SARTORIUS

Simplifying Progress

Transformation of upstream bioprocessing in the digital era

World Bioprocessing Pharma 4.0 Summit– October 2021

Sartorius in brief

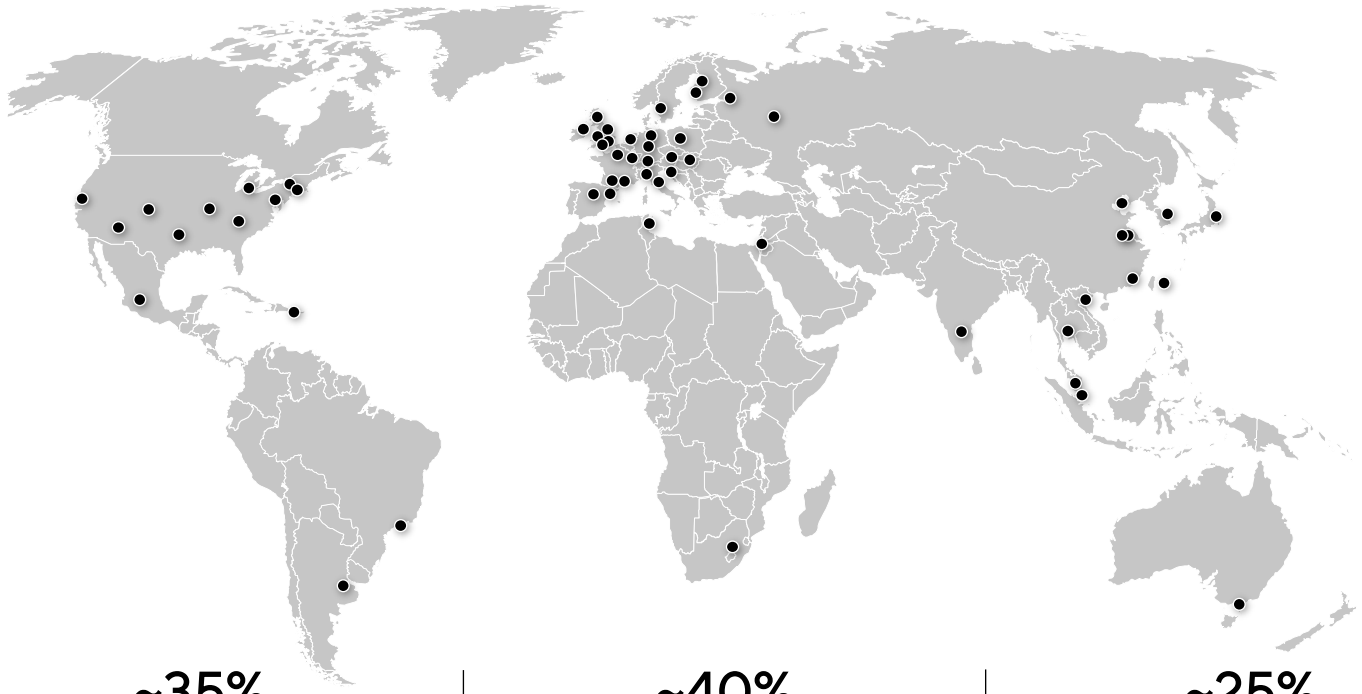
60+
Locations worldwide,
headquartered in Göttingen, Germany

10,600+
Employees[1]

~€2.3bn
Sales revenue[1]

29.6%
EBITDA margin[1,2]

~€23.6bn
Sartorius AG market capitalization;
included in relevant indices in Germany



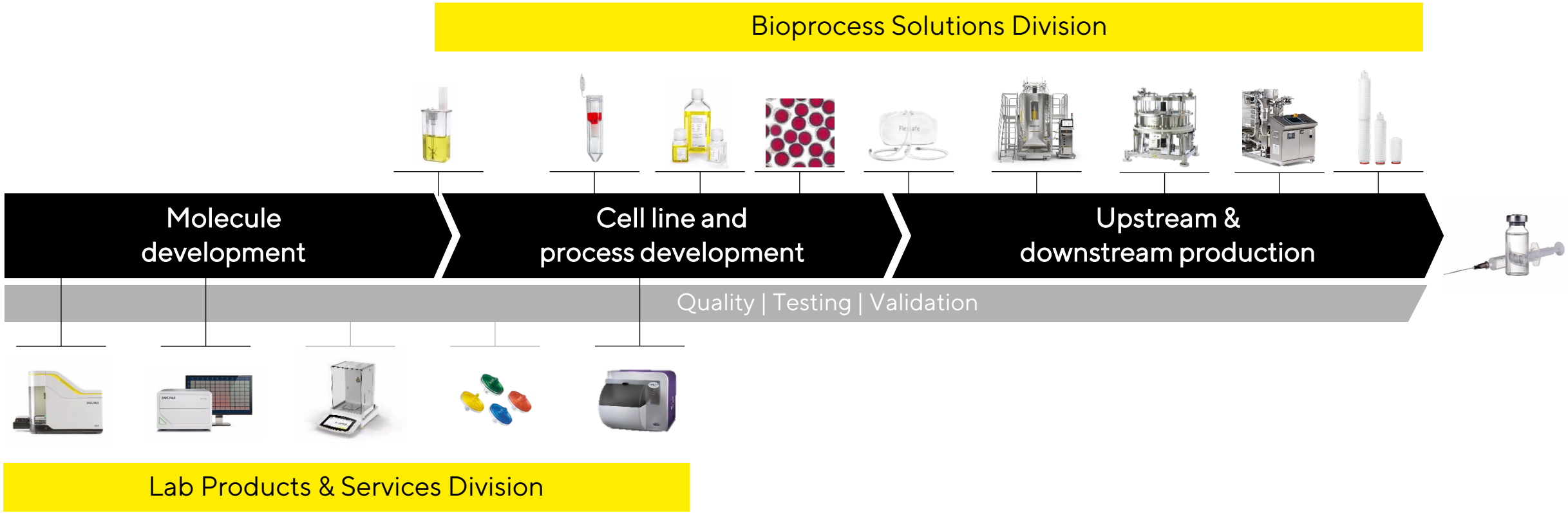
~35%
Sales revenue
Americas

~40%
Sales revenue
EMEA

~25%
Sales revenue
Asia | Pacific

1 As of December 31, 2020, 2 Underlying EBITDA

Strategic focus on the biopharma market



Sartorius Corporate Research

- New ideas to concepts & novel applications aligned with Sartorius strategy (mission/vision)
- Securing of early stage IP positions
- Identify, nurture & enable technology creation with an understanding of end use
- Network with leading academia, consortia, research industry partner and opinion leaders
- Collaborative projects/programmes & funding

Summary

WHAT	WHY	HOW
Current practices in upstream bioprocessing	Shifting paradigms in biopharma R&D strategy	Making value out of data using modeling tools
The Biosimulator a generic upstream hybrid modeling structure	Unifying workflows from product development to manufacturing	Future perspectives and reflections on in-silico bioprocessing

