ERA CoBioTech (ERA-Net Cofund on Biotechnologies)

ACHEMA2018

Kick-off session: "Biotechnology for a sustainable bioeconomy"

Title: ComRaDes
Project name: COMputation for RAtional DESign: From lab to industry with success

Name: Henk Noorman

Com
Ra
Des

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant 722361

Frankfurt am Main, 13.06.2018

Project partners

- Partners:
  - DSM Sinochem Pharmaceuticals, NL
  - Technical University Delft, NL
  - University Liege, B
  - Syngulon, B
  - University Stuttgart, D
- Total project budget: 2 M€
- Project start: July 25, 2018

Topic area and scientific approaches

- Sustainable production and conversion of different types of feedstocks and bioresources into added value products
- Scientific approaches:
  - Synthetic biology
  - Systems biology
  - Bioinformatic tools
  - Biotechnological approach(es)

Introduction

- Project objectives (problem to be solved):
  - Moving to bio-based economy
  - Use of microorganisms to convert renewable feedstocks into added-value products

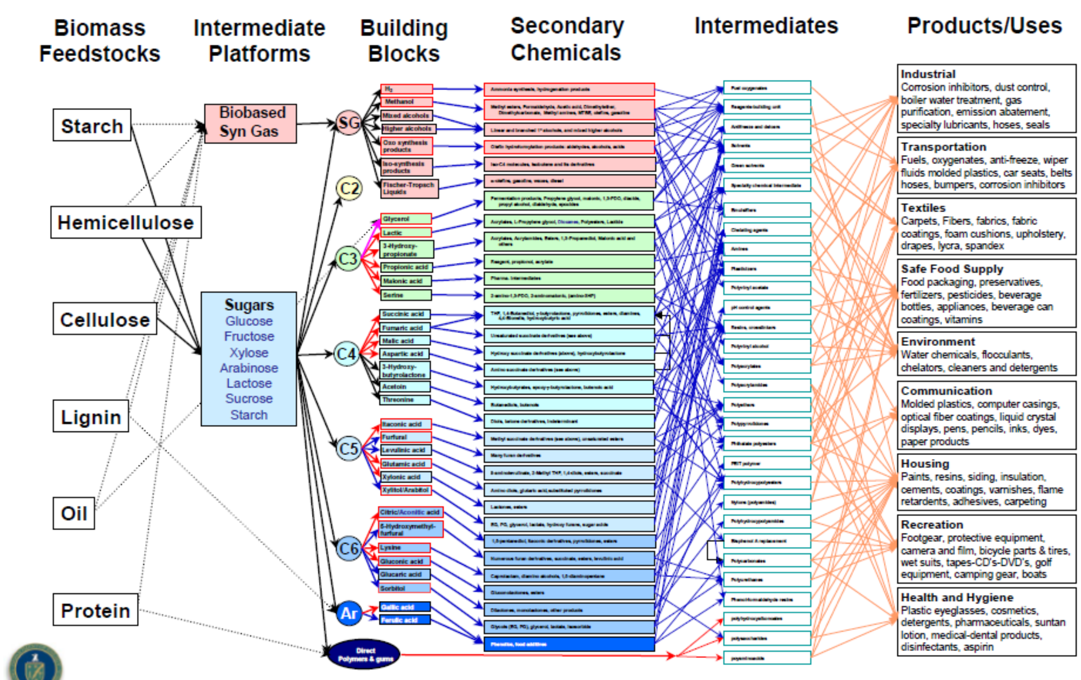


Figure 3 – Analogous Model of a Biobased Product Flow-chart for Biomass Feedstocks

Werpy and Petersen, PNNL/NREL report 2004

ERA CoBioTech

Com
Ra
Des

Introduction

- Project objectives (problem to be solved):
  - Moving to bio-based economy
  - Use of microorganisms to convert renewable feedstocks into added-value products

Titer
Rate
Yield

Productivity (g/l.h)

Lactic acid: 150 (cell recycling)
Ethanol: 82 (ISPR, cell recycling)
Sorbitol: 38
Gluconate: 19 (cell retention, pure O_2)
Succinate: 15 (cell retention, ISPR)
1-butanol: 10 (immobilized cells)
Valine: 6 (metabolic engineering)

Yield (g/g, % of max)

