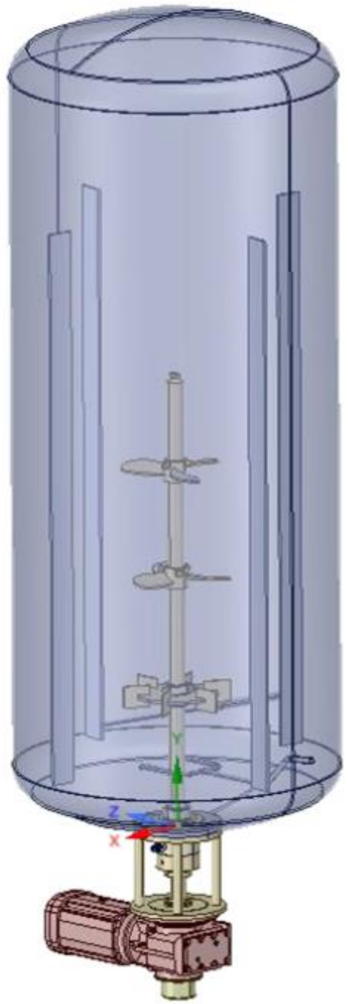
Present design

Parameter	Unit	3000L
Number of stirrers	pcs	3
Tip Speed	m/s	1.67
Vessel working volume	L	2000

INITIALIZATION

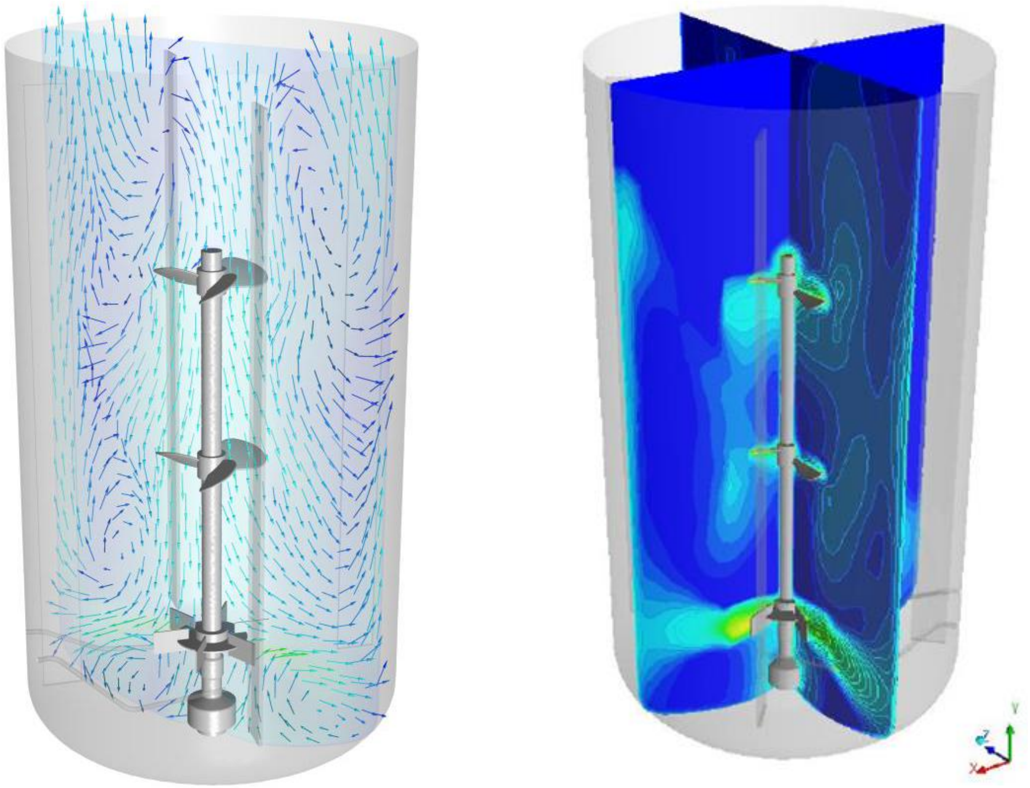
Single-phase steady state fluid analysis in order to:

- Assess the overall flow field distribution
- Investigate wall shear stress distribution at rotor tips
- Evaluate power input to the stirrer without bubbles



FLOW FIELD DISTRIBUTION

- Axial flow regime
  - 2x propeller impellers generate a downward pumping flow along the shaft toward the base of the vessel
- Heterogenous flow pattern
  - Low turbulence
- Disruption in flow pattern
  - Rushton turbine counters the axial pumping effect



SHEAR STRESS

- Shear stress at the Rushton turbine
  - Shear rate too low to break up bubbles

- Low shear stress at the propeller
  - Energy transformed to axial flow pattern

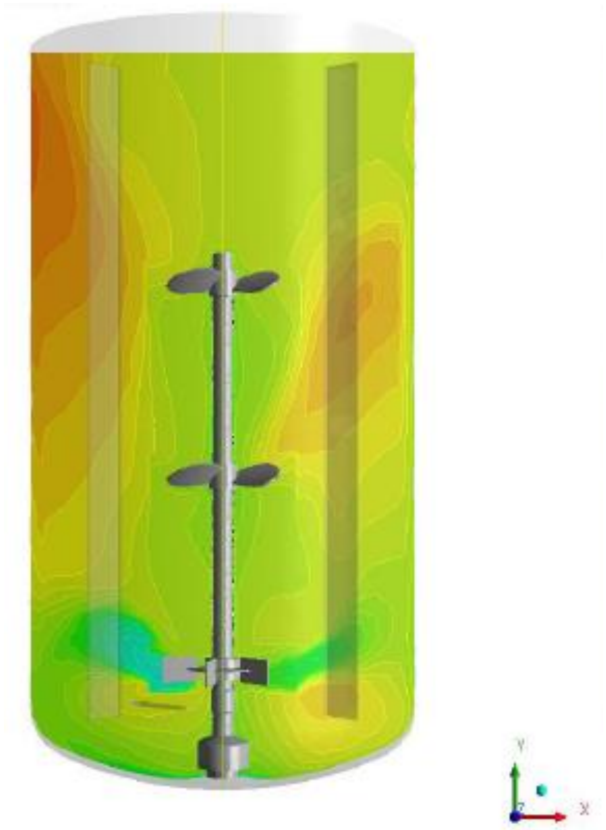
POWER INPUT WITHOUT AERATION

- Low power input
  - Highest input for the Rushton
  - Non-critical for the requisite heat transfer

Parameter	Torque (Nm)	Power (KW)
Bottom impeller	-9.21	143.4
Middle impeller	-0.75	11.6
Top impeller	-1.13	17.3
Total	11.08	173

K_LA - BUBBLE SIZE DISTRIBUTION

- Heterogenous distribution
  - Smaller bubbles closer to stirrer and base
  - Larger bubbles/agglomeration in the upper levels
- Radial flow pattern
  - Rushton turbine counters the axial pumping effect
- Coalescence along the vessel wall
  - Bubbles pushed outward to the vessel wall boundary by Rushton turbine
  - Rise up with axial flow regime

