



Performance Limits in Feedback Control of Biomass in Continuous Fermentation

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Why track biomass at all?

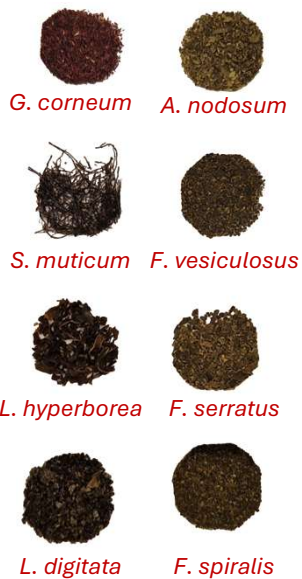


Figure 1: Bioreactor at NTNU's Microbial Feedback Control laboratory.

The monoculture case

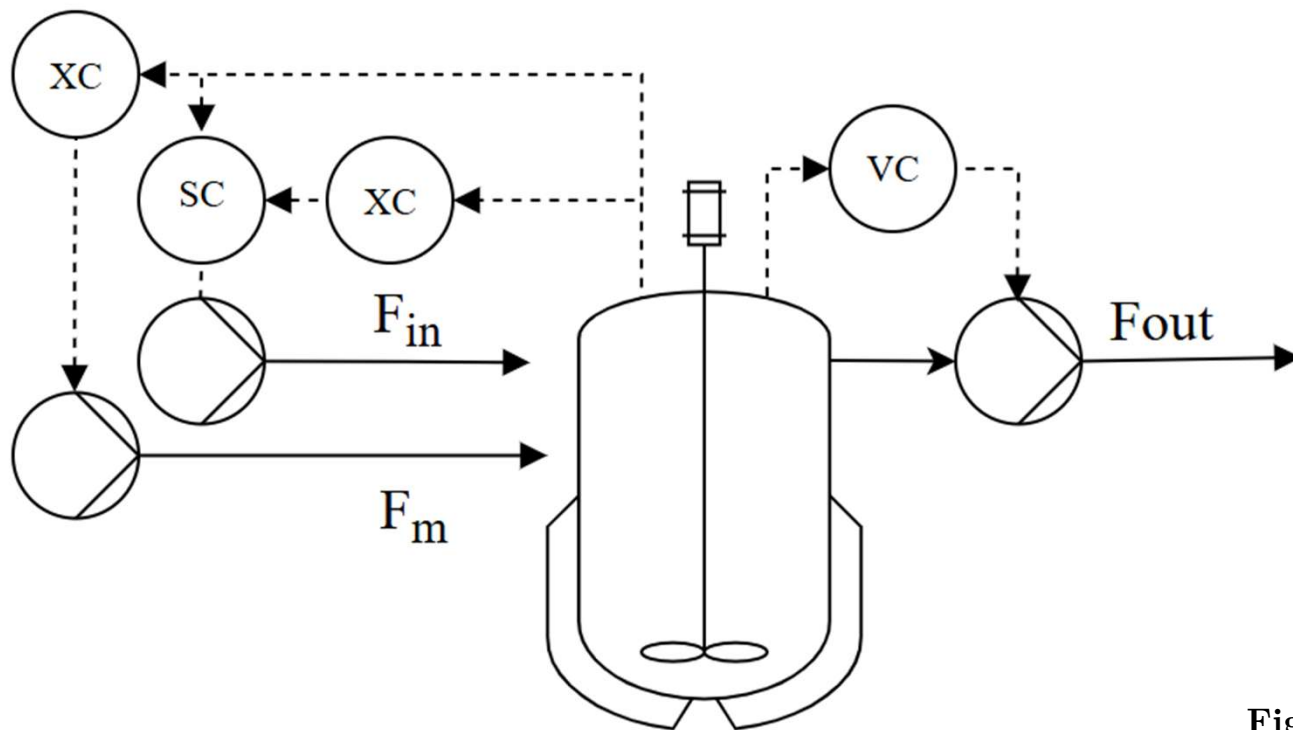


Figure 1: Bioreactor at NTNU's Microbial Feedback Control laboratory. 3

The monoculture case

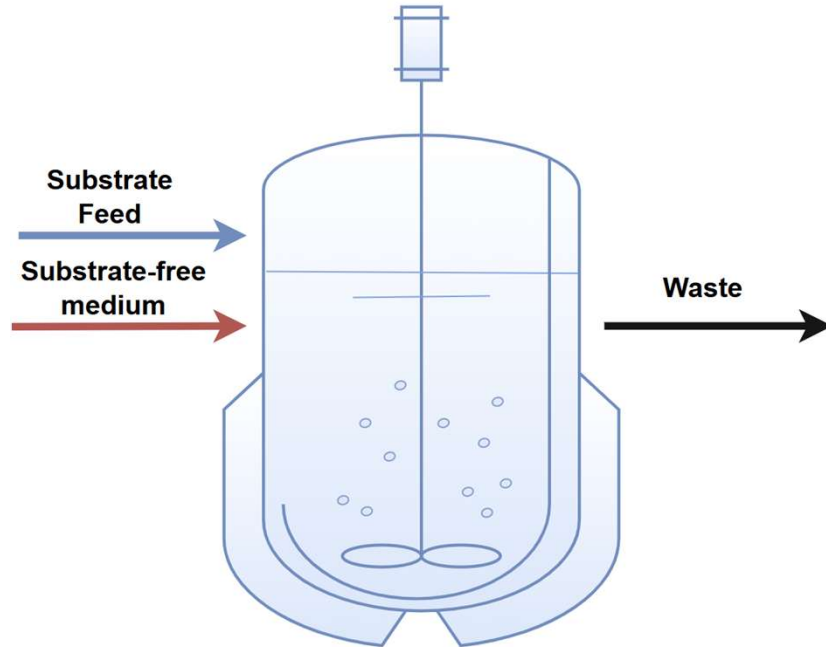
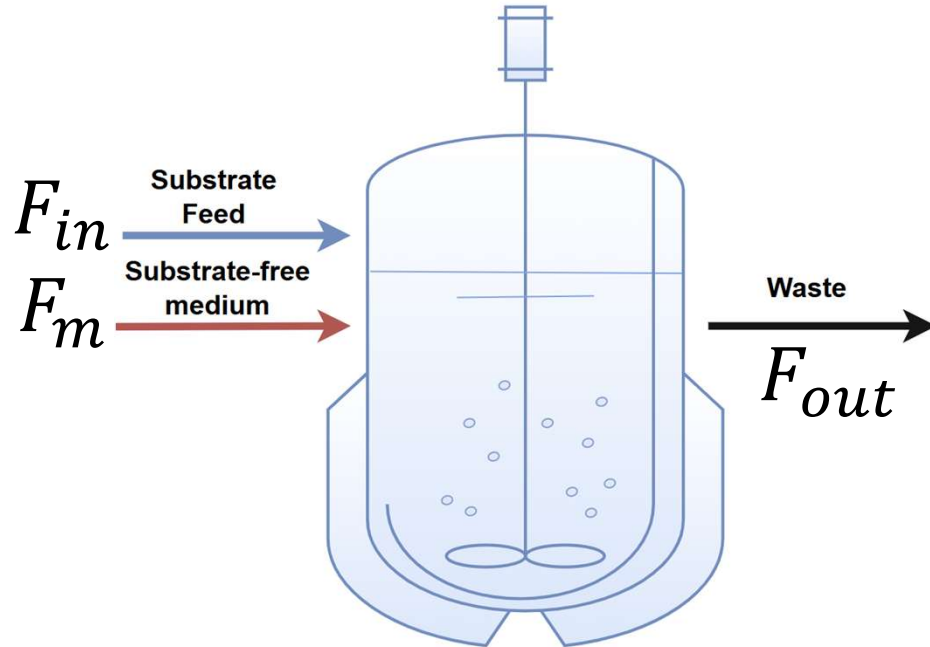


Figure 2: Aerated continuous stirred tank reactor (CSTR).