Lactic acid: 1.00 (~100%)
Citric acid: 0.88 (80%)
Acetic acid: 0.80 (80%)
Glutamate: 0.60 (80%)
Ethanol: 0.51 (96%)
Lysine: 0.44 (74%)
1-Butanol: 0.36 (85%)
Methane: 0.27 (~100%)

Titer (g/l)

Gluconate: 504
Sorbitol: 300
Xylitol: 244
Erythritol: 240
Citric acid: 240
Mannitol: 237
Lactate: 231
Valine: 227
Acetic acid: 203
Ethanol: 170
2,3 Butanediol: 152
Succinate : 146
1,3-Propanediol: 141
Gluatamate: 141
Threonine: 118
1,4 Butanediol: 115

Published best key performance Indicators of commercial products

Straathof, Chem. Rev. 114 (2014) 1871-1908

Introduction

- Project objectives (problem to be solved):
  - Moving to bio-based economy
  - Use of microorganisms to convert renewable feedstocks into added-value products
  - Takes long time (5 years), costly (10 M€)

Noorman, Heijnen, *Chem. Eng. Sci.* (2017)

Introduction

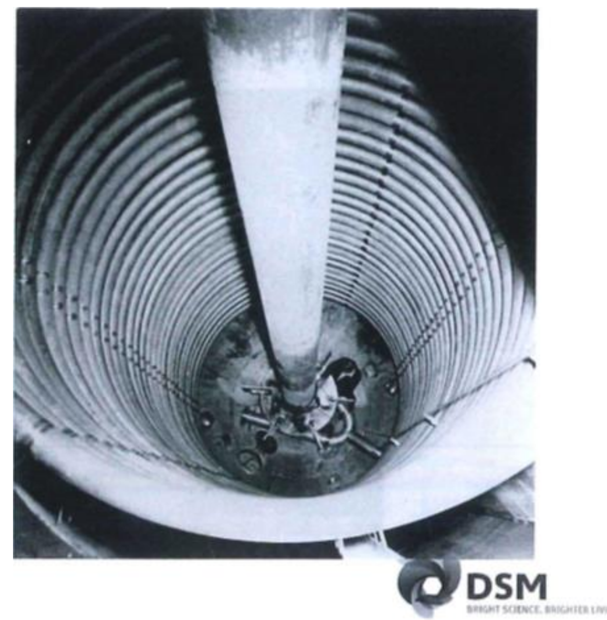
- Project objectives (problem to be solved):
  - Moving to bio-based economy
  - Use of microorganisms to convert renewable feedstocks into added-value products
  - Takes long time (5 years), costly (10 M€)
  - Bottleneck of bringing synthetic biology innovations to the factories

Scale-up

Lab vs. Industry:

Conditions not the same!

Scale-down

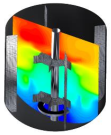


Noorman, Heijnen, *Chem. Eng. Sci.* (2017)

Introduction

- Project objectives (problem to be solved):
  - Moving to bio-based economy
  - Use of microorganisms to convert renewable feedstocks into added-value products
  - Takes long time (5 years), costly (10 M€)
  - Bottleneck of bringing synthetic biology innovations to the factories

Scale-up fail



Lab vs. Industry:

Conditions not the same!

Introduction

- Project objectives (problem to be solved):
  - Moving to bio-based economy
  - Use of microorganisms to convert renewable feedstocks into added-value products
  - Takes long time (5 years), costly (10 M€)
  - Bottleneck of bringing synthetic biology innovations to the factories

Bioprocess Development must become

- Cheaper: 10 M€ → 2 M€
- Faster: 5 y → 1 y
- Better: TRY (titer, rate, yield) closer to the maximal possible
- Less risky: no full-scale problems

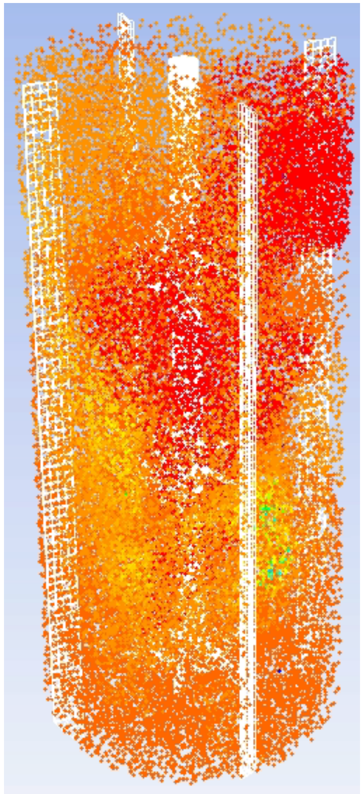
Titer
Rate
Yield

Noorman, Heijnen, *Chem. Eng. Sci.* (2017)

