On the trade-off between experimental effort and information content in optimal experiment design

Dries Telen, Filip Logist, Eva Van Derlinden and **Jan Van Impe**
BioTeC & OPTEC, Dept. of Chemical Engineering, KU Leuven

Outline

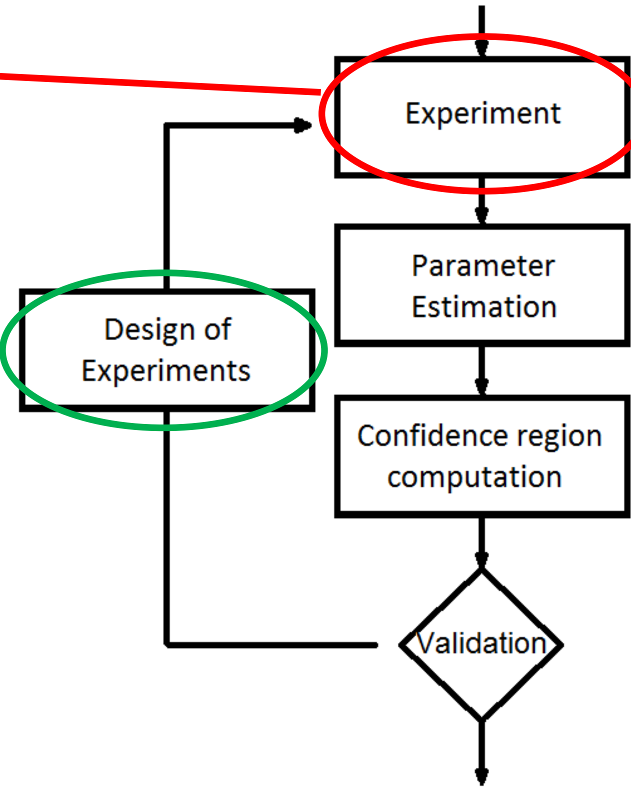
- Introduction
- Background
- Example
- Conclusions

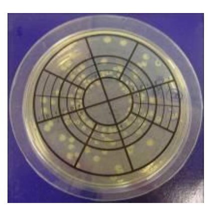
Modelling bioprocesses

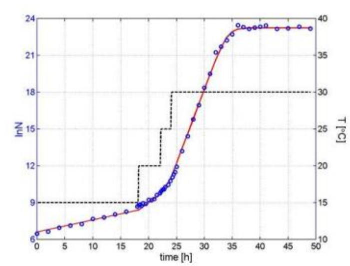
- Dynamic models for biochemical processes are appealing, but ... need to be constructed first!

Cost & labor intensive

Reduce exper-imental burden







Outline

- Introduction
- Background
- Example
- Conclusions

Optimal experiment design: parameter estimation

- Dynamic optimization problem:

$$\min_{\mathbf{u}} J$$

subject to:

$$\frac{dx(t)}{dt} = f(x(t), u(t), p, t)$$

$$0 = b(x(t_0))$$

$$0 \geq c(x(t), u(t), p, t)$$

- $J(\mathbf{F})$ scalar function
  Fisher information matrix (FIM):

