Computational Methods Supporting Process Intensification

Krühne, Ulrich

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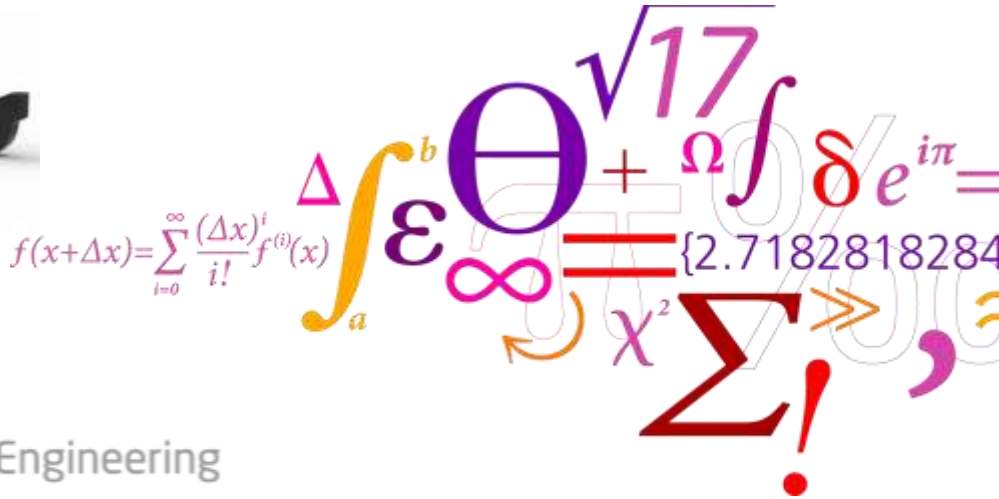
Ulrich Krühne
Senior Researcher, PhD

Center for Process Engineering and Technology (PROCESS)
Department of Chemical and Biochemical Engineering,
Technical University of Denmark



DTU Chemical Engineering
Department of Chemical and Biochemical Engineering

Overview

- Introduction and Motivation
- Modeling at the Department
- CFD
- CFD for advanced cell growth optimization
- Biocatalysis and CFD
- Pilot scale Biodiesel production
- Conclusion

Ulrich Krühne

- MSc. (Technical University Berlin), PhD (Technical University Denmark)
- Senior Researcher, Technical University of Denmark, Dept. Chemical and Biochemical Engineering

- A little history:
  - PhD (1996-2000; DTU Lyngby, Copenhagen)
  - Celtor Biosystems A/S (2000-2003 Copenhagen, Santa Clara Ca.,) since 2001 CEO of the Danish Entity
  - 2003-2011 Danish Technological Institute (Senior Consultant/Teamleader/Program Leader microfluidics)
  - Since 1st of March 2011 Senior Research at the DTU
  - From 1st of September 2012 Assoc. Professor

- Research interests:
  - Modeling (mechanistic models, chemometrics, CFD)
  - Microbioreactors and Microfluidics
  - Process Analytical Technology (fermentation, organic synthesis-based pharmaceutical production, continuous production of pharmaceuticals, design of PAT systems …)
  - Process dynamics, process control

Introduction and Motivation

- **Definition: Process Intensification** (**PI**) is an engineering expression that refers to making changes that render a manufacturing or processing design *substantially improved* in terms of
- energy efficiency,
- cost-effectiveness or
- enhancement of other qualities.

- Through PI, biotech companies strive to enhance production of biological products (*i.e.* in fermentation units or other bioreactors), by decreasing energy consumption, increasing reaction rates, reducing wasted energy and costs associated with waste products, improving purification steps, reducing equipment size, increasing safety and operational simplicity, *etc*. In doing so, companies can increase the sustainability of their company activities.

Modelling efforts at the Process group

Data-driven models

John Prausnitz has rightly said:
"Models come and go, but good data are forever!".

- Chemometrics (PCA, PLS, …) applied to NIR, MWF, but also traditional process data
- Soft sensors

- Driver?
  - Process Analytical Technology (PAT) guidance
  - QbD, Design space

- Challenges
  - Filamentous organisms
  - Multi-purpose / multi-product plants: robustness of calibrations / switching between productions

On-line monitoring of fermentation processes

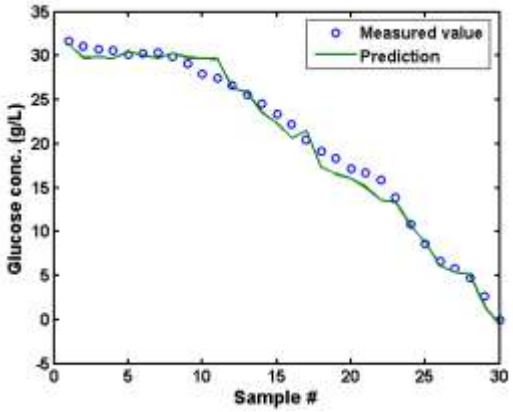
Glucose, air, base

NIR measurements:

Biomass, glucose, NH_4^+

On-line measurement:

CO_2, dissolved O_2, temperature, pH, Base addition, etc.



On-line monitoring of fermentation processes

Main results:

Cervera A.E. et al. (2009) Application of near-infrared spectroscopy for monitoring and control of cell culture and fermentation. Biotechnology Progress, 25, 1561-1581. Review

Ödman P. et al. (2009) On-line estimation of biomass, glucose and ethanol in *Saccharomyces cerevisiae* cultivations using in-situ multi-wavelength fluorescence and software sensors. Journal of Biotechnology, 144, 102-112.

Petersen N. et al. (2010) In situ near infrared spectroscopy for analyte-specific monitoring of glucose and ammonium in *Streptomyces coelicolor* fermentations. Biotechnology Progress, 26, 263-271

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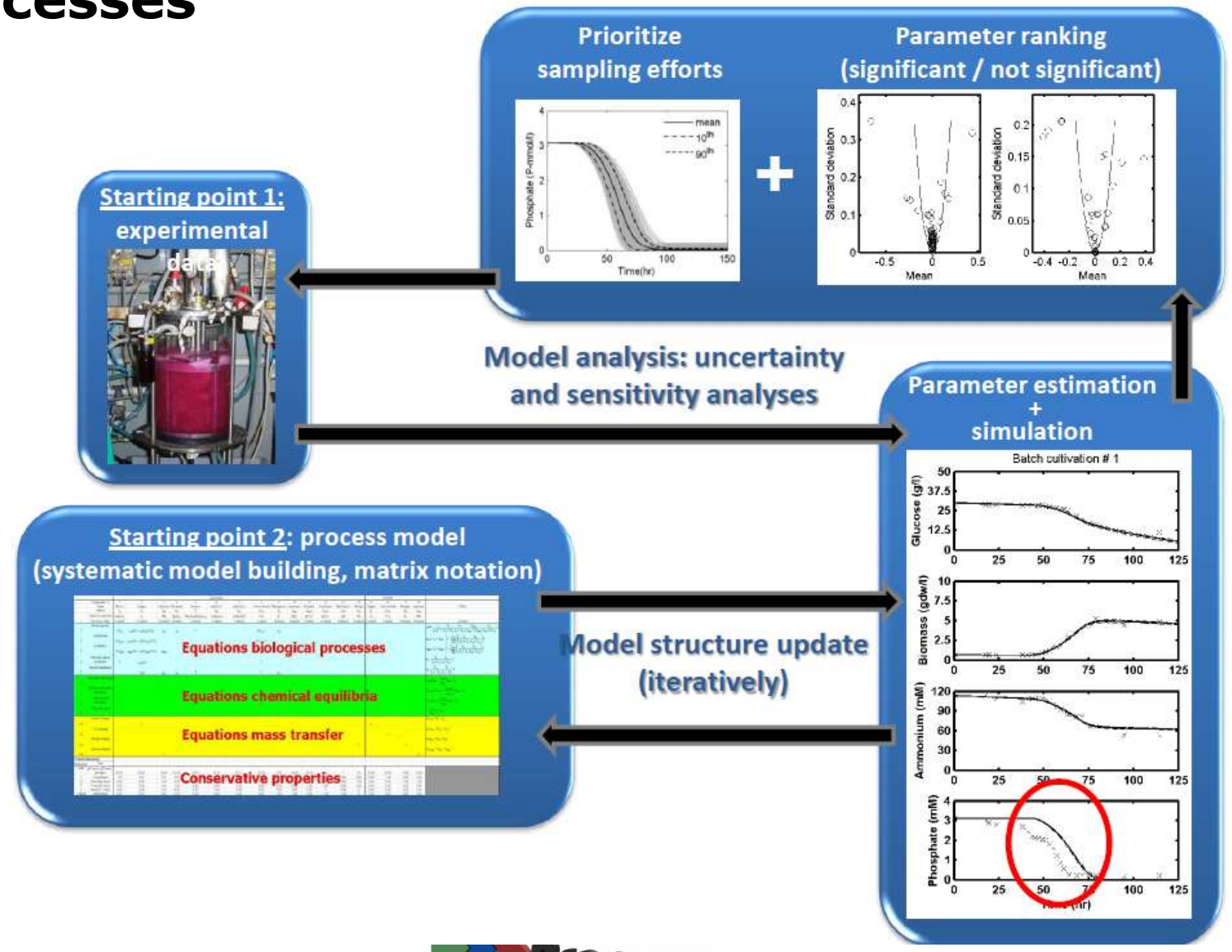
Mechanistic models