Figure 1: Bioreactor at NTNU's Microbial Feedback Control laboratory. 4

The monoculture case

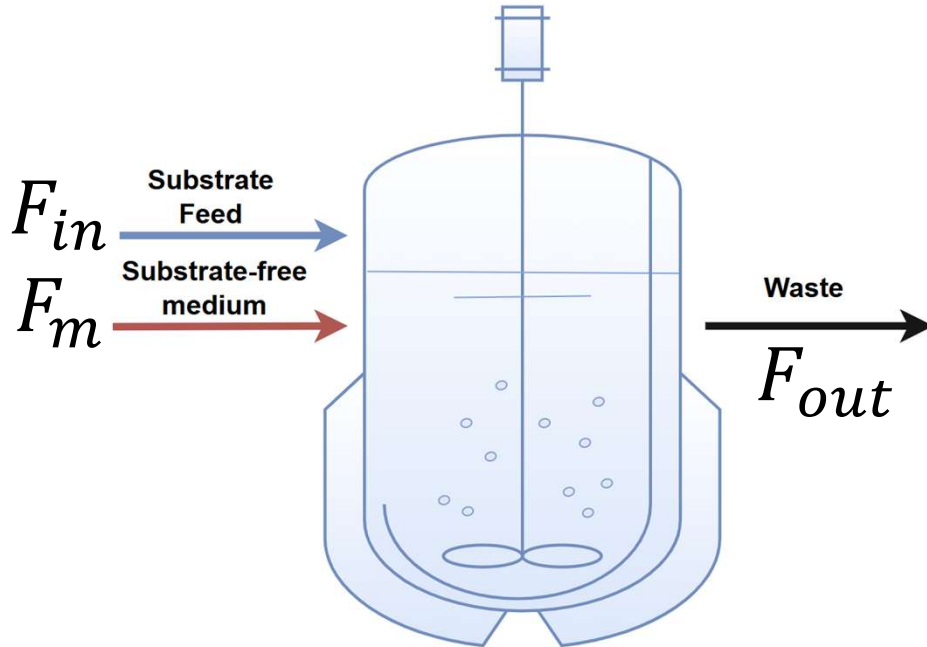


$$\frac{dV}{dt} = F_{in} + F_m - F_{out},$$

Figure 2: Aerated continuous stirred tank reactor (CSTR).



The monoculture case



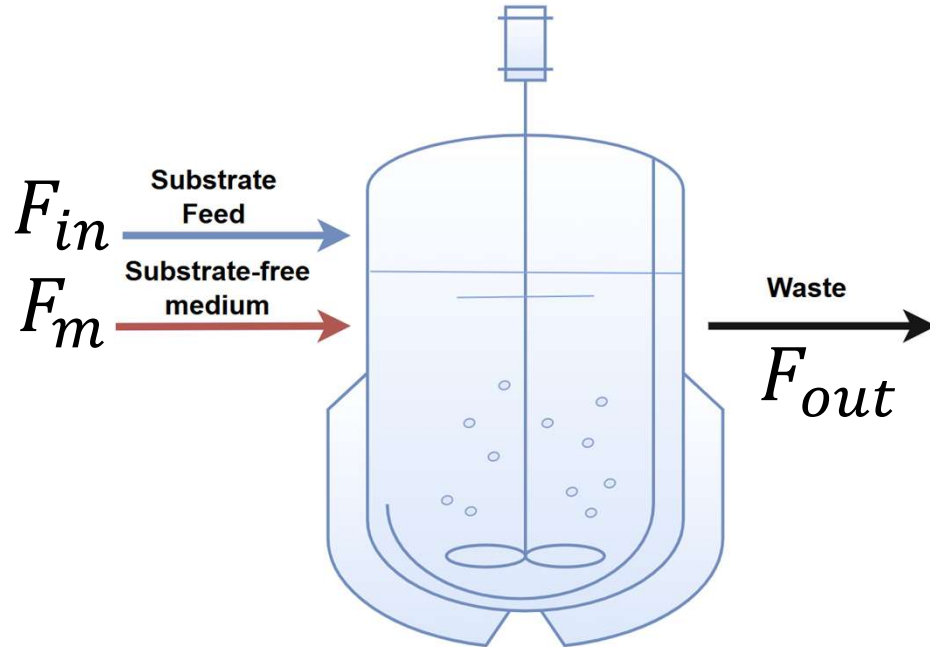
$$\frac{dV}{dt} = F_{in} + F_m - F_{out},$$

$$\frac{dX}{dt} = -\left(\frac{F_{in} + F_m}{V}\right)X + \mu X - k_d X,$$

Figure 2: Aerated continuous stirred tank reactor (CSTR).



The monoculture case



$$\frac{dV}{dt} = F_{in} + F_m - F_{out},$$

$$\frac{dX}{dt} = -\left(\frac{F_{in} + F_m}{V}\right)X + \mu X - k_d X,$$

$$\frac{dS}{dt} = (S_{in} - S)\left(\frac{F_{in}}{V}\right) - S\left(\frac{F_m}{V}\right) - \mu \frac{X}{Y_{XS}},$$

Figure 2: Aerated continuous stirred tank reactor (CSTR).



The monoculture case

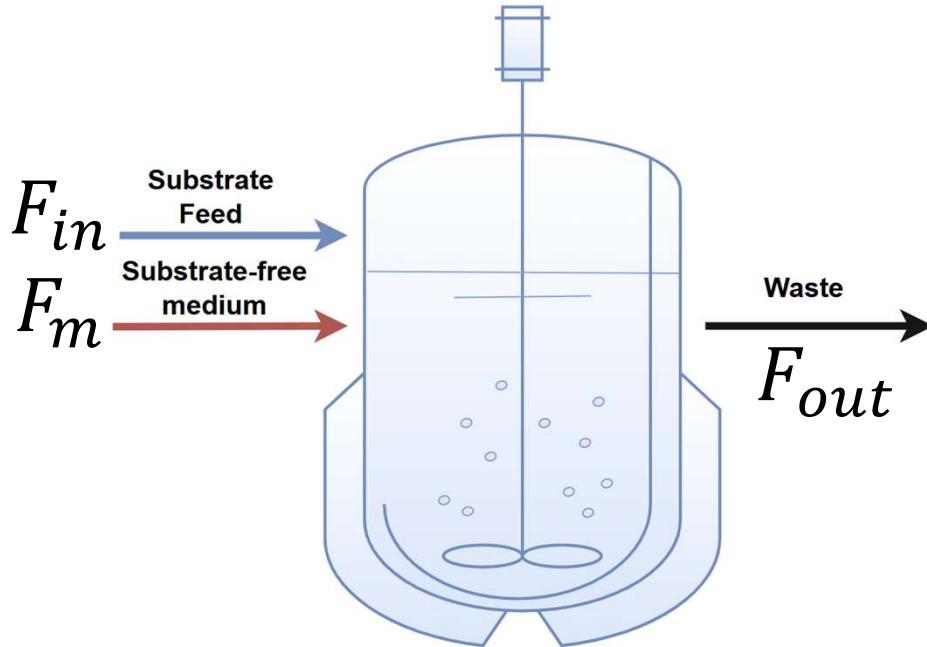


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$$\mu = \mu_{max} \left(\frac{S}{K_s + S} \right).$$



The monoculture case

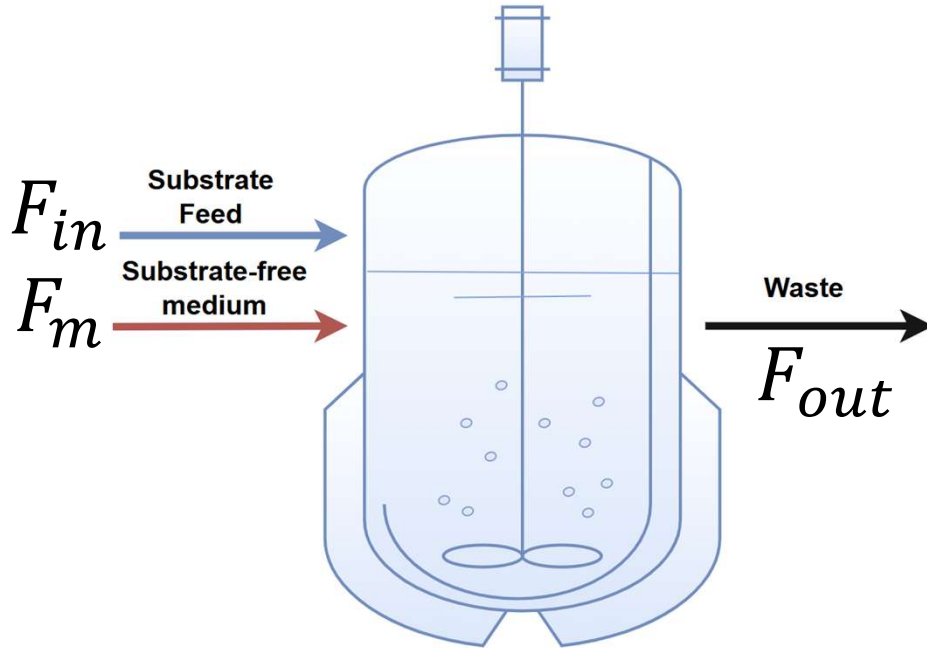


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$$\mu = \mu_{max} \left(\frac{S}{K_s + S} \right)$$

$$K_s \approx 0.007 \text{ g/L}$$



The monoculture case

Two controlled variables and three manipulated flow rates.