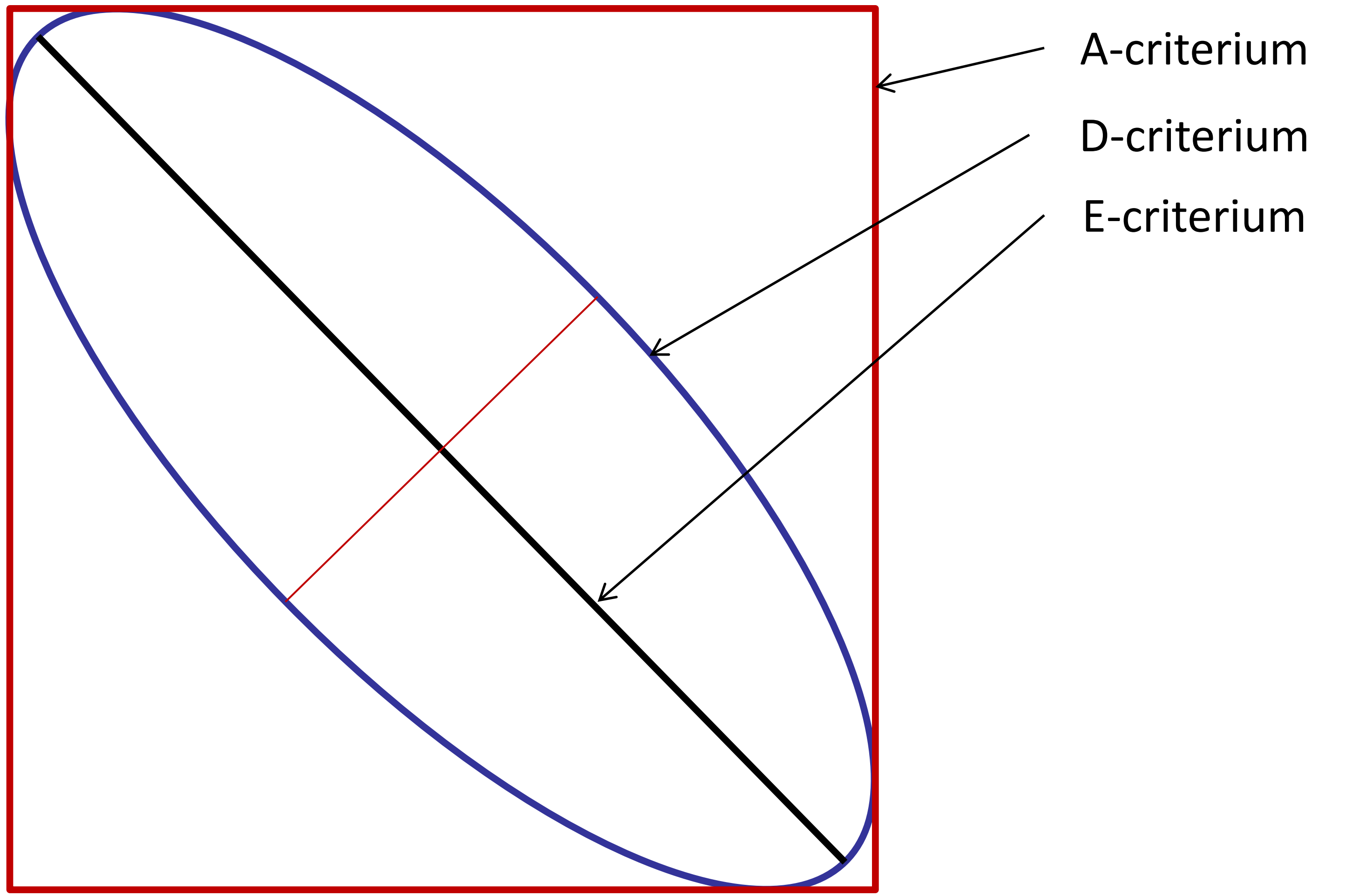
$$\mathbf{F} = \int_0^T \left(\frac{\partial \mathbf{y}}{\partial \mathbf{p}}(t)\right)^{\mathrm{T}} \mathbf{Q} \left(\frac{\partial \mathbf{y}}{\partial \mathbf{p}}(t)\right) dt$$

Optimal experiment design

- 2 key ingredients in FIM:
  - **Sensitivity functions**: $\frac{\partial \mathbf{y}}{\partial \mathbf{p}}(t)$
  - Inverse variance-covariance matrix of measurement errors: $\mathbf{Q}$
- Different scalar functions J possible:
  - A-criterium: min (trace $\mathbf{F}^{-1}$)
  - D-criterium: max (det $\mathbf{F}$)
  - E-criterium: max ($\lambda_{\min}$ ($\mathbf{F}$))
  - Modified E-criterium: min ($\frac{\lambda_{\max}}{\lambda_{\min}}$ ($\mathbf{F}$))