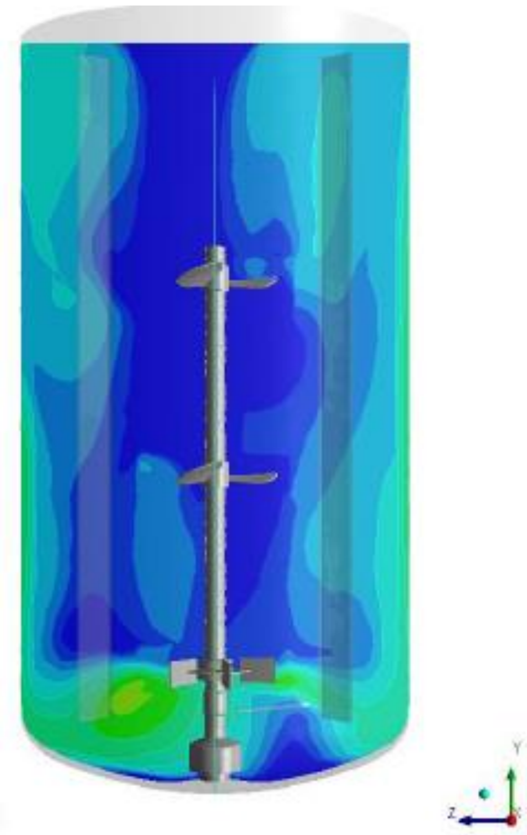


K_LA – OXYGEN TRANSFER PLOT

- Heterogenous oxygen absorption
  - Vessel aeration is good, but the phase interaction is too small owing to agglomerated bubbles

- Bubble diameter is important for the k_La value
  - Best k_La at the sparger => ideal diameter
  - Low k_La at the shaft => to small

Ideal bubble diameter ≈ 3mm
Optimized gas/liquid boundary

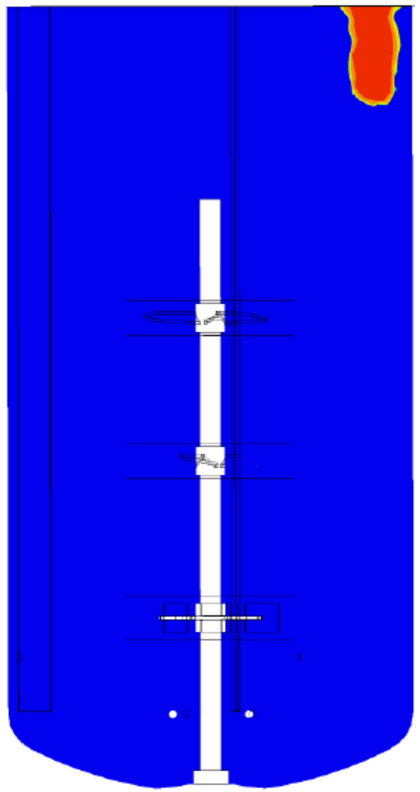


MIXING t= 0 sec

- Introduce 2l of a tracer solution to the established flow (same properties)

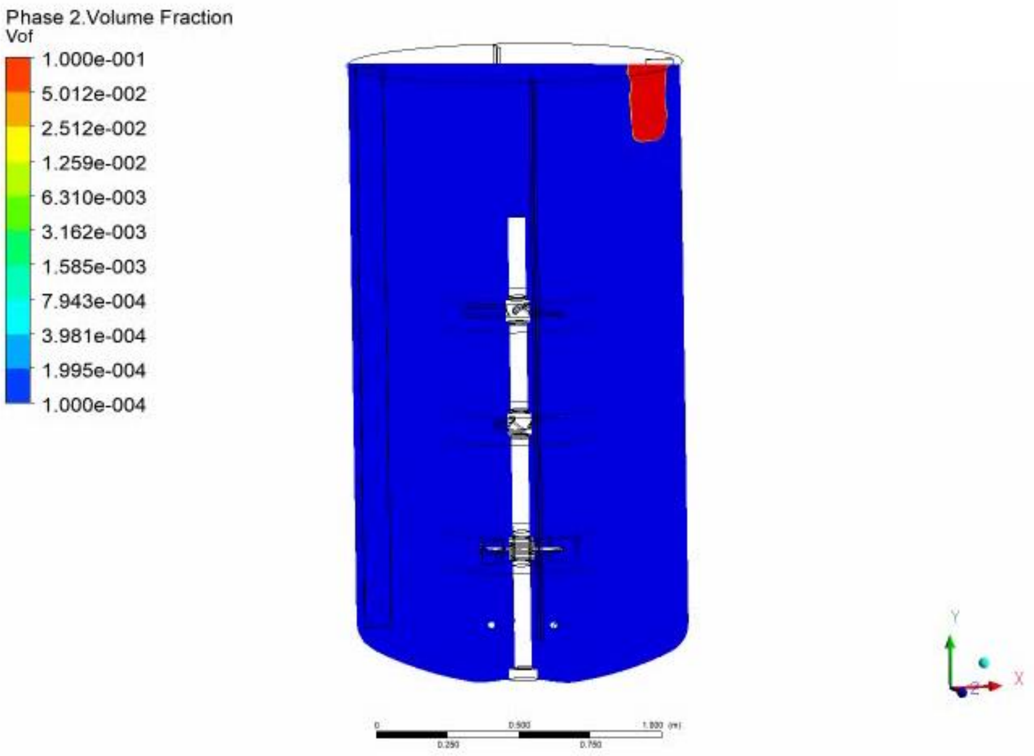
- Add the new fluid to the worst-case position (behind a baffle)

- Investigate mixing over time (60 seconds)



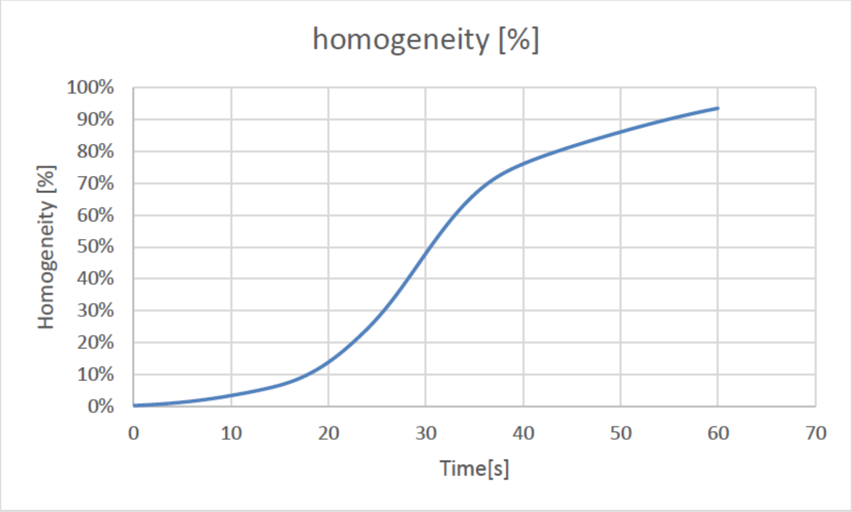
MIXING PROFILE

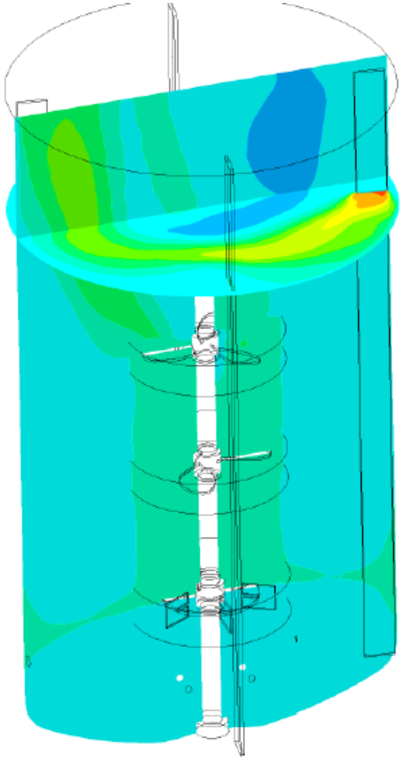
- The tracer fluid follows the flow pattern
  - Suction to the shaft
  - Upwards along the wall



MIXING t= 60 sec

- Mixing time increased as fluid swirls/circulates behind the baffle
  - Fluids with a quick response time (e.g. acid/base) or high viscosity (glucose) should be added close to the stirrer shaft
  - Addition from the top or special nozzle design
- After 60 seconds, the homogeneity is 94%