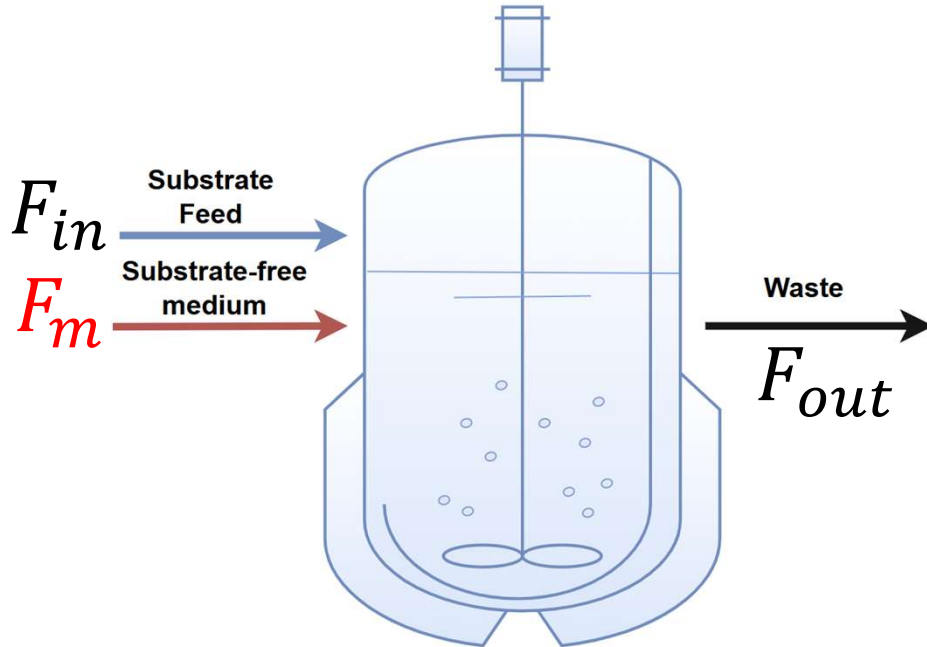


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The monoculture case

- Open-loop exponential feeding

$$\frac{d\mathbf{V}}{dt} = F_{in} + F_m - F_{out},$$

$$\frac{d\mathbf{X}}{dt} = -\left(\frac{F_{in} + F_m}{V}\right)X + \mu X - k_d X,$$

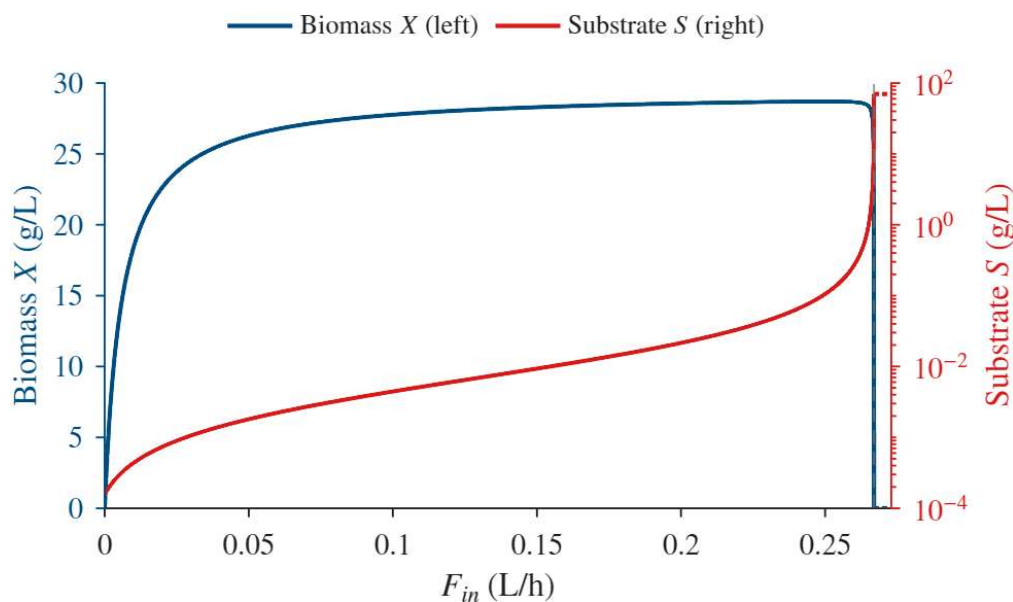
$$\frac{dS}{dt} = \boxed{(S_{in} - S)\left(\frac{F_{in}}{V}\right)} - S\left(\frac{F_m}{V}\right) - \boxed{\mu \frac{X}{Y_{XS}}},$$

$$\mu = \mu_{max} \left(\frac{S}{K_s + S} \right).$$



The monoculture case

- Proportional-Integral-Derivative (PID) control



$$\frac{dV}{dt} = F_{in} + F_m - F_{out},$$

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The monoculture case

- Open-loop exponential feeding

$$\frac{d\mathbf{V}}{dt} = F_{in} + F_m - F_{out},$$

- Proportional-Integral-Derivative (PID) control

$$\frac{d\mathbf{X}}{dt} = -\left(\frac{F_{in} + F_m}{V}\right)X + \mu X - k_d X,$$

- Model predictive control (MPC)

$$\frac{dS}{dt} = (S_{in} - S)\left(\frac{F_{in}}{V}\right) - S\left(\frac{F_m}{V}\right) - \mu \frac{X}{Y_{XS}},$$

- (Robust) Koopman-MPC

$$\mu = \mu_{max} \left(\frac{S}{K_s + S} \right).$$

- Reinforcement learning



The monoculture case

- Starvation at steady-state
- Substrate is directly controlled

$$\frac{dV}{dt} = F_{in} + F_m - F_{out},$$

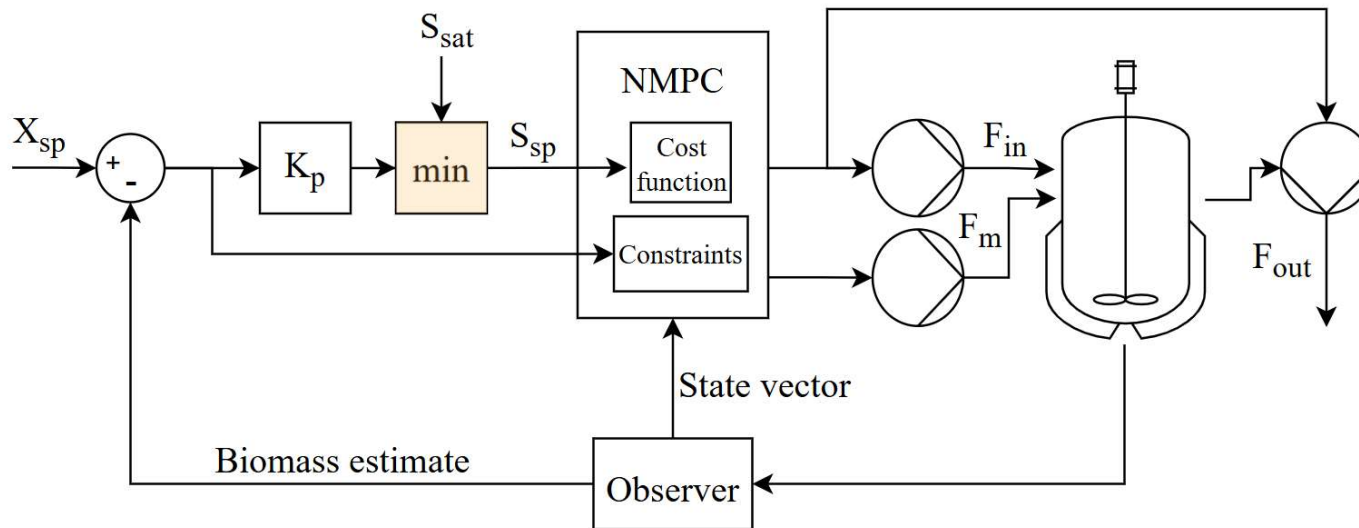
$$\frac{dX}{dt} = -\left(\frac{F_{in} + F_m}{V}\right)X + \mu X - k_d X,$$

