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Advanced computational tools to enhance continuous monoclonal antibody production

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1. Konstantinov, K.B. and C.L. Cooney, White Paper on Continuous Bioprocessing May 20-21, 2014 Continuous Manufacturing Symposium. Journal of Pharmaceutical Sciences, 2015. 104(3): p. 813-820. 2. Kiparissides, A., M. Koutinas, C. Kontoravdi, A. Mantalaris, and E.N. Pistikopoulos, 'Closing the loop' in biological systems modeling — From the in silico to the in vitro. Automatica, 2011. 47(6): p. 1147-1155. 3. Aumann, L. and M. Morbidelli, A continuous multicolumn countercurrent solvent gradient purification (MCSGP) process. Biotechnology and Bioengineering, 2007. 98(5): p. 1043-1055. 4. Pistikopoulos, E.N., N.A. Diangelakis, R. Oberdieck, M.M. Papathanasiou, I. Nascu, and M. Sun, PAROC—An integrated framework and software platform for the optimisation and advanced model-based control of process systems. Chemical Engineering Science, (0). 5. Dua, P., K. Kouramas, V. Dua, and E.N. Pistikopoulos, MPC on a chip-Recent advances on the application of multi-parametric model-based control. Computers and Chemical Engineering, 2008. 32(4-5): p. 754-765.

Advanced computational tools to enhance continuous monoclonal antibody production

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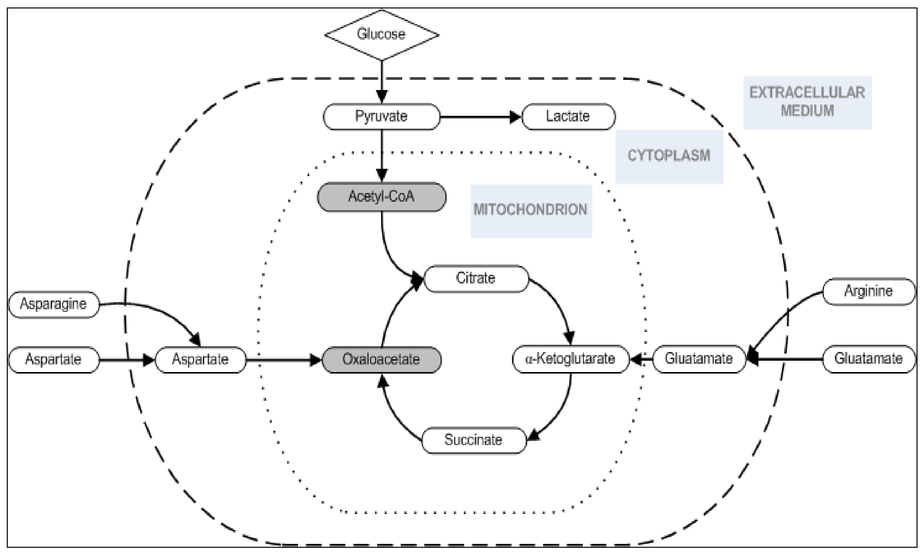
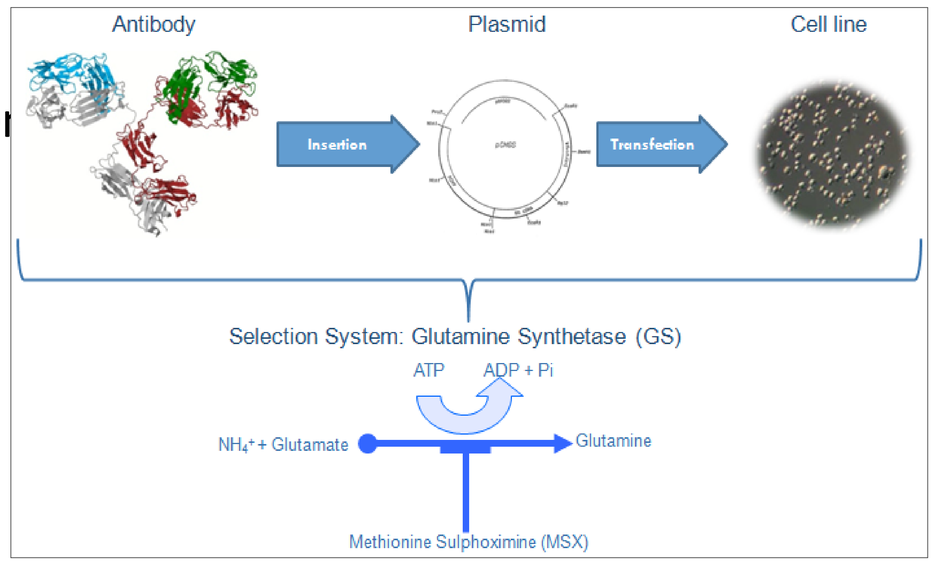
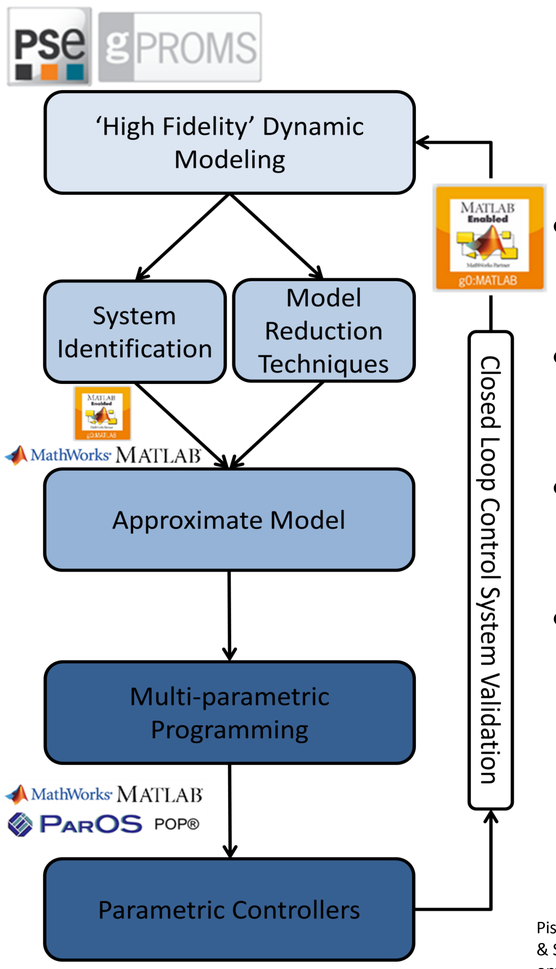
The System