EVALUATING PROCESS EQUIVALENCE OF EXISTING 3000L BIOREACTOR

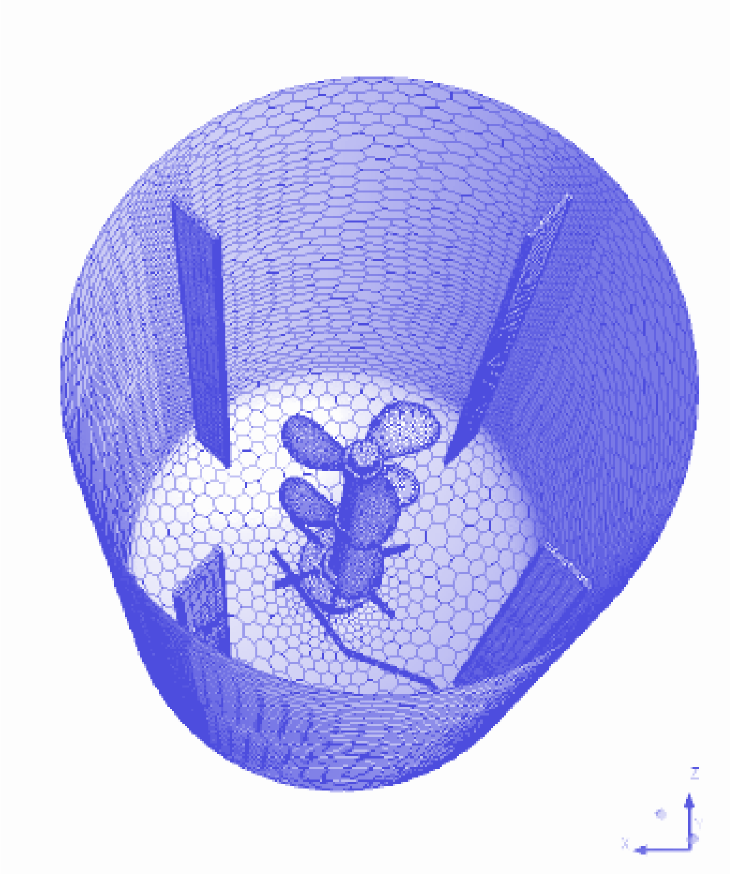
	Parameter	Unit	3000L
General	Number of stirrers	pcs	3
	Tip Speed	m/s	1.67
	Vessel working volume	L	2000
Aeration	Bubble size (Min/Max)	mm	3 / 4.5
	k_La	1/h	1.82
Mixing	Power	W	173
	Homogeneity (H_{60sec})	%	94

SCALE DOWN 1500L

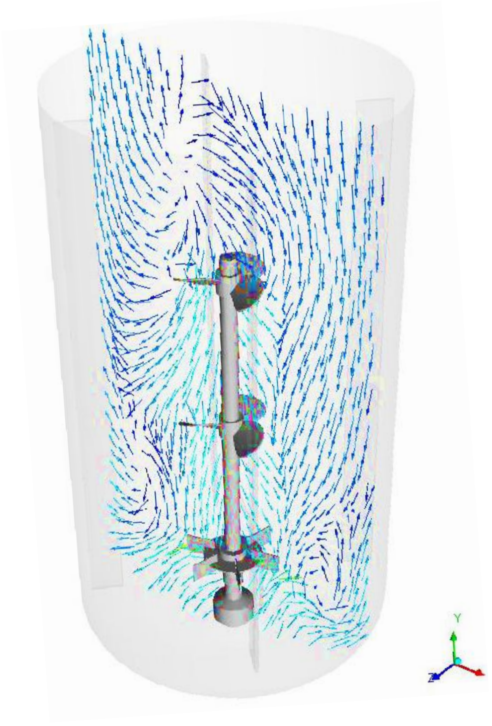
DOES THE 1500L VESSEL PERFORMANCE MATCH THE 3000L VESSEL?

START CONDITIONS

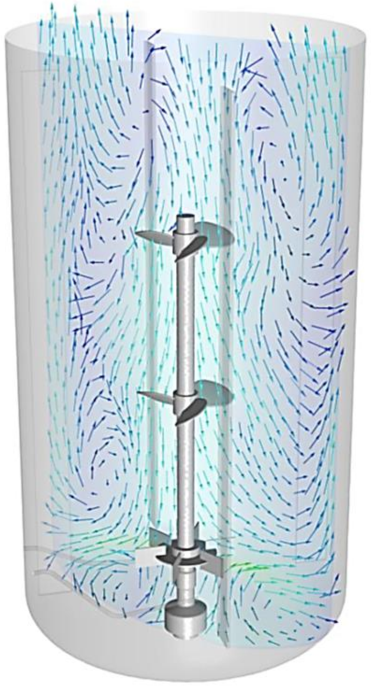
- Geometrical scale down
  - H/D Vessel
  - d/d0 Stirrer
  - 3 impellers / same kind
  - Tip speed 1.67m/s