1. Systems of ordinary differential equations (ODEs) – traditional unstructured models / structured models
2. Population Balance models (PDEs)
3. Computational Fluid Dynamics (CFD) (**Ulrich Krühne**)
4. 1+3
5. 2+3
6. Multi-scale models

– **Purpose**:

- Building up/storing process knowledge
- Generate ideas for experimental work (model analysis)
- Focus experimental work (sensitivity analysis)
- Reactor design / comparison of fermentation technologies
- Development of control strategies
- Economic analysis

Mechanistic modeling of fermentation processes



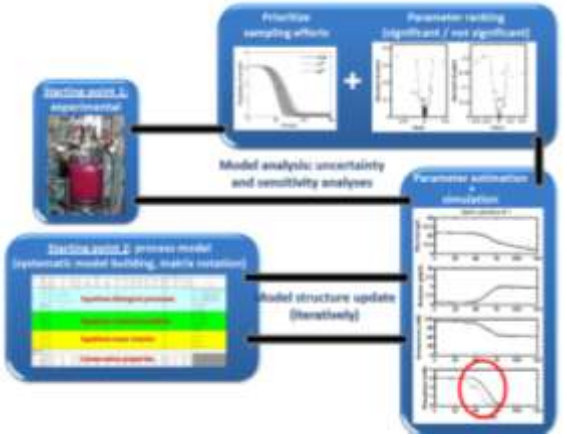
Mechanistic model – matrix representation

- Example: matrix description of Monod-Herbert aerobic growth model

Component, *i*	C_1	C_2	C_3	**Rates, r_j**
Symbols	S_S	S_O	X	
Units	C-mol/L	mol/L	C-mol/L	C-mol X/(L.h)
Process, *j*				
1. Growth	$-1/Y_{X,S}$	$-1/Y_{X,O}$	1	$\mu_{max} \frac{S_S}{S_S + K_S} X$
2. Decay	0	$-1/\gamma_X$	-1	$k_d X$

Mechanistic modelling of fermentation processes

Main results:



Sin G. et al. (2008) Matrix notation for efficient development of first-principles models within PAT applications: Integrated modeling of antibiotic production with *Streptomyces coelicolor*. Biotechnology and Bioengineering, 101, 153-171.

Sin G. et al. (2009) Good modelling practice (GMoP) for PAT applications: Propagation of input uncertainty and sensitivity analysis. Biotechnology Progress, 25, 1043-1053.

Gernaey K.V. et al. (2010) Application of mechanistic models to fermentation and biocatalysis for next generation processes. Trends in Biotechnology, 28, 346-354. Review / opinion article.

PBM Main results:

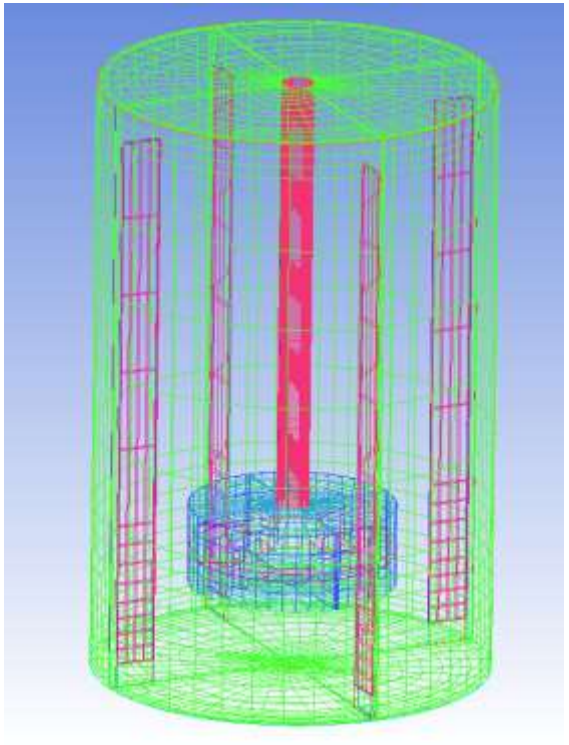
Lencastre Fernandes R. et al. (2011) Experimental methods and modeling techniques for description of cell population heterogeneity. Biotechnology Advances, 29, 575-599. Review

CFD

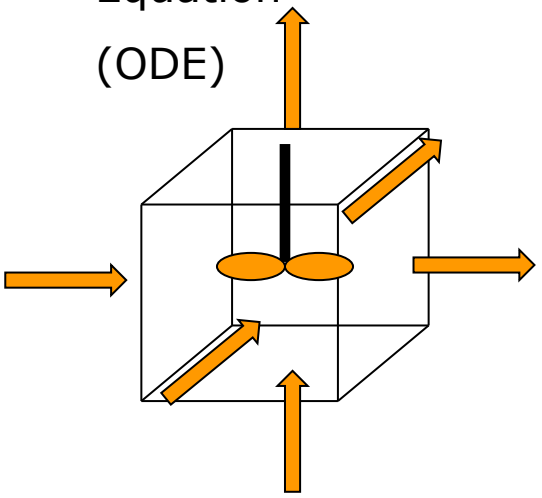
- **How it works**

Partial Differential Equation (PDE)

$$\rho \frac{Du_i}{Dt} = -\nabla p + \rho \mathbf{g}$$

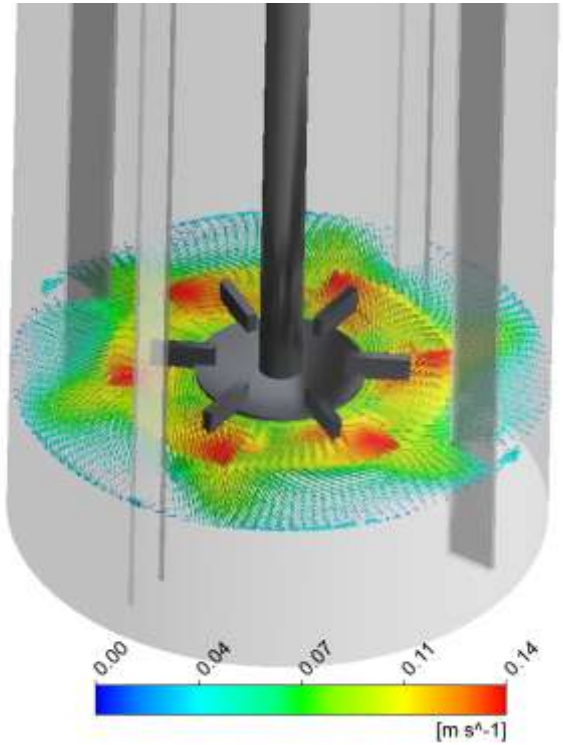


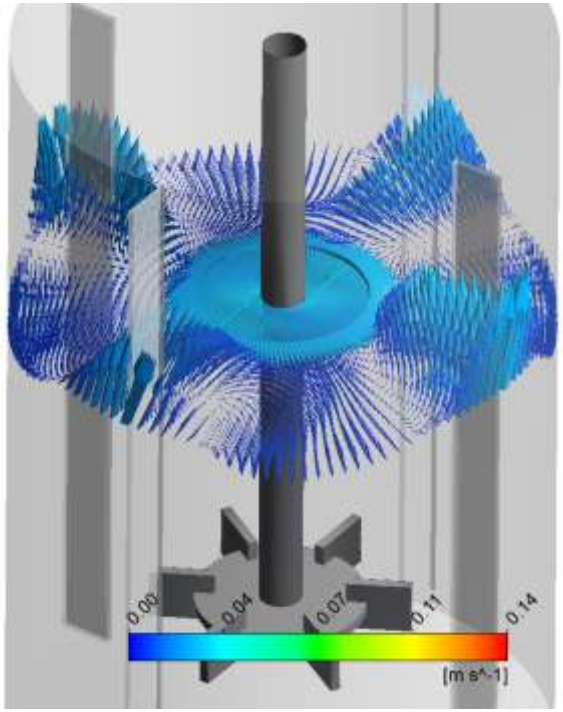
Many Ordinary Differential Equation (ODE)



