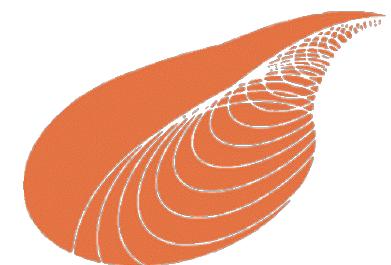


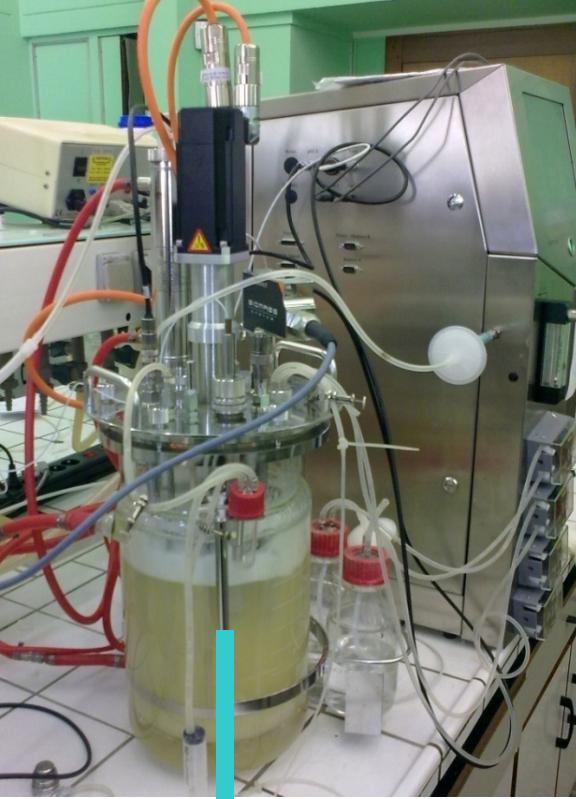


Some experiments with recursive least squares extremum-seeking: fed-batch yeast and continuous micro-algae cultures

Laurent Dewasme

Automatic Control Laboratory





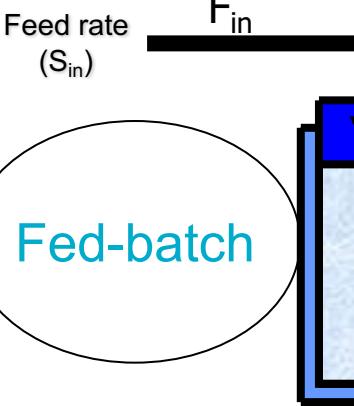
Introduction



Biotechnology



Process Optimization

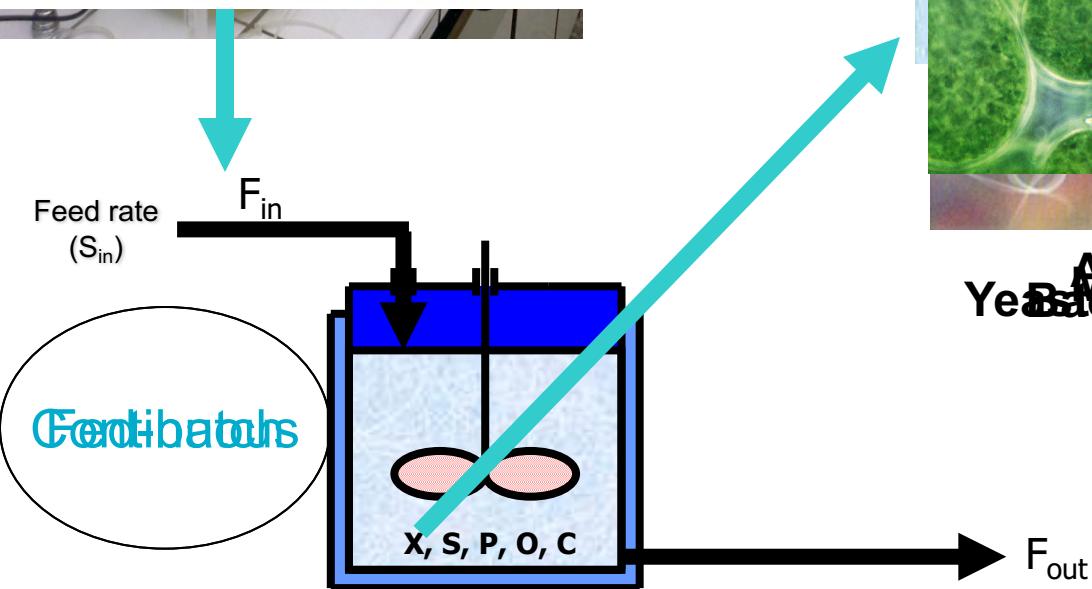
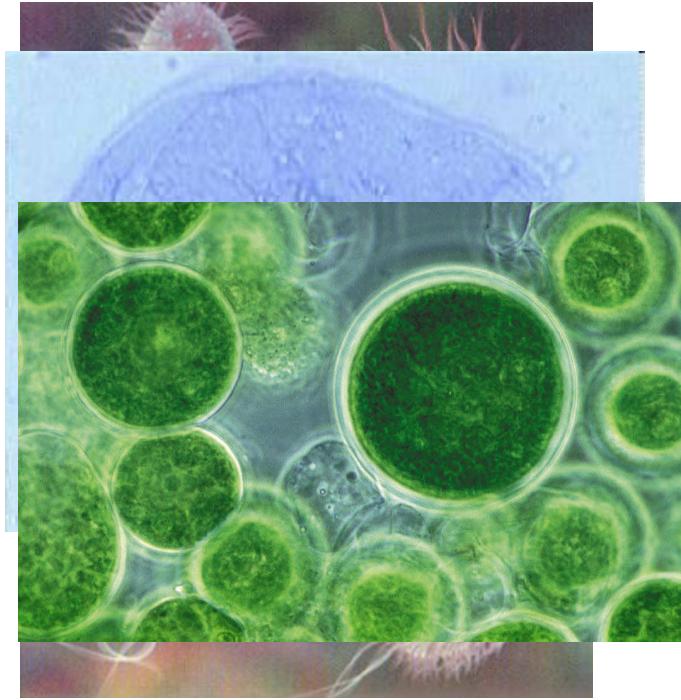
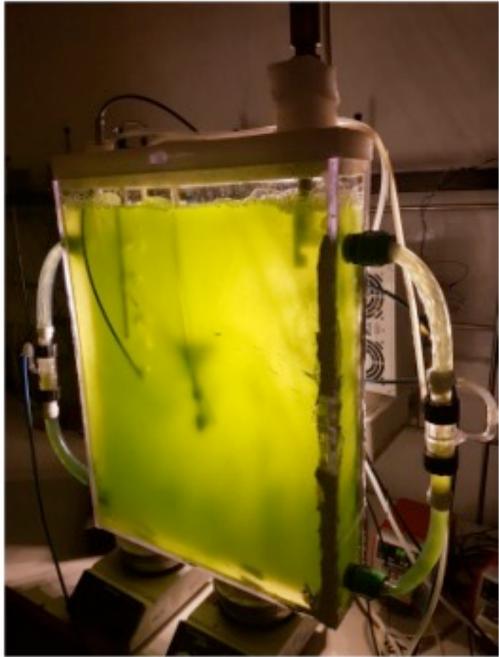