FLOW FIELD DISTRIBUTION

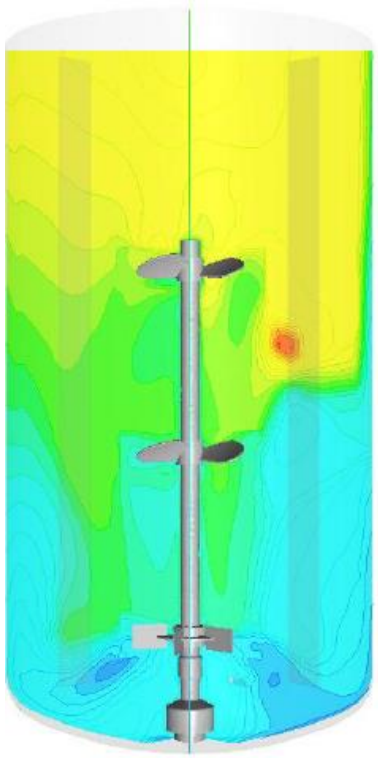


1500L

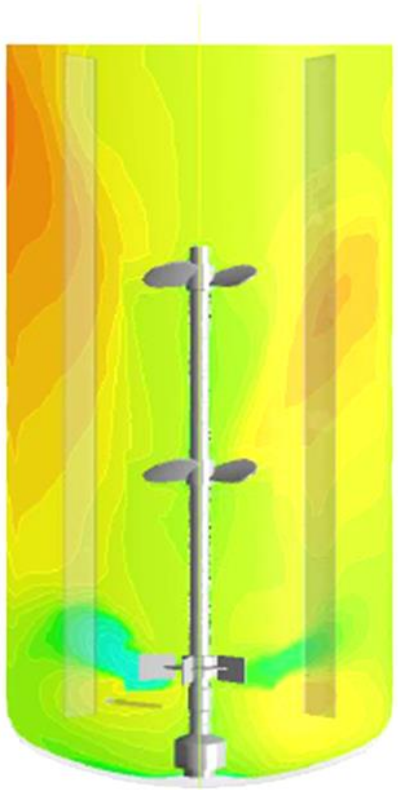


3000L

BUBBLE DIAMETER

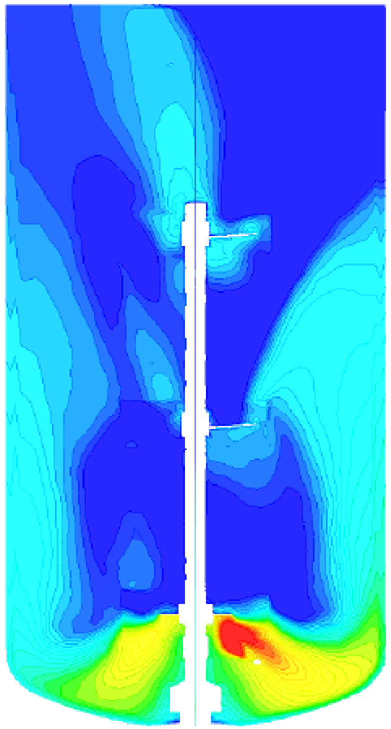


1500L

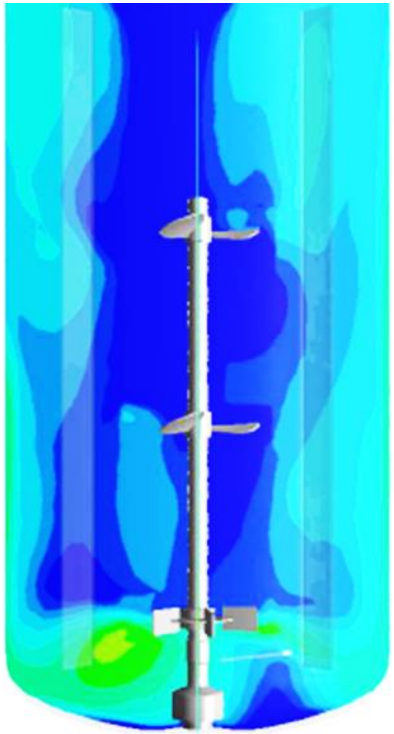


3000L

K_La

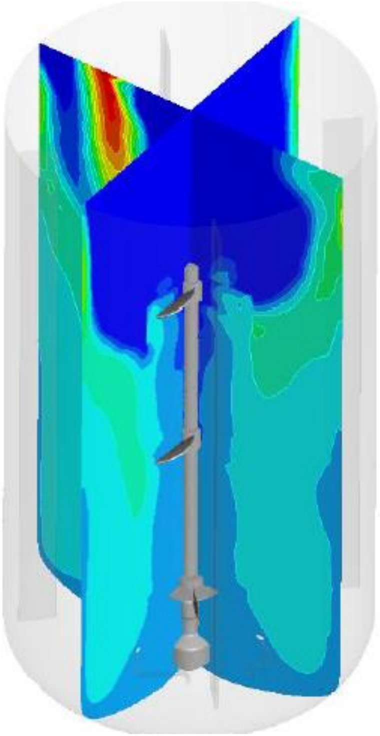


1500L

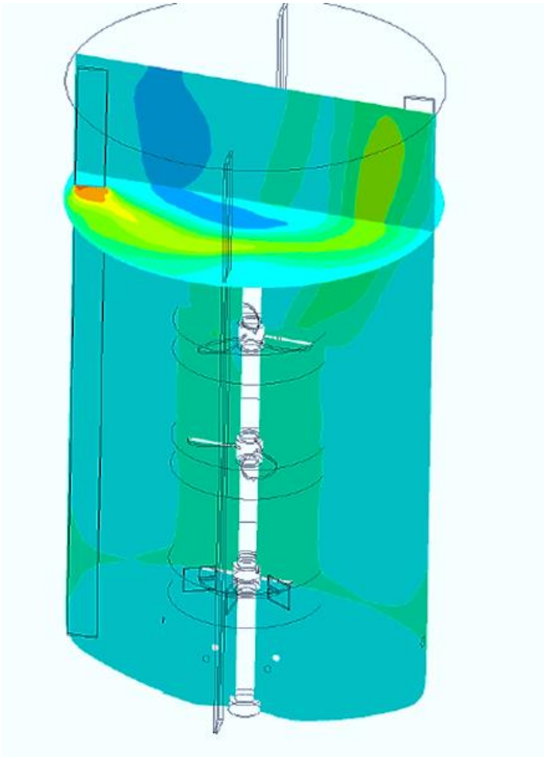


3000L

MIXING t= 60 sec



1500L



3000L

SIMULATION RESULT COMPARISON

	Parameter	Unit	3000L	1500L
General	Number of stirrers	pcs	3	3
	Tip Speed	m/s	1.67	1.67
	Vessel working volume	L	2000	1000
Aeration	Bubble size (Min/Max)	mm	3 / 4.5	1 / 4.1
	k_La	1/h	1.82	3.15
Mixing	Power	W	173	77
	Homogeneity (H_{60sec})	%	94	92

OPTIMIZATION OF 1500L

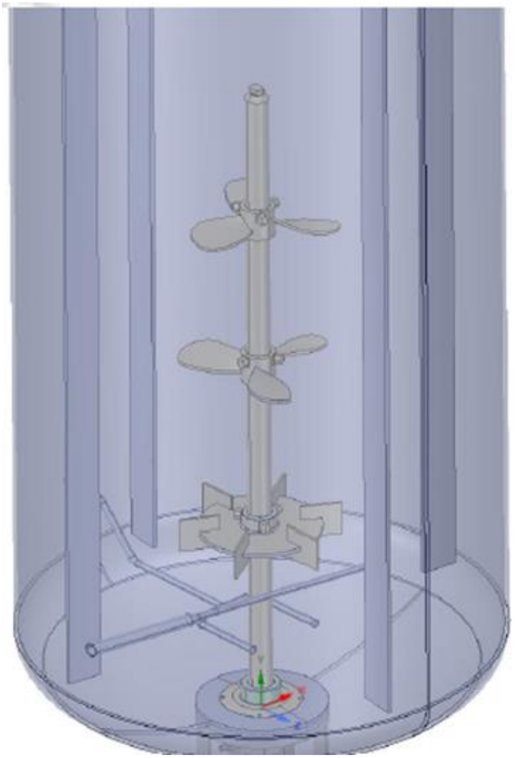
CONCLUSIONS

- Small bubbles improve the oxygen transfer
- High dwell time improves the oxygen transfer efficiency
- Homogenous flow pattern creates a good mixing performance

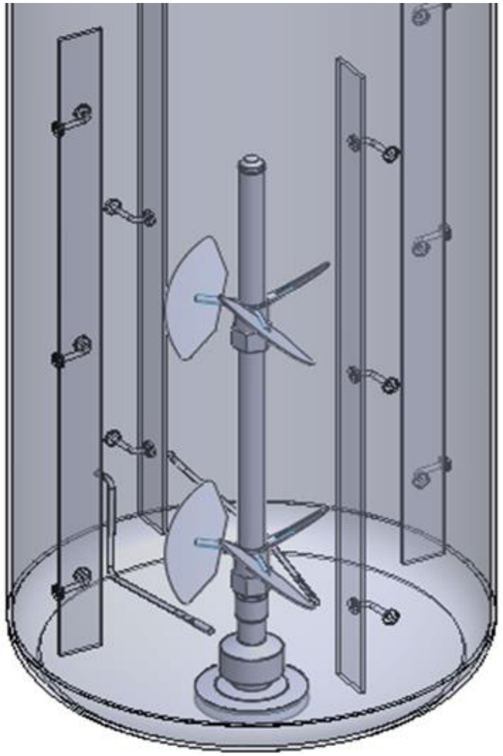
- Rushton turbine performance is insufficient => higher shear rates are required