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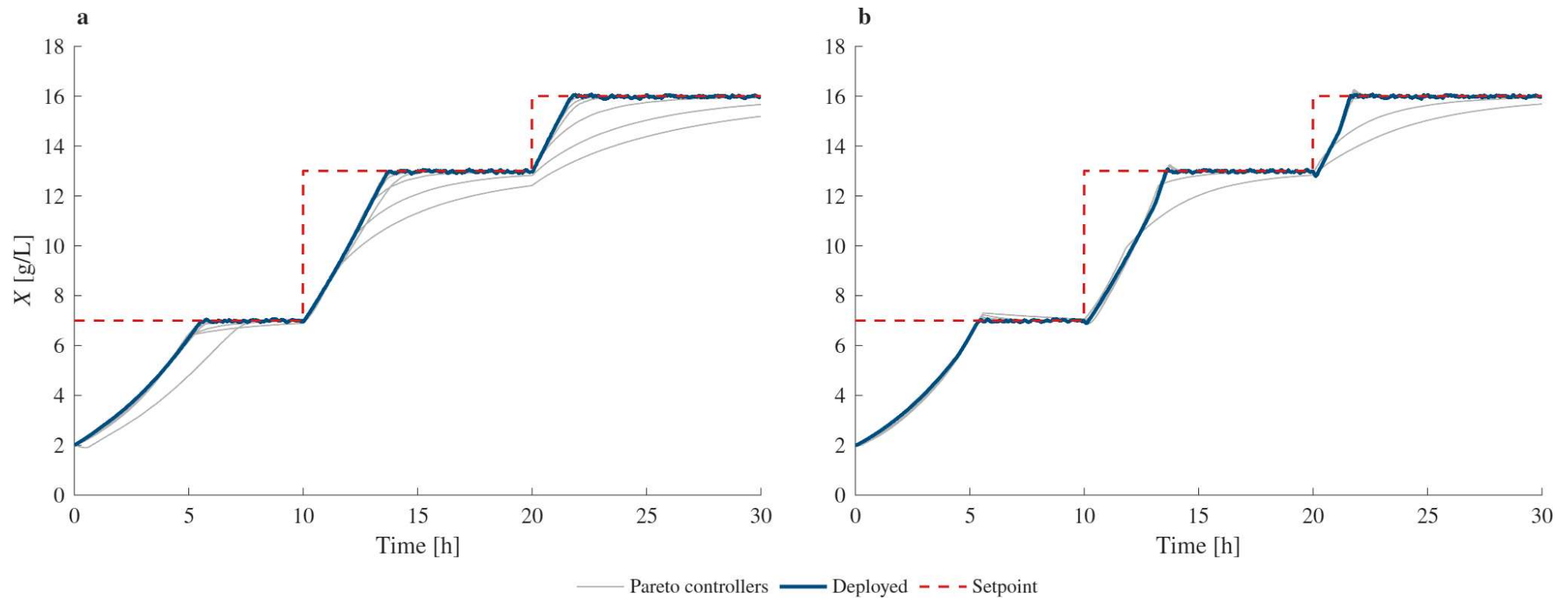
Model Predictive Control



- Substrate setpoint is constrained
- Outer loop gain is model-based
- A supervisory logic toggles the inflow constraints

Figure 2: Proposed architecture, adapted from *Model predictive control with supervisory substrate targeting for multi-setpoint biomass control in continuous bioprocesses* by Carmel, et al., 2026.

Model Predictive Control

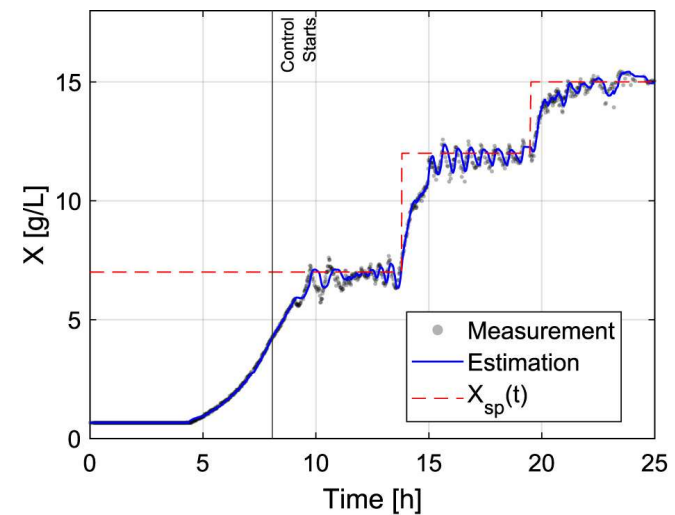
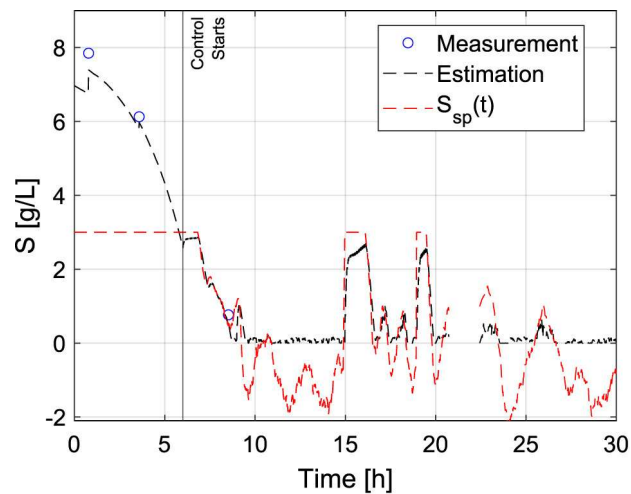




Model Predictive Control

Model predictive control with supervisory substrate targeting for multi-setpoint biomass control in continuous bioprocesses

[Lipe Carmel](#), [Giacomo Sartori](#), [Chinmay Patwardhan](#), [Christopher Sørmø](#), [Nadav Bar](#)   [Show more](#) 