Geometrical interpretation

Joint confidence interval: 2 parameter case

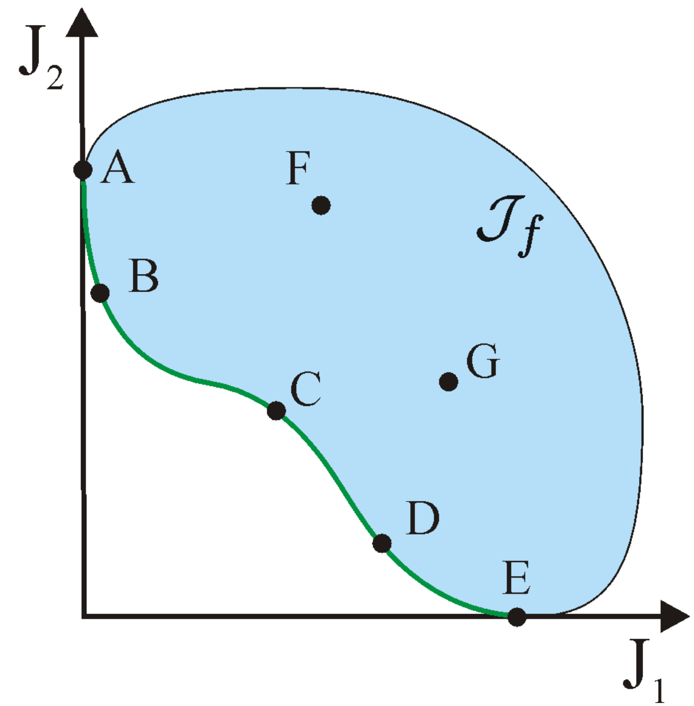


Multi-objective optimization

- Not a single but a **set** of Pareto optimal solutions:

$$\text{minimise } \{J_1(\mathbf{y}), \ldots, J_m(\mathbf{y})\}$$
$$\mathbf{0} \leq \mathbf{g}(\mathbf{y})$$
$$\mathbf{0} = \mathbf{h}(\mathbf{y})$$

A feasible point $\mathbf{y}^*$*, is Pareto optimal there does not exist another feasible point* $\mathbf{y}$*, such that* $J_i(\mathbf{y}) \leq J_j(\mathbf{y}^*)$ *for all* i *and* $J_j(\mathbf{y}) < J_j(\mathbf{y}^*)$ *for at least one* j*.*



In order to enhance real-time decision making
a fast and accurate generation of alternatives is required.

Multi-objective optimization

Evolutionary algorithms

$\rightarrow$ directly tackle MO via gradual evolution to Pareto front

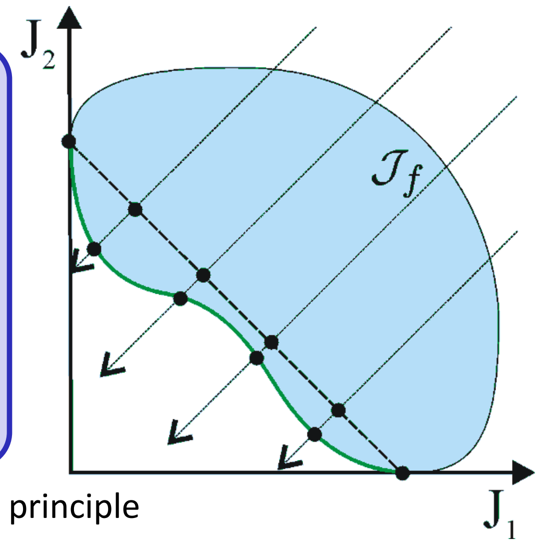
Scalarisation algorithms

$\rightarrow$ convert MO into series of single objective problems

$\rightarrow$ exploit fast deterministic gradient based methods

Examples:

- Weighted Sum (WS)
- ε-constraint (ε-Con)
- Normal Boundary Intersection (NBI)
- (Enhanced) Normalized Normal Constraint ((E)NNC)



NBI principle

OPTEC
K.U.Leuven Optimization in Engineering Center

BioTeC BIOPROCESS TECHNOLOGY & CONTROL

- Intro
- **Background**
- Example
- Conclusions

KATHOLIEKE UNIVERSITEIT LEUVEN

Software: ACADO (Multi-Objective)

Automatic Control And Dynamic Optimization Toolkit

- Open Source (LGPL) **www.acadotoolkit.org**
- User-friendly: close to mathematical syntax
- Self-contained: only need C++ compiler
- Code extensibility: use C++ capabilities

Direct optimal control:

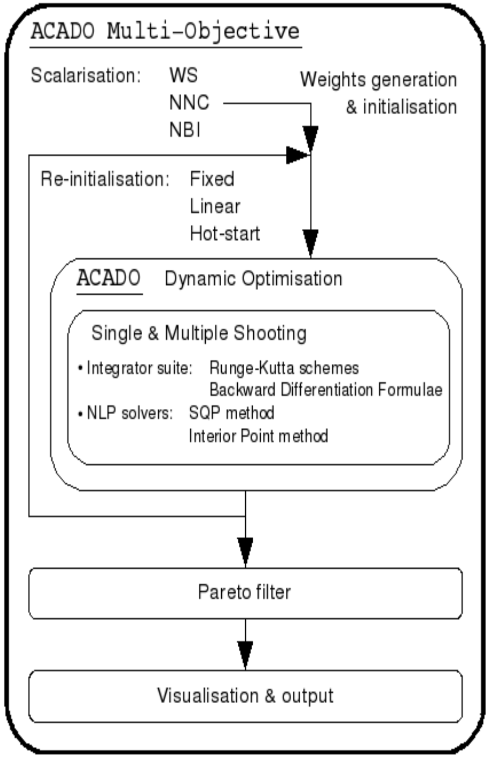
- Single & Multiple Shooting
- Automatic Differentiation

Scalarisation approaches:

- Weighted Sum (WS)
- (Enhanced) Normalized Normal Constraint ((E)NNC)
- Normal Boundary Intersection (NBI)

(Houska et al. 2011, Logist et al. 2010,2011.)

Schematic view of
`ACADO Multi-Objective`



Outline

- Introduction
- Background
- Example
- Conclusions

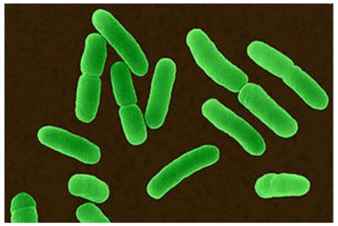
Predictive microbiology case study

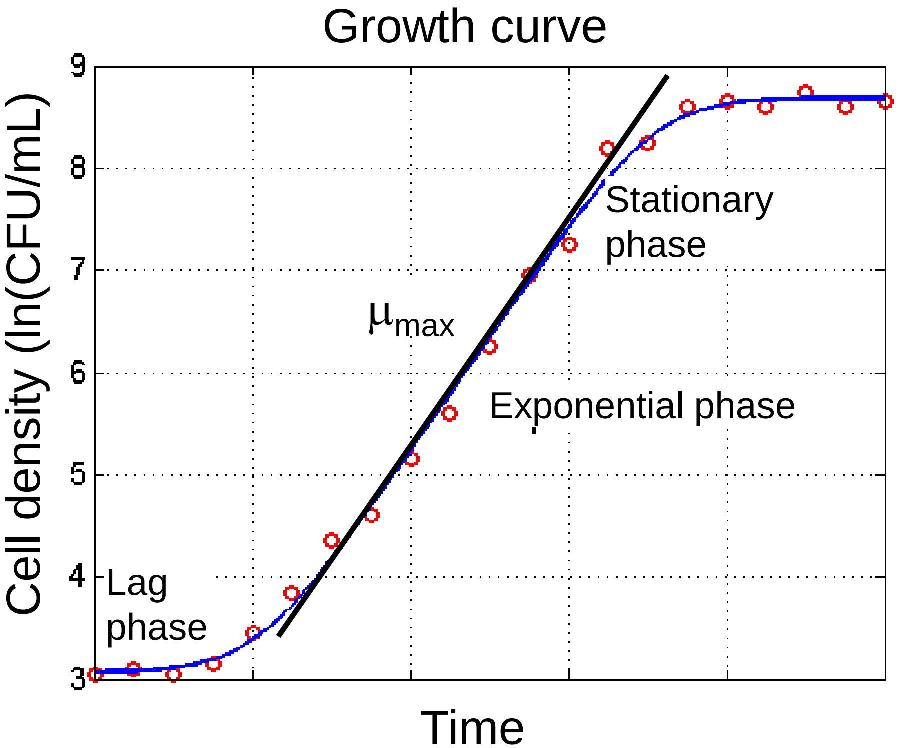
- Intro
- Background
- **Example**
- Conclusions

- Model equations:

$$\frac{dn}{dt} = \frac{Q}{Q+1}\mu_{max}(T(t))[1 - \exp(n - n_{max})]$$

$$\frac{dQ}{dt} = \mu_{max}(T(t))Q$$





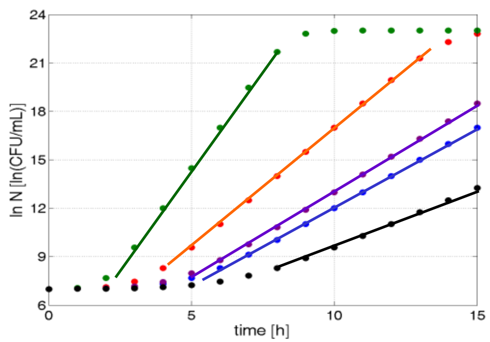
Predictive microbiology case study

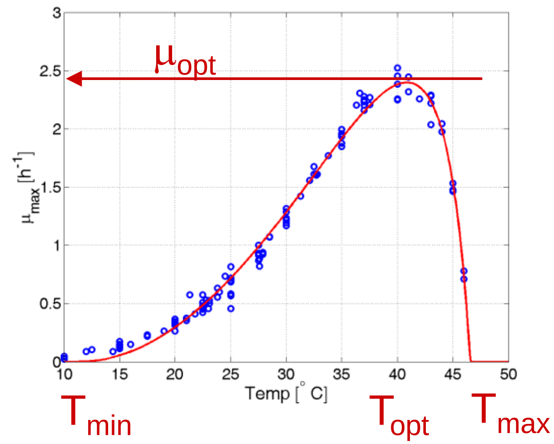
- Temperature dependency: $\mu_{max} = \mu_{opt}\gamma(T)$

$$\gamma(T) = \frac{(T-T_{min})^2(T-T_{max})}{(T_{opt}-T_{min})[(T_{opt}-T_{min})(T-T_{opt})-(T_{opt}-T_{max})(T_{opt}+T_{min}-2T)]}$$

Cardinal temperature model with inflection (CTMI)

Van Derlinden et al., 2010





- Two objectives:
  - **max** (information content)
  - **min** (experimental load)