Axial pumping systems can help to improve cell processes

GENERATE HOMOGENOUS FLOW REGIME



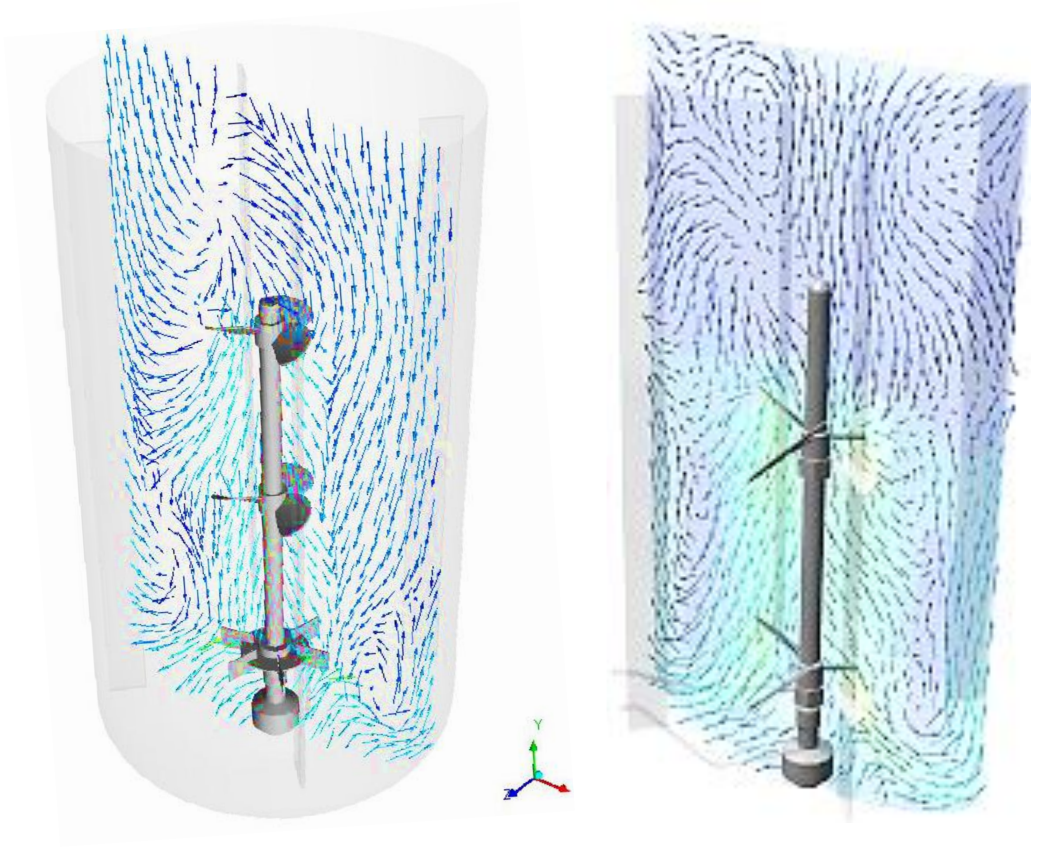
1500 L



Bioengineering Design

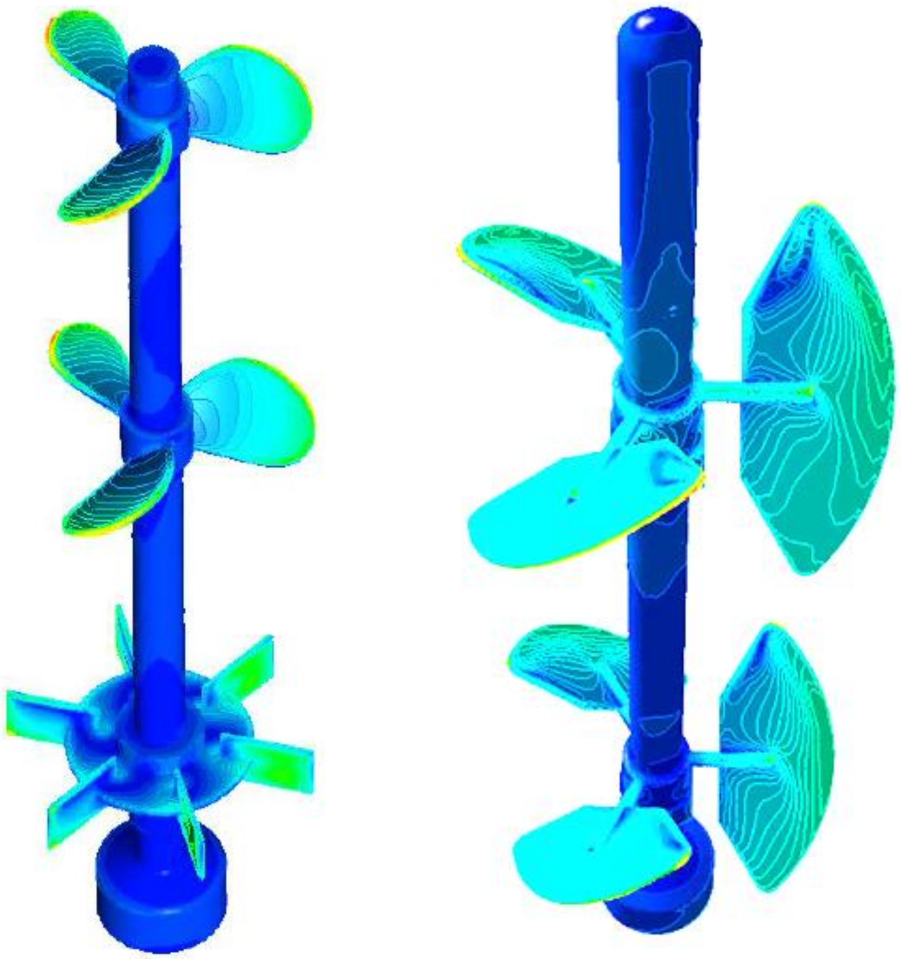
FLOW FIELD DISTRIBUTION

- Homogenized velocity profile in the Bioengineering proposed design
- Flow appears largely turbulent in the Bioengineering design



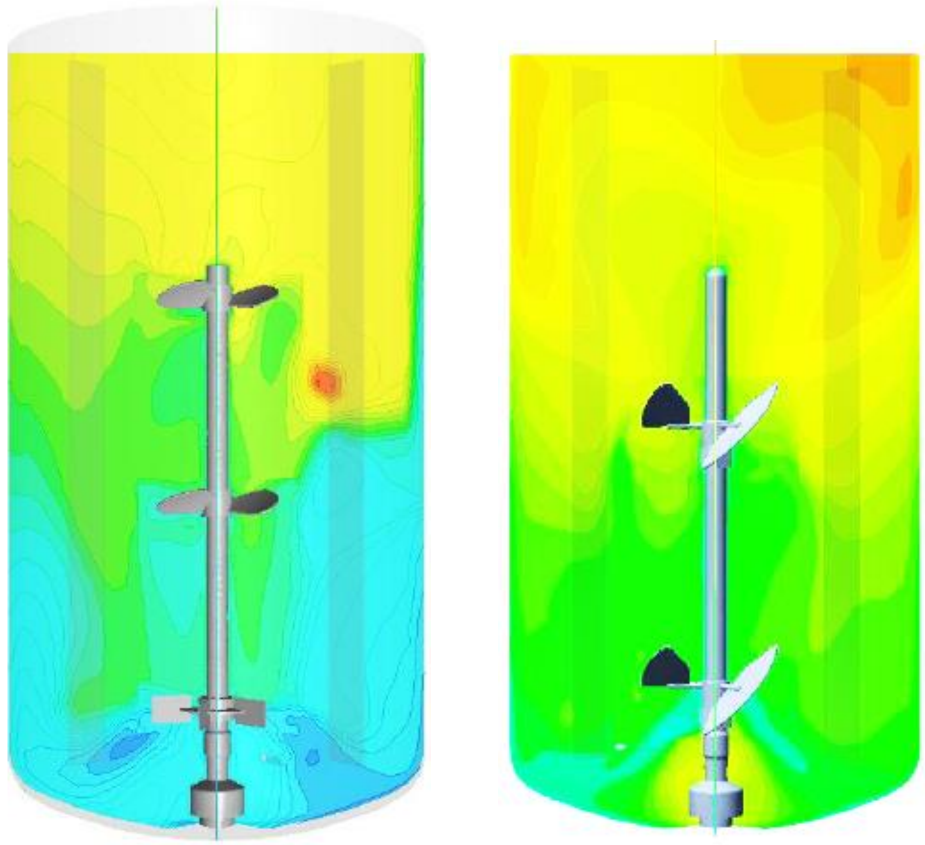
SHEAR STRESS

- Low shear stress at the Propeller and Pitched Blade
  - Energy will be transformed to axial flow pattern
  - Specific pumping volume for pitched blade system is higher