PID Design

- Cascade control for biomass (substrate in an inner loop)
- Level controlled by outflow with feedforward action
- Substrate-free medium used conditionally to dilute biomass excess
- Tuning is based on linear model identification in simulated data

$$\frac{dV}{dt} = F_{in} + F_m - F_{out},$$

$$\frac{dX}{dt} = -\left(\frac{F_{in} + F_m}{V}\right)X + \mu X - k_d X,$$

$$\frac{dS}{dt} = (S_{in} - S)\left(\frac{F_{in}}{V}\right) - S\left(\frac{F_m}{V}\right) - \mu \frac{X}{Y_{XS}},$$

$$\mu = \mu_{max} \left(\frac{S}{K_s + S} \right).$$

PID Design

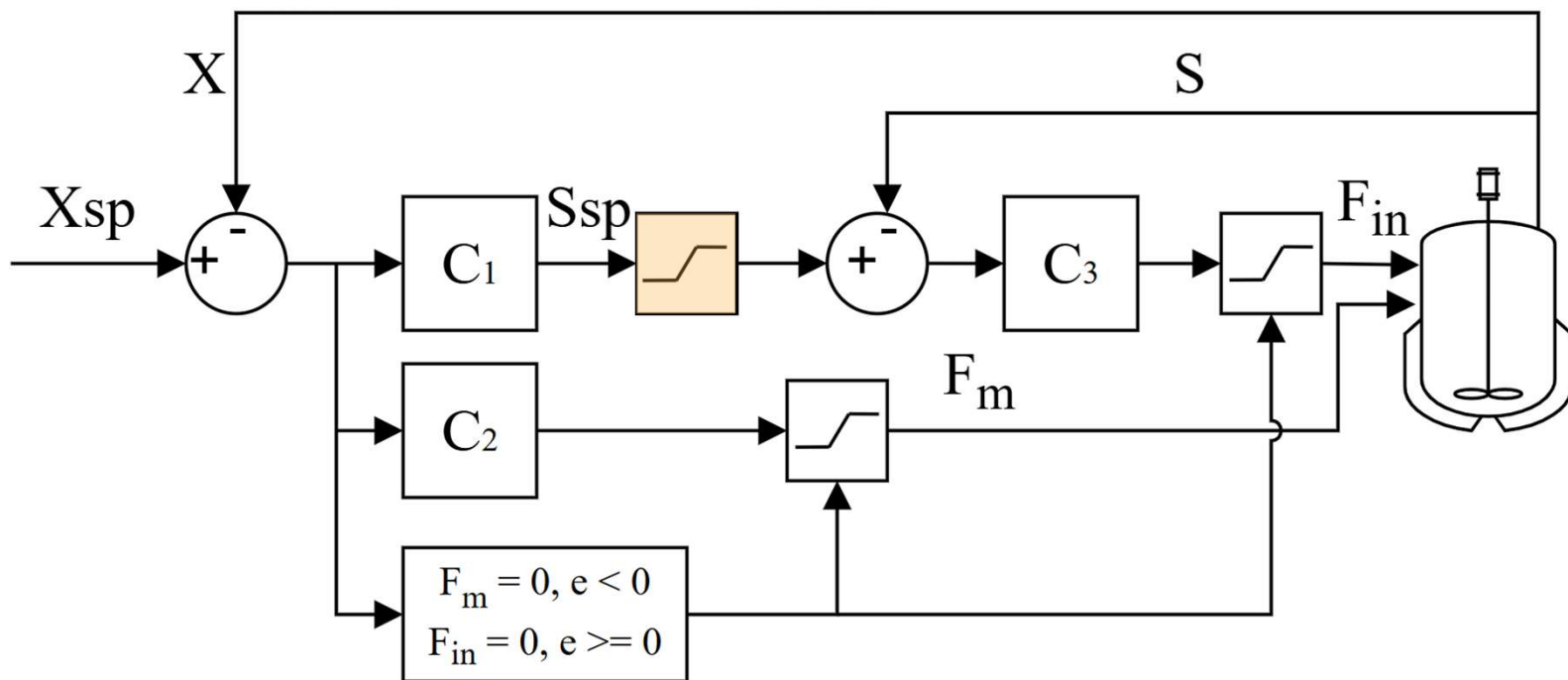


Figure 2: Proposed PID architecture. Volume control and antiwind-up loops have been omitted from the diagram.



Performance Limitation

- *Ideal* tracking is bound by maximum growth and death rates

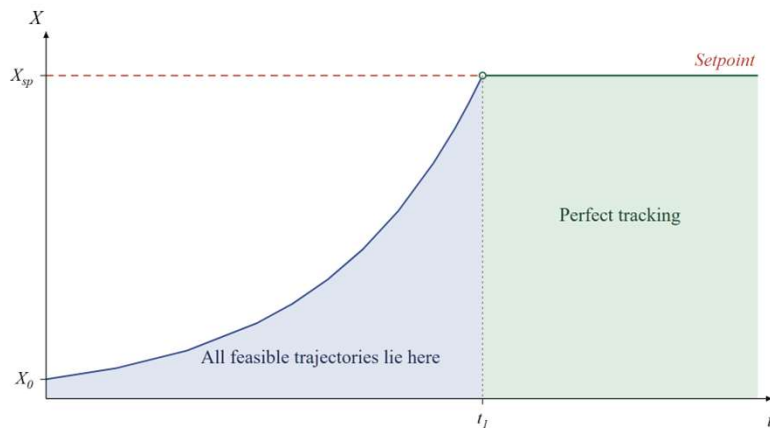


Figure 4: Illustrative example of perfect biomass tracking.

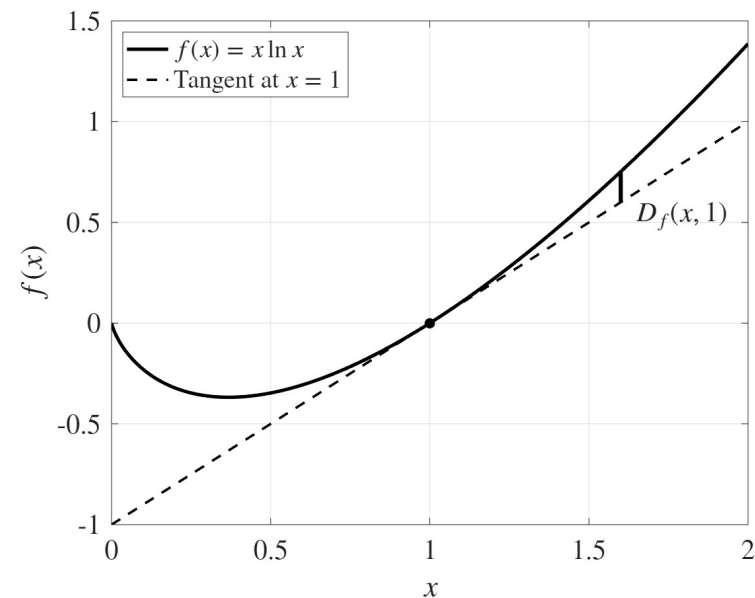
$$\text{IAE}_{\text{ideal}} = \frac{1}{\mu_{\max} - k_d} \left[X_{sp} \ln \left(\frac{X_{sp}}{X_0} \right) - (X_{sp} - X_0) \right]$$

Performance Limitation



- *Ideal* bound coincides with the Bregman divergence:
 $D_f(X_{sp}, X_0), f(x) = x \cdot \ln(x)$

$$\text{IAE}_{\text{ideal}} = \frac{1}{\mu_{\max} - k_d} \left[X_{sp} \ln \left(\frac{X_{sp}}{X_0} \right) - (X_{sp} - X_0) \right]$$



Performance Limitation



- **Assumption:** A minimum **continuous** feed rate is required to prevent substrate depletion, resulting in:

$$\frac{dS}{dt} = (S_{in} - S) \left(\frac{F_{in}}{V} \right) - S \left(\frac{F_m}{V} \right) - \mu \frac{X}{Y_{XS}}$$

$$\frac{dX}{dt} = \left(\mu_{max} - k_d - \frac{\mu_{max} X}{S_{in} Y_{XS}} \right) X$$

Performance Limitation



- **Assumption:** A minimum **continuous** feed rate is required to prevent substrate depletion, resulting in:

$$\frac{dX}{dt} = \left(\mu_{max} - k_d - \frac{\mu_{max}X}{S_{in}Y_{XS}} \right) X,$$

$$X_{ss} = \frac{S_{in} (\mu_{max} - k_d)}{\mu_{max} Y_{XS}^{-1}},$$

$$IAE^* = \frac{X_{sp} \ln \left(\frac{X_{sp}}{X_0} \right) + (X_{ss} - X_{sp}) \ln \left(\frac{X_{ss} - X_{sp}}{X_{ss} - X_0} \right)}{\mu_{max} - k_d}.$$



Performance Limitation

- **Equilibrium concentration imposes a bound on performance**

$$\text{IAE}_{\text{ideal}} = \frac{1}{\mu_{\max} - k_d} \left[X_{sp} \ln \left(\frac{X_{sp}}{X_0} \right) - (X_{sp} - X_0) \right]$$