Fed-batch

Goal: productivity optimization.

- Bioprocess?
- Application?
 - Wastewater
 - Bioethanol treatment
 - Food
 - Microalgae cultures
 - Vaccines
 - Fermentations
 - Wine
 - Beer
 - Biopolymer
 - Water purification

Introduction



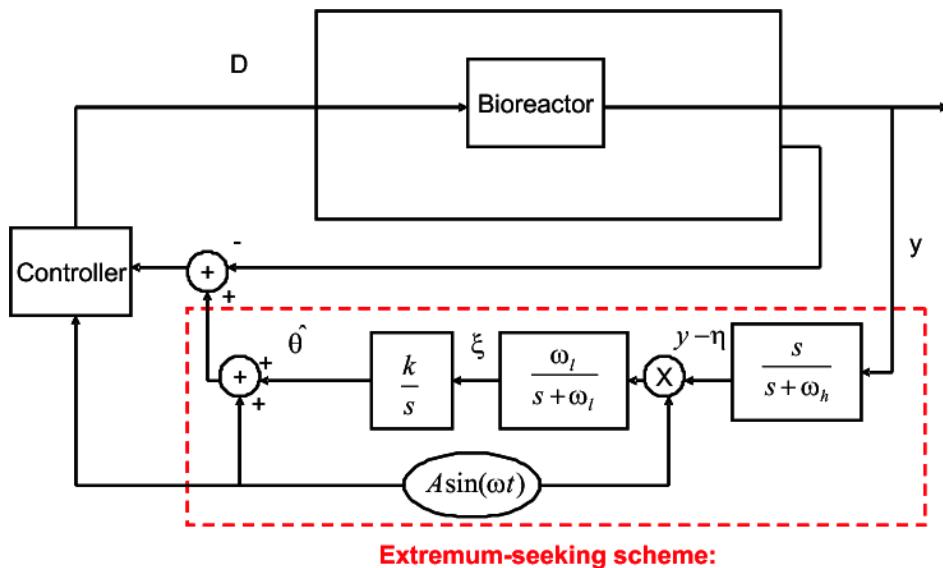
Animal cells
Bacterial cells
Yeast cells (Saccharomyces cerevisiae)

Outline

- Optimizing bioprocess productivity – Real-time optimization
 - Optimizing productivity of fed-batch cultures (yeasts)
 - Optimizing productivity of continuous cultures (μ algae): collaboration with UQAR.

Optimizing bioprocess productivity – RTO

- Real-time optimization (RTO)¹:
 - Model parameter adaptation (Batch-to-batch);
 - Modifier adaptation (Gradient and constraint cost functions match with those of the plants);
 - Direct input adaptation (Extremum-seeking)^{2,3}.



$$y = f(\hat{\theta} + A \sin(\omega t))$$
$$\dot{\hat{\theta}} = k\xi$$
$$\dot{\xi} = -\omega_l \xi + \omega_l (y - \eta) A \sin(\omega t)$$
$$\dot{\eta} = -\omega_h \eta + \omega_h y$$

Extremum-seeking scheme:

Bank of filters

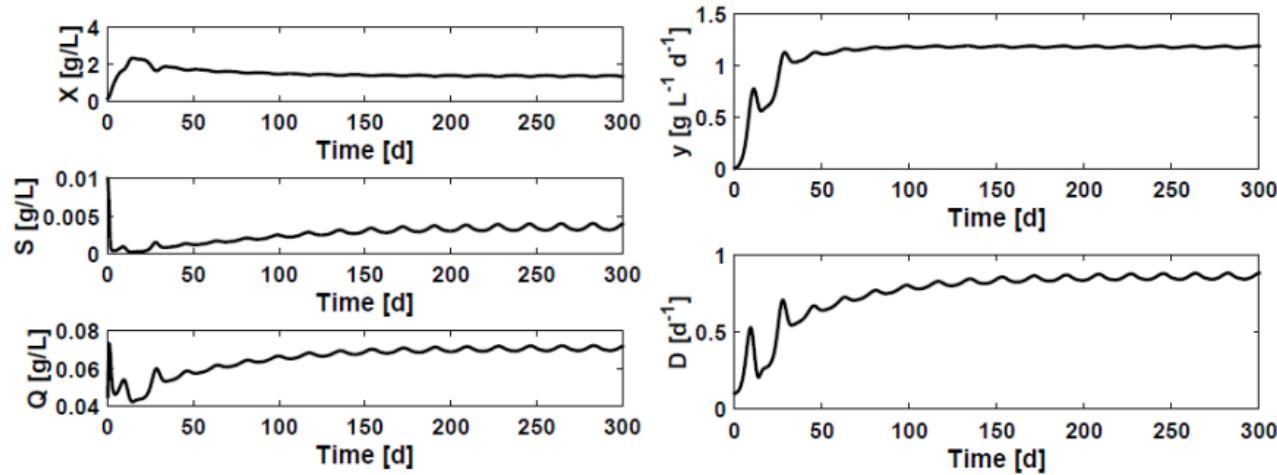
¹ B. Chachuat, B. Srinivasan, D. Bonvin, Adaptation strategies for real-time optimization, Computers and Chemical Engineering 33 (2009) 1557–1567

² K. B. Ariyur and M. Krstic, *Real-time Optimization by Extremum-seeking Control*, wiley-interscience ed. John Wiley & Sons, INC, 2003.