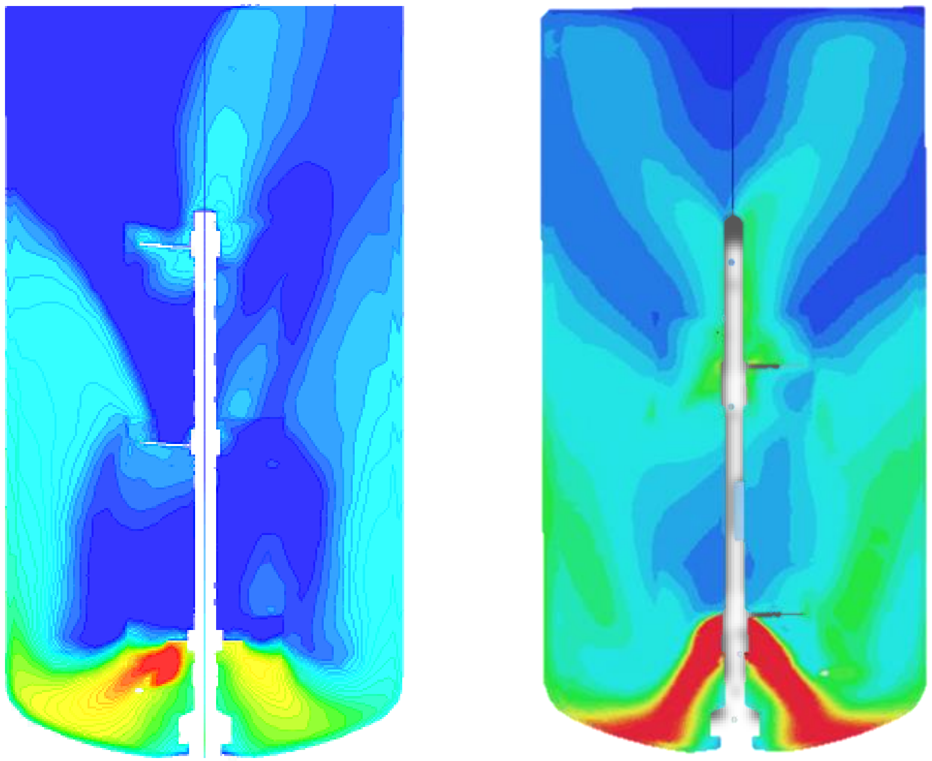
BUBBLE DIAMETER

- Smaller bubbles in the current design
- BUT: Bubble distribution homogeneity in Bioengineering design is significantly increased
  - The downwards oriented pitched blade stirrers are efficiently keeping smaller bubbles below the top third part of the fluid thanks to a strong recirculation cell.

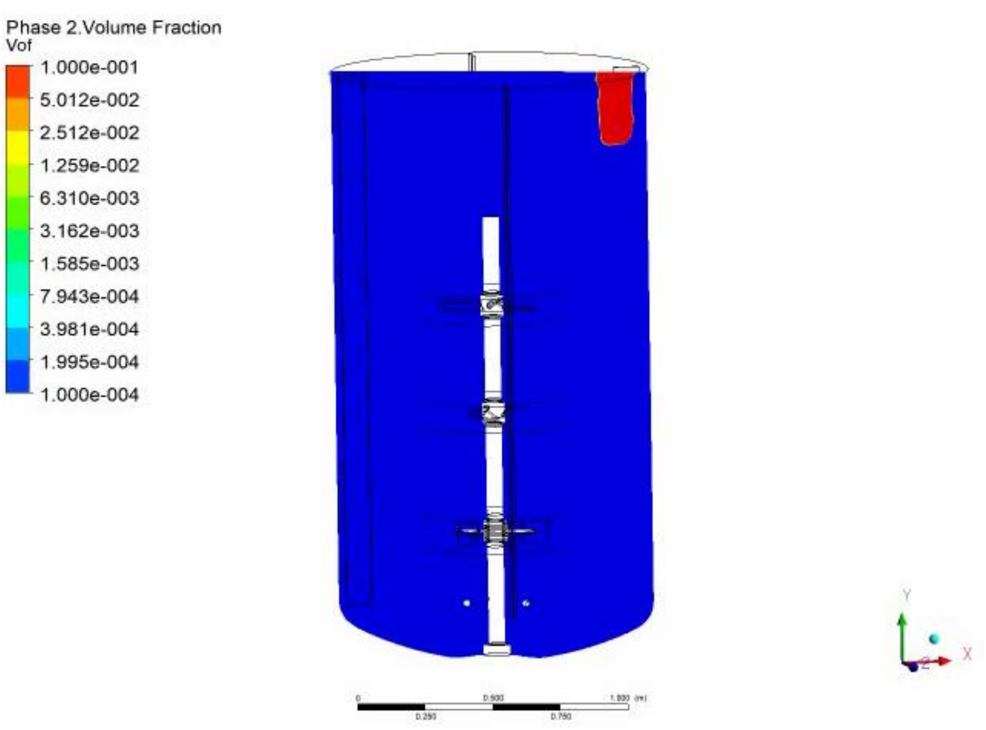


K_La

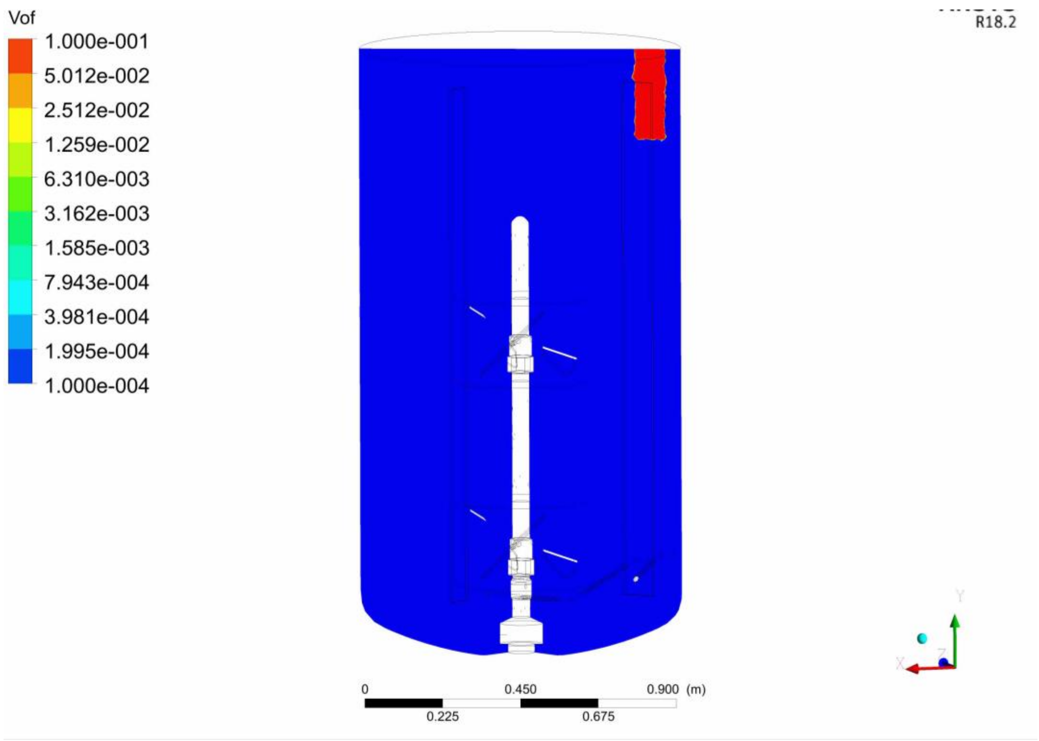
- Downward flow keeps the bubbles in suspension
- This phenomenon increases gas residency time and maximizes the oxygen transfer
- Homogeneous Oxygen absorption