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Performance Limitation

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Performance Limitation



- Equilibrium concentration imposes a bound on performance, *and it is a design choice*

$$\text{IAE}_{\text{ideal}} = \frac{1}{\mu_{\max} - k_d} \left[X_{sp} \ln \left(\frac{X_{sp}}{X_0} \right) - (X_{sp} - X_0) \right]$$

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Performance Limitation



Integral of the absolute error, normalized by the realistic lower bound

$$\text{IAE}_x = \frac{1}{\text{IAE}^*} \int |X - X_{sp}| dt$$

Sum of the Total Variation of the input signal

$$\text{TV} = \sum_{j=1}^3 \int_0^{20} |\dot{u}_j(t)| dt, j \in \{1, 2, 3\}$$

Performance Limitation

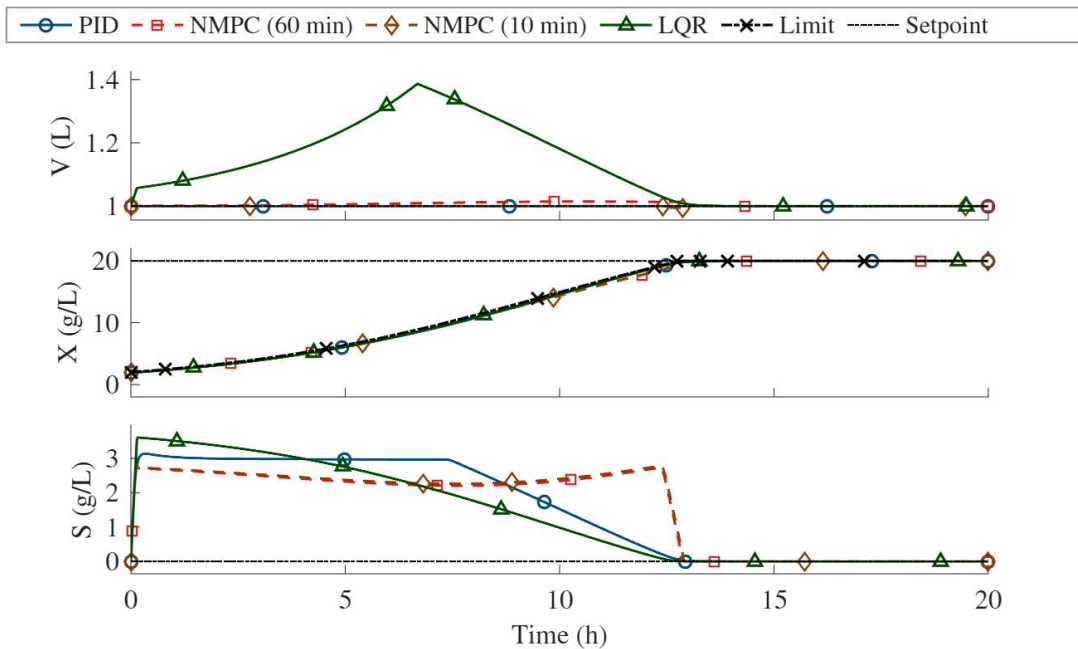


Figure 5: Closed loop simulations of NMPC, PID, and LQR (optimal tuning).

Controller	IAE _x (%)	TV	IAE _v (Lh)
Theoretical	100		
LQR	102.39	0.008	2.3694
PID	102.75	0.117	0.0000
NMPC (1h)	103.40	0.042	0.1052
NMPC (10 min)	103.45	0.034	0.0036

Table 1: Performance of the simulated controllers. All achieve near IAE* biomass tracking; thus, **selection should prioritize robustness, TV and level control.**

Filtering

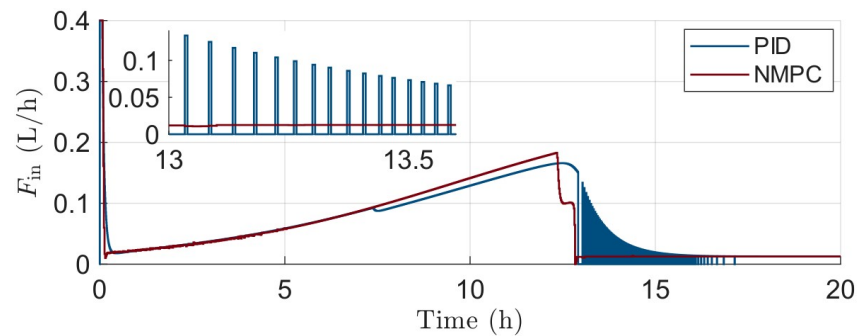


Figure 6: Feed stream comparison between NMPC A and PID.

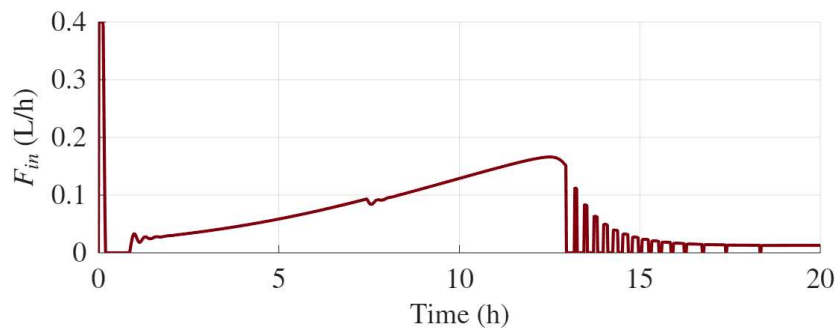
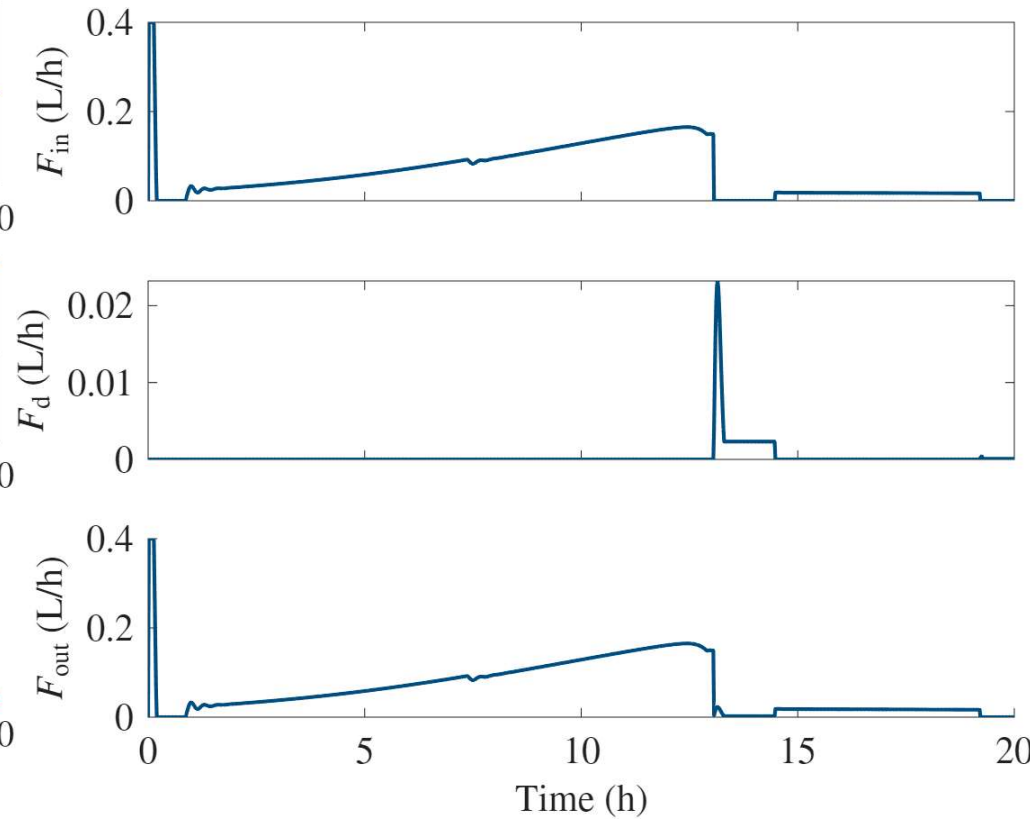
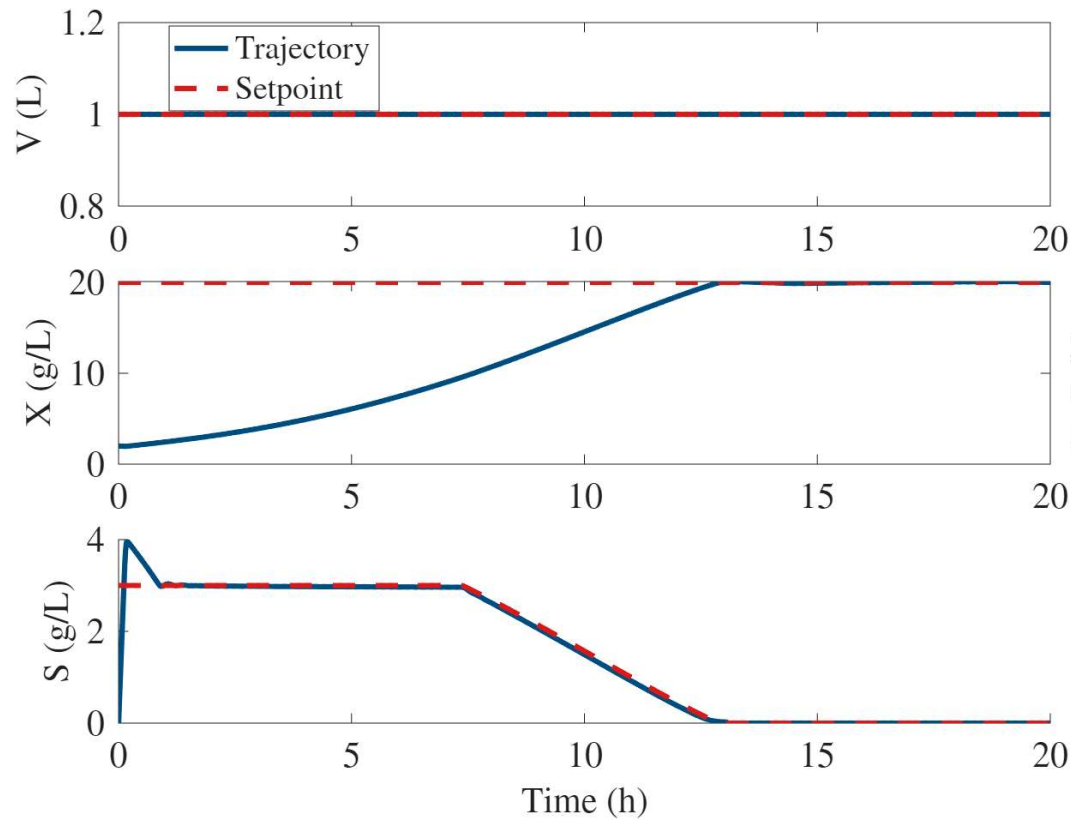