³ D. Dochain, M. Perrier, M. Guay, Extremum-seeking control and its applications to process and reaction systems: A survey. Mathematics and Computers in Simulation 82 (3, 2011) 369-380.

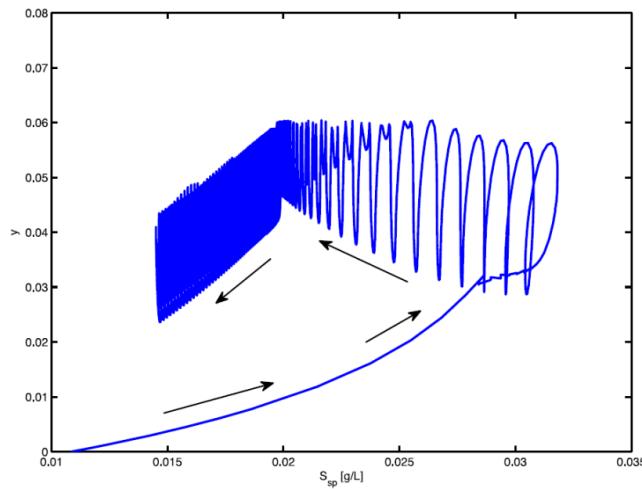
Optimizing bioprocess productivity – RTO

- Main issues/limitations of BOFES application to bioprocesses:
 - Slow (filters)-fast (controller) dynamics



Optimizing bioprocess productivity – RTO

- Main issues/limitations of BOFES application to bioprocesses:
 - Reaches the neighborhood of the optimum, depending on the excitation which should be as small as possible:
 - growth inhibition by a specific metabolite (byproduct, light intensity,...) → drift!



Optimizing bioprocess productivity – RTO

- Main issues/limitations of BOFES application to bioprocesses:
 - **Practical implementation** is difficult and ES parameter design is, most of the time, achieved by **trial and error** even if, for what concerns the excitation (dither signal) effect, literature provides studies for particular nonlinear processes^{4,5}.
 - **Practical guidelines** are necessary, based on the assumed cell growth rate (process time constant), sampling (bioprocesses = continuous-discrete processes) → **Empirical rules.**

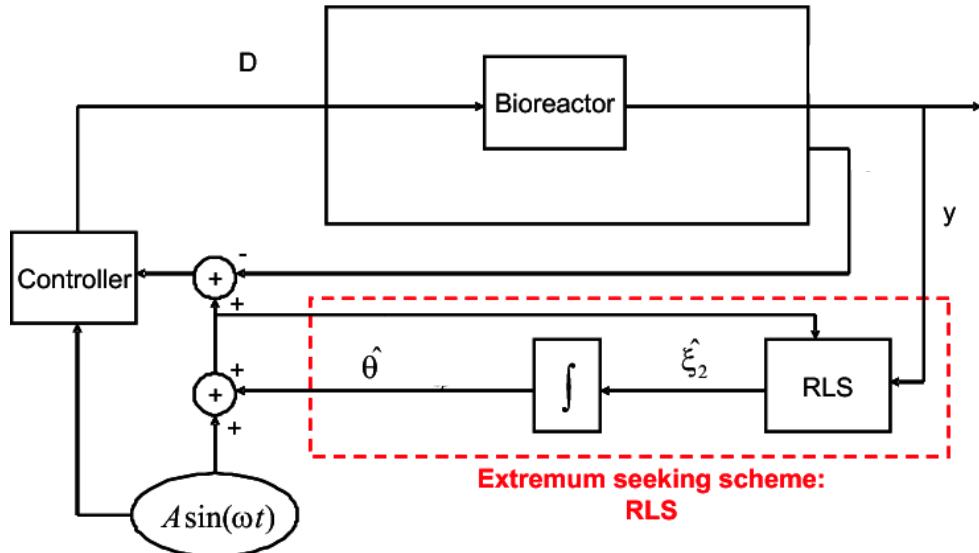
⁴ Y. Tan, D. Nesić, and I. Mareels, “On the choice of dither in extremum seeking systems: A case study,” *Automatica*, vol. 44, pp. 1446–1450, 2008.

⁵ M. Chioua, B. Srinivasan, M. Guay, and M. Perrier, “Dependence of the error in the optimal solution of perturbation-based extremum seeking methods on the excitation frequency,” *The Canadian Journal of Chemical Engineering*, vol. 85, no. 4, pp. 447 – 453, 2008.

Optimizing bioprocess productivity – RTO

▪ Solutions:

- PI extremum-seeking⁵
- Recursive least squares extremum-seeking^{6,7}.



$$e = y - \hat{\xi}\Phi$$

$$\dot{\hat{\xi}} = KR^{-1}\Phi^T e$$

$$\dot{R} = K(\Phi^T\Phi - \lambda R)$$

⁵ M. Guay, D. Dochain, A proportional-integral extremum-seeking controller design technique, Automatica 77 (2017) 61-67

⁶ L. Dewasme, B. Srinivasan, M. Perrier, A. Vande Wouwer, Extremum-seeking algorithm design for fed-batch cultures of microorganisms with overflow metabolism, Journal of Process Control 21 (2011) 1092-1104

⁷ M. Chioua, B. Srinivasan, M. Guay, M. Perrier, Performance improvement of extremum seeking control using recursive least square estimation with forgetting factor, IFAC-PapersOnLine 49 (7, 2016) 424-429.

Optimizing bioprocess productivity – practical cases

- **Optimizing productivity of fed-batch cultures (yeasts)**
- Optimizing productivity of continuous cultures (μ algae): collaboration with UQAR.