Intro

Background

Example

Conclusions

Predictive microbiology case study

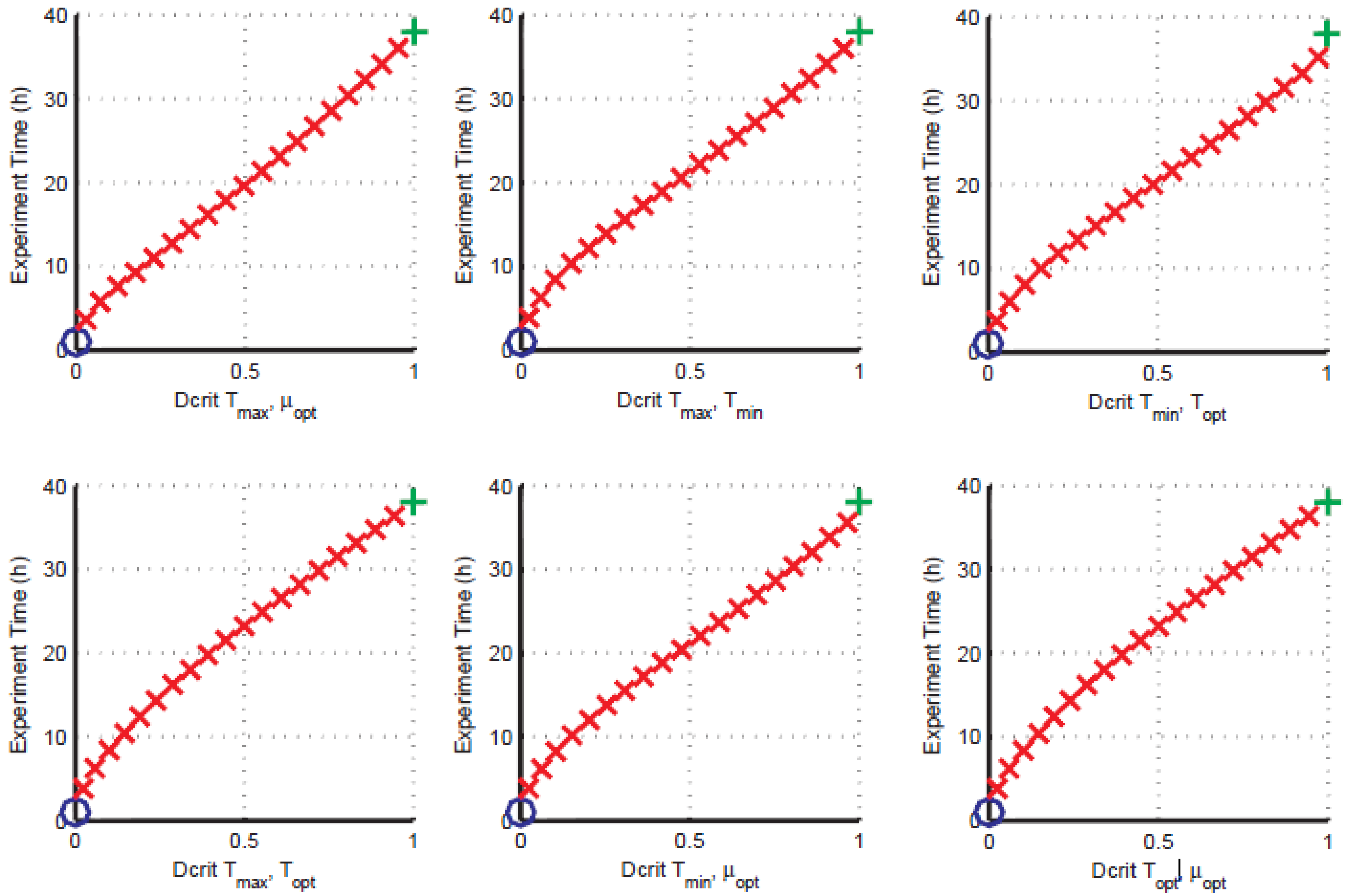
Aim

- Provide efficiently and accurately the Pareto set of information content versus experimental effort

- Control input is a piecewise linear temperature profile which is allowed to change at most 5°C/h.

(Van Derlinden et al., 2010)