Figure 7: PID with second order Butterworth filter on states.

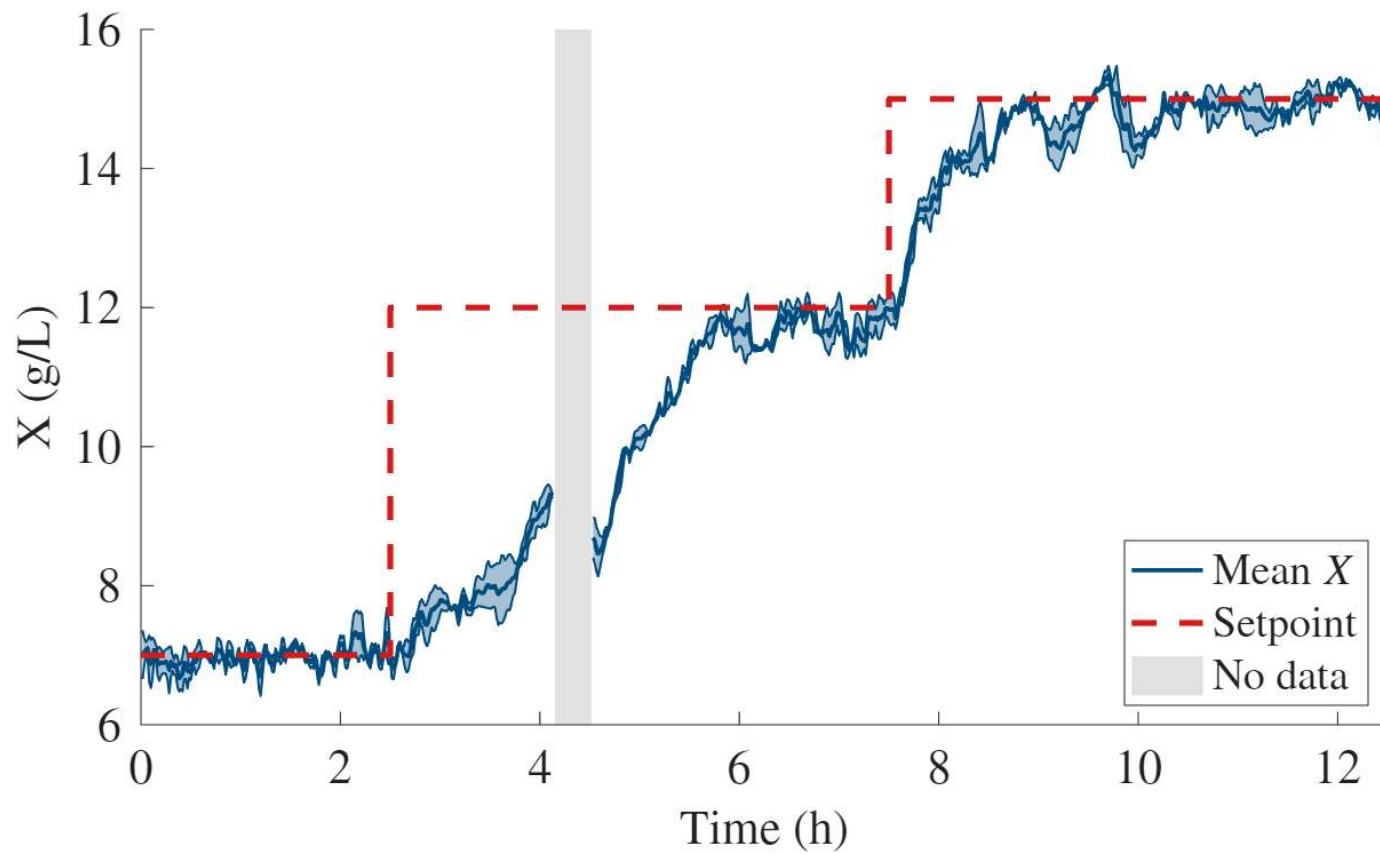
Controller	IAE _x (%)	TV	IAE _v (Lh)
Theoretical	100		
LQR	102.39	0.008	2.3694
PID	102.75	0.117	0.0000
PID (low pass)	102.78	0.073	0.0000
NMPC (1h)	103.40	0.042	0.1052
NMPC (10 min)	103.45	0.034	0.0036

Table 2: Performance of the simulated controllers. The PID equipped with a Butterworth and NMPC show comparable tracking performance.