Practical cases – Yeasts

- Generic mechanistic model of culture of strains with overflow metabolism:

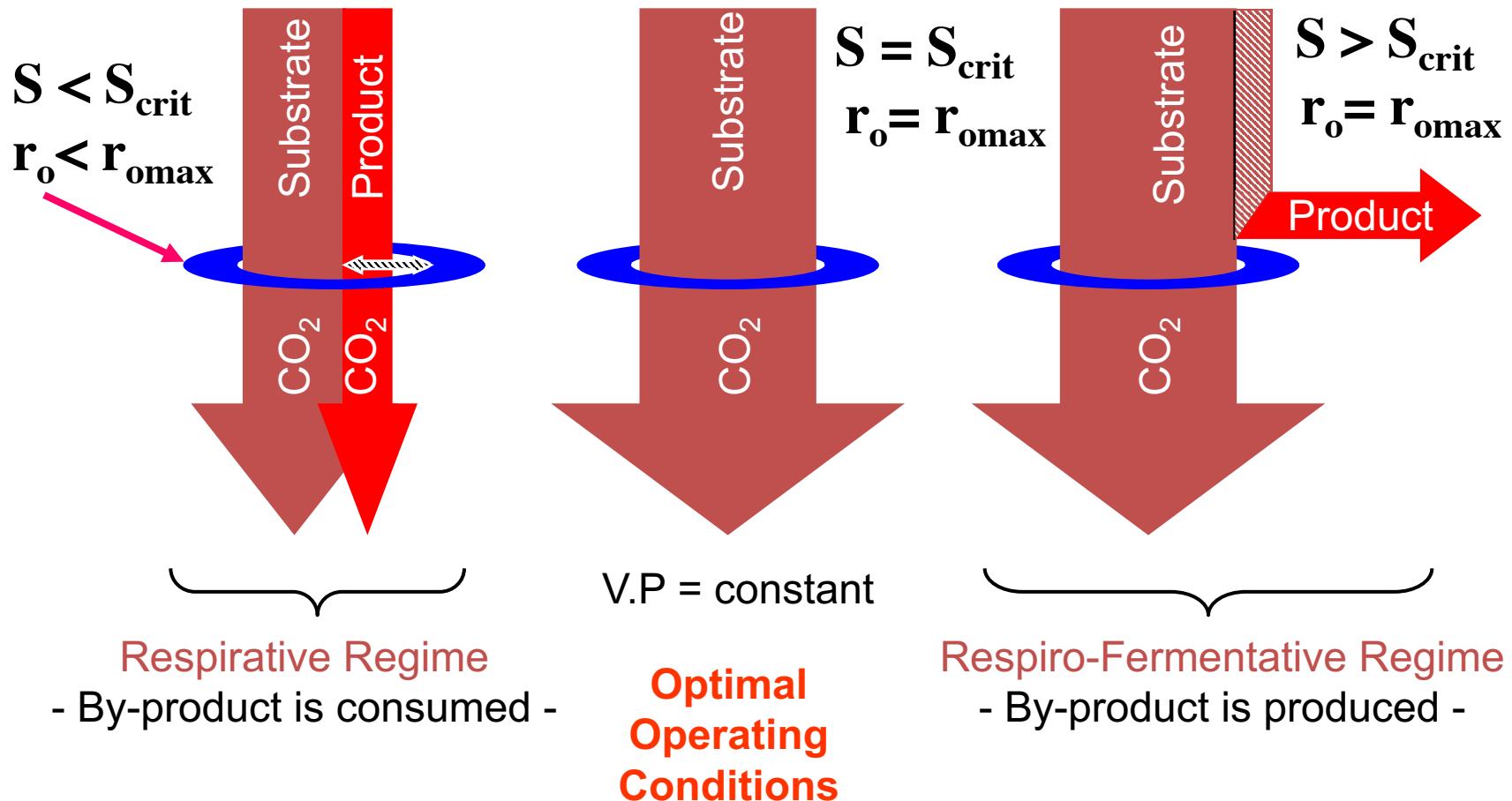
- Substrate oxidation: $k_{S1}S + k_{O1}O \xrightarrow{r_1 X \cap} k_{X1}X + k_{C1}C$
- Fermentation: $k_{S2}S + k_{O2}O \xrightarrow{r_2 X \cap} k_{X2}X + k_{P2}P + k_{C2}C$
- Byproduct oxidation: $k_{P3}P + k_{O3}O \xrightarrow{r_3 X \cap} k_{X3}X + k_{C3}C$

- Mass balances:

$$\begin{bmatrix} \dot{X} \\ \dot{S} \\ \dot{P} \\ \dot{O} \\ \dot{C} \end{bmatrix} = \begin{bmatrix} k_{X1} & k_{X2} & k_{X3} \\ -k_{S1} & -k_{S2} & 0 \\ 0 & k_{P2} & -k_{P3} \\ -k_{O1} & -k_{O2} & -k_{O3} \\ k_{C1} & k_{C2} & k_{C3} \end{bmatrix} \cdot \begin{bmatrix} r_1 \cdot X \\ r_2 \cdot X \\ r_3 \cdot X \end{bmatrix} - D \cdot \begin{bmatrix} X \\ S \\ P \\ O \\ C \end{bmatrix} + \begin{bmatrix} 0 \\ S_{in} \cdot D \\ 0 \\ OTR \\ 0 \end{bmatrix} - \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ CTR \end{bmatrix}$$

Practical cases – Yeasts

- Limited respiratory capacity (overflow metabolism):



Practical cases – Yeasts

- Control objectives:

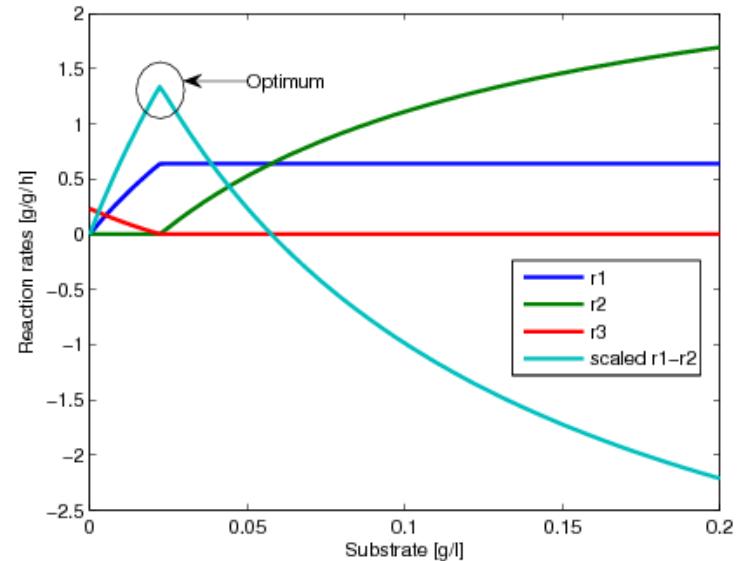
- Optimal operating conditions: $S = S_{crit}$ and $r_2 = r_3 = 0$

$$S_{crit} = \frac{K_S r_o}{k_5 \mu_S - r_o}$$

- Reformulation:

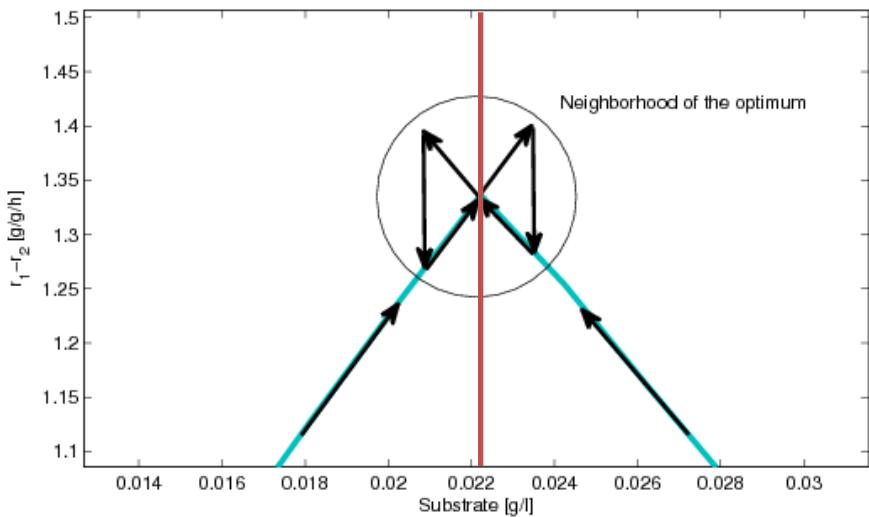
$$\max_{S_{crit}} Y_x = \max_{S_{crit}} \frac{1}{t_f} \frac{V(t_f)X(t_f) - V_0 X_0}{S_{in}(V(t_f) - V_0)}$$

$$\Leftrightarrow \max_{S_{crit}} (r_1 - r_2)X = \max_{S_{crit}} (\varphi_1 - \varphi_2)$$



Practical cases – Yeasts

- Neighborhood of the optimum



Extremum → « cusp »!

$$r_1 - r_2 = \begin{cases} r_1 = \frac{\mu_S S}{S + K_S} \text{ if } S \leq S_{crit}^- \\ r_{1_{max}} - r_2 = \frac{2r_O}{K_{OS}} - \frac{\mu_S S}{S + K_S} \text{ if } S \geq S_{crit}^+ \end{cases}$$

$$(r_1 - r_2)' = \begin{cases} r'_1 = \frac{\mu_S K_S}{(S + K_S)^2} \text{ if } S \leq S_{crit}^- \\ (r_{1_{max}} - r_2)' = -\frac{\mu_S K_S}{(S + K_S)^2} \text{ if } S \geq S_{crit}^+ \end{cases}$$

$$e = y - \hat{\xi}\Phi$$

$$\dot{\hat{\xi}} = KR^{-1}\Phi^T e$$

$$\dot{R} = K(\Phi^T \Phi - \lambda R)$$

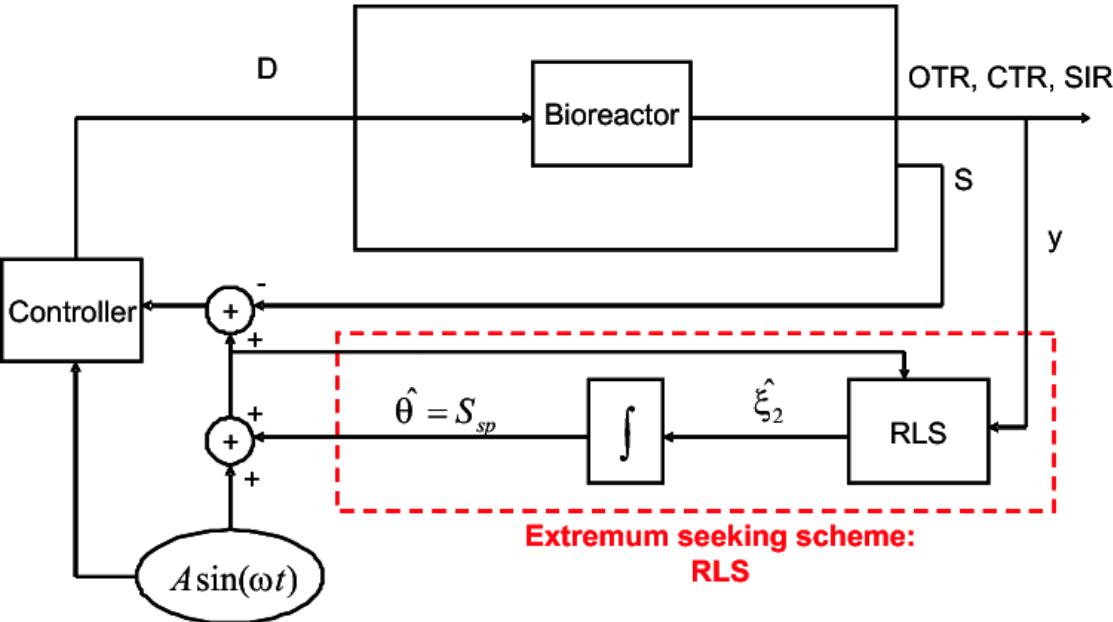
$$\hat{\xi} = \begin{bmatrix} \hat{\xi}_1 & \hat{\xi}_2 \end{bmatrix}$$

$$\Phi = \begin{bmatrix} 1 & S_{crit} \end{bmatrix}$$

$$\dot{\hat{S}_{crit}} = k_i \hat{\xi}_2$$

Practical cases – Yeasts

- RLS strategy:



$$e = y - \hat{\xi}\Phi$$

$$\dot{\hat{\xi}} = KR^{-1}\Phi^T e$$

$$\dot{R} = K(\Phi^T\Phi - \lambda R)$$

$$\dot{\hat{S}}_{crit} = k_i \hat{\xi}_2$$

$$\hat{\xi} = \begin{bmatrix} \hat{\xi}_1 & \hat{\xi}_2 \end{bmatrix}$$

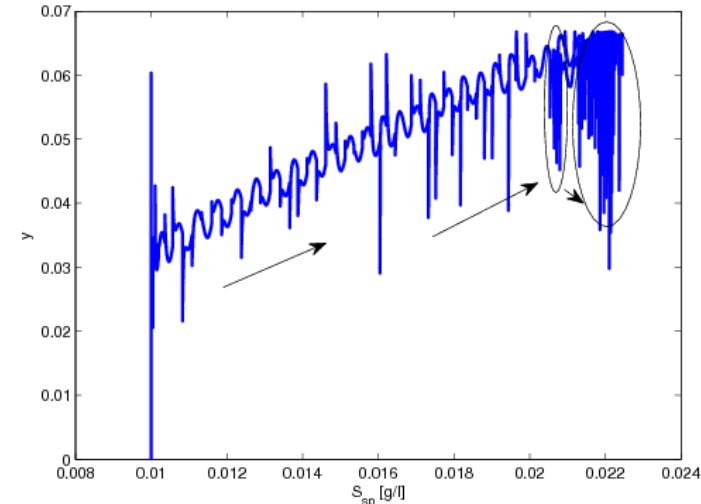
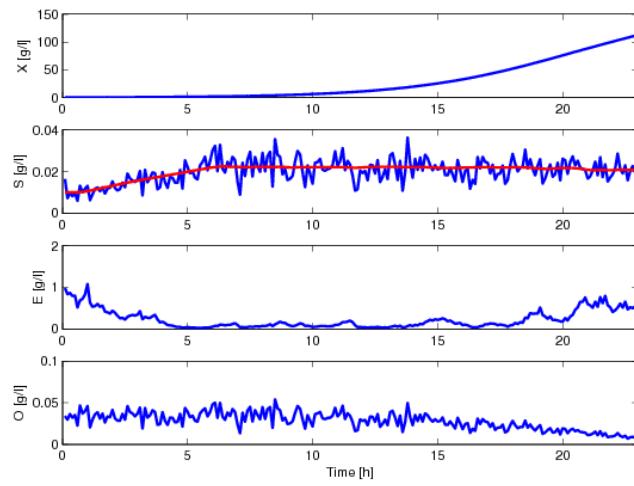
$$\Phi = \begin{bmatrix} 1 & S_{crit} \end{bmatrix}$$

Practical cases – Yeasts

- Numerical results:

- Application to classical small scale (20 liters) cultures of *S. cerevisiae* (baker's yeast model).
- Initial and operating conditions:

$X_0 = 0,4\text{g/l}$, $S_0 = 0,05\text{g/l}$, $E_0 = 1\text{g/l}$, $O_0 = 0,035\text{g/l}$, $V_0 = 5\text{l}$ and $S_{\text{in}} = 350\text{g/l}$.

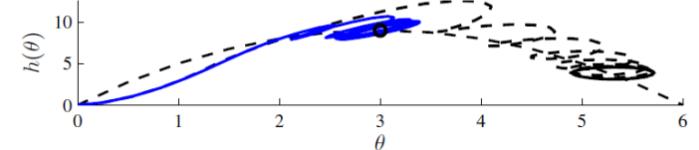
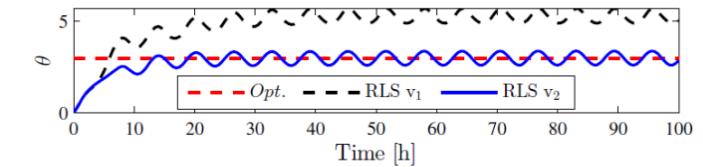
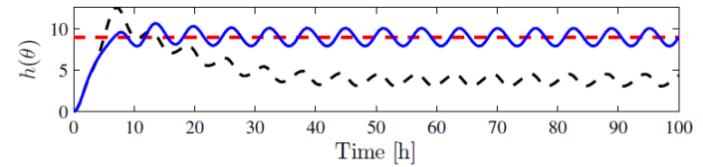
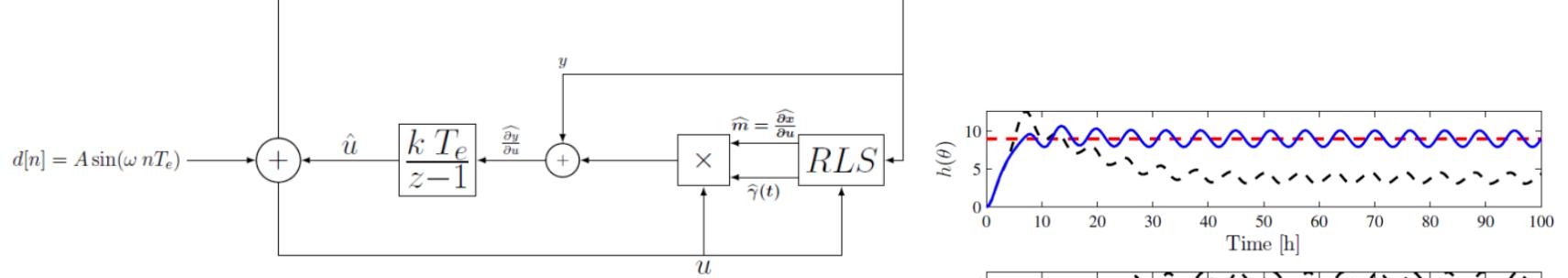
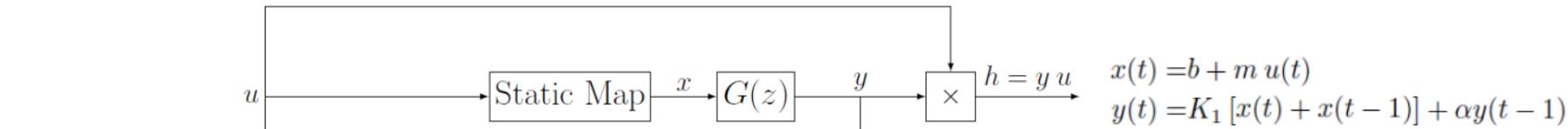


Optimizing bioprocess productivity – practical cases

- Optimizing productivity of fed-batch cultures (yeasts): previous PhD thesis work.
- Optimizing productivity of continuous cultures (μ algae): collaboration with UQAR.