MIXING PERFORMANCE COMPARED



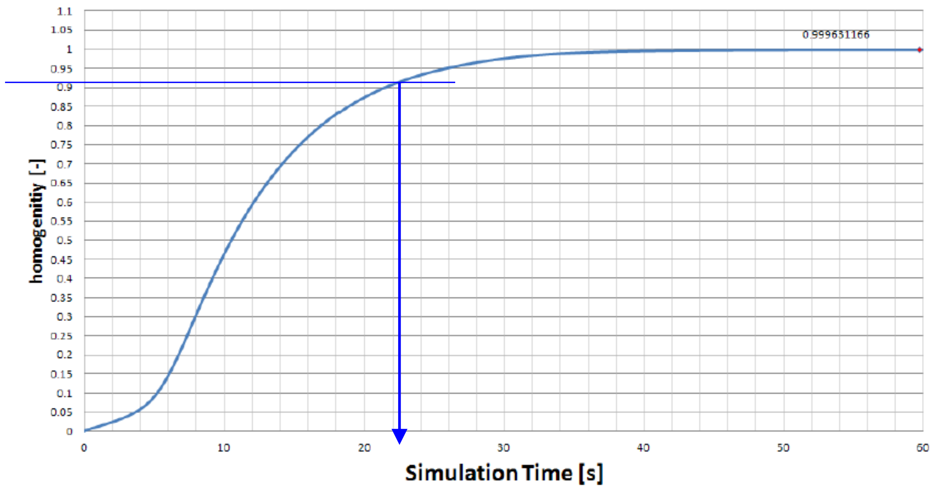
3000L

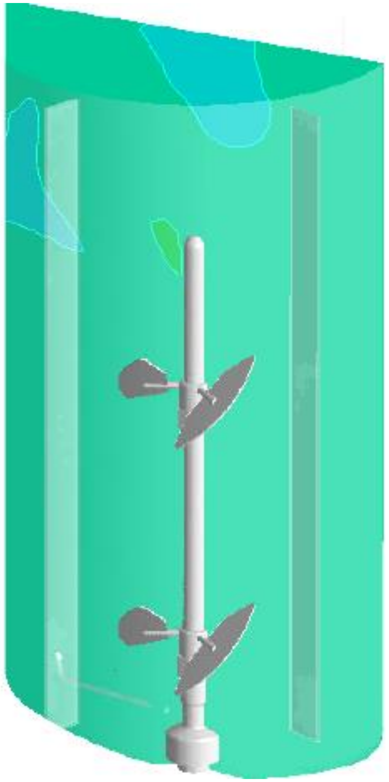


Bioengineering Design

MIXING t= 30 sec

- Injected tracer fluid is pulled down by the axial flow
- Recirculation results in a shorter mixing time
- Tracer volume fraction is homogeneously integrated after 26 seconds



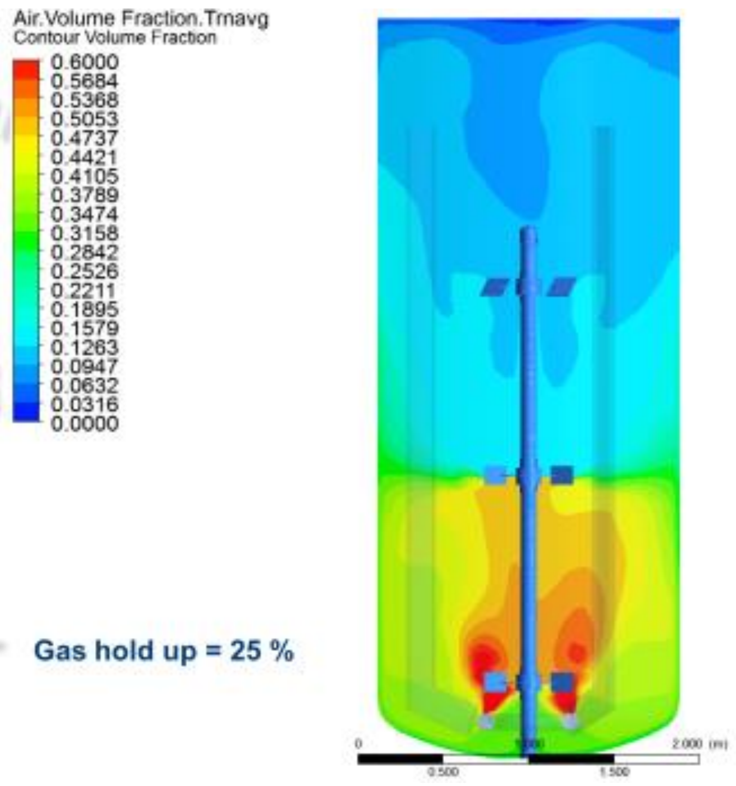


SIMULATION RESULT COMPARISON

	Parameter	Unit	3000L	1500L	Bioengineering
General	Number of stirrer	pcs	3	3	2
	Tip Speed	m/s	1.67	1.67	1.67
	Vessel working volume	L	2000	1000	1000
Aeration	Bubble size (Min/Max)	mm	3 / 4.5	1 / 4.1	1.9/6.1
	k_La	1/h	1.82	3.15	13.0
Mixing	Power	W	173	77	85
	Homogeneity (H_{60sec})	%	94	92	99