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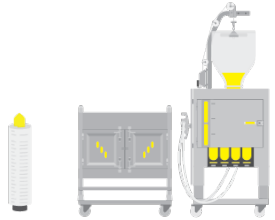
Manufacturing of biopharmaceuticals

Large molecules (> 20k atoms) produced by living cells culture

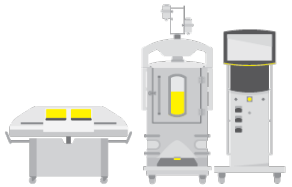
Molecule development → **Cell line and process development** → **Upstream & downstream production**

Upstream
Production of the desired drug

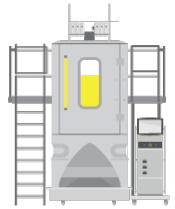


Culture media preparation

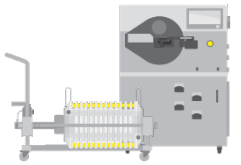
Seed cultivation



Scale-up

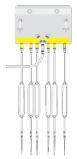


Production



Clarification & centrifugation

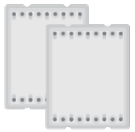
Downstream
Isolation and filling of the desired drug



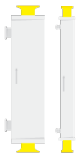
Final filling

Cryo-preservation

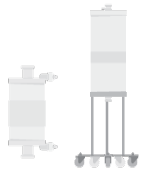
Sterile filtration



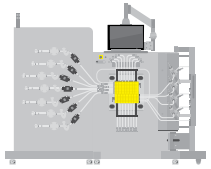
Concen-tration



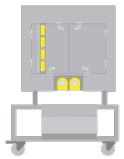
Virus removal filtration



Polishing



Chromato-graphy



Viral clearance

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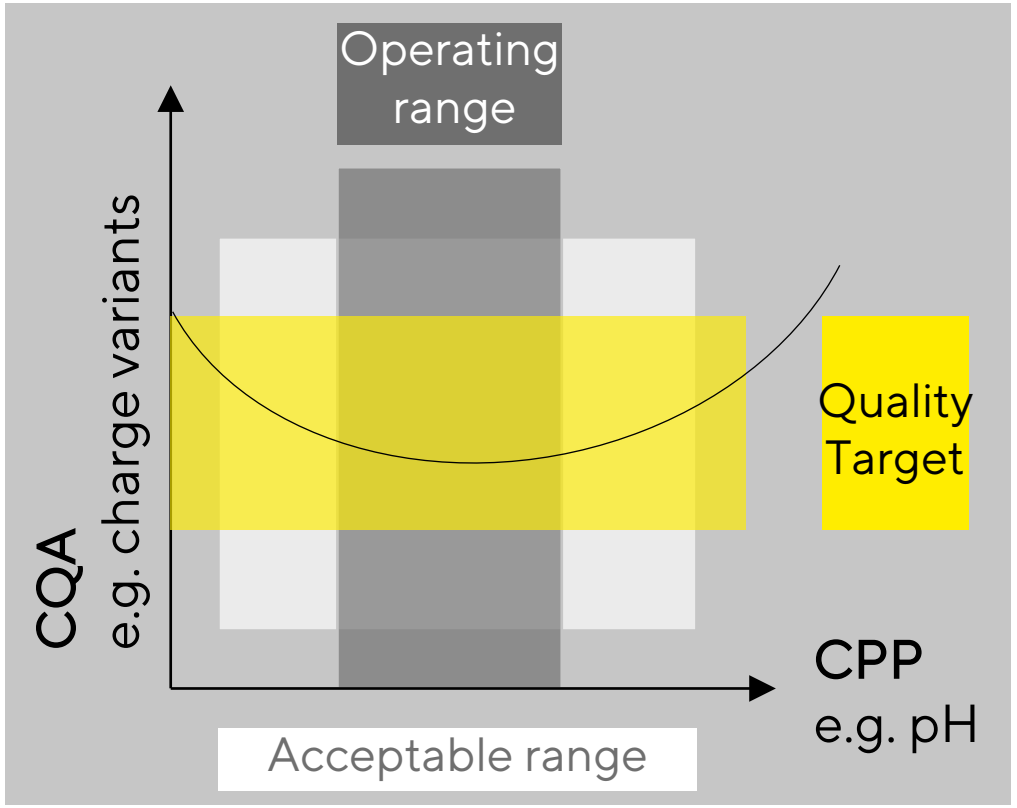
Bioprocess Performance Evaluation

CPPs are determined to ensure consistent and reproducible CQAs acquisition

Product

Critical **Q**uality **A**ttributes

physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired **product quality***



Critical **P**rocess **P**arameters

process variables impacting CQAs that must be monitored to ensure the quality standard of the product

Process

While multiple researches have highlighted the potential benefit to shift the focus **from CPPs to CQAs**, process performance is still mainly evaluated in **process space** using Risk Analysis, DOE and MVDA

*definition from ICH Q8(R2) annex

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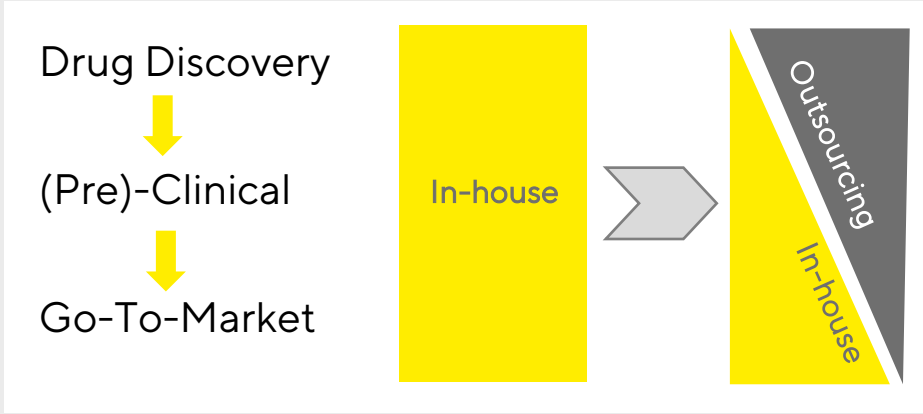
Challenging the biopharma R&D strategy

R&D cost are growing faster over an average investment period than actual revenues over the same period