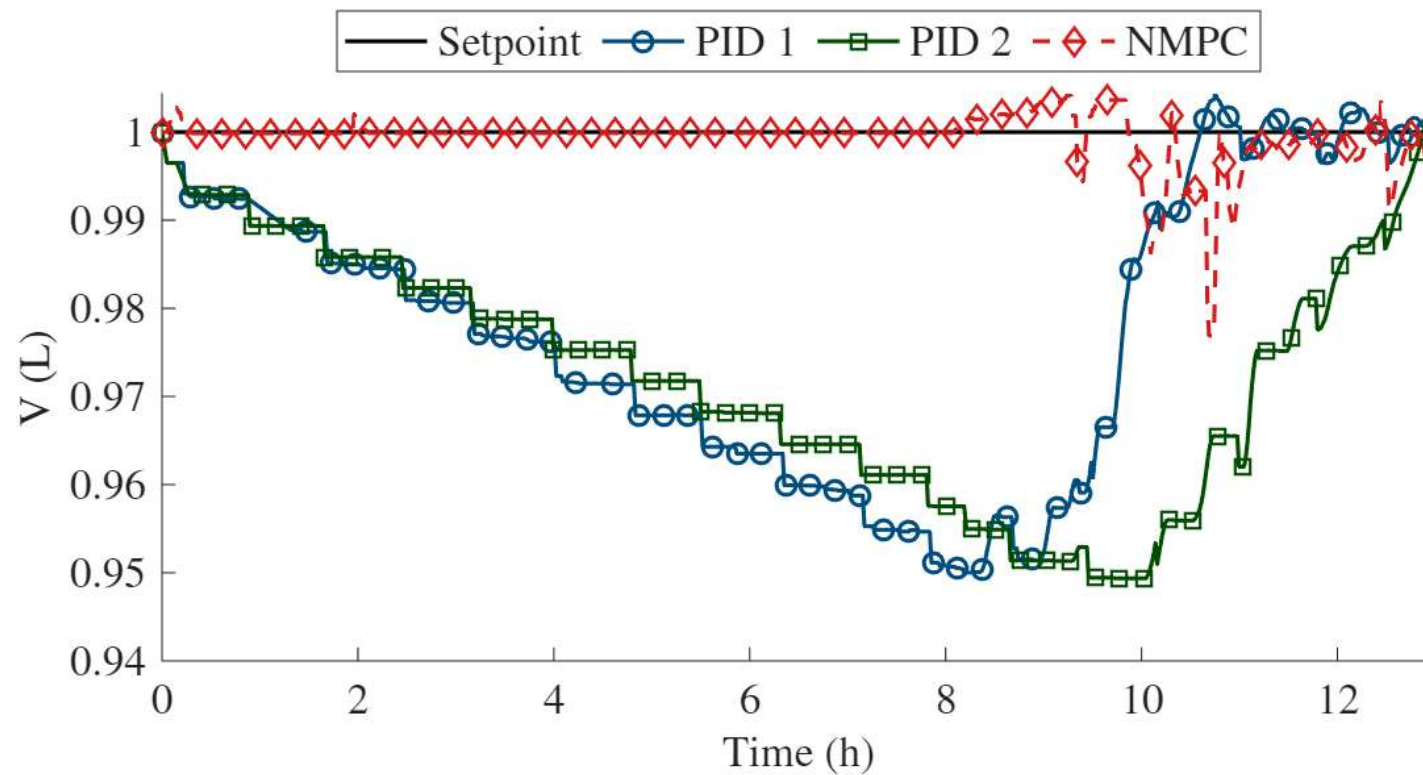
Filtering with Deadband



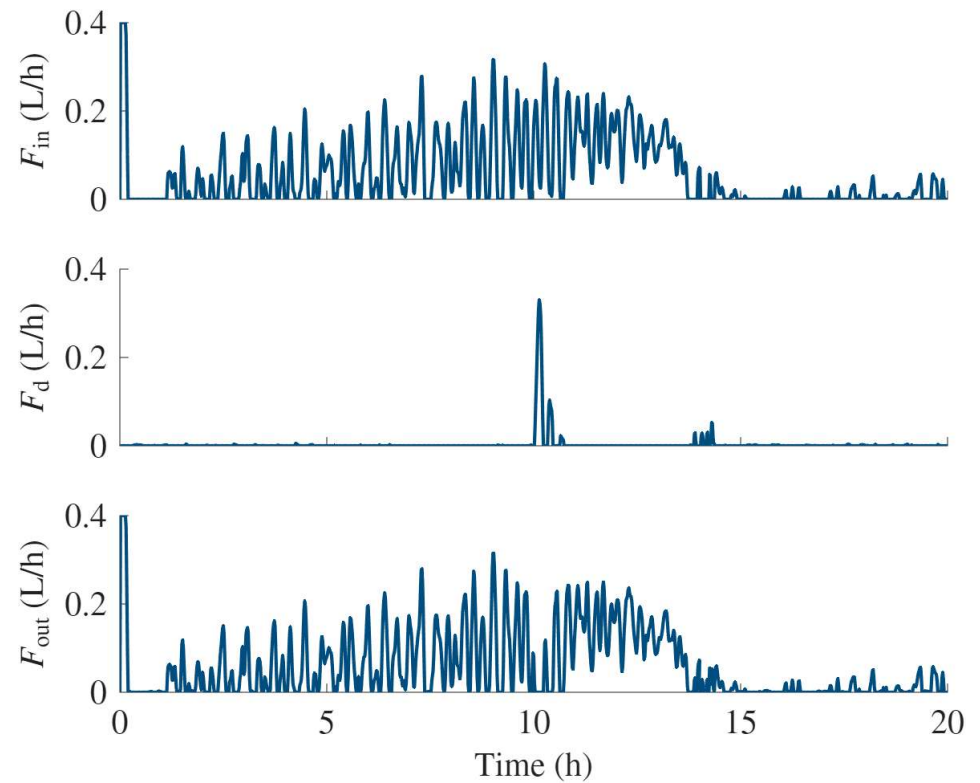
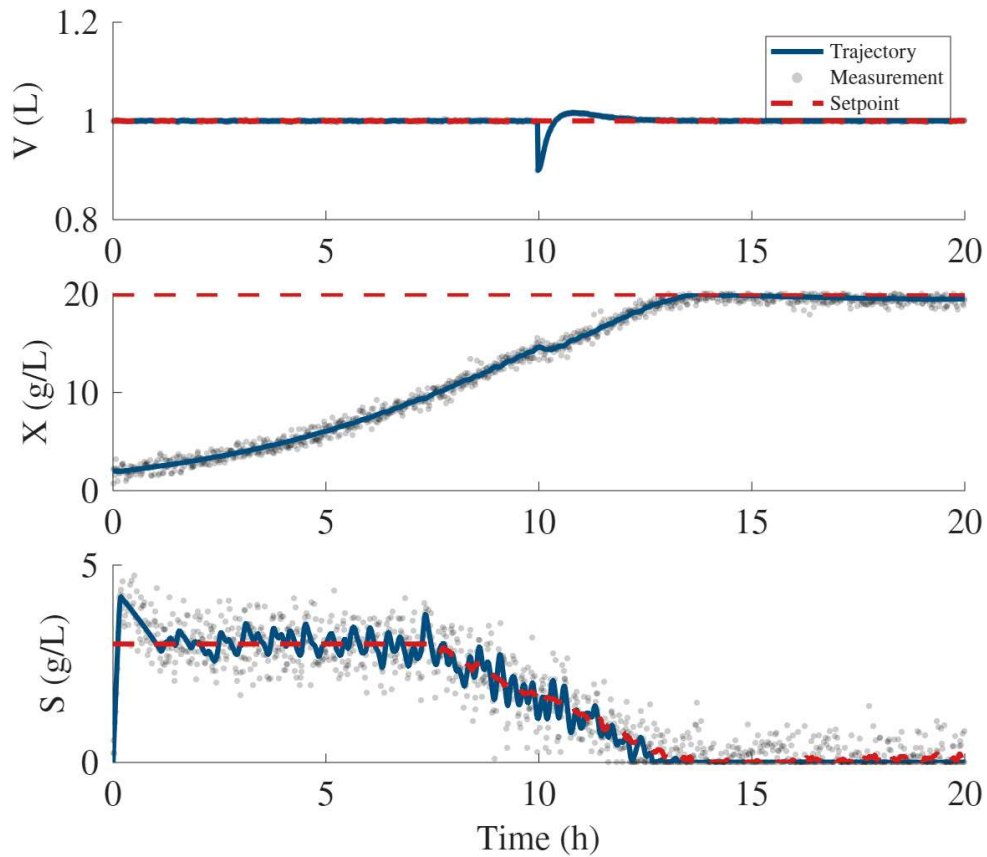
Experimental Results



Volume Oversight



Volume Oversight



Conclusion

1. **Biomass tracking is possible with simple control strategies**
2. **$IAE_x \leq 105\% IAE^*$ is achievable in simulations**
3. **The main open practical challenge is robust and smooth control**

Future work:

1. *Validate optimal MPC tuning*
2. *Generalize to multiple strains*



Thank you!