CFD

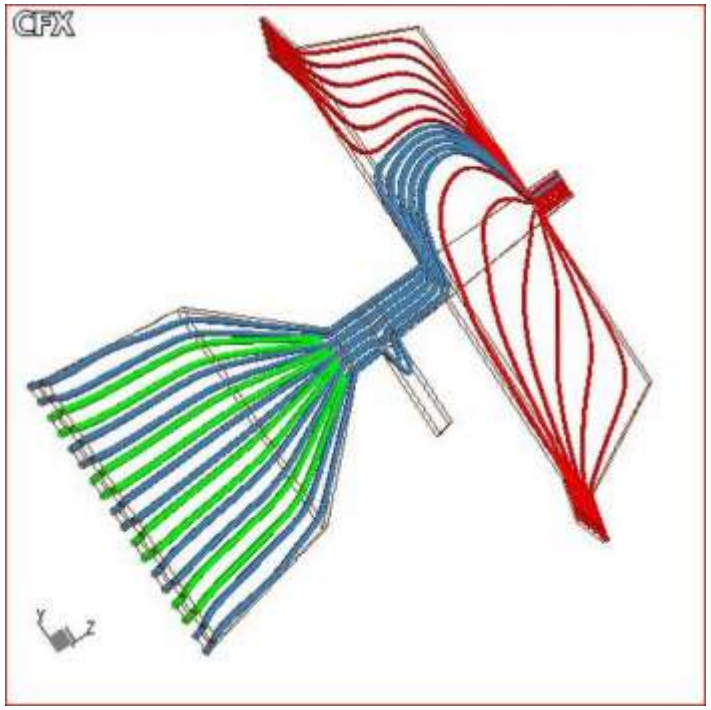
- **How it works**

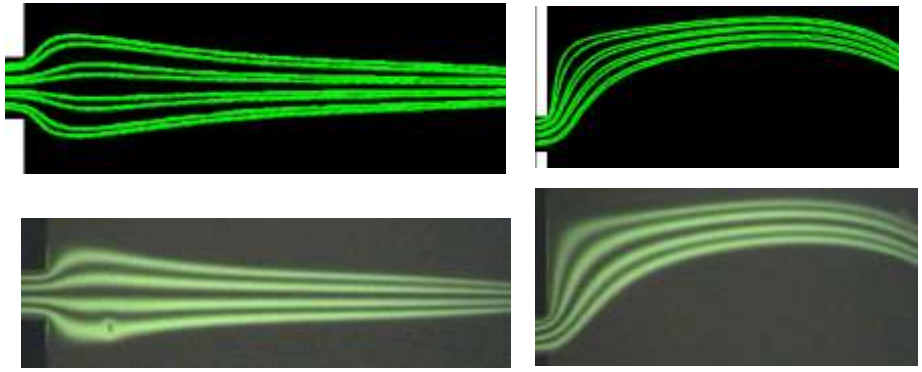




But does CFD work?

Hydrodynamic focussing





Micro and Nanosystems, 2010, 2, 249-260 249

A Transient 3D-CFD Model Incorporating Biological Processes for Use in Tissue Engineering

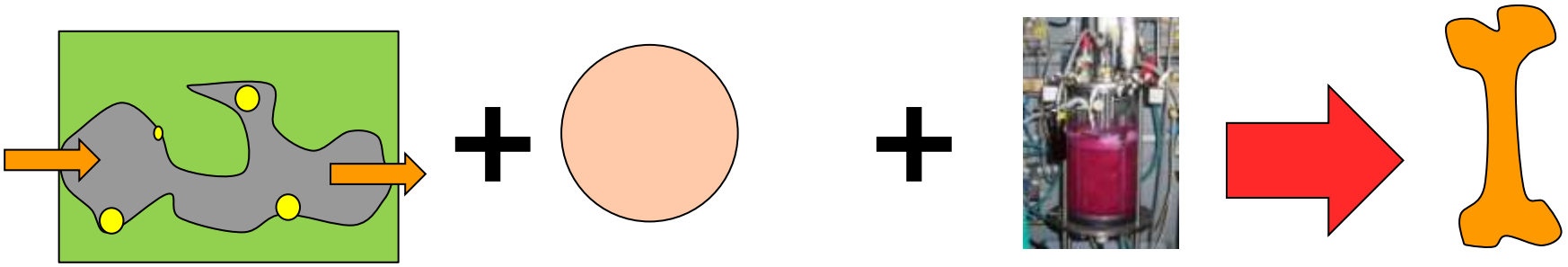
U. Krühne*,[1], D. Wendt[2], I. Martin[2], M.V. Juhl[1], S. Clyens[1] and N. Theilgaard[1]

[1]*Danish Technological Institute, Denmark*

[2]*Departments of Surgery and of Biomedicine, University Hospital Basel, Switzerland*

Abstract: In this article a mathematical model is presented in which the fluid dynamic interaction between the liquid flow in a scaffold and growing cells is simulated. The model is based on a computational fluid dynamic (CFD) model for the representation of the fluid dynamic conditions in the scaffold. It includes furthermore a simple biological growth model based on Michaelis Menten type kinetics for the growth of cells. The model includes biomass, substrate and oxygen as the most important growth limiting components in the system. Furthermore the growth, decay and maintenance respiration of the cells are considered in the model. In a variation of the model the growth of the biomass is influenced by the fluid dynamic induced shear stress level, which the cells are exposed to. In parallel an experimental growth of stem cells has been performed in a 3D perfusion reactor system and the culturing has been stopped after 2, 8 and 13 days. The development of the cells is compared to the simulated growth of cells and it is attempted to draw a conclusion about the impact of the shear stress on the cell growth.

Keywords: Computational fluid dynamics (CFD), bioreactor, tissue engineering, scaffold, micro pores, fluid structure interaction.



Activation of scaffold surfaces, through impregnation with active substances/plasma activation, in order to achieve specific cell adhesion

Table 1. Biological Model

Process	X_{BM}	C_{O_2}	C_S	Rate vector
Decay	-1	-	-	$k_d \cdot X_{BM}$
Growth	1	$-Y_{O_2}$	$-Y_S$	$\mu_{max} \cdot \frac{C_{O_2}}{C_{O_2}+K_{O_2}} \cdot \frac{C_S}{C_S+K_S} \cdot \text{Factor} \cdot \text{strain rate factor} \cdot fw \cdot X_{BM}$
Maintenance respiration	-	$-Y_{rO_2}$	$-Y_{rS}$	$r_r \cdot X_{BM}$

$$\frac{dX_{BM}}{dt} = -k_d \cdot X_{BM} + \mu_{max} \cdot \frac{C_{O_2}}{C_{O_2}+K_{O_2}} \cdot \frac{C_S}{C_S+K_S} \cdot \text{Factor} \cdot \text{strain rate factor} \cdot fw \cdot X_{BM}$$

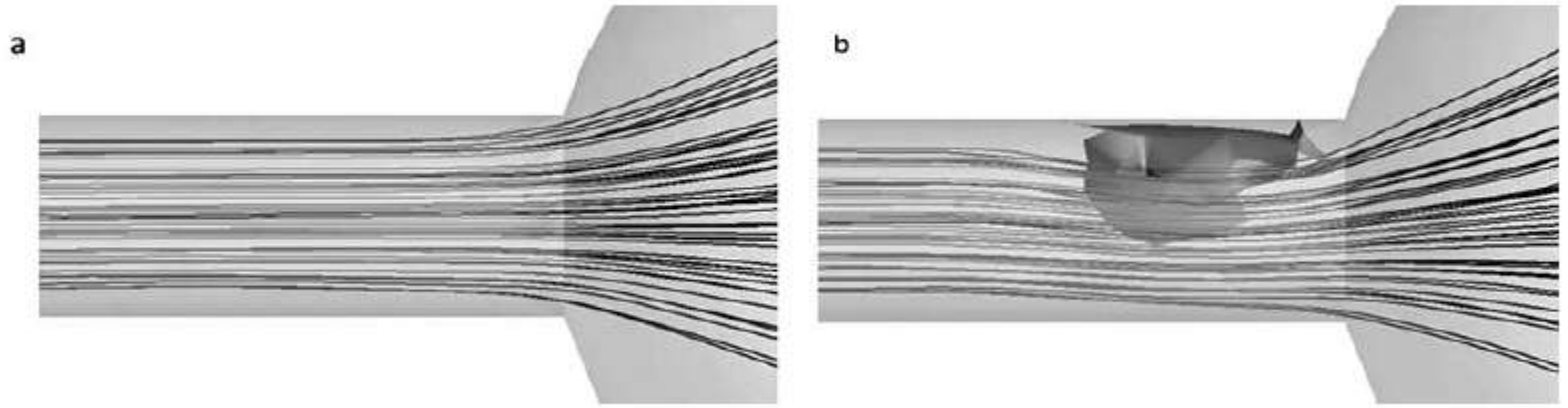
Table 2. Parameter for the Biological Model

Parameter	Value	Units
μ_{max}	3	$kg\ m^{-3}\ s^{-1}$
Arbitrary wall function	fw = 1 for $X_W >= 1\ 10^{-5}$ fw = 0 for $X_W < 1\ 10^{-5}$	1
Decay rate	$k_d = 0.1$	$kg\ m^{-3}\ s^{-1}$
Factor	0 for $X_{BM} \geq 0.95$ 1 for $X_{BM} < 0.95$	1 1
Oxygen respiration rate for maintenance	$Y_{rO_2} = 1$	$kg\ m^{-3}\ s^{-1}$
Oxygen saturation concentration	$K_{O2} = 0.05$	1
Respiration rate	$r_r = 1$	$kg\ m^{-3}\ s^{-1}$
Stoichiometric coefficient for oxygen throughout growth	$Y_{O_2} = 1$	1
Stoichiometric coefficient for substrate throughout growth	$Y_S = 1$	1
strain rate factor	Shear Strain Rate < 218 → SSF = 0,00459 [s] SSR Shear Strain Rate > 218 →SSF = -0,00459 [s] SSR+2	1 1
Substrate respiration rate for maintenance	$Y_{rS} = 1$	$kg\ m^{-3}\ s^{-1}$
Substrate saturation concentration	$K_S = 0.05$	1
ν_{app}	$5\ 10^{-3}\ 1\ X_{BM} \geq 0.95$ $1\ 10^{-3}\ 1\ X_{BM} < 0.95$	$kg\ m^{-1}\ s^{-1}$ $kg\ m^{-1}\ s^{-1}$