Introduction

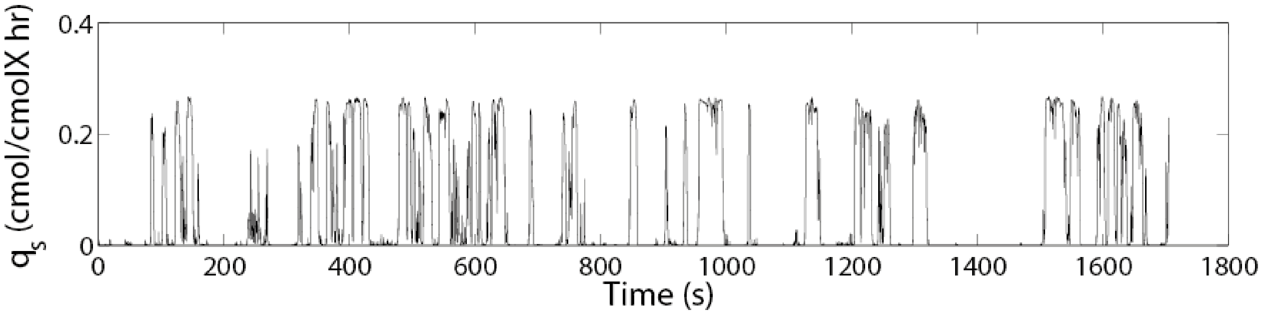
Lagrangian CFD approach

- Scientific approach: High-precision scale-down and improved scale-up performance via computation-driven, rational design



- Track many microbes, register their adventures
  - Developed by Lapin and Reuss (2004, 2006)

Track ~10^3 - 10^5 particles
Record "Lifelines"



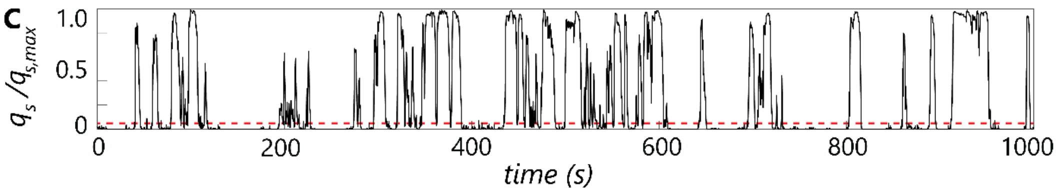
Glucose uptake (q_s) from the organism point of view

Lapin, A., et al., *I&EC Research* (2004) and *Chem. Eng. Sci.* (2006)