This **NOT** due to a lack of Innovation or Market

Law of diminishing returns ? Kelvin Stott

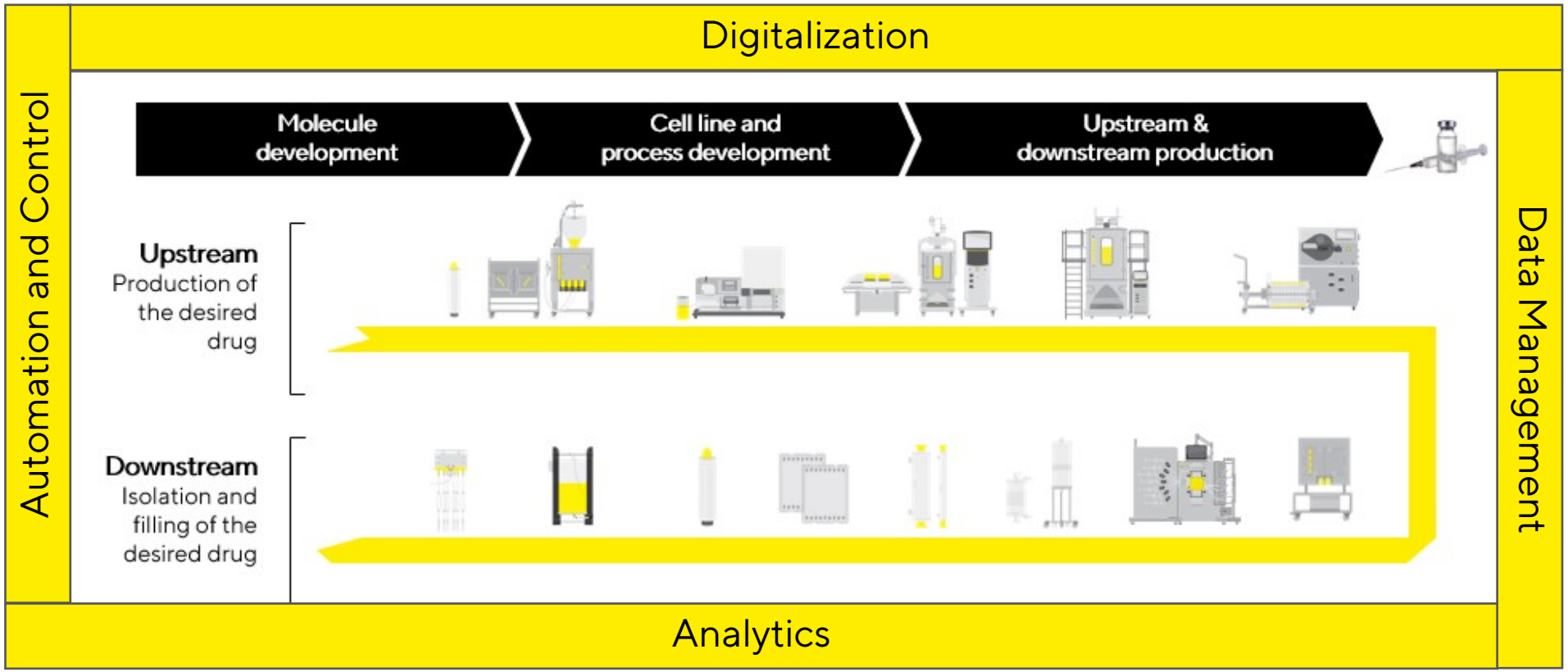
Inherent unpredictability of drug discovery and outdated business model? Standish Fleming



Outsourcing to external entrepreneurial and research community to lower the cost and increase the agility to face market disruption

Source : articles on R&D model and outsourcing in biopharma by **Andrii Buvailo** in BiopharmaTrend

Acceleration of Operational Tasks



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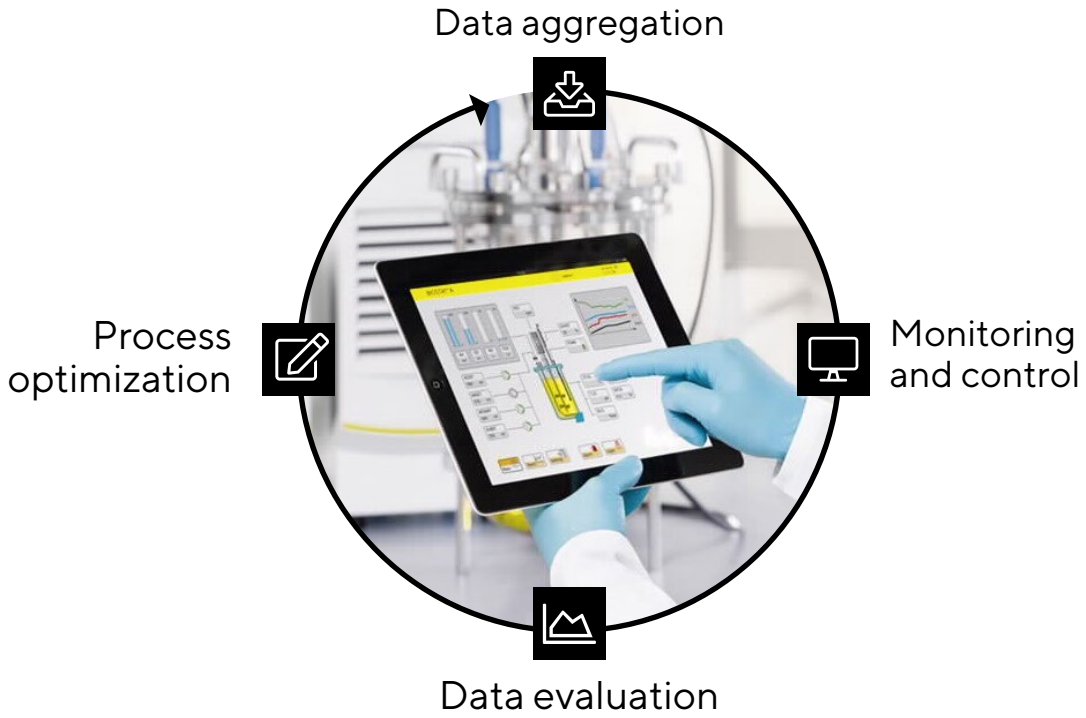
Process DOT* in the biopharmaceutical industry

Status
- Largely trial and error development
- Large amounts of complex heterogeneous data
- Long, costly development times