Table 3. Components of the Biological Model

Component	Symbol	Units
Arbitrary wall concentration	X_W	1
Biomass concentration level	X_{BM}	1
Oxygen concentration Level	C_{O_2}	1
Substrate concentration level	C_S	1

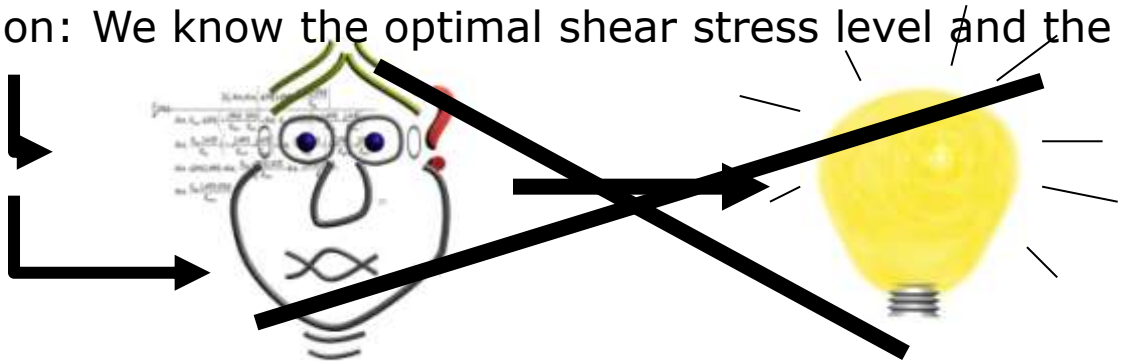
Fluid structure interaction impact



Evolutionary strategy for implant optimisation

Fact: Biological experiments have shown that cell grow better due to perfusion

Assumption: We know the optimal shear stress level and the model is sufficient

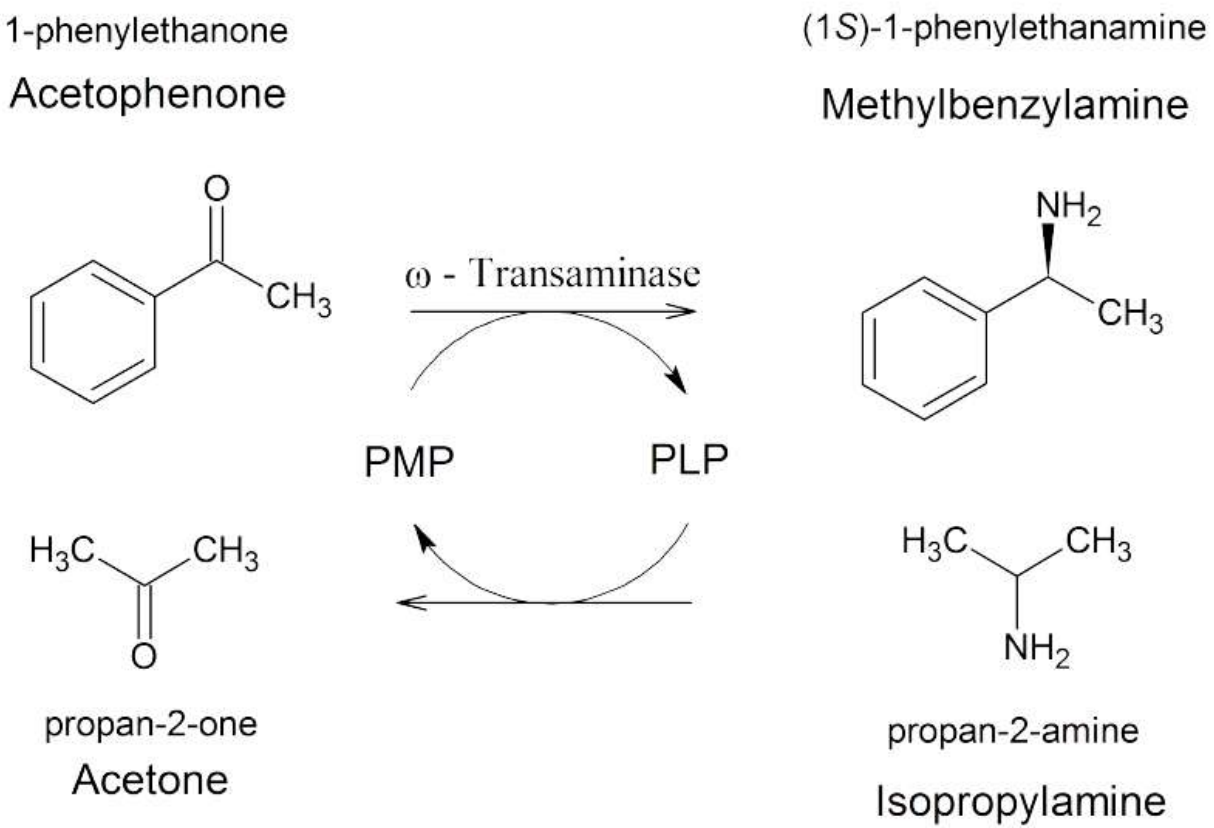


Geometry

Transient changes of the geometry

Autobone optimal pore shape

Biocatalysis



Biocatalysis

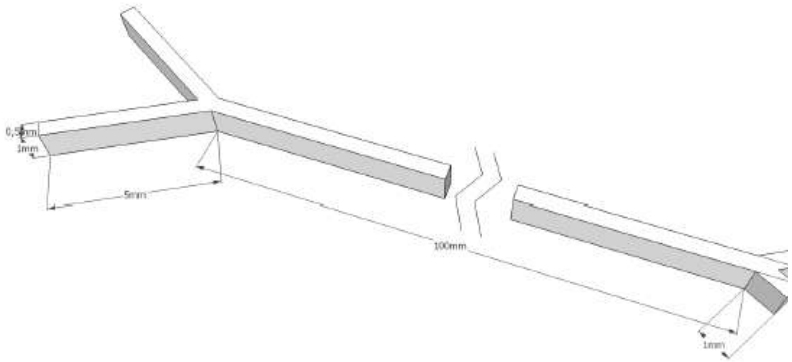


Figure 3.2: Schematic drawing of the YY-reactor

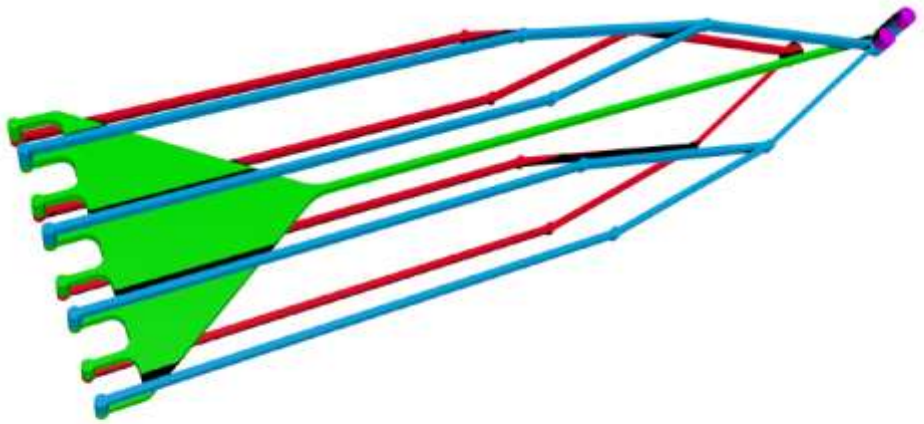
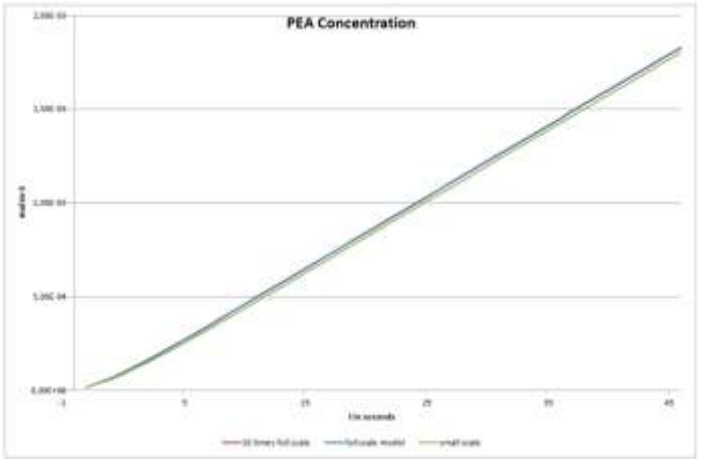
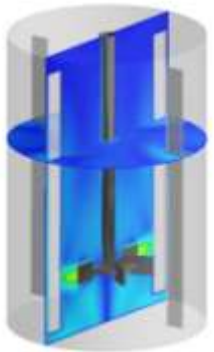


