FerroFlow: unlocking simulation software for Bioprocesses - control strategy for penicillin fermentation case study

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Purpose of the study

A standard methodology is developed for fermentation modeling using AVEVA Process simulation (APS). Based on the Indpensim dataset[1] for penicillin fermentation, the results demonstrate the potential for chemical engineering software to be used for bioprocess modeling and optimization of cost of production and feeding strategy for fermentation. This project is part of FerroFlow, a pre-CVR startup that aims to develop bioprocess unit operations using chemical engineering software.

Characterization

IN	Products
Sugar	Penicillin G
PAA	Biomass
Nutrients	CO_2
O_2	Citric Acid
H_2SO_4	
H_2O	
Soybean oil	

- ✓ Component modeling (penicillin, biomass)
- ✓ Thermodynamic model choice (ideal gas law)
- ✓ Indpensim model (Goldrick et al. 2015[1])

Physics

✓ k_La (Goldrick et al. 2015[1])

$$k_La = a\left(\frac{P_t}{V_l}\right)^b u_s^c\, \mu_{app}^d \left(1-\frac{Q_{oil}}{V_l}\right)^e$$

$$P_{stir} = P_{ug}\, E_1 \left(\frac{Q_g}{N\, V_l}\right)^{E_2} \left(\frac{N^2 D_i^4}{g d_w V_l^{\frac{2}{3}}}\right)^{E_3}$$

✓ Viscosity (Goudar et al. 1999[2])

$$\mu_{app} = K\,\gamma^{n-1}$$

$$\gamma = k_s N$$

k_s: Metzner and Otto constant
N: impeller speed

✓ DO_2, DCO_2 (Villadsen et al. 2015[3])

$$r_{Na} = k_La\,(O_{2,sat} - DO_2)$$

$$O_{2,sat} = y_{O_2,in} P \times 0.027 \times e^{\frac{1142}{T}} M_{O_2}$$

Biology

Based on established methodology in Villadsen et al., Bioreaction Engineering Principles[3]

- *Product reaction*

$$Sugar + Y_{OS,p}\; O_2 + Y_{NS,p}\; NH_3 + Y_{S_2S,p}\; PAA + Y_{S_3S,p}\; H_2SO_4 \Leftrightarrow Y_{PS,p}\; Penicillin + Y_{CS,p}\; CO_2 + Y_{WS,p}\; H_2O$$

$$RQ_{p,theoric} = \frac{Y_{CS,p}}{Y_{OS,p}}$$

- *Growth reaction*

$$Sugar + Y_{OS,g}\; O_2 + Y_{NS,g}\; NH_3 + Y_{S_2S,g}\; PAA \Leftrightarrow Y_{XS,g}\; Biomass + Y_{P_2S,g}\; Citric\ Acid + Y_{CS,g}\; CO_2 + Y_{WS,g}\; H_2O$$