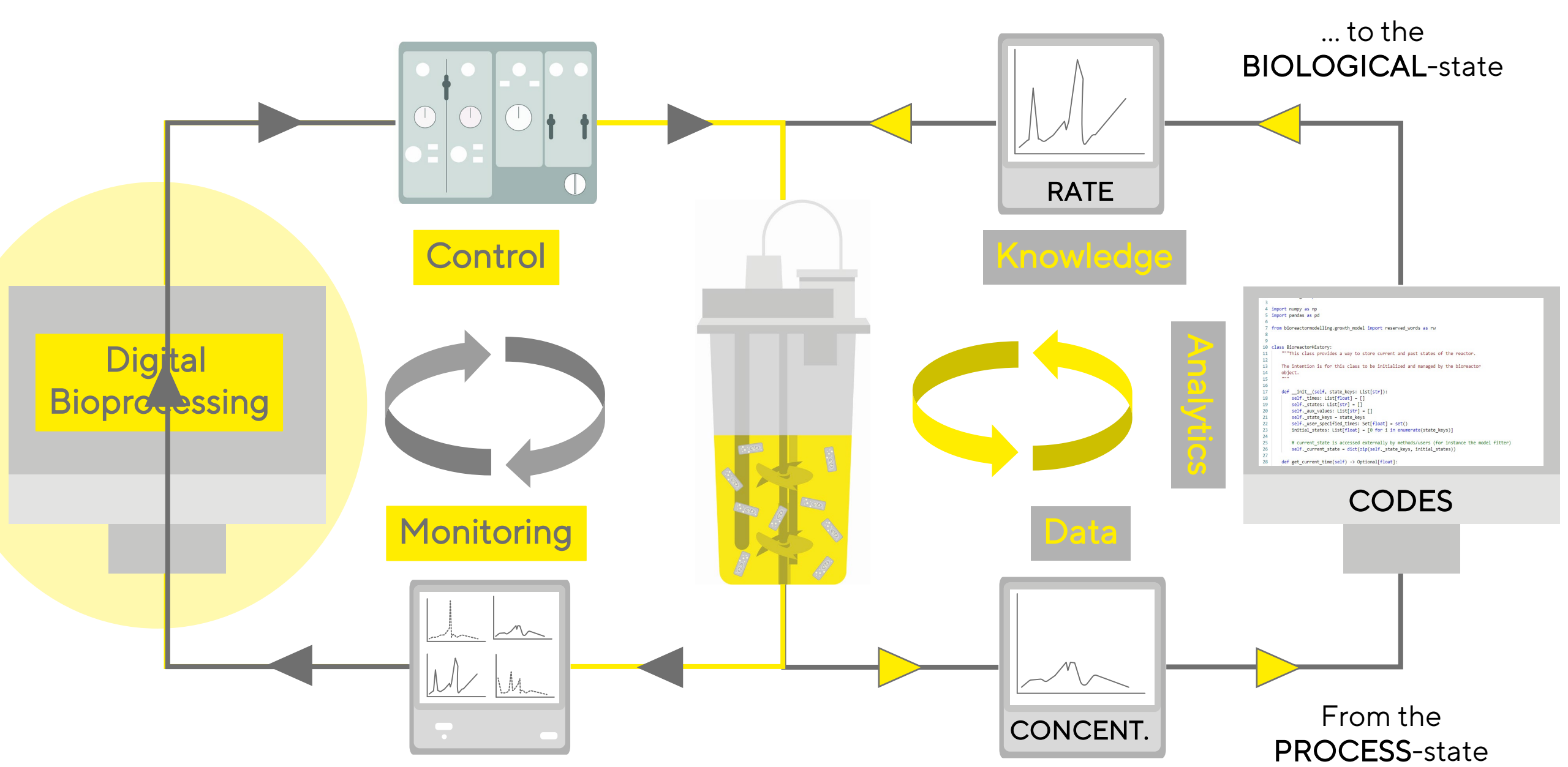
Challenges
- Complex biology not fully understood
- Non-stationary, non-linear and stochastic behaviors
- Standard workflows do not yet exist

Opportunities
- In-silico modeling and simulation
- Real-time analytics and process optimization



- ✓ Rapid prototyping and process development
- ✓ Improved process performance and product quality
- ✓ De-risked transfer to manufacturing

*DOT = Design, Optimization and Transfer


... to the
BIOLOGICAL-state
RATE
Control
Knowledge
Digital
Bioprocessing
Analytics
CODES
Monitoring
Data
CONCENT.
From the
PROCESS-state

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The Biosimulator

Substrate

Model calibrated from measured data

Transferrable to new cell lines

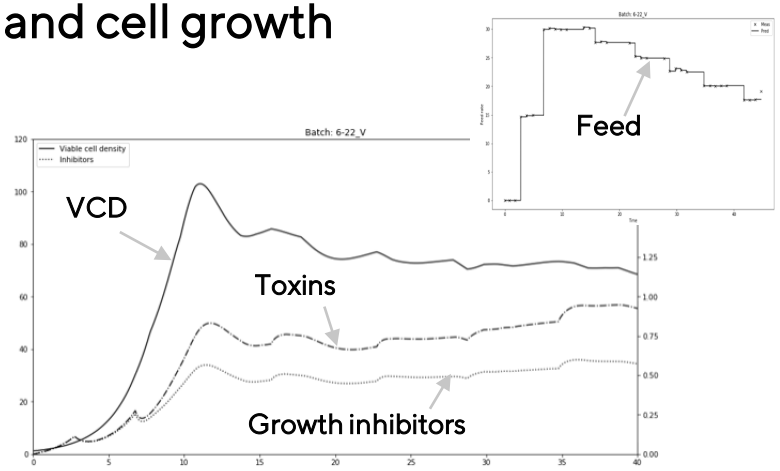
Hybrid State Space

Mechanistic Process

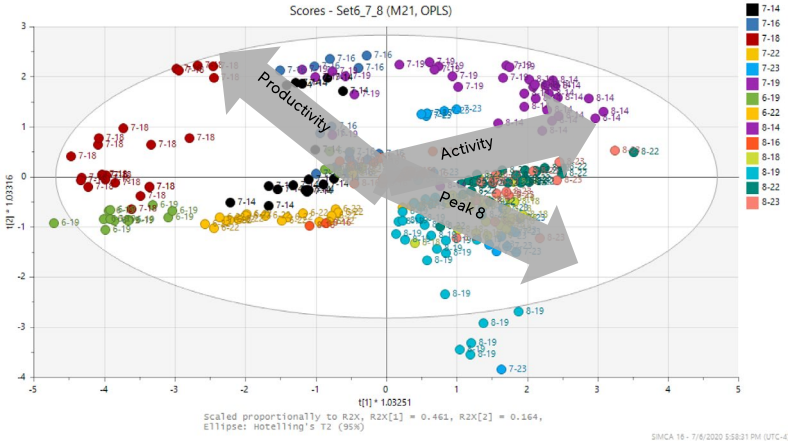
Data-driven Metabolic

Product

Link between process operation and cell growth



What are the cells doing?