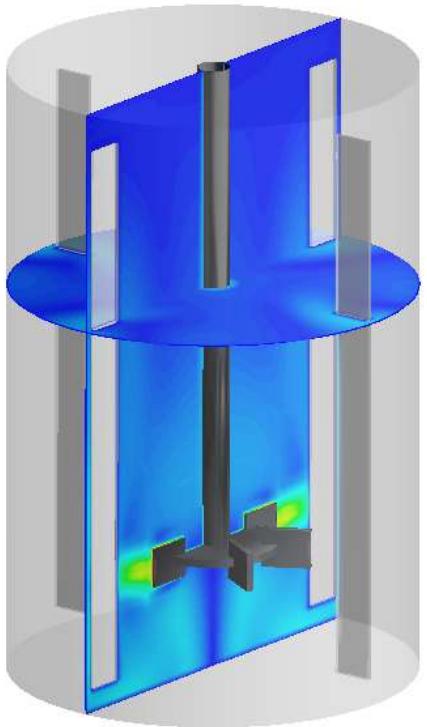
Figure 3.3: Shows the 3 dimensional structure of the 8 stream reactor

CFD

$$\frac{d}{dt}[PEA] = \frac{[E_0]\cdot Kcat_f Kcat_r \left(a[IPA]\cdot[APH] - b\frac{[ACE]\cdot[PEA]}{K_{EQ}} \right)}{Kcat_r \cdot K_{APH}\cdot a[IPA]\cdot\left(1+\frac{[PEA]}{K_{SPEA}}+\frac{[IPA]}{K_{SIPA}}\right)+Kcat_r\cdot K_{IPA}\cdot[APH]\cdot a\left(1+a\frac{[APH]}{K_{SAPH}}+b\frac{[ACE]}{K_{SACE}}\right)+}$$
$$Kcat_f\cdot\frac{K_{PEA}\cdot[ACE]}{K_{EQ}}\cdot b\left(1+a\frac{[APH]}{K_{SAPH}}+b\frac{[ACE]}{K_{SACE}}\right)+Kcat_f\cdot\frac{K_{ACE}\cdot[PEA]}{K_{EQ}}\cdot b\left(1+b\frac{[PEA]}{K_{SPEA}}+a\frac{[IPA]}{K_{SIPA}}\right)+$$
$$Kcat_r\cdot a[IPA]\cdot[APH]+Kcat_f\cdot\frac{K_{PEA}\cdot a[IPA]\cdot[ACE]}{K_{EQ}\cdot K_{PIPA}}+Kcat_f\cdot b\frac{[ACE]\cdot[PEA]}{K_{EQ}}+$$
$$Kcat_r\cdot\frac{K_{IPA}\cdot[APH]\cdot[PEA]}{K_{PPEA}} \qquad (7)$$







Biocatalysis

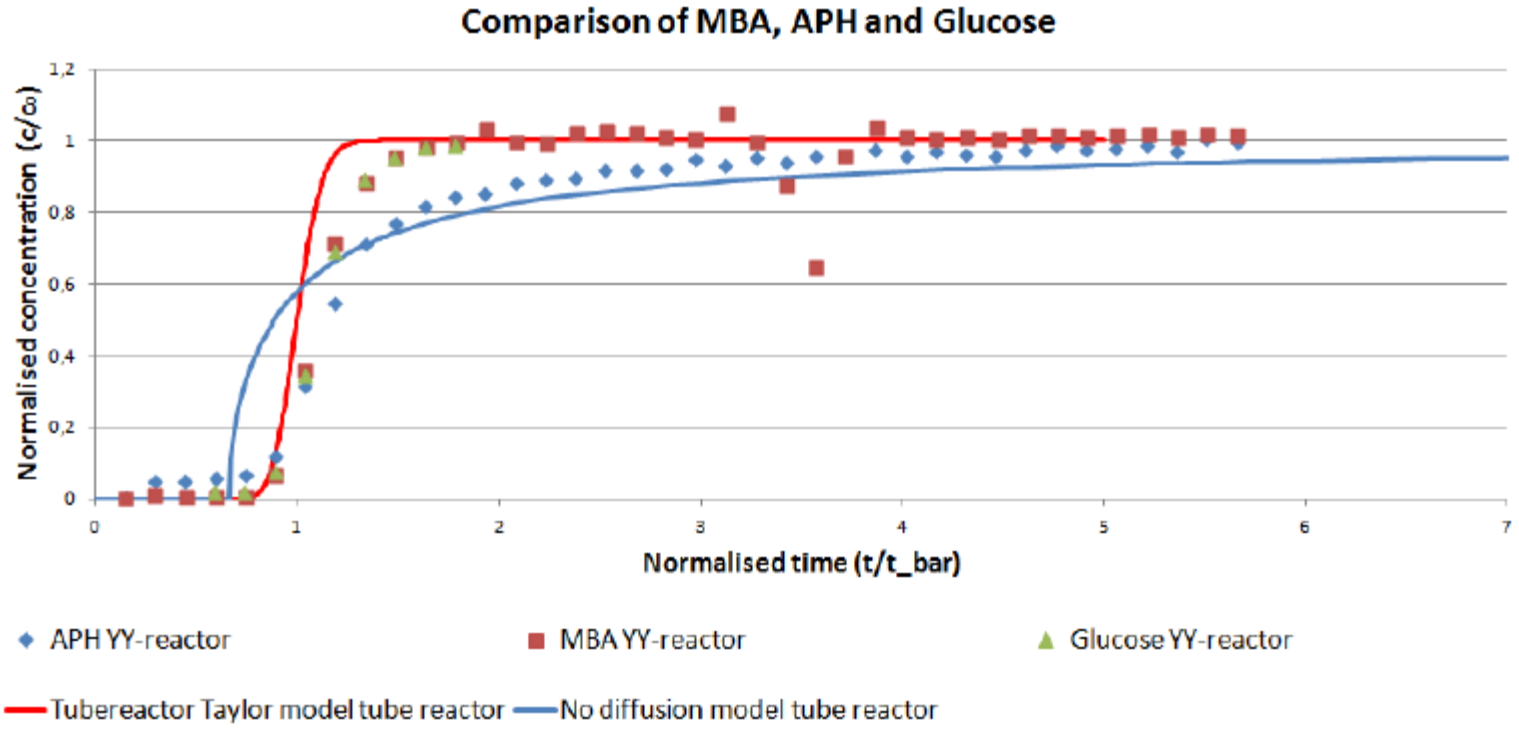


Figure 6.15: Comparison of the concentration profiles of MBA, APH and glucose

Biocatalysis

Table 6.7: Measured average concentration in different reactor designs and residence time for reaction test

	MBA			APH		
	6.66 min	30 min	60 min	6.66 min	30 min	60 min
8 stream	0.051	1.049	1.689	1.943	9.895	9.030
YY-reactor	0.034	0.999	1.418	2.339	16.703	13.016
Batch	0.052	0.309	0.714	1.964	17.546	18.178

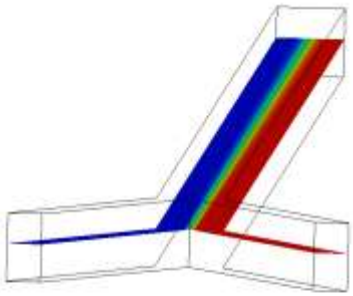
Figure 5.6: Principle of the substrate delivery and product removal experiment

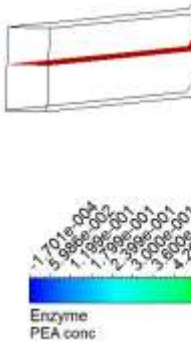
Biocatalysis CFD

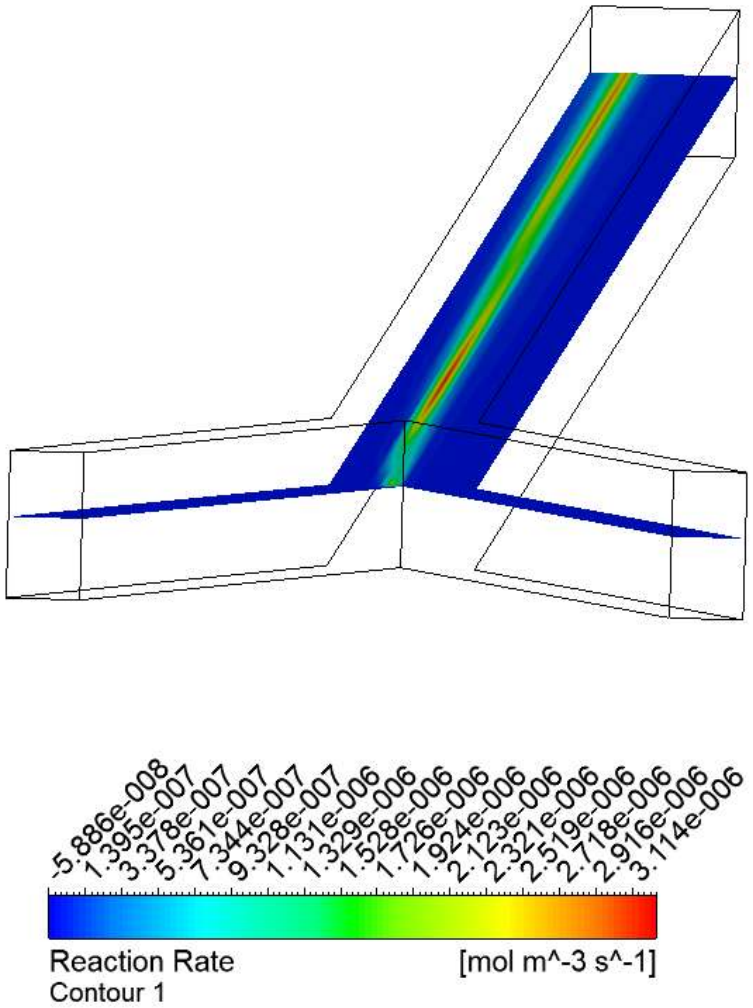
Assumptions:

$D_{APH} << D_{MBA} \sim D_{enzyme} \sim D_{IPA} \sim D_{ACE}$

K_{SAPH} is very small





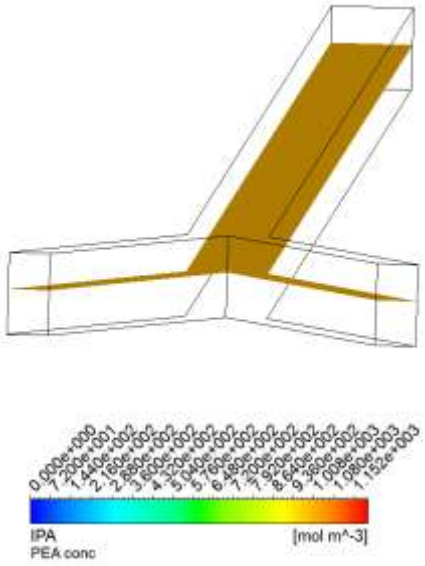


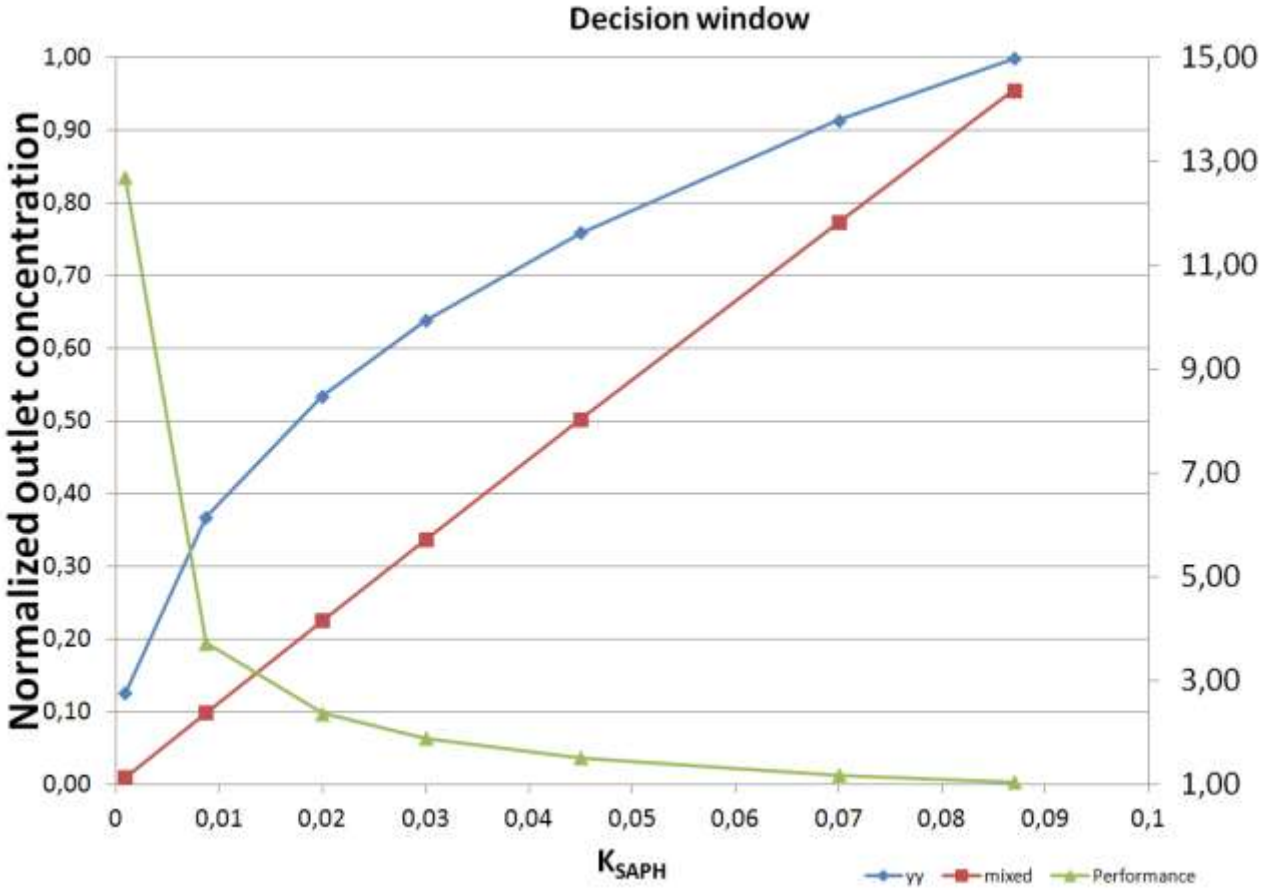
Biocatalysis CFD

Same assumptions

But in both channels everything

Completely mixed





What is Biodiesel ?