Pareto fronts



Intro

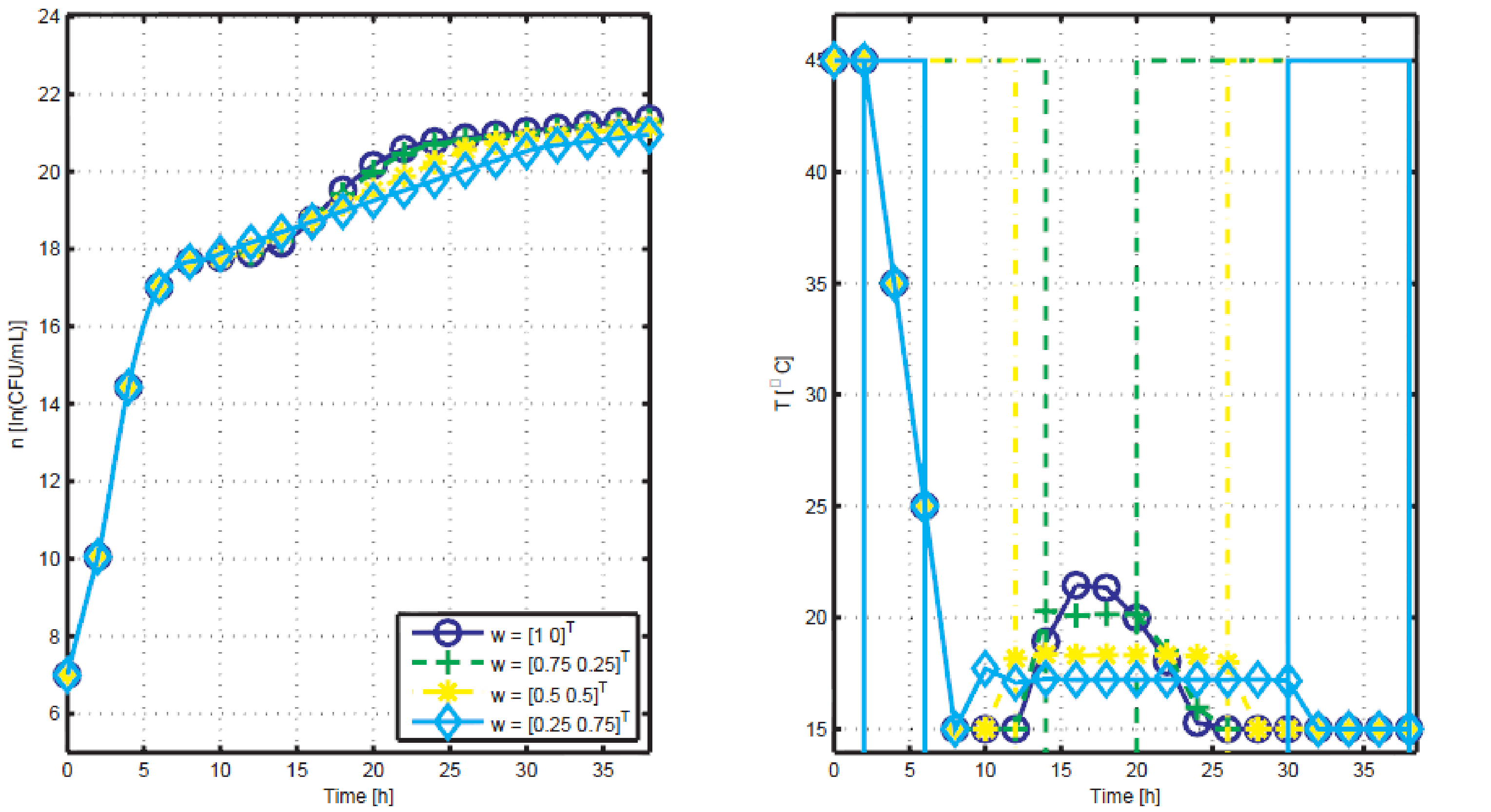
Background

Example

Conclusions

Designed experiments for $D_{T_{opt},\mu_{opt}}$

State | Temperature



Outline

- Introduction
- Background
- Example
- Conclusions

OPTEC
K.U.Leuven Optimization in Engineering Center

Intro

Background

Example

Conclusion

KATHOLIEKE UNIVERSITEIT
LEUVEN

Conclusion

- Advanced multi-objective optimisation techniques provide in a *systematic way* insight in possible alternatives

- Experiments change with (less/more) experimental time available

References

1. F. Logist, B. Houska, M. Diehl and J. Van Impe. Fast Pareto set generation for nonlinear optimal control problems with multiple objectives. Structural and Multidisciplinary Optimization, 42, 591-603 , 2010.
2. E. Walter and L. Pronzato, 1997. Identification of Parametric Models from Experimental Data, Springer.
3. B. Houska, H. Ferreau, M. Diehl. ACADO Toolkit - An Open-Source Framework for Automatic Control and Dynamic Optimization. Optimal Control Applications & Methods, 32, 398-312, 2011.
4. E. Van Derlinden, K. Bernaerts, and J. Van Impe. Simultaneous versus sequential optimal experiment design for the identification of multi-parameter microbial growth kinetics as a function of temperature. Journal of Theoretical Biology, 264, 347–355, 2010.

Thank you for your attention!

Acknowledgements

http://www.kuleuven.be/optec/

Center-of-Excellence
Optimization in Engineering (PFV/10/02)

Institute for the Promotion of Innovation through Science and Technology in Flanders (IWT-Vlaanderen).

Belgian chemistry and life sciences federation essenscia.

where chemistry meets life sciences