$$RQ_{g,theoric} = \frac{Y_{CS,g}}{Y_{OS,g}}$$

- *Maintenance reaction*

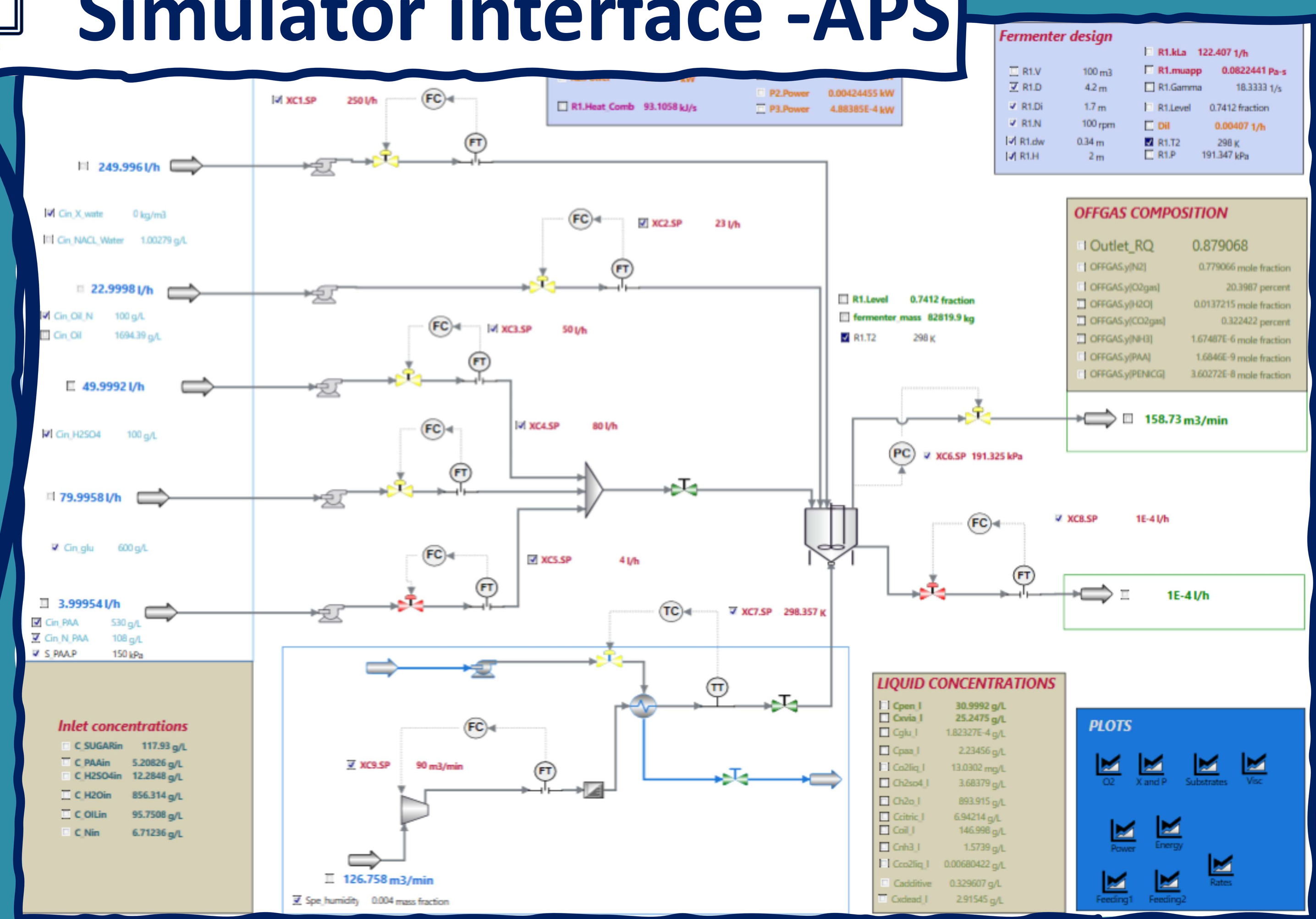
$$m_s\; Sugar + m_o\; O_2 + \Leftrightarrow m_s\; CO_2 + m_w\; H_2O$$

$$RQ_{m,theoric} = \frac{m_c}{m_o} = 1$$

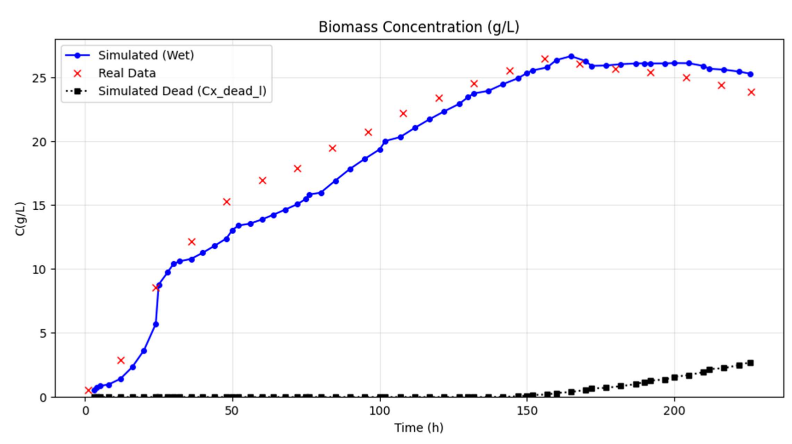
Calculated From data[1]

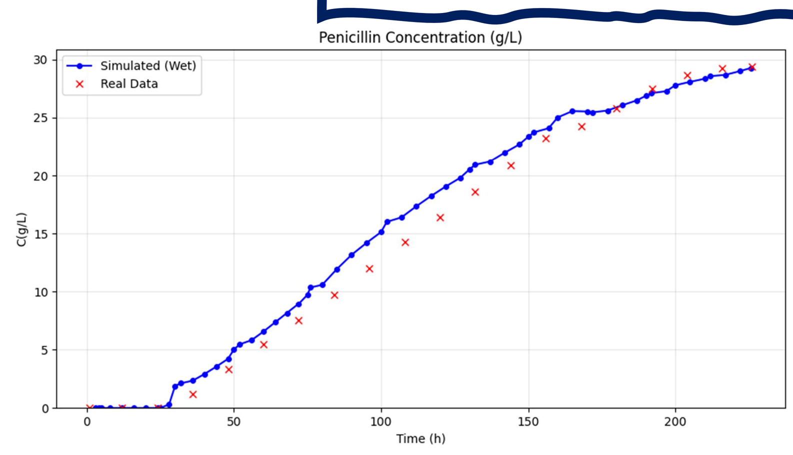
Scientific advantage → Allows direct testing of alternative product formations if balances do not reconcile with measured industrial data