Vegetable oil

or

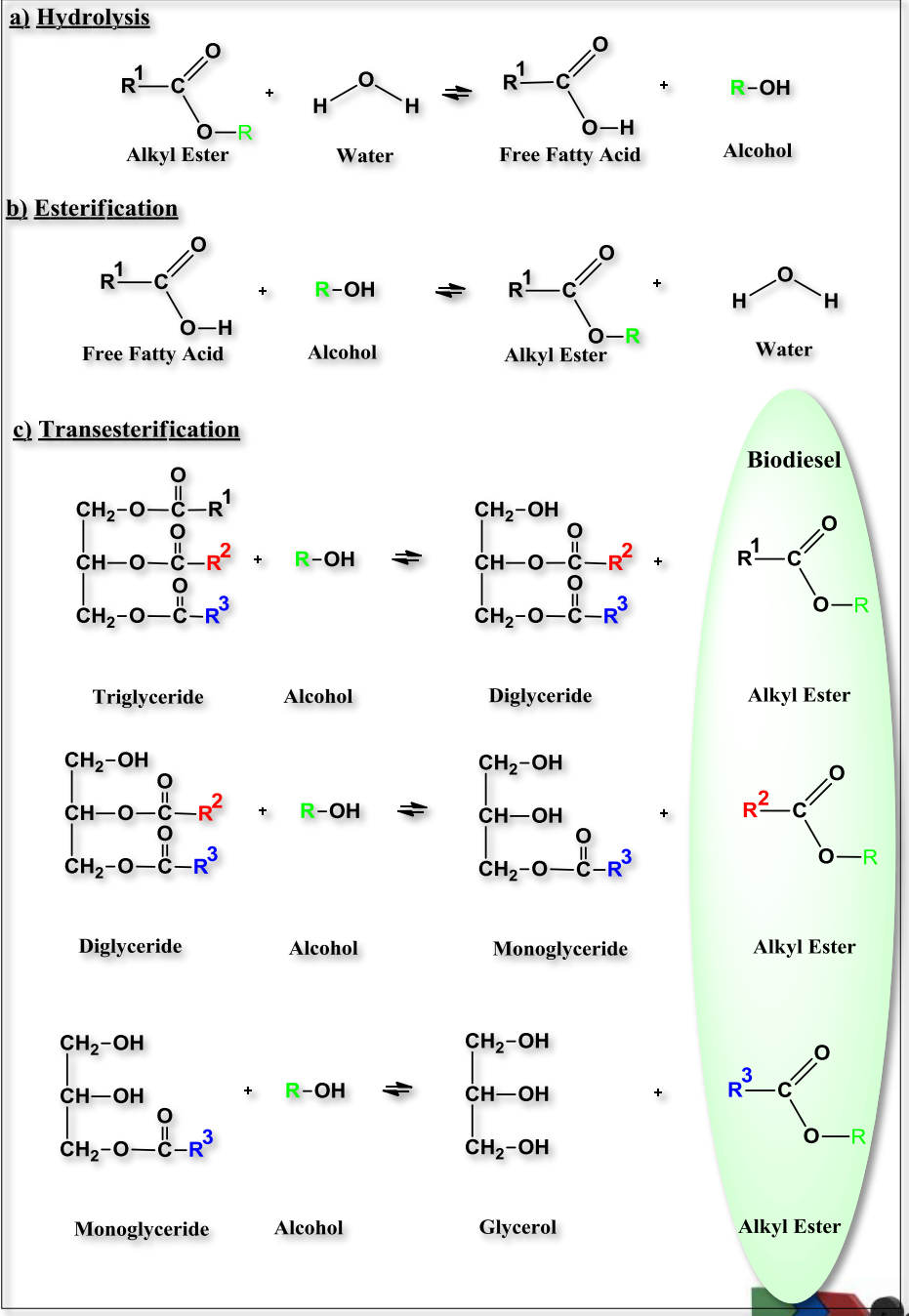
Waste oil and fats

+

Alcohol

Catalyst

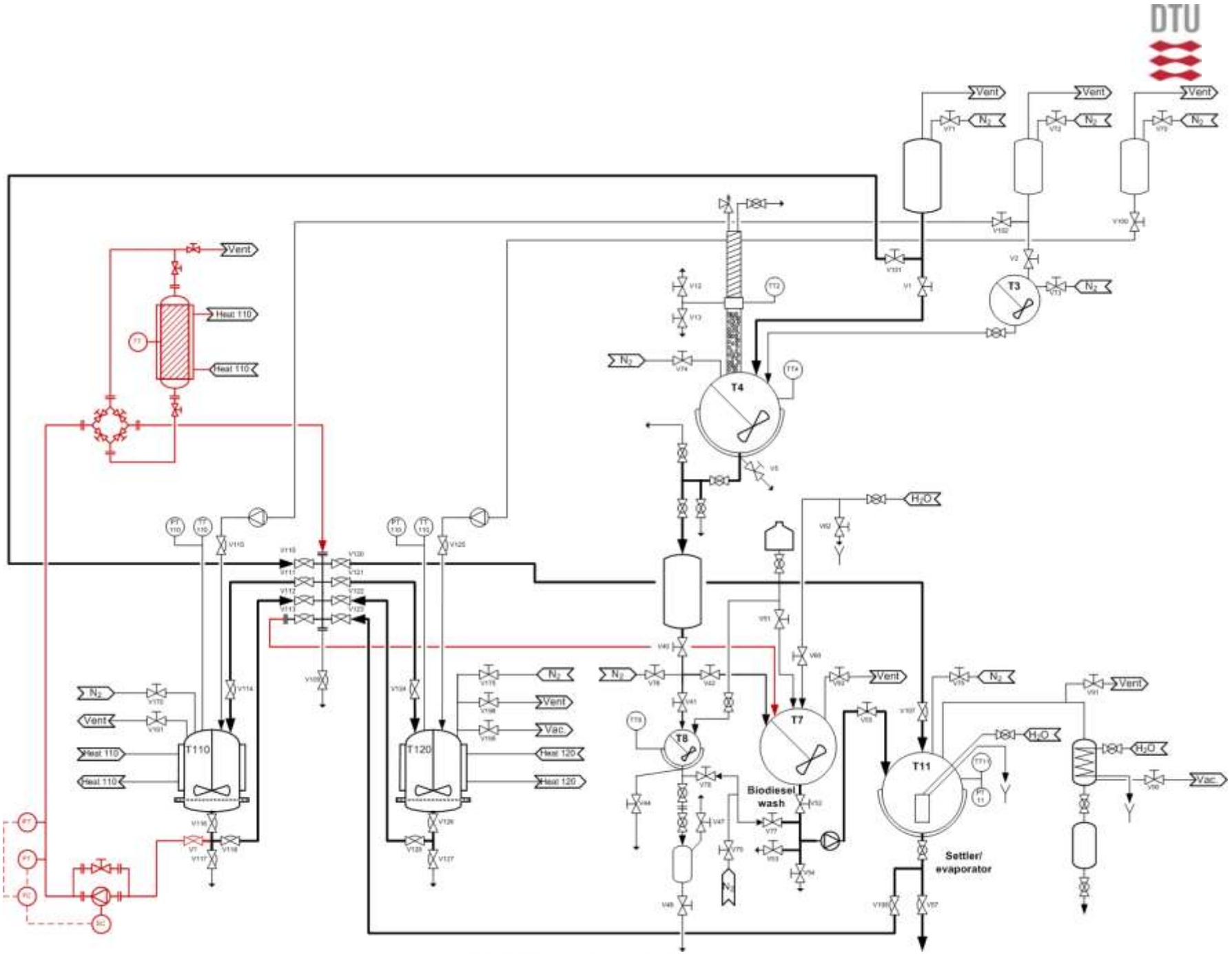
Biodiesel



- Cetane number and heating value similar to that of petroleum diesel
- Strong candidate to supplement petroleum diesel

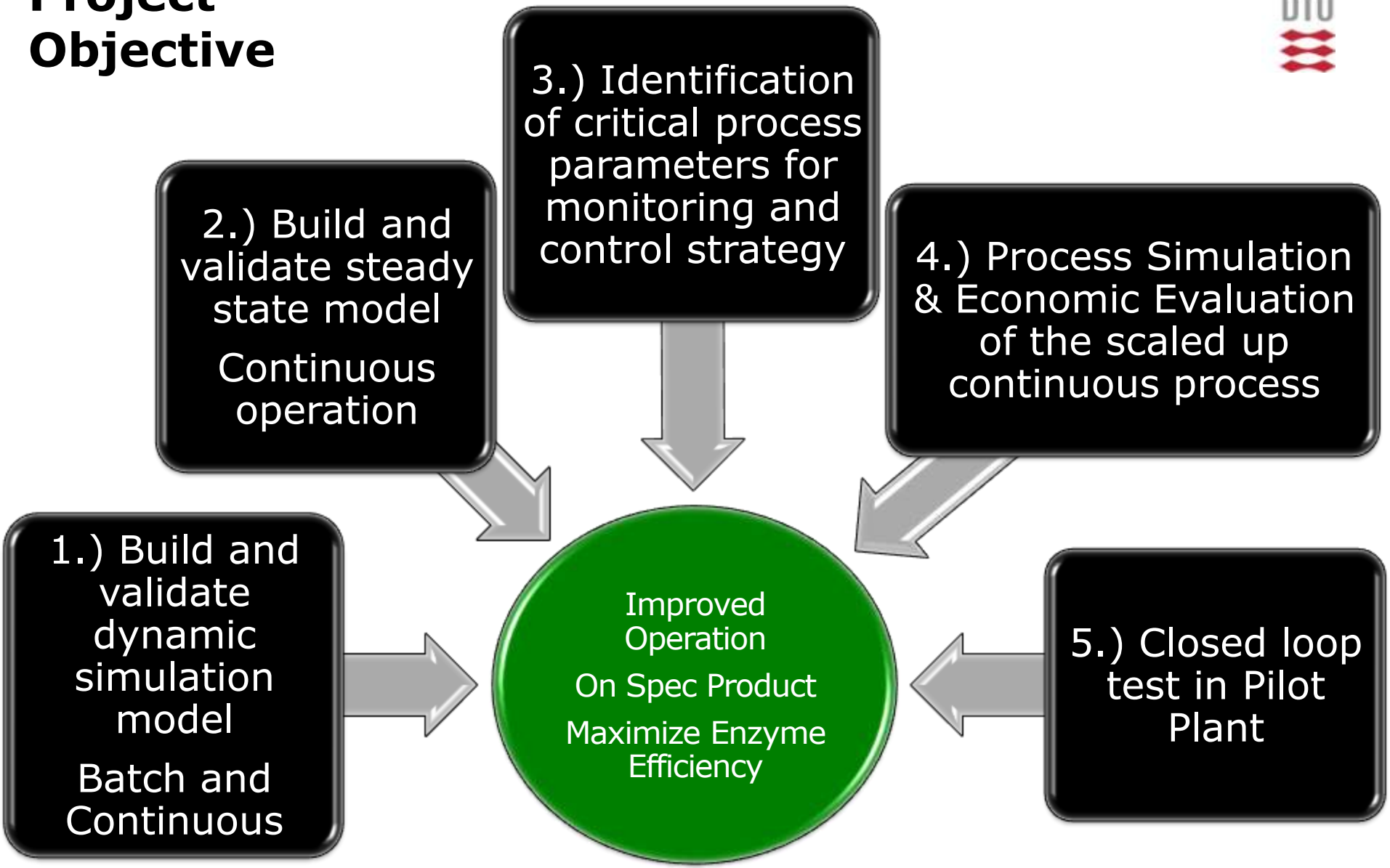
Pilot Scale Biodiesel

- Designed to handle all discussed processes
  - Pre-treatment in column (single pass or recirculation) or STR (batch)
  - Transesterification with immobilized enzyme in STR (fed-batch)
  - Transesterification with free enzyme (fed-batch)
  - Esterification to in-spec product in column or STR (drying can be done in plant)


DTU
Vent
N2
Heat 110
T110
T120
T3
T4
T7
T8
T11
H2O
Vac.
Heat 120
Biodiesel wash
Settler/ evaporator