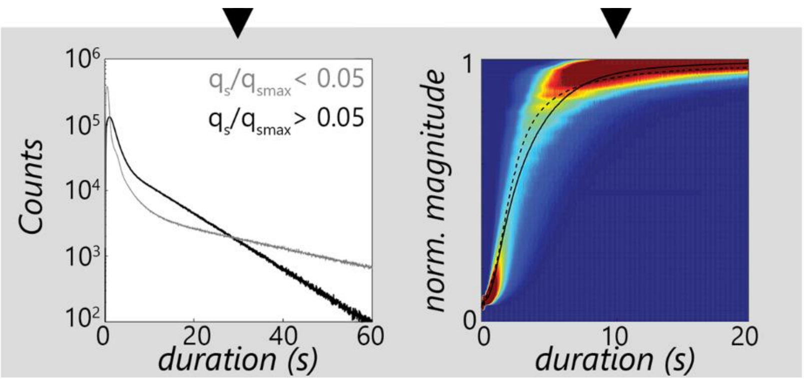
Introduction

Industry to lab: lifeline scale-down

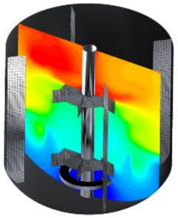
1. Simulate reactor, collect lifelines

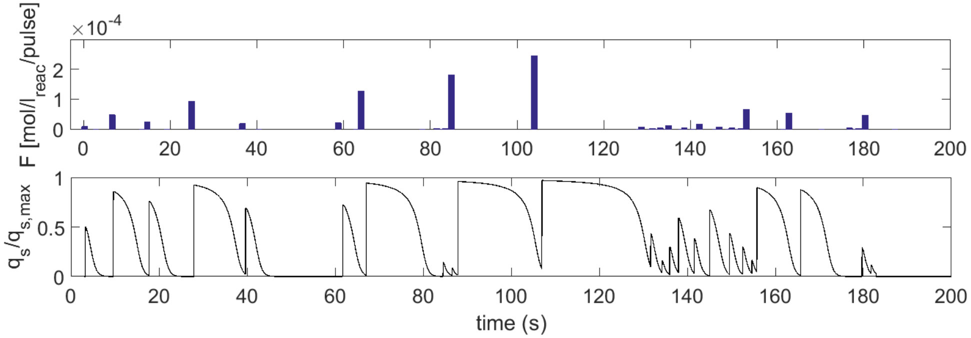


2. Analyze lifelines: Fluctuation statistics



3. Invert statistics: Scale-down design



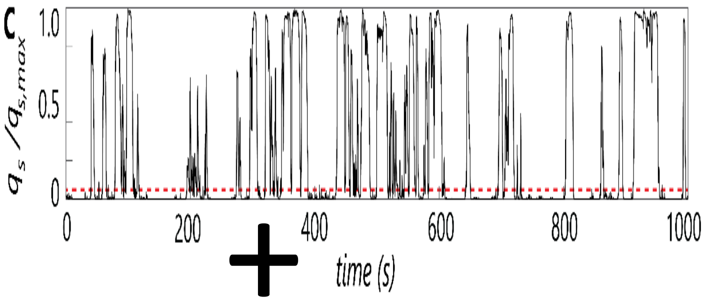


Haringa et al., *Chem eng sci.* 2017
Haringa et al., *Eng. Life Sci.* 2016

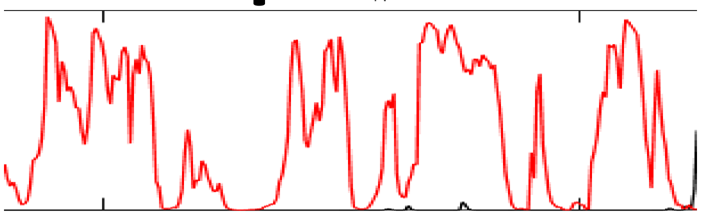
Confidential

Missing link 1

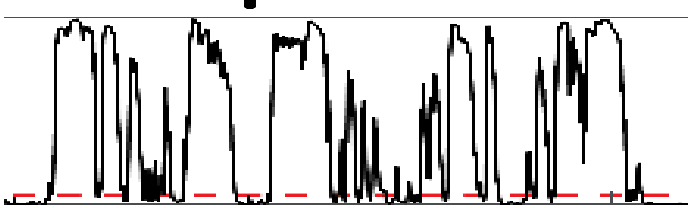
Impact of multiple sources of extracellular (bioreactor) noise