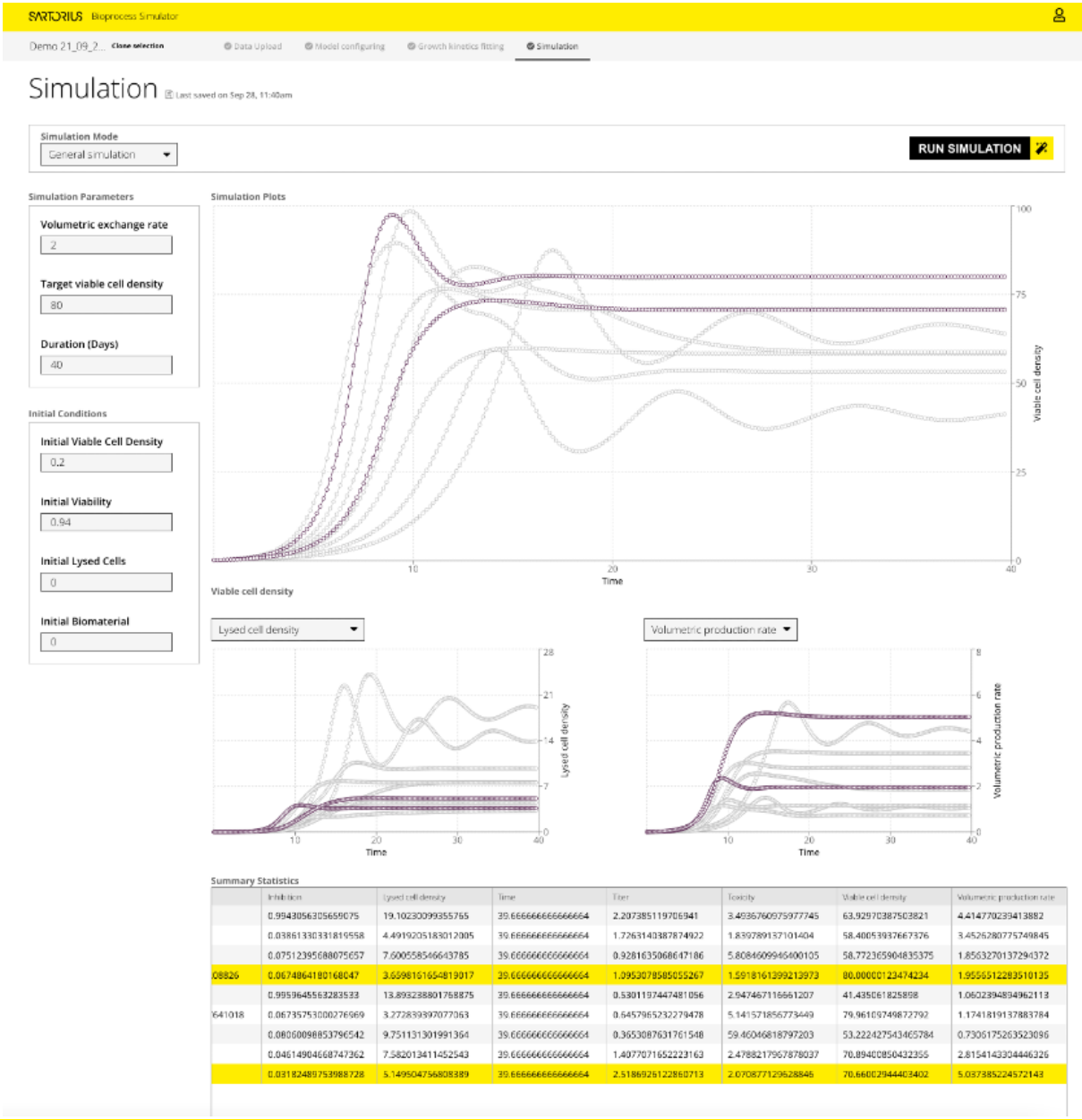
Commercial Product for Process Development

- Two workflows

  - ❑ **Clone selection for intensified and perfusion**
    - Forecast multiple cell line's performance in media exchange

  - ❑ **Digital twin for *in-silico* experimentation**
    - What-if analysis: test impact of process adjustments on growth and product yield
    - Operating mode: transfer between fed-batch, intensified and perfusion
    - Media optimization
    - Critical Quality Attribute predictions

- Web/cloud based application (PC/tablet/iPad)
  - Integration in Umetrics Studio (2022)



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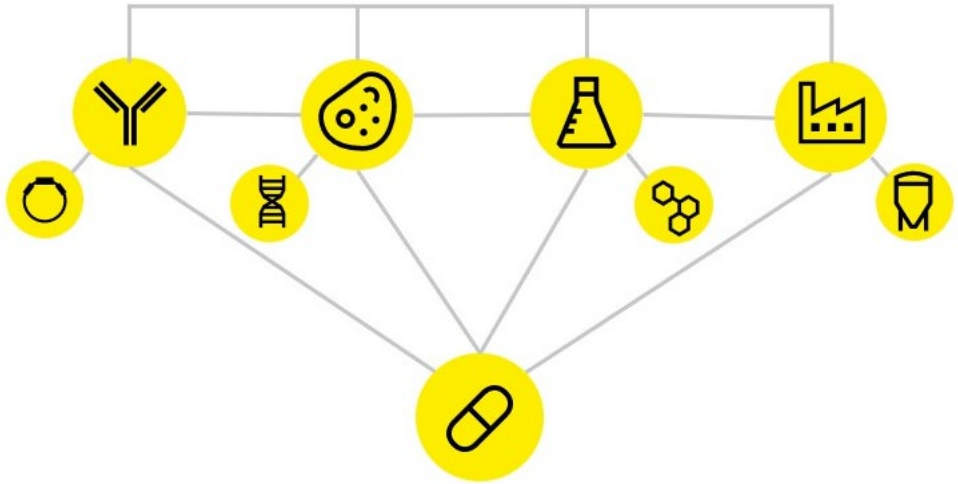
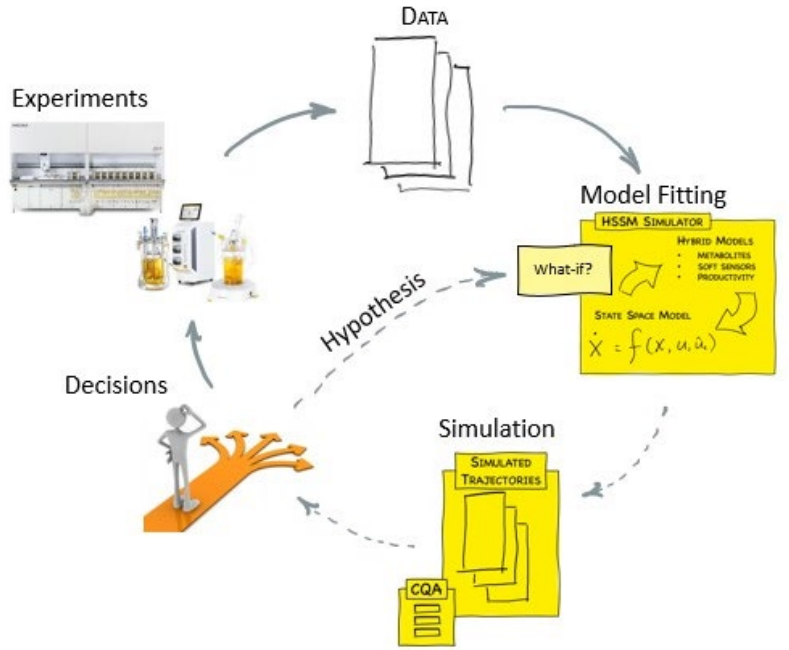
In-silico Experimentation Workflow

Systems thinking





Process Development

- Enhanced clone selection
- Digital Twin: *Insilico* experimentation
- Optimization (fed-batch or intensified/continuous)

Manufacturing / Advanced control

- Intensified/continuous control
- Soft sensors
- Supervisory control (up/down-stream)

Engineering Studies

- Sizing and configuration of unit operations
- Plant costing
- End-to-end economic optimization

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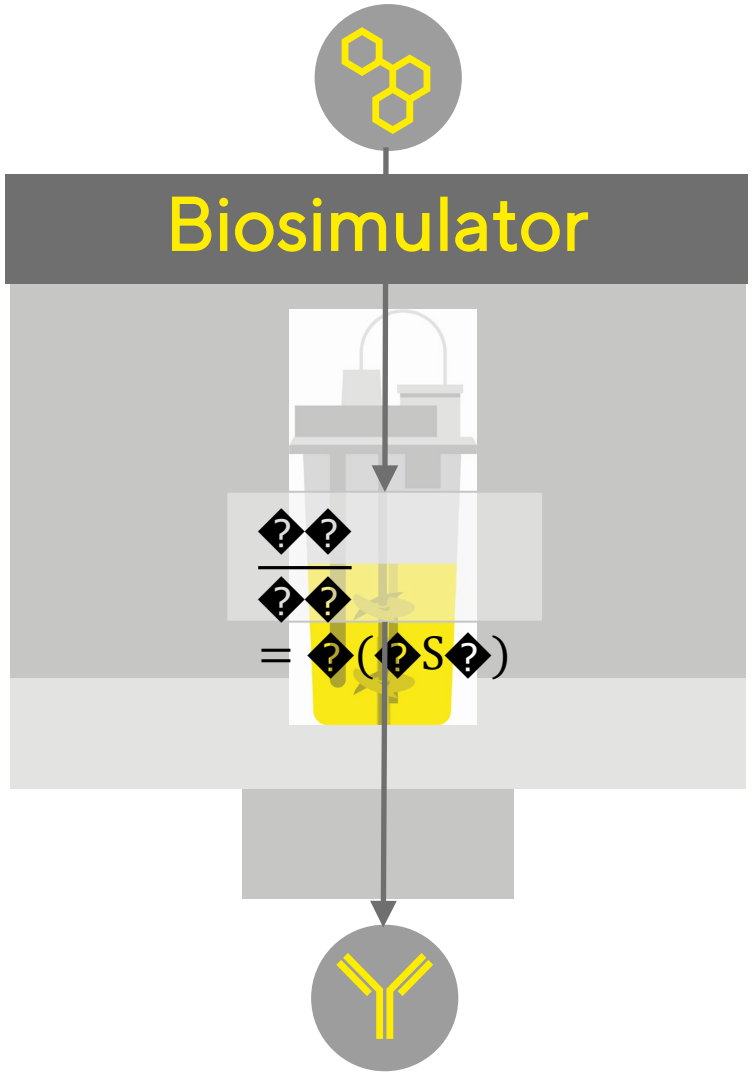
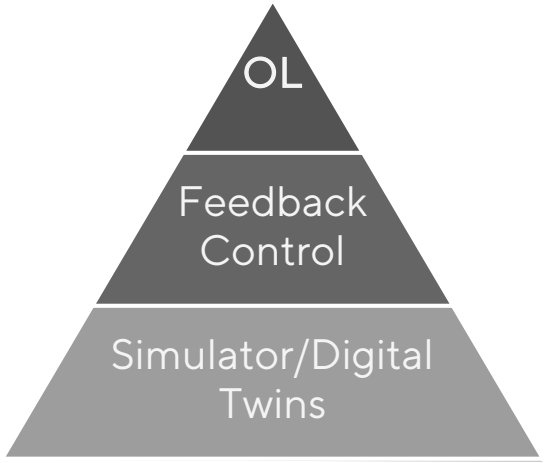
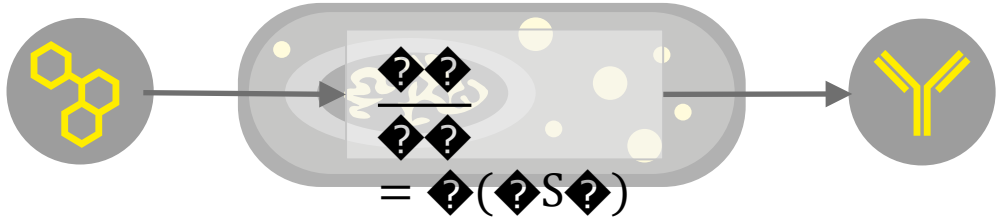
Research Roadmap





Biological Systems modeling

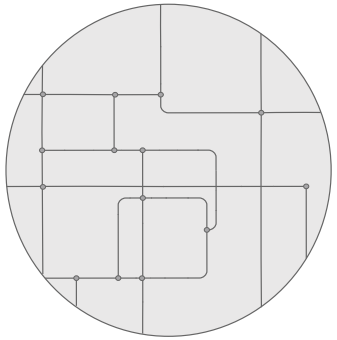


Process development

Analyze of process parameters influence

Macro

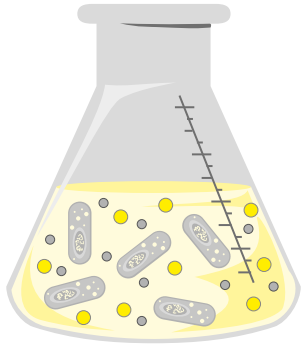
Optimization and control



Process engineering

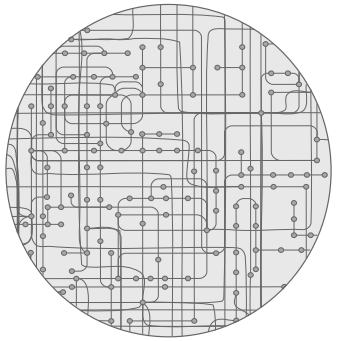
Media design

Identification of potential growth booster



Micro

Description and understanding



Systems Biology

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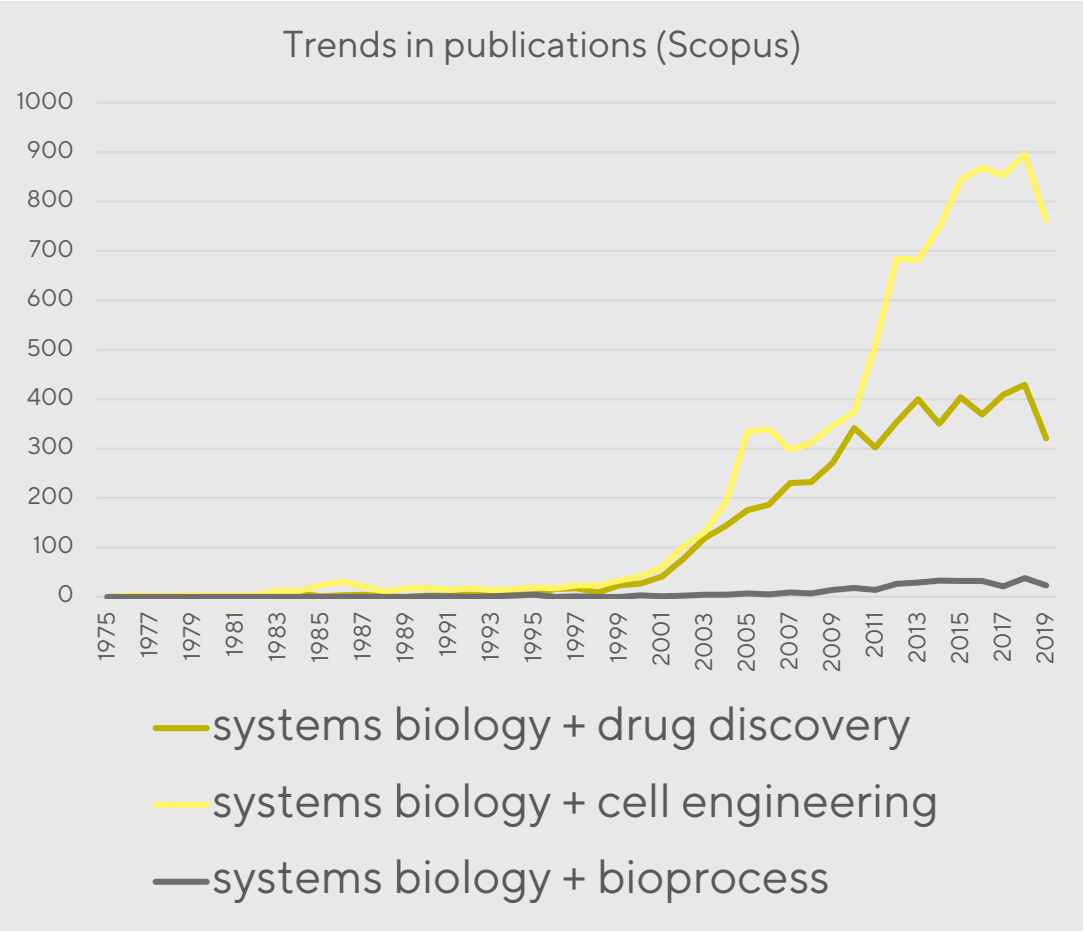
Systems Biology for Process DOT*

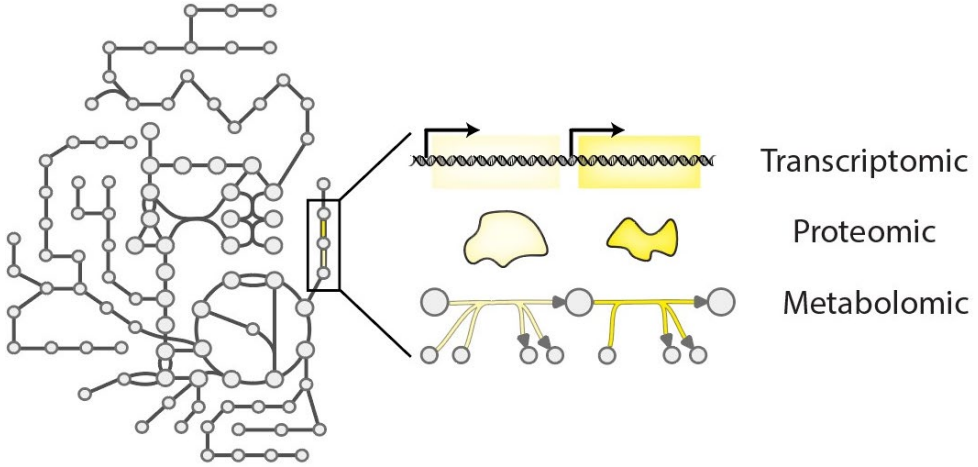
Note : Multiple reasons have been highlighted as main factors currently limiting the adoption of systems biology tools**



Metabolic Networks

enable the coherent organization of large datasets into biological networks

➔ provide non-intuitive insights on biological systems that *in vivo* experiments alone cannot provide

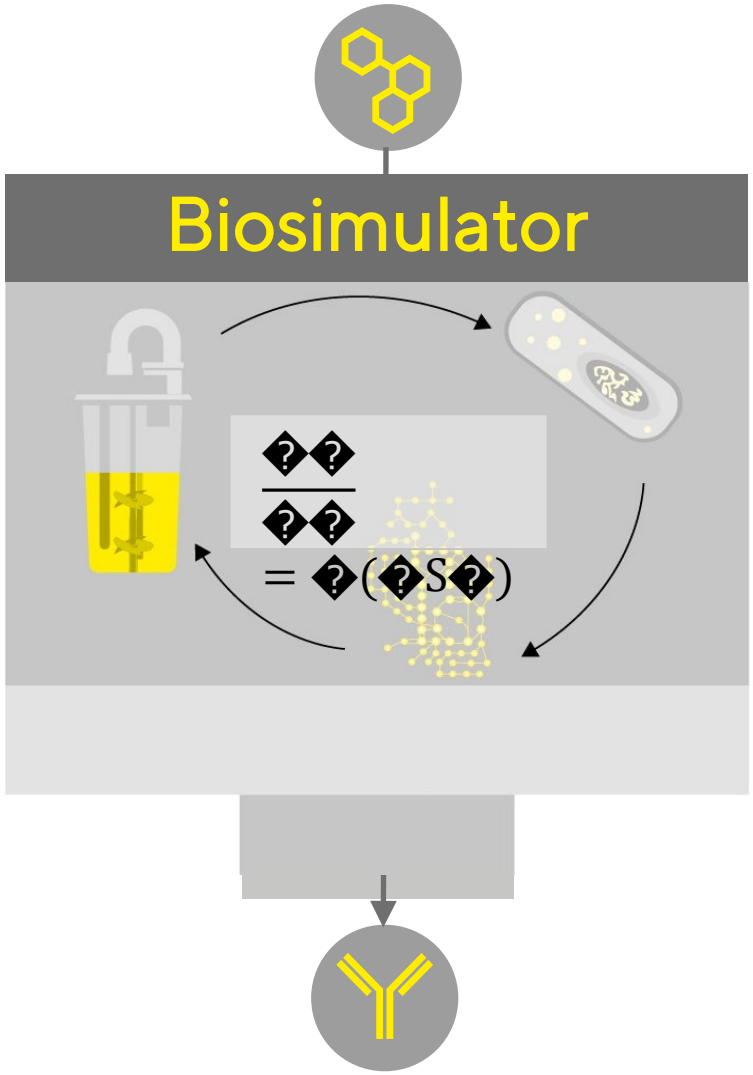


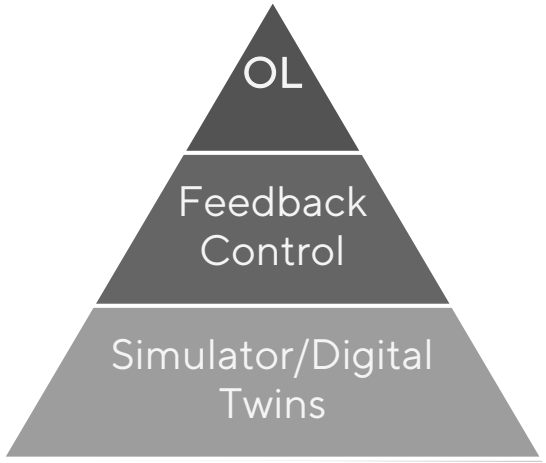
➔ **link between genotype and phenotype**

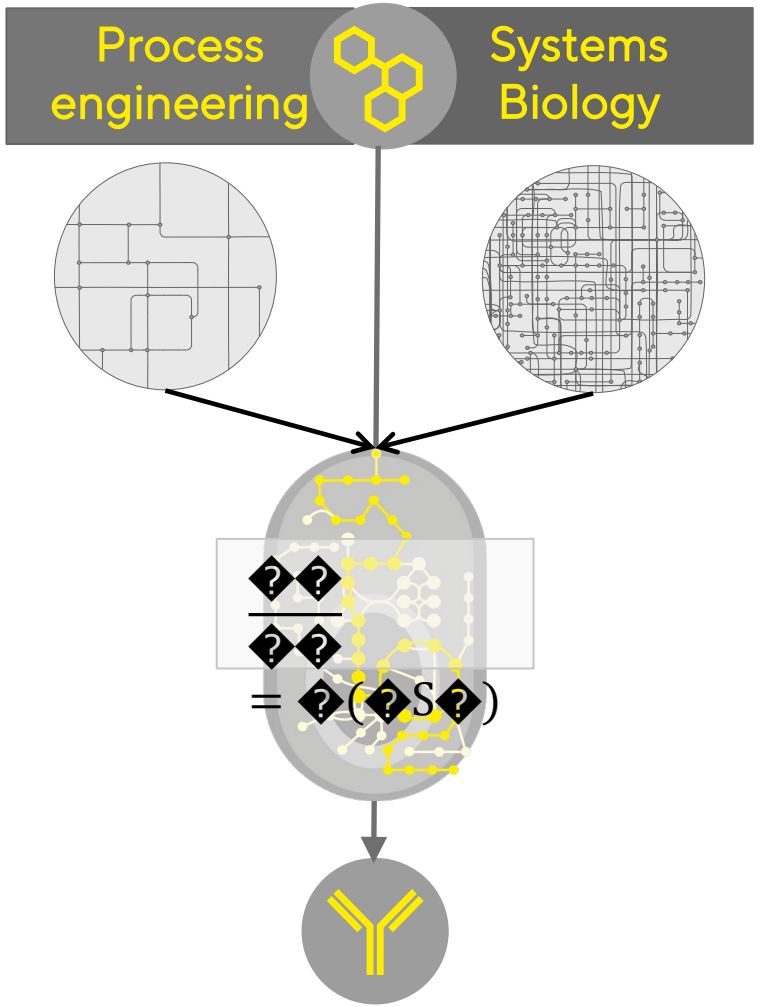
*DOT = Design, Optimization and Transfer

** Richelle *et al. npj Syst Biol Appl* 6, 6 (2020).
Towards a widespread adoption of metabolic modeling tools in biopharmaceutical industry: a process systems biology engineering perspective.

Research Roadmap







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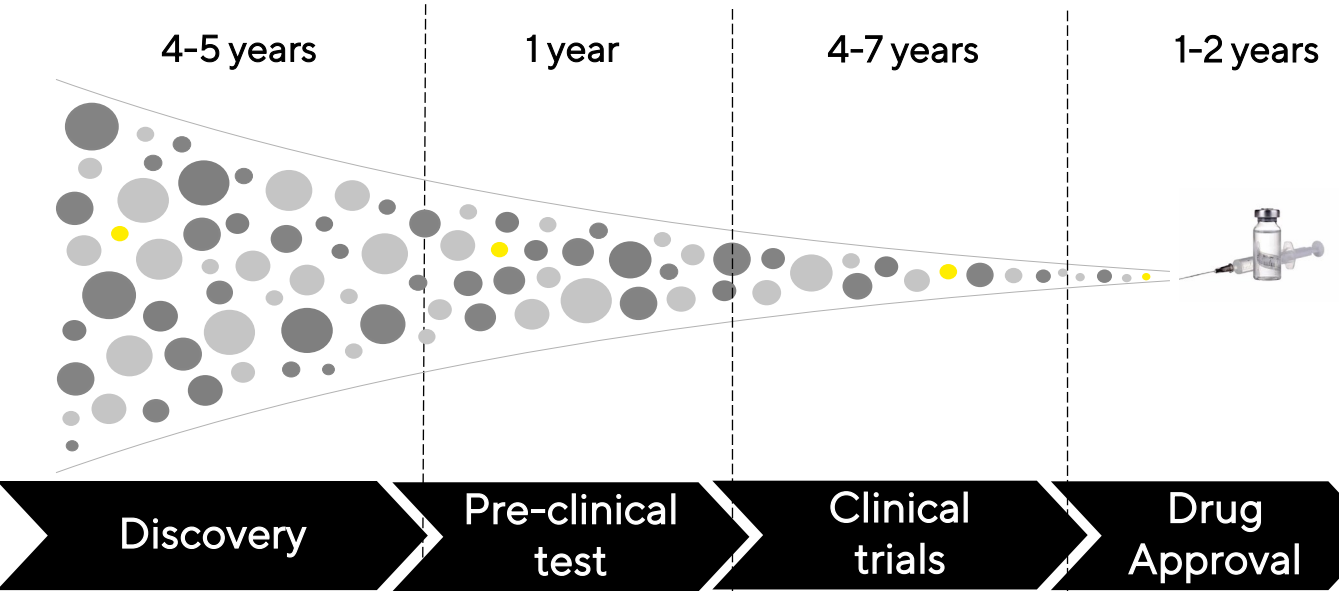
Future outlook on drug development

Only one out of 10,000 new drug candidates reaches the market



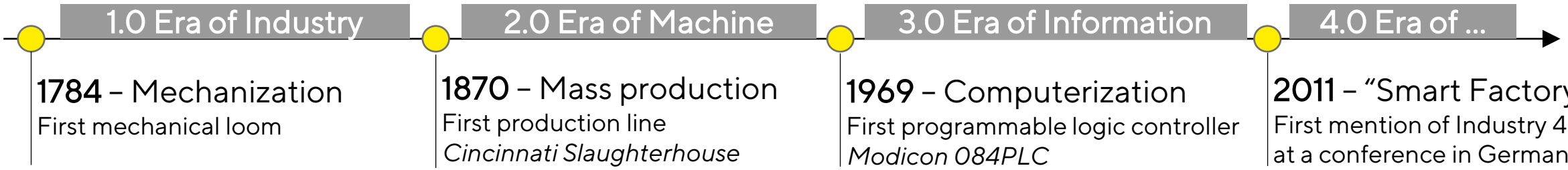
>10 years
From discovery until approval

>€2bn
Average costs of developing a successful drug

~10%
Probability of clinical success (Phase I to approval)

Schematic example of biologic drug discovery with data from the Association of the British Pharmaceutical Industry

Food for thoughts – Bioprocessing 4.0



"The [AI] field's heavy use of statistical techniques to pick regularities in masses of data is unlikely to yield the explanatory insight that science ought to offer". Noam Chomsky, 2012

NUMERIC	VS	FEATURE
DIGITAL		COGNITIVE

➔ **Shifting existing paradigm for defining regulated biomanufacturing processes from data- to knowledge-based approaches**

* Interview of Noam Chomsky by Yarden Katz in The Atlantic – *"Noam Chomsky on where AI went wrong"*

Thank you.

Acknowledgments

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