Project Objective

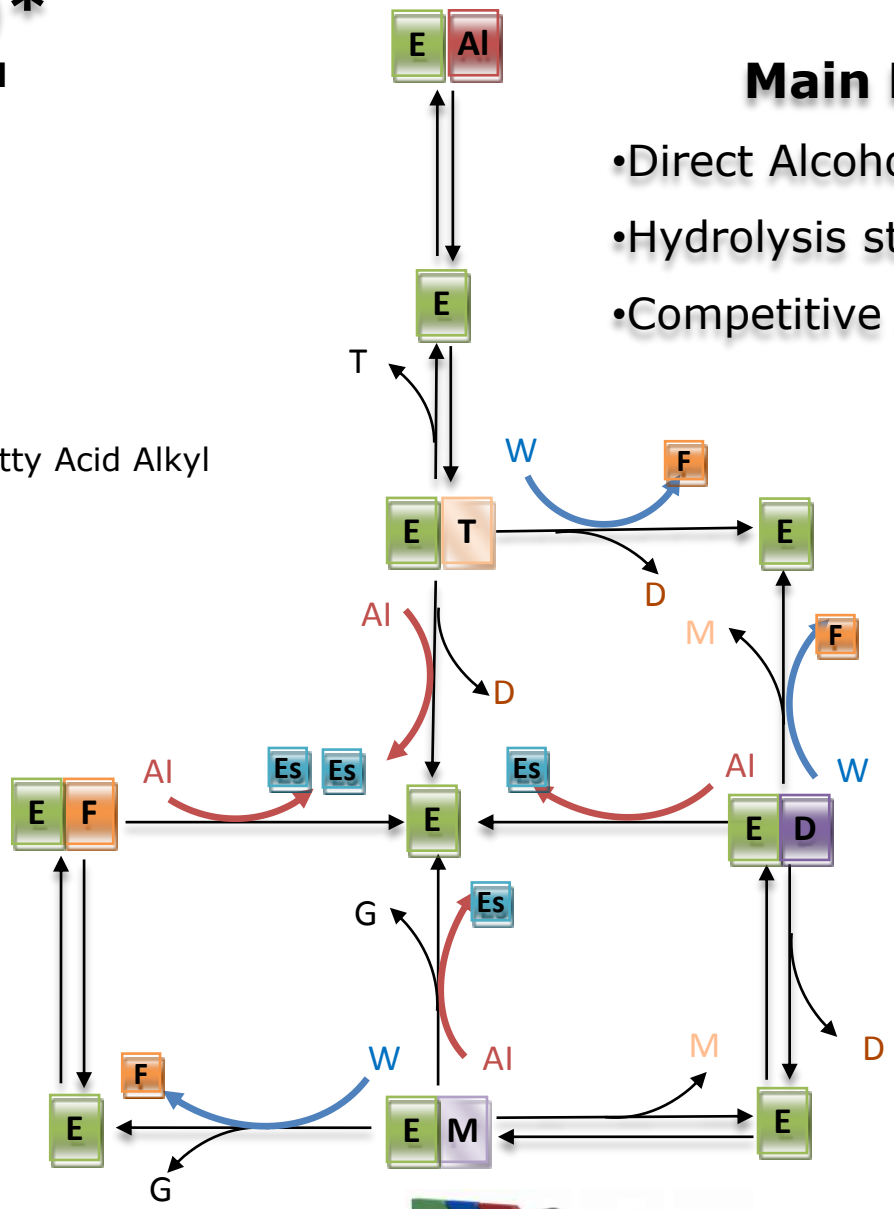
Project Objective



Transesterification Modelling (Kinetics)*

Legend

- E — Enzyme
- Al — Alcohol
- T — Triglyceride
- D — Diglyceride
- M — Monoglyceride
- Es — Ester/FAAE (Fatty Acid Alkyl Ester)
- F — Free Fatty Acid
- G — Gycerol
- W — Water
- → Hydrolysis
- → Esterification

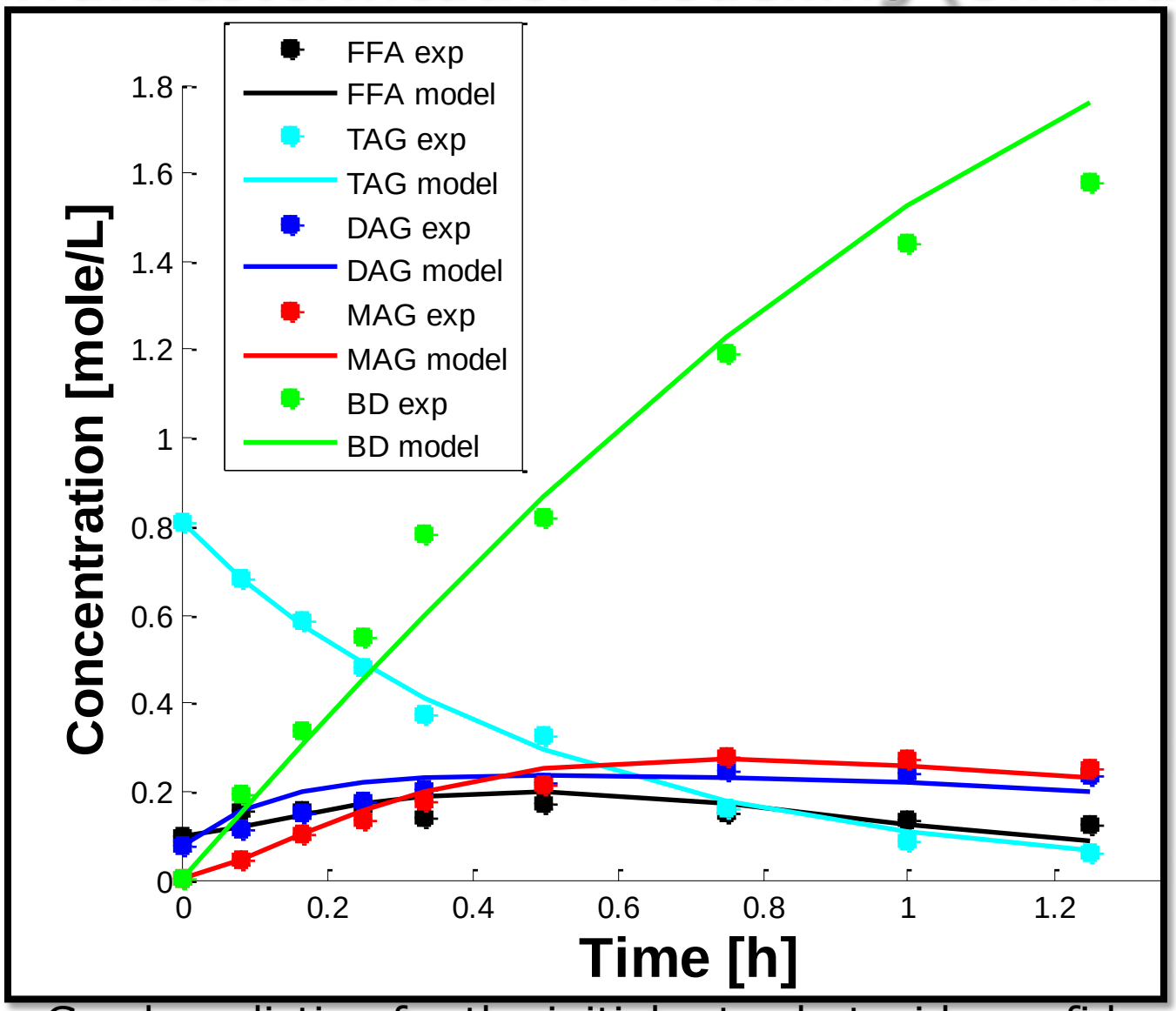


Main Model Assumptions

- Direct Alcoholysis of TAG to produce FAAE
- Hydrolysis step to produce FFA
- Competitive alcohol inhibition

* B Cheirsilp, Impact of transesterification mechanisms on the kinetic modeling of biodiesel production by immobilized lipase, Biochem.Eng.J. 42 (2008) 261-269

Transesterification Modelling (Simulation)



Conditions

- 1L Batch Reactor
- 500 g Rapeseed Oil
- 200 rpm, 35° C
- 5 w/w% TL HC
- 1eq 96 vol % Ethanol

Main Assumptions

- Mass transfer limitations ignored
- Competitive alcohol inhibition
- No enzyme deactivation

Good prediction for the initial rates but wide confidence intervals

Conclusions

- Models come and go and help to understand your data, generating knowledge which is staying forever
- If you want to intensify a process you must understand your data. Modeling is a useful starting point for this ☺
- Models can help to reduce your experimental efforts (DoE)
- CFD and microreactors can be a powerful tool for gaining understanding in biocatalysis and process intensification and scale-up
- You can perform experiments under conditions which are otherwise difficult or impossible
- You can indeed investigate minute amount of samples with reduced time effort
- High throughput screening by parallelization numbering out rather than scale up
- Very relevant for low production volumes (e.g. pharmaceuticals)
- An excellent tool for high content screening

Questions?

- My contact details
  - ulkr@win.dtu.dk

Ulrich Krühne
Department of Chemical and Biochemical Engineering
Technical University of Denmark
Building 229
DK-2800 Kgs. Lyngby
Denmark
Phone: +45 45 25 29 74