- GS-NS0 cell culture syste
- **5** Key compounds:
  - Glucose
  - Glutamate
  - Arginine
  - Asparagine
  - Aspartate



PAROC Framework and Software Platform



- **Model-based** controller development.
- **Seamless, in-silico** validation.
- Software **interoperability**
- Map of solutions on small, embedded devices (**MPC-on-a-chip**).

Pistikopoulos, E. N., Diangelakis, N. A., Oberdieck, R., Papathanasiou, M. M., Nascu, I. & Sun, M. 2015. PAROC—An integrated framework and software platform for the optimisation and advanced model-based control of process systems. *Chemical Engineering Science,* 136, 115-138.

System Identification & Multi-parametric Programming Problem

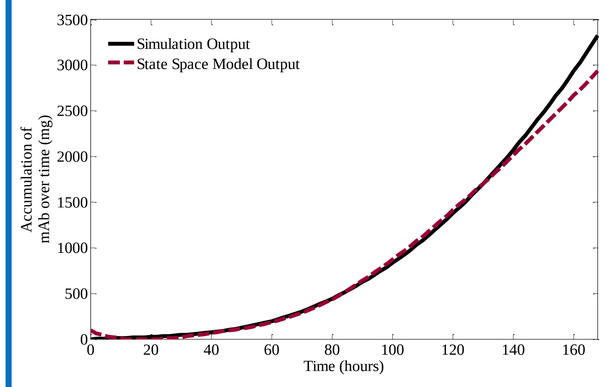


Figure 2 Comparison between the process model output (simulation output, –) and the designed state space model (state space model output, - - -).

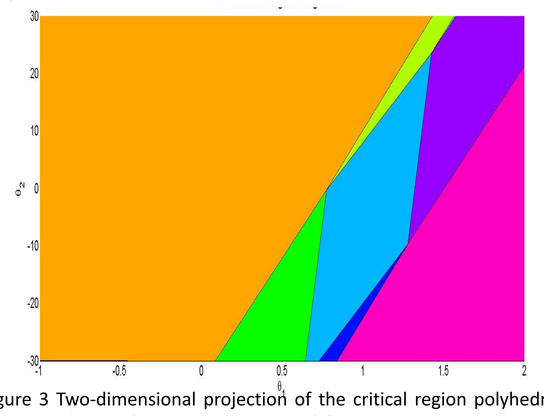


Figure 3 Two-dimensional projection of the critical region polyhedral corresponding to the six state space model.