Practical cases - μ algaе

- Importance of process output dynamics: assumption of Hammerstein-Wiener model → convergence impact!



$$\begin{aligned} \widehat{\frac{\partial h}{\partial u}} &= \widehat{\frac{\partial u \cdot y}{\partial u}} = y + u \frac{\widehat{\partial y}}{\partial u} \\ &= y + u \frac{\widehat{\partial y}}{\partial x} \frac{\widehat{\partial x}}{\partial u} \\ &= y + u \widehat{\gamma}(t) \widehat{m} \end{aligned}$$

$$\widehat{\gamma}(t) = \frac{y(t)}{\widehat{m}u(t) + \widehat{b}}$$

Practical cases - μ alga

- Micro-algae continuous culture model of *Isochrysis galbana*⁸:

$$\begin{aligned}\dot{X} &= \mu(Q, I, \theta) X - D X - R X \\ \dot{S} &= -\rho(S, Q) X + D(S_{in} - S) \\ \dot{Q} &= \rho(S, Q) - \mu(Q, I, \theta) Q \\ \dot{I}^* &= \delta \mu(Q, I, \theta) (\bar{I} - I^*)\end{aligned}$$

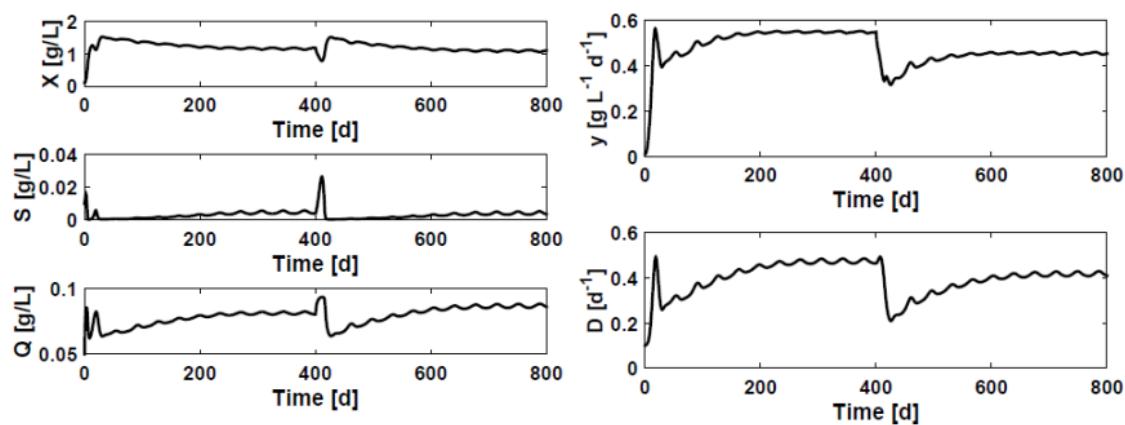
$$\mu(Q, I, \theta) = \mu_{max} \frac{I}{K_{sI} + I + \left(\frac{I^2}{K_{II}}\right)} \left(1 - \frac{Q_{min}}{Q}\right)$$

$$\rho(S, Q) = \rho_{max} \frac{S}{S + K_S} \left(1 - \frac{Q}{Q_{max}}\right)$$

BOFES on a static map

Operating Conditions :

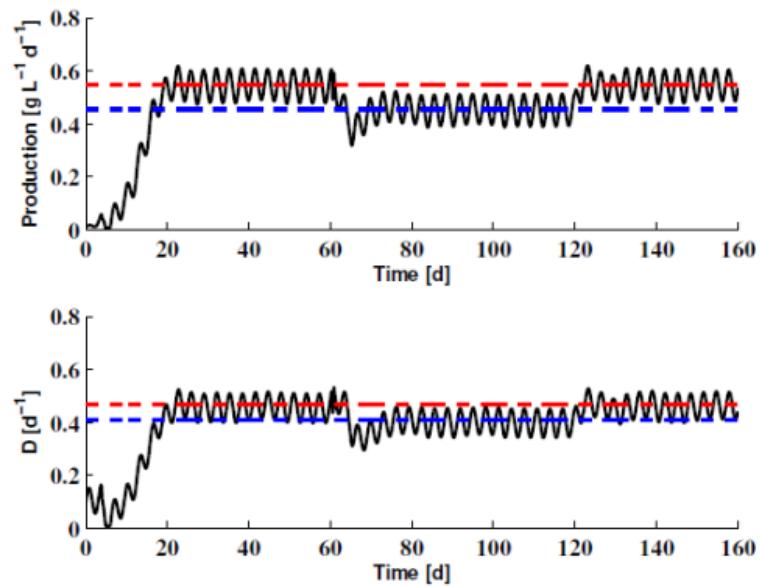
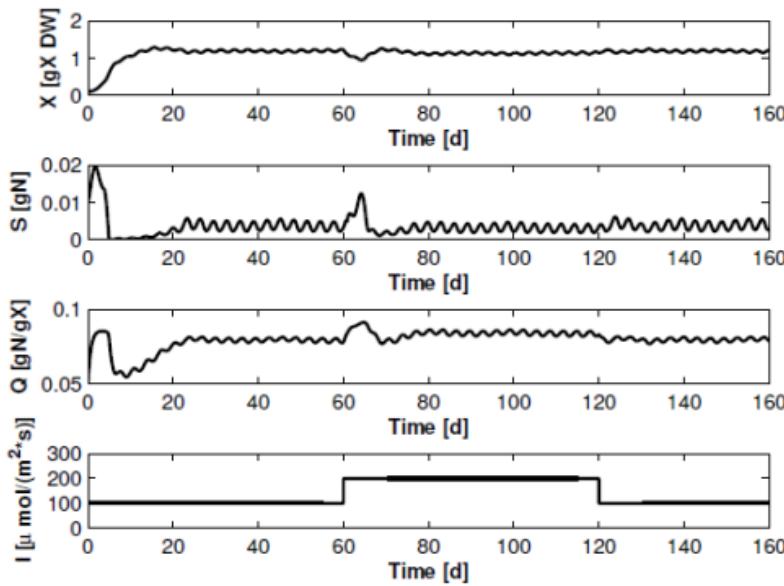
$$I = 100 \mu\text{mol m}^{-2}\text{s}^{-1} \text{ if } t < 400 \text{ else } I = 200 \mu\text{mol m}^{-2}\text{s}^{-1}$$



⁸ O. Bernard, B. Rémond. Validation of a simple model accounting for light and temperature effect on microalgal growth. Bioresource Technology 123 (2012) 520-527.