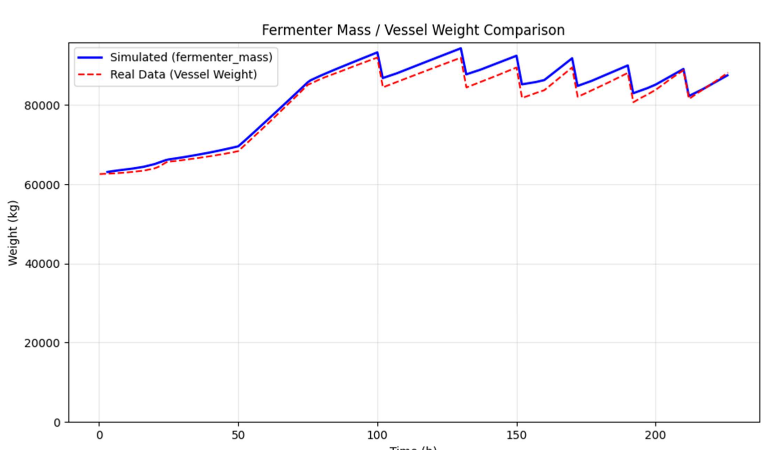
Simulator interface -APS

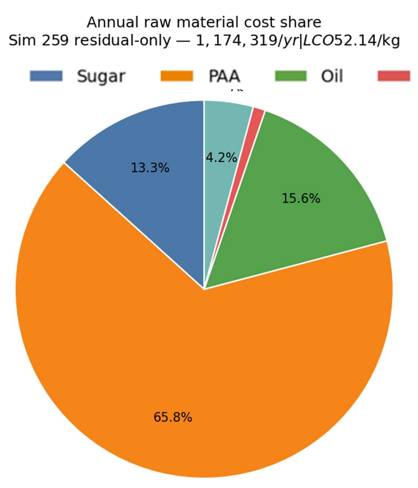


Validation - Optimization





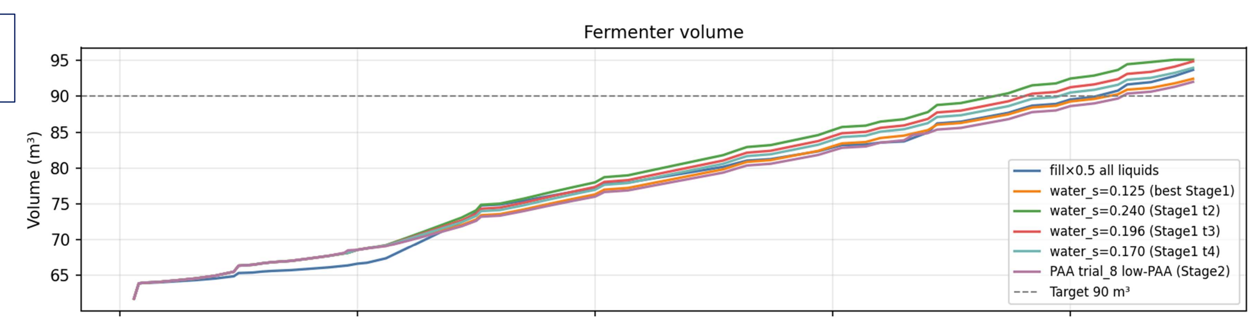




- ✓ Penicillin and biomass concentration, k_La, viscosity and fermenter mass validated
- ✓ Optimization based on 2 targets: LCO minimization and final fermenter volume
- ✓ Optuna optimization in Python
- ✓ Constraints: variation of feeding of water for discharge and precursor (PAA) feeding

Levelized Cost of Operation (LCO)

Before opti	After opti
\$52.14/kg	\$36.86/kg



KEY RESULTS

Standard methodology for fermentation modeling → Techno-economic assessment capabilities for bioprocess → Optimization of fermentation control and feeding strategy in APS

[1] Goldrick S, Ştefan A, Lovett D, Montague G, Lennox B. The development of an industrial-scale fed-batch fermentation simulation. J Biotechnol. 2015 Jan 10;193:70-82. doi: 10.1016/j.jbiotec.2014.10.029
[2] Goudar CT, Strevett KA, Shah SN. Influence of microbial concentration on the rheology of non-Newtonian fermentation broths. Appl Microbiol Biotechnol. 1999 Mar;51(3):310-5. doi: 10.1007/s002530051396. PMID: 10222579.
[3] John Villadsen , Jens Nielsen , Gunnar Lidén, Bioreaction Engineering Principles, Springer, 2011