Sugar concentration and uptake rate



Oxygen concentration and uptake rate

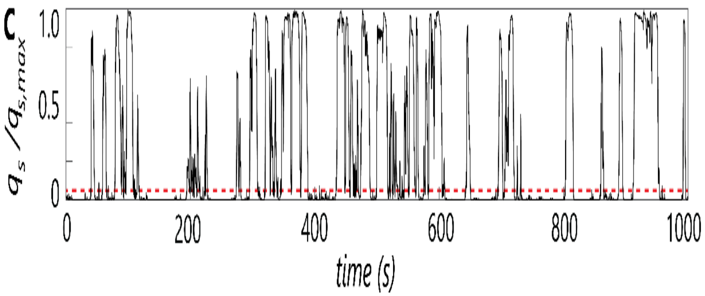


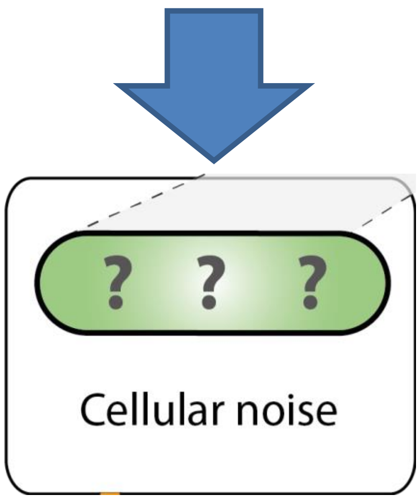
Shear rate gradients

Cumulative effects - intensified impact

Missing link 2

Impact of extracellular (bioreactor) noise on intracellular (biological) noise

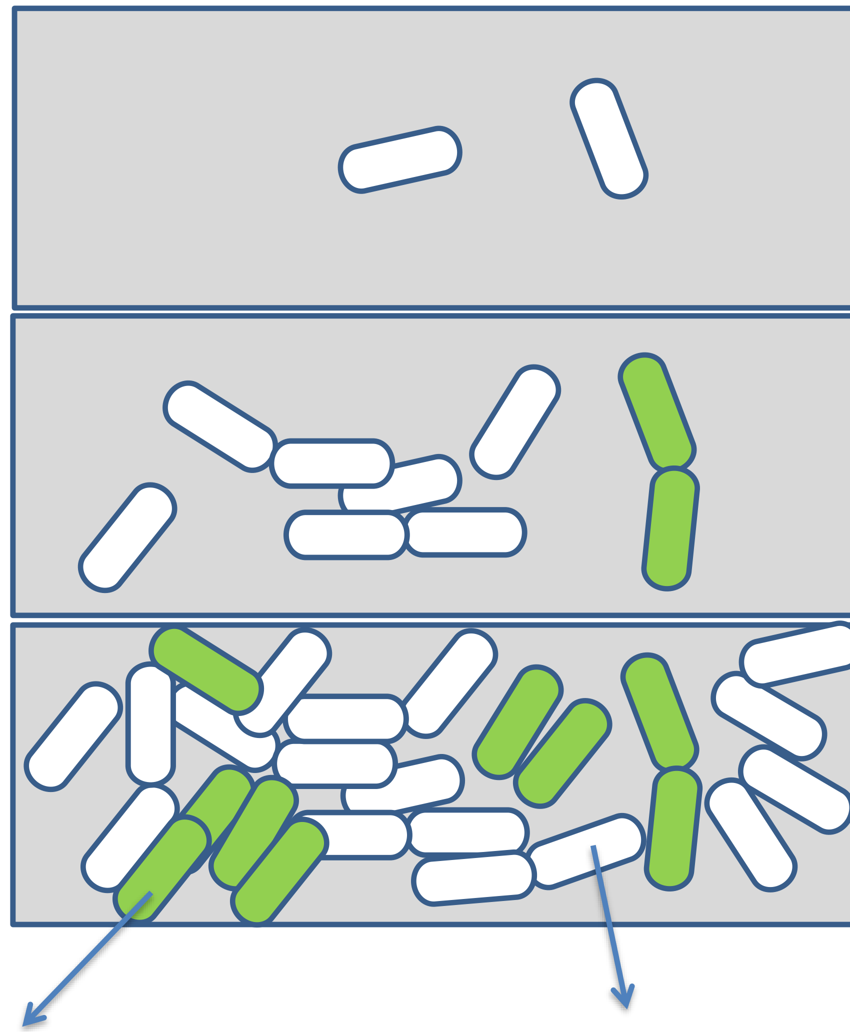




t = 0 min

t = 50 min

t = 100 min



Colony 1 with heterogeneous GFP expression

Colony2 without GFP expression

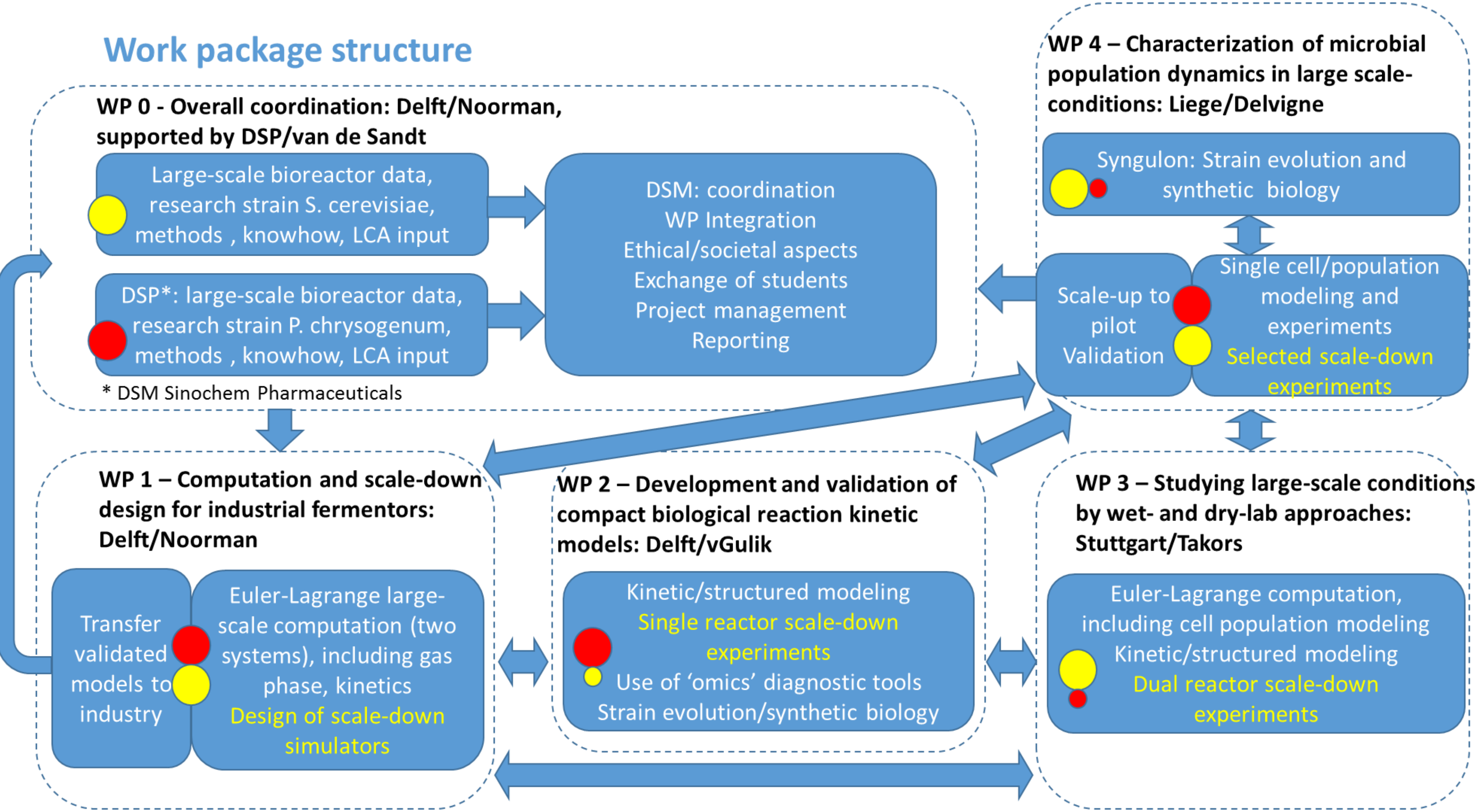
ERA CoBioTech

Confidential

Com Ra Des

Project plan

Work package structure

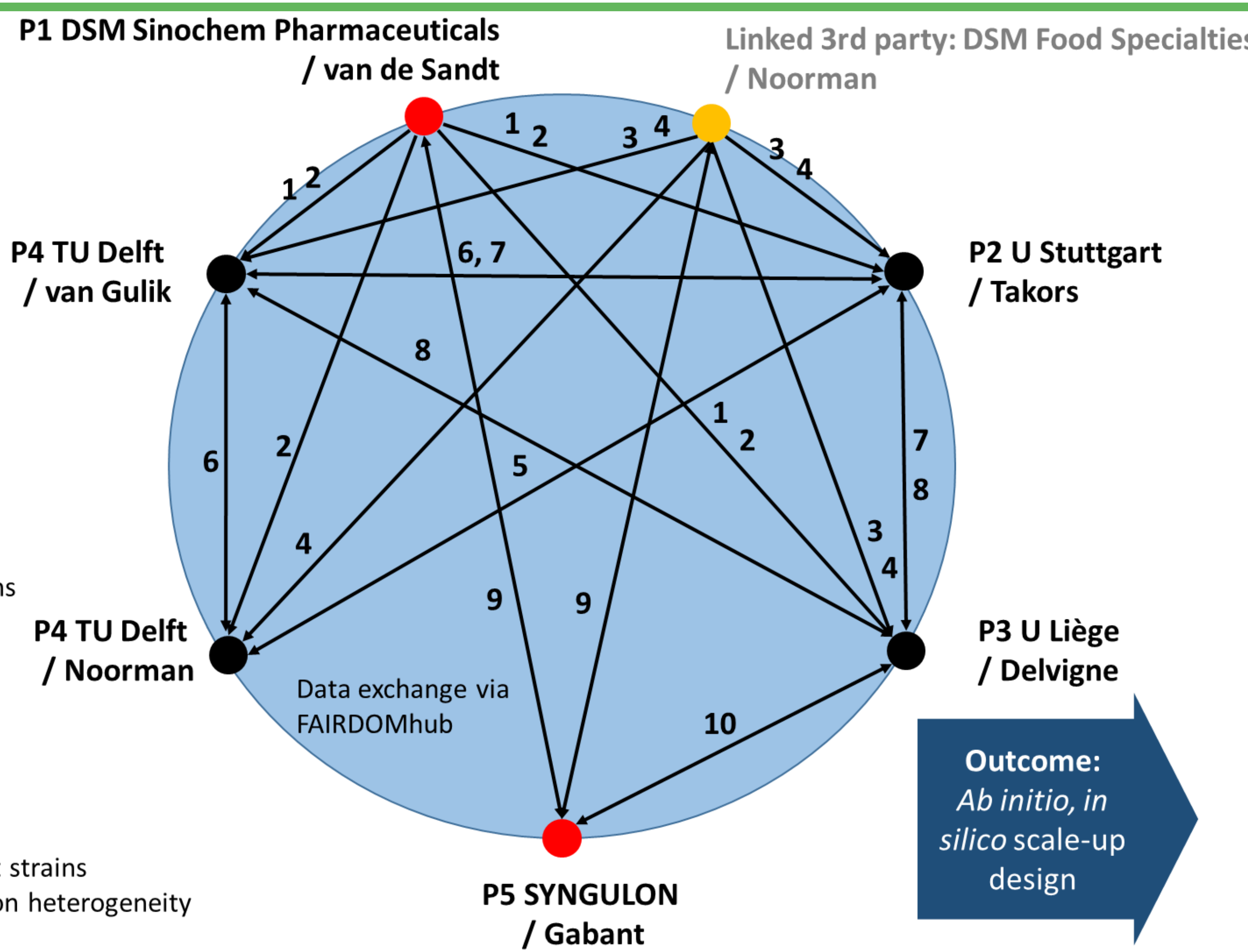


Penicillium chrysogenum

Saccharomyces cerevisiae

Confidential

Project interaction map



1: *P. chrysogenum* strains
2: industrial conditions
3: *S. cerevisiae* strains