Practical cases - μ alga

- Micro-algae continuous culture model of *Isochrysis galbana*⁸:
RLSES with H-W assumption



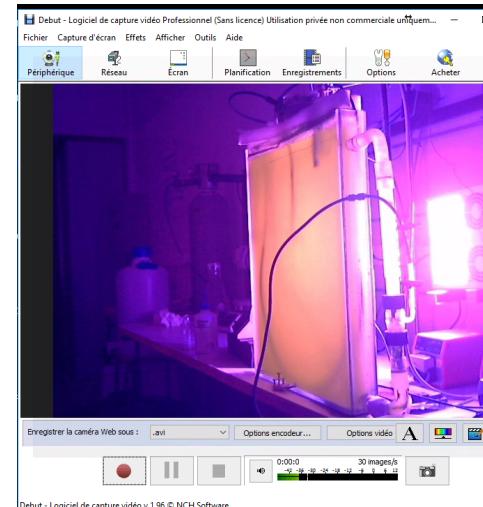
⁸ O. Bernard, B. Rémond. Validation of a simple model accounting for light and temperature effect on microalgal growth. Bioresource Technology 123 (2012) 520-527.

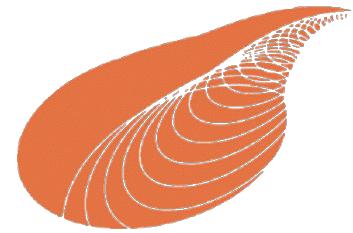
Conclusion

- RLSES offers the possibility to accelerate the convergence towards the extremum (see also PIES for fast convergence);
- The method is not model-based and requires only the existence of a convex objective function (a priori knowledge);
- It has the advantage to be very practical and not difficult to implement on a real plant;
- Some references:
 - L. Dewasme, B. Srinivasan, M. Perrier, A. Vande Wouwer, Extremum seeking algorithm design for fed-batch cultures of microorganisms with overflow metabolism, *Journal of Process Control* 21 (2011), 1092-1104
 - L. Dewasme, Y. Samyudia, A. Vande Wouwer. Modeling and optimization of bioethanol production process. *19th IEEE International Conference on System Theory, Control and Computing (ICSTCC)*, 37-42, Cheile Gradistei - Fundata, Romania (2015)
 - L. Dewasme, C. G. Feudjio Letchindjio, I. Torres Zuniga, A. Vande Wouwer, Micro-algae productivity optimization using extremum-seeking control. *25th Mediterranean Conference on Control and Automation (MED)*, Valetta, Malta (2017).
 - C. G. Feudjio Letchindjio, J.-S. Deschênes, L. Dewasme, A. Vande Wouwer, Extremum-seeking based on a Hammerstein-Wiener representation. Submitted to *10th IFAC Symposium on Advanced Control of Chemical Processes (ADCHEM)*, Shenyang, China (2018).

Perspectives

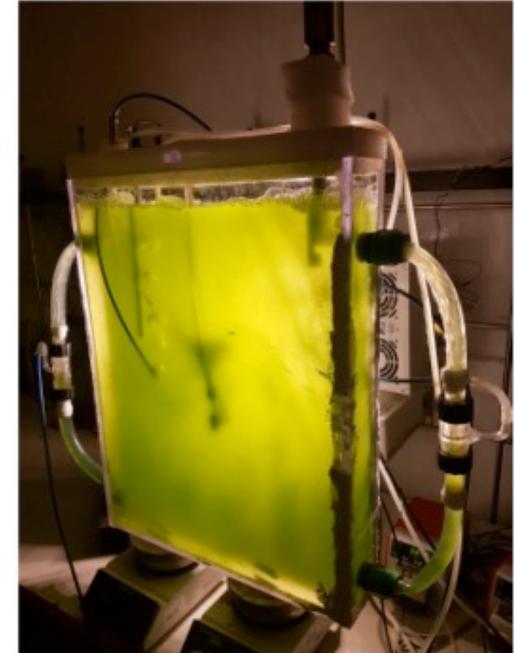
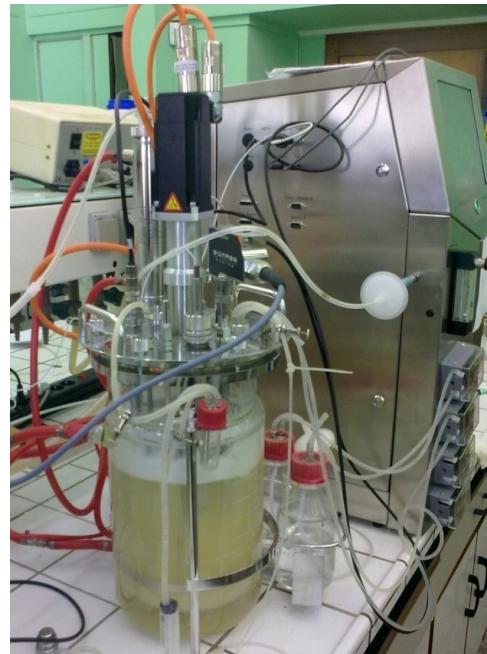
- Mathematical characterization of the H-W RLSES with other efficient ES strategies through benchmark examples from the literature
- Extension of the μ alga model accounting for light and chlorophyll effects
- Application to a real plant located in UMons (using *Dunaliella tertiolecta* → currently running)





Thank you for your attention!

IAP VII/19 - DYSCO



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