- **2** states
- **2** hours sampling time
- ~**95%** fit on the process model

- Output Horizon: **2**
- Control Horizon: **2**
- **4** Parameters

High-fidelity Dynamic Modeling

Volume	Viable Cells	Dead Cells	Total Cells
$\frac{dV}{dt} = F_{in}$	$\frac{dVX_v}{dt} = VX_v(\mu - \mu_d)$	$\frac{dVX_d}{dt} = VX_v\mu_d$	$X_t = X_V + X_d$

Growth Rate

$$\mu = \mu_{max}\left(\frac{[GLC]}{K_{glc}+[GLC]}\right)\left(\frac{[GLU]}{K_{glu}+[GLU]}+\frac{[ARG]}{K_{arg}+[ARG]}\right)\left(\frac{[ASP]}{K_{asp}+[ASP]}+\frac{[ASN]}{K_{asn}+[ASN]}\right)$$

Death Rate

$$\mu_d = \mu_{d,max}\left(\frac{K_{glc,lim}}{K_{glc,lim}+[GLC]}+\frac{K_{glu,lim}}{K_{glu,lim}+[GLU]}+\frac{K_{arg,lim}}{K_{arg,lim}+[ARG]}+\frac{K_{asp,lim}}{K_{asp,lim}+[ASP]}+\frac{K_{asn,lim}}{K_{asn,lim}+[ASN]}\right)$$

Glucose and Lactate

$$\frac{d(V[GLC])}{dt} = -VX_v(Q_{x,glc}+Q_{glyc,glc}+Q_{tca,glc})+F_{in}[GLC]_{in}$$

$$\frac{d(V[LAC])}{dt} = -VX_v * 2 * Q_{glyc,glc}$$

$$Q_{x,glc} = \mu/Y_{x,glc} \qquad Q_{glyc,glc} = \left(\frac{\mu}{Y_{gly,glc}}+M_{gly,glc}\right) \qquad Q_{tca,glc} = \left(\frac{\mu}{Y_{tca,glc}}+M_{tca,glc}\right)$$

Amino Acids Balance

$$\frac{d(V[AA])}{dt} = -VX_v(Q_{x,AA}+Q_{tca,AA})+F_{in}[AA]_{in}$$

$$Q_{x,AA} = \mu/Y_{x,glu} \qquad Q_{tca,AA} = \left(\frac{\mu}{Y_{tca,AA}}+m_{tca,AA}\right)$$

Monoclonal antibody

$$\frac{d(V[mAb])}{dt} = VX_v m_{mAb,x}$$

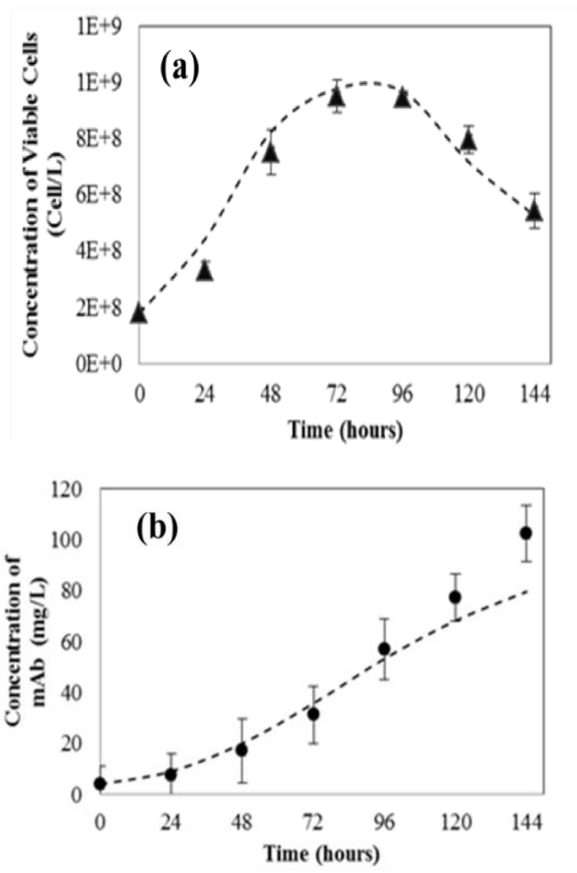


Figure 1. Comparison of simulation results and experimental data for the GS-NS0 Batch Cultures: (a) Concentration of viable cells (Cells/L): (▲) Experimental Results (---) Predictive Model Results. (b) mAb concentration (mg/L): (●) Experimental Results (---)Predictive Model Results. The experimental data used here are obtained from Kiparissides et al. (2015).