4: industrial conditions
5: *cfd* approaches
6: kinetic models
7: metabolomics data
8: proteomics data
9: engineering of robust strains
10: analysis of population heterogeneity

Outcome:
Ab initio, in silico scale-up design

Special items in project plan

- Data management plan: Will be hosted by the DSM data platform with back-up at TU Delft
- Dissemination & Communication Manager: Prof. Frank Delvigne, covering following activities:
  - establishing and updating dissemination and outreach strategy, plan and dissemination;
  - dealing with open access to publications;
  - giving support while implementing the communication activities;
  - networking and community building;
  - raising target groups awareness about project results.

Expected outcomes

- *Outcomes to be achieved:*

- accelerating the bioprocess development including plant start-up by at least 20% (e.g. from 5 to 4 years), which could after 10 years further develop into a factor 5 (from 5 to 1 year).
- developing guidelines for constructing strains such that they are robust enough for harsh production conditions
- the early identification of scale-up sensitive properties of novel producers to ensure efficient use of manpower and research capacities
- reducing of the order of 10's of tonnes of CO_2 emission per large-scale fermentation
- reducing the energy requirements of at least 10%, i.e. in the order of 10 MWh, per run executed on industrial scale
- reducing by at least 20% the development budget (e.g. from 10 M€ to 8 M€), which could after 10 years further advance to a factor 5 (from 10 to 2 M€)