FIELD REPORTS

FLOODING


Air.Volume Fraction.Trnavg
Contour Volume Fraction
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0.5368
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0.4737
0.4421
0.4105
0.3789
0.3474
0.3158
0.2842
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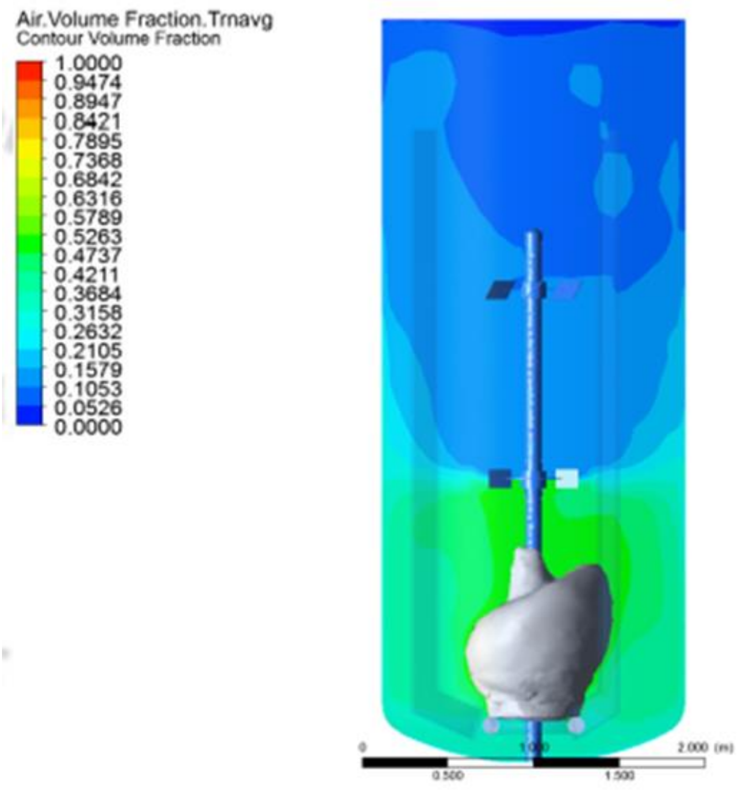
0.2211
0.1895
0.1579
0.1263
0.0947
0.0632
0.0316
0.0000
Gas hold up = 25 %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Contour Volume Fraction
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0.4737
0.4211
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0.1053
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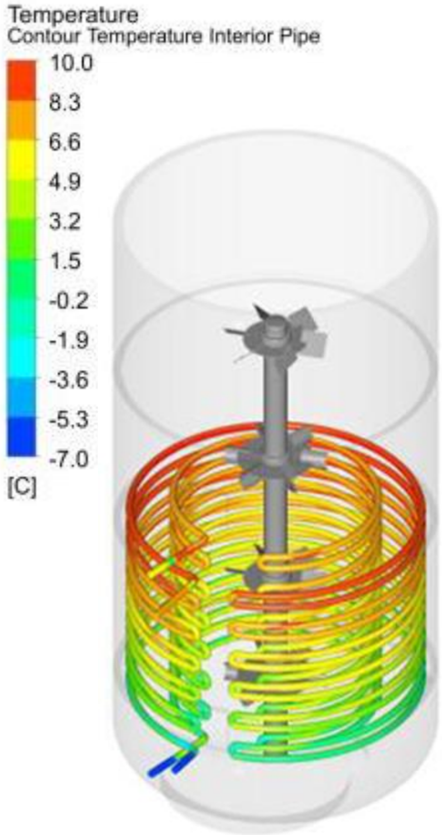
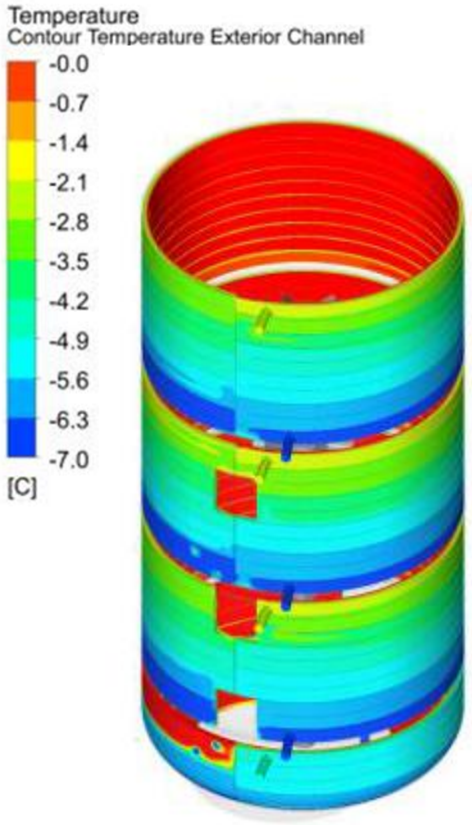
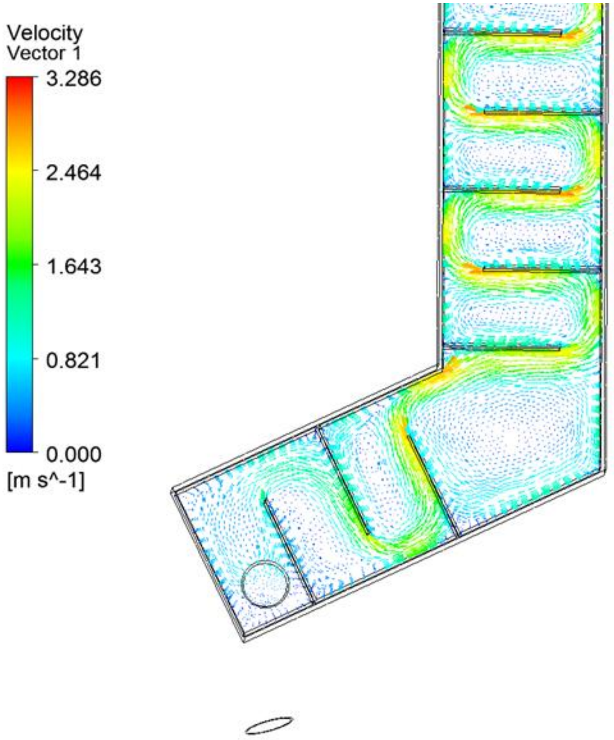
METABOLIC HEAT / POWER INPUT

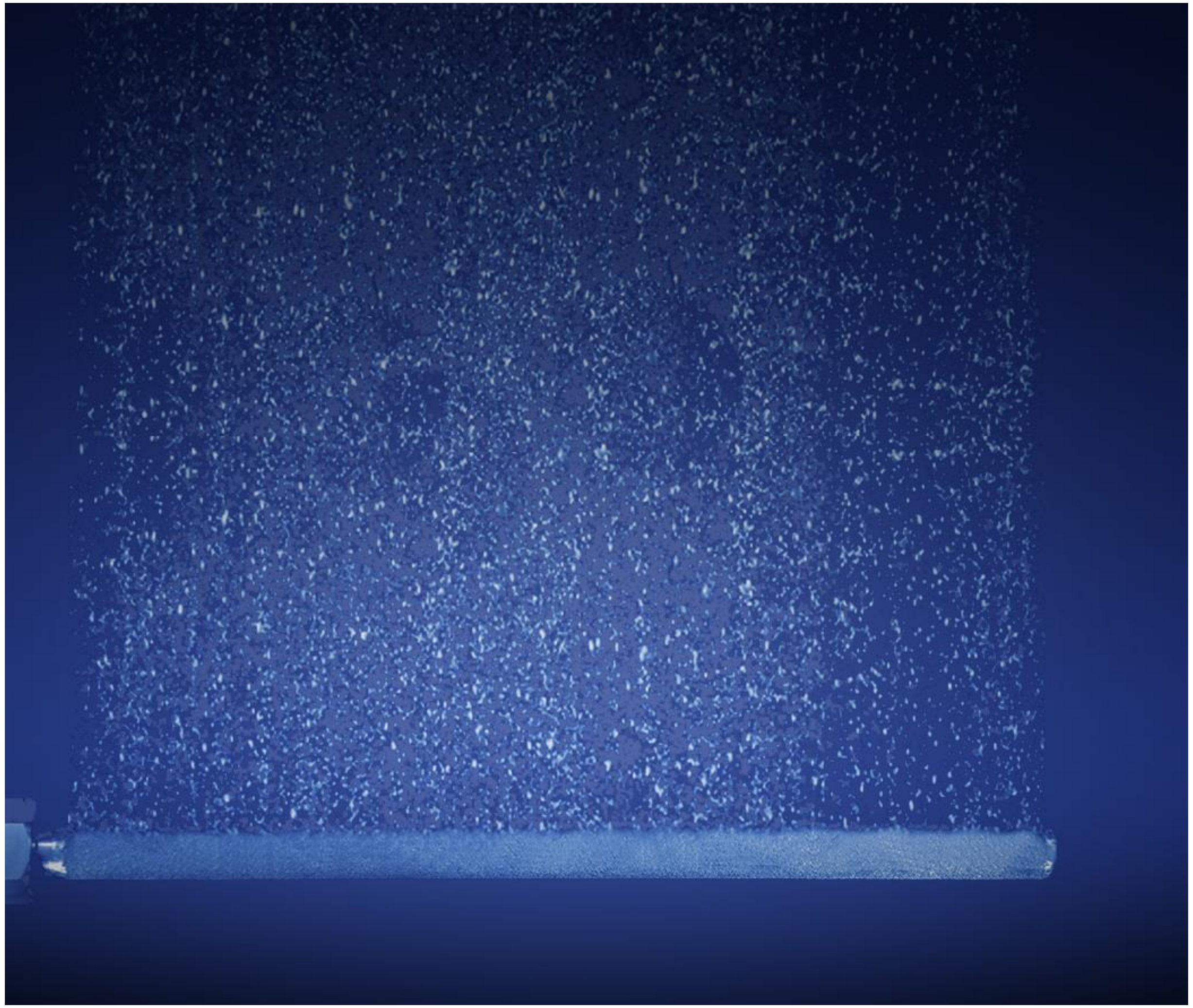






MICROSPARGER

- Reduced oxygen consumption: ≥20%
- Reduced cultivation time: 4h
    - Pore size optimized
    - Bubble diameter adjusted
    - Inlet pressure defined



THANK YOU

BIOENGINEERING