Kiparissides, A., Pistikopoulos, E. N. & Mantalaris, A. 2015. On the model-based optimization of secreting mammalian cell (GS-NS0) cultures. Biotechnology and Bioengineering, 112, 536-548.

- **25** Differential and Algebraic Equations.
- **26** Differential and Algebraic Variables.
- **25** Parameters.

'Closed-loop' Validation

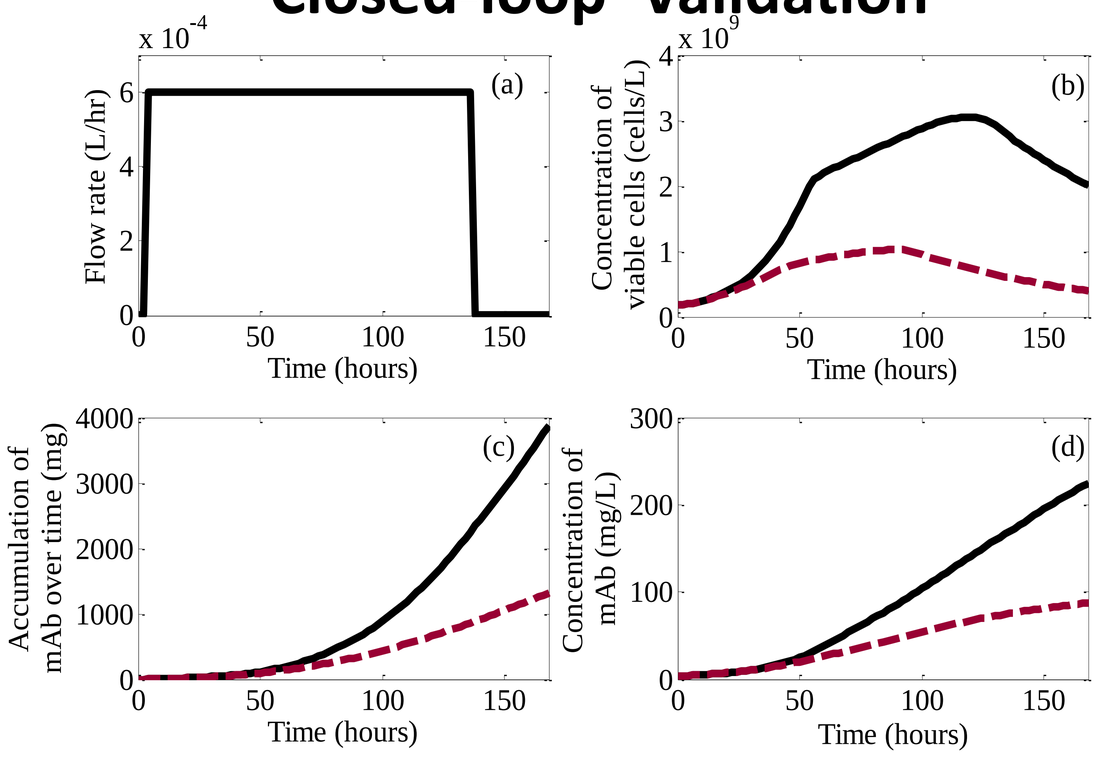


Figure 4 Results from the in-silico, 'closed-loop' validation of the controller for 168 hours culture time: (a) profile of the flow rate (L/hr) (input) as indicated by the controller and comparison of the system performance under the operation of the controller (–) and without controller (- - -)_ for: (b) concentration of viable cells (mg/mL), (c) accumulation of mAb (mg) and (d) mAb concentration (mg/L).

- **Increased** culture **productivity**.
- **Prolonged** culture **times**.
- **Increased** cell **density**.
- **Smart** control input – **biological** significance.

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