Modular Design and Supervisory Control for Economic Resilience in Continuous Pharmaceutical Manufacturing

Tuse Asrav

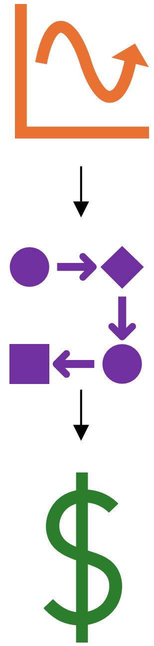
Supervisors: Prof. Gürkan Sin, SR. Merlin Alvarado-Morales

Process Systems Engineering Research Center, PROSYS, DTU

Conventional Continuous Manufacturing

- Custom-built design
- Integrated process units
- Fixed capacity

The challenge: Operating under uncertain demand



Capacity mismatch

Low demand → Underutilized capacity

High demand → Capacity bottleneck

Off-design operation

Residence time shifts → Conversion / selectivity penalties → Higher unit production cost

Modular Continuous Manufacturing

- Standardized design
- Interchangeable units
- Scalable capacity

How does modular design address this challenge?

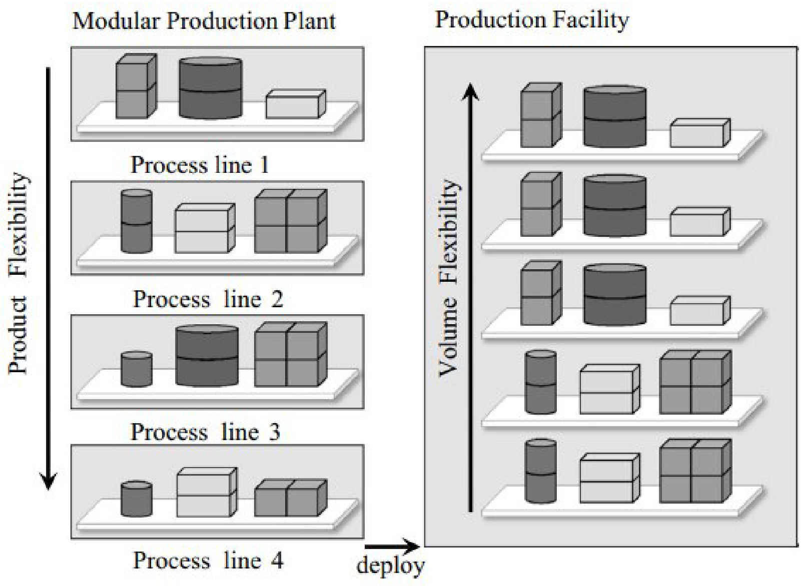
Multiple standardized reactor modules

Adjustable active volume

➢Activate or bypass modules as throughput changes

Improved operating flexibility

➢Favorable operating conditions across different throughputs



Becker, T., Bruns, B., Lier, S., & Werners, B. (2021). Decentralized modular production to increase supply chain efficiency in chemical markets: An example of polymer production. *Journal of Business Economics.*

Modular Design and Supervisory Control

2 Sampling for Market Demand Uncertainty

Scenario I: Fixed-Rate Stochastic CAGR	**Scenario II:** Time-Dependent Stochastic CAGR

D(t=1,..,n)

3 Sensitivity Analysis

1. Evaluate plant performance across the demand range for different configurations
2. Determine optimal switching points

Switching Thresholds

4 Supervisory Layer (Python)

1. Check Logic: D(t) vs Switching thresholds
2. Decision Logic: Determine control action u(t)

Discrete Control Signal u(t=1,…,n)

1 Process Synthesis, Design & Simulation

Modular Plant
1. Module Definition & Sizing **2.** Topology
3. Flexible Flowsheet Design

Model Constraