Advanced
Fermentation
Technology

19 mars 2026

Adoption of miniaturized and automated approaches to assist R&D for bioprocess developments

Olivier GALY, Toulouse White Biotechnology

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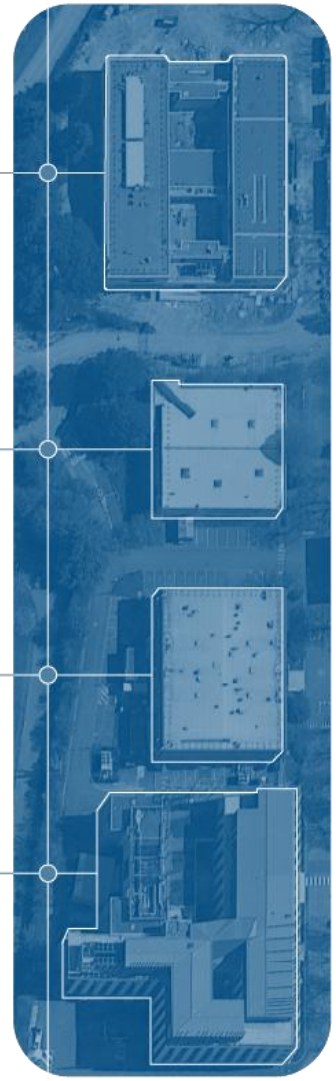
INRAE INSA TOULOUSE cnrs

Toulouse White Biotechnology, an innovative device in the heart of The Toulouse Biotech Alley



Toulouse White Biotechnology
TWB

Technological hall (2027)

CRITT Bio-Industries

Toulouse Biotech Institute
TBI

CORE TECHNOLOGICAL PLATFORMS

30 M€
direct investment in state-of-the-art platforms

60 FTE
dedicated to inhouse platforms

2 HTS
strain engineering platforms
(including nanoliter) – automated cloning, transformation, screening

Bioprocess from 50 ml to 300 L, with DSP,
next to come up to 2 m³

Versatile analytics including **cytometry**

Protein design & screening platform

Direct connection to Genotoul GENOPOLE TOULOUSE
cutting-edge metabolomics & fluxomics, Genome & transcriptome, proteomics, molecular screening, phenotyping, bioinformatics

CORE SCIENTIFIC COMPETENCES

400 Scientists

@ TWB:
- Metabolic modelling
- Strain engineering
- Fermentation & bioprocess development
- Data sciences

@ CRITT BIO-INDUSTRIES:
- DSP
- Industrialization
- Biocatalysis

@ TBI:
- Fermentation
- Microbial engineering & mathematical modeling
- Physiology
- Metabolic engineering
- Biocatalysis
- Sustainable chemical engineering

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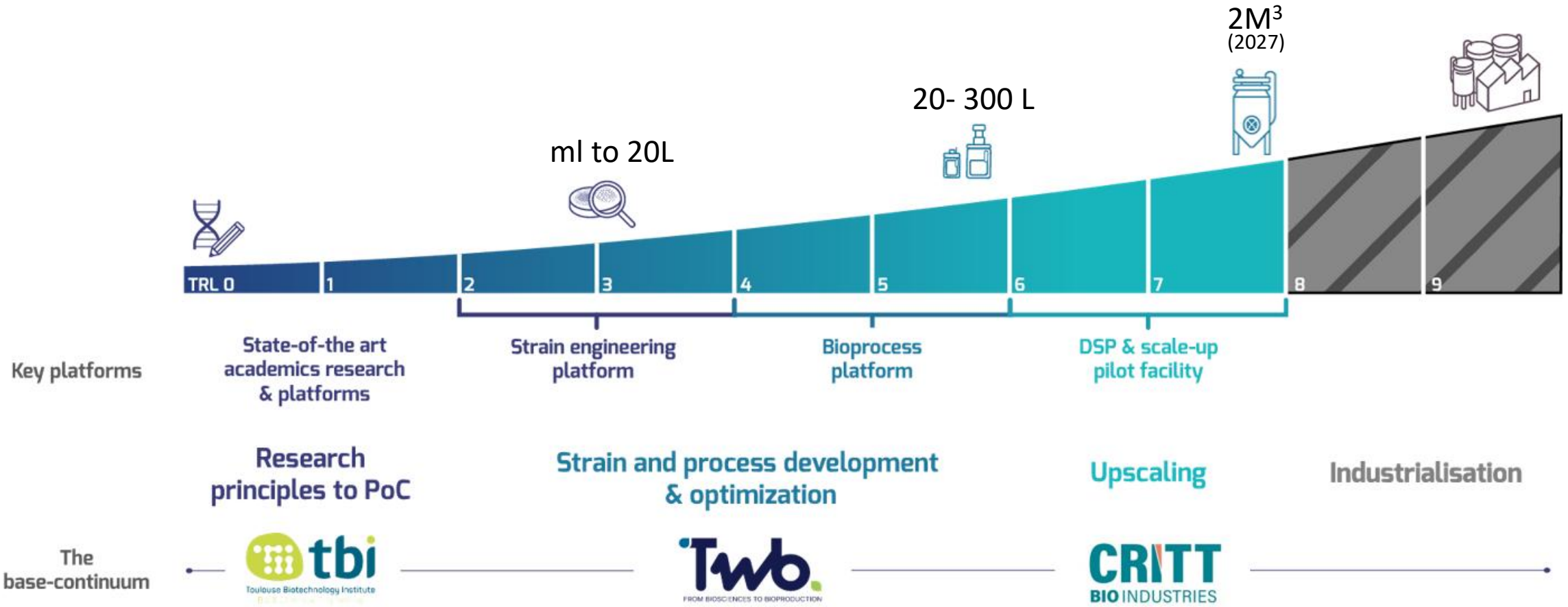

Two
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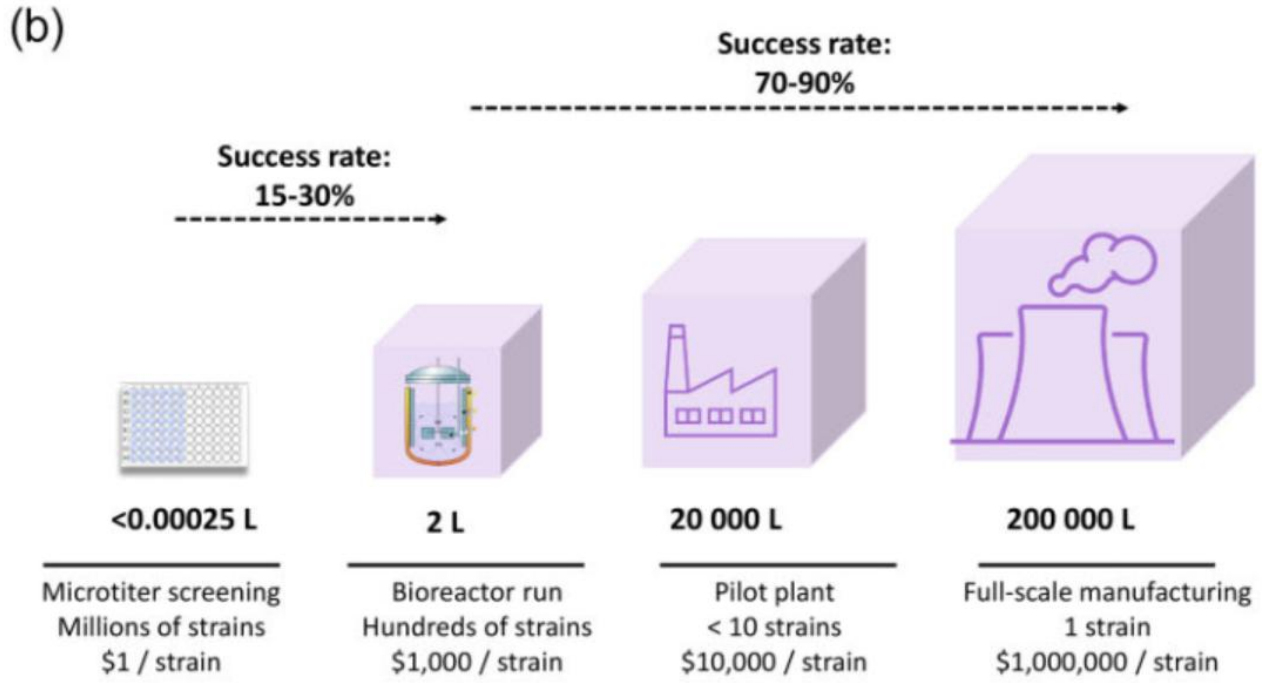
"Scale-up is still an art not a science."

A. Humphrey (1998)



Optimizing the strain engineering process for industrial-scale production of bio-based molecules
Eric Abbate et al. 2023

"Scale-up is still an art not a science."

A. Humphrey (1998)

€€€

Cost per run
Each pilot / industrial batch consumes media, time and capacity.

weeks

Per iteration
Slow turnaround limits the design–build–test–learn loop.

n ≈ 1

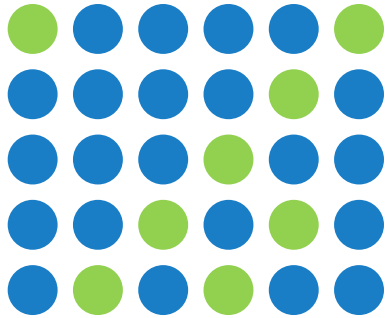
Design space
Few conditions testable at scale
→ optima are missed.
→ incomplete exploration of experimental space

learn from a scaled experiment is a slow & costly process.

Move the learning to me microscale

Industrial fermentor

scale-down



Thousands of parallel micro-cultures

THE CONDITION

Valid only when the microscale model is representative of at-scale conditions.

Everything that follows concerns the acquiring — and strengthening — of this representativeness

What cells face above 1 m³ — and microscale doesn't

1. **Concentration gradients**
   Substrate · O_2 · pH — circulating cells see feast–famine lifelines; the microwell stays uniform.

2. **Pressure → dissolved CO_2**
   Head + back-pressure raise dissolved CO_2 and cycle gas solubility; negligible in a ml scale

3. **Heterogeneous shear**
   High peak shear at the impeller plus sparging / bubble forces; gentle and uniform at µL.

4. **Heat removal**
   Metabolic heat difficult to remove above ~5 m³; the microscale is trivially isothermal.

5. **Generations & point feeds**
   More generations → genetic drift; feed and base enter as local extremes, not pre-mixed.

What could makes a microscale model predictive?

Objective is not to mimic everything — Just identify and control the few parameters that drive correlation to at-scale performance.

O_2

Oxygen transfer

Match kLa and OUR/OTR so the cell sees comparable oxygen supply.

f(t)

Feeding regime

Reproduce substrate delivery — constant, linear or exponential — not just the endpoint.

DO·pH

Controlled environment

Online DO and pH control closes the gap with a regulated production reactor.

τ

Mixing & regimes

Account for gradient exposure; a microwell is near-ideally mixed, the tank is not.

σ

Data quality

Reproducibility and traceability so small effects survive build/test noise.

✓

Defined readouts

Scale-relevant outputs (biomass, titer, yield) that transfer across scales.

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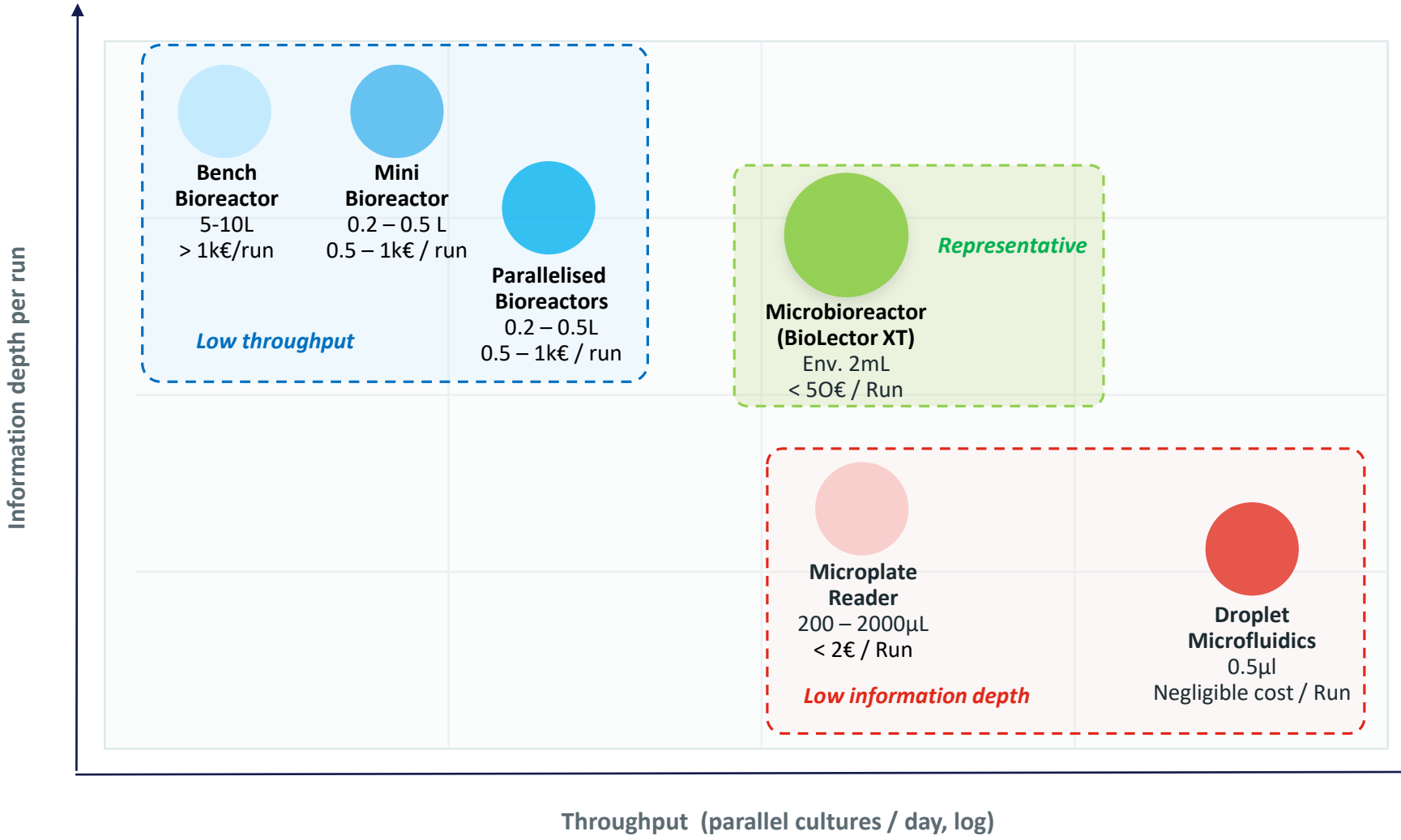
Miniaturized fermentation platforms as scale-down simulators



No platform maximizes both axes.

Online microbioreactors mixes parallelism and capacity to access essential metrics (biomass, DO, pH, fluorescence).

That is the zone where a screening capacity & predictability is better

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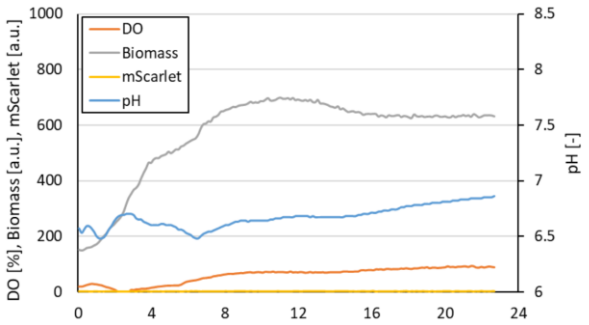
CASE STUDY · 1 OF 2

Vibrio natriegens: exploring the design space at microscale



BioLector XT microbioreactor
With online monitoring suite:

- Biomass
- DO
- pH
- mScarlet fluorescence

Parameters screened in parallel

Glycerol	**20 · 30 · 50 g/L**
Inoculation density	**OD_{600} 0.1 – 0.5**
Induction timing	**early ↔ late**
Feeding strategy	**constant · linear · exponential**
Feed medium	**1× VN / 4× VN**

→ Large design space, minimal reagent & waste
Cost-effective hypothesis testing before achieving any liter scale experiment

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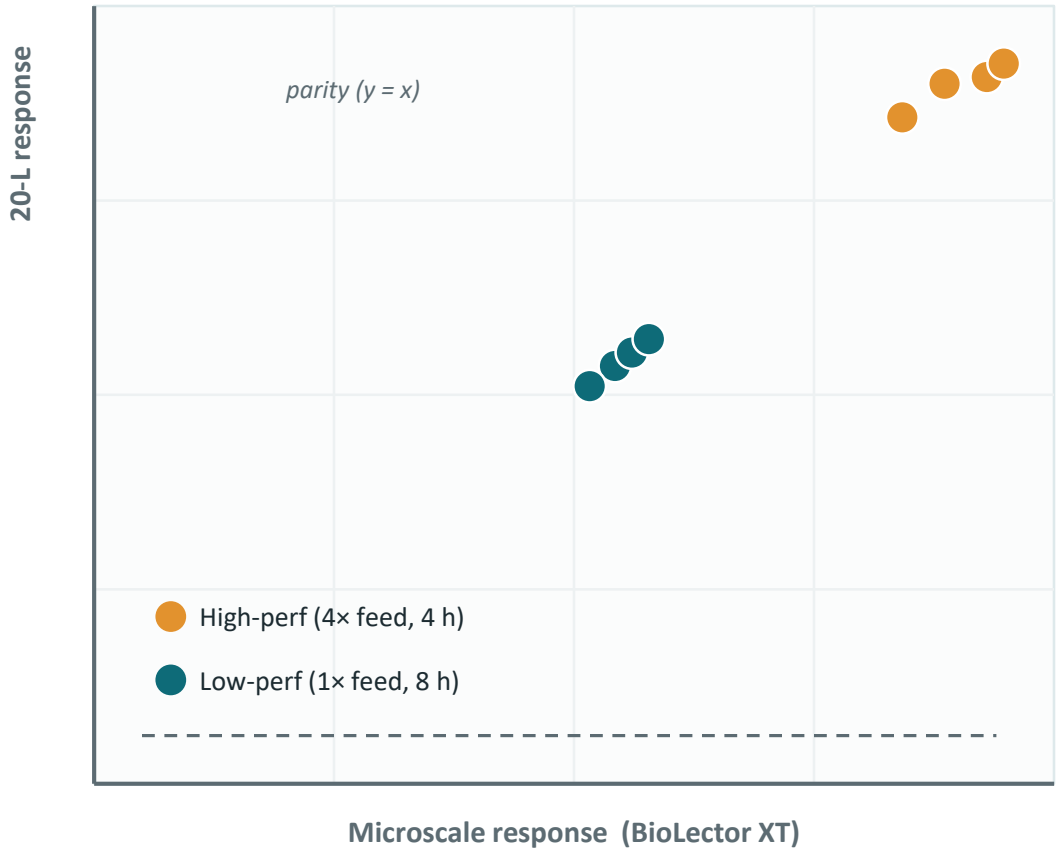
Microscale predicts the 20-L bioreactor behaviour



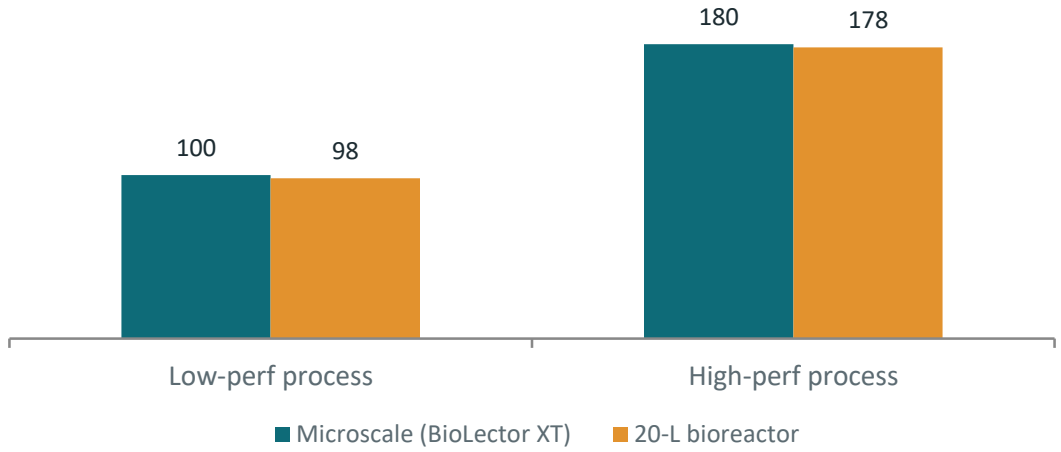
illustrative — representative of TWB transfer data

1.8×

higher biomass for the high-performance process

— and the ratio is preserved at both scales.

Biomass (a.u.) — micro ≈ 20 L



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Where microscale breaks — and how we close the gap

Where it breaks

Near-ideal mixing. The microwell is homogeneous; the production tank is not.

No lifelines. Cells never see the substrate / DO gradients of a large reactor.

Transport ≠ reproduced. Hydrodynamics and circulation times don't scale down by themselves.

How we bridge it

1 **Rational scale-down**

CFD / regime analysis reconstructs at-scale gradients in the small device — re-introducing the lifelines microscale misses.

2 **Computation upstream**

DoE, data-driven design & ML shrink the experimental search space, so each microscale run is spent where it matters.

Computation is the enabler — not the hero.

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TWB Team

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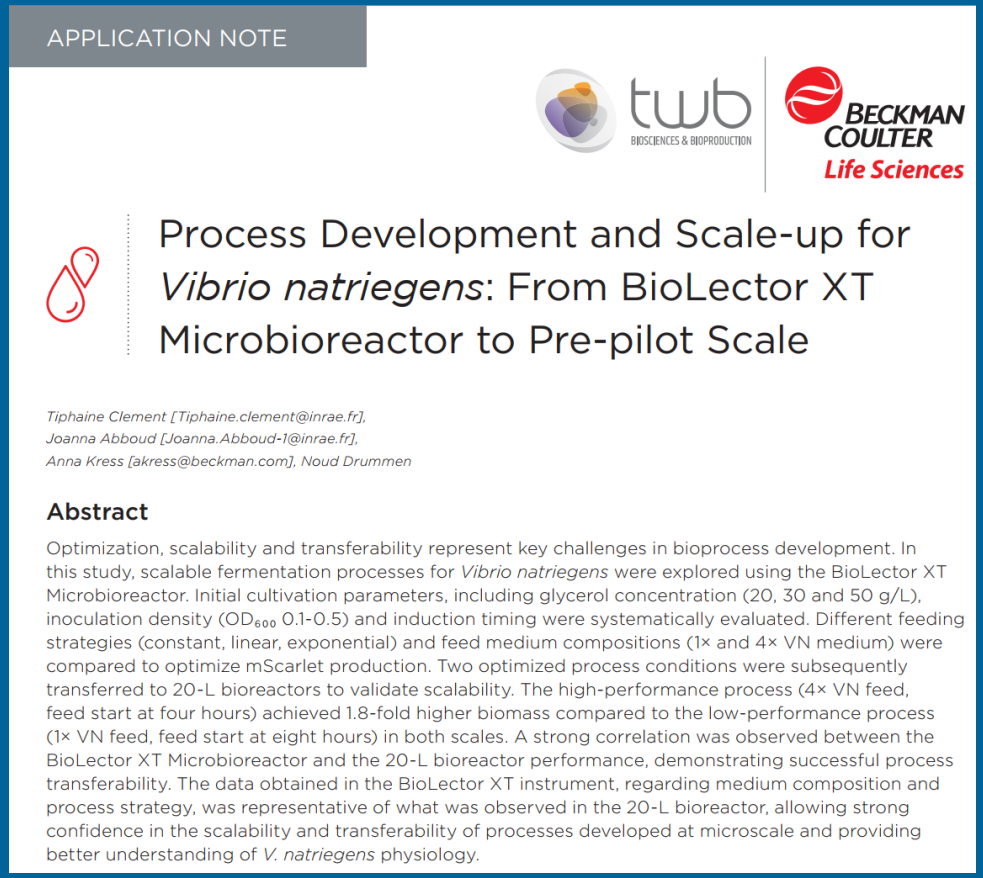

APPLICATION NOTE

twb BIOSCIENCES & BIOPRODUCTION | BECKMAN COULTER Life Sciences

Process Development and Scale-up for *Vibrio natriegens*: From BioLector XT Microbioreactor to Pre-pilot Scale

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Joanna Abboud [Joanna.Abboud-1@inrae.fr],
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Abstract

Optimization, scalability and transferability represent key challenges in bioprocess development. In this study, scalable fermentation processes for *Vibrio natriegens* were explored using the BioLector XT Microbioreactor. Initial cultivation parameters, including glycerol concentration (20, 30 and 50 g/L), inoculation density (OD_{600} 0.1-0.5) and induction timing were systematically evaluated. Different feeding strategies (constant, linear, exponential) and feed medium compositions (1× and 4× VN medium) were compared to optimize mScarlet production. Two optimized process conditions were subsequently transferred to 20-L bioreactors to validate scalability. The high-performance process (4× VN feed, feed start at four hours) achieved 1.8-fold higher biomass compared to the low-performance process (1× VN feed, feed start at eight hours) in both scales. A strong correlation was observed between the BioLector XT Microbioreactor and the 20-L bioreactor performance, demonstrating successful process transferability. The data obtained in the BioLector XT instrument, regarding medium composition and process strategy, was representative of what was observed in the 20-L bioreactor, allowing strong confidence in the scalability and transferability of processes developed at microscale and providing better understanding of *V. natriegens* physiology.

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