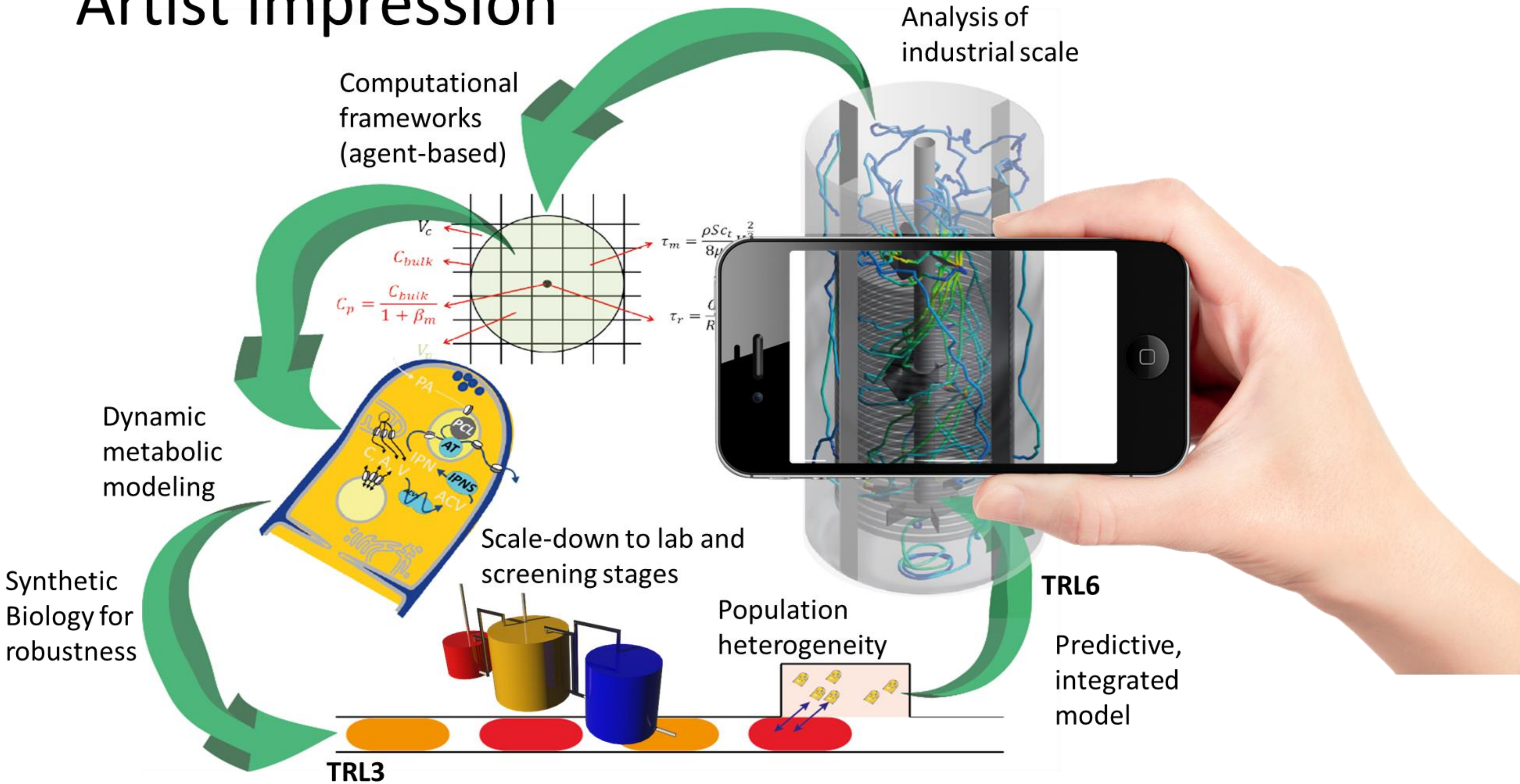
Expected outcomes

- *Planned implementation and exploitation of results:*

The projects should fall within TRL3-6: ComRaDes uses two real life examples to develop and demonstrate its approach. Its final delivery is a working framework, that can be used by industry not only for the two cases used but in principle for 'any' engineered micro-organism and its application in sustainable biotech. The research part of ComRaDes is at TRL 3-4, the final delivery at TRL 5-6. The presence of DSM Sinochem Pharmaceuticals as active partner in our consortium guarantees focus on reaching TRL 6, i.e. demonstrating our approach on existing processes from industry.

Summary

Artist impression



Delvigne and Noorman, *Microbial Biotechnology* (2017)

Contact details

- Coordinator: Henk Noorman, henk.noorman@dsm.com
- Partners:
  - Emile van de Sandt, DSM Sinochem Pharmaceuticals, NL
  - Walter van Gulik ,Technical University Delft, NL
  - Frank Delvigne, University Liege, B
  - Philippe Gabant, Syngulon, B
  - Ralf Takors, University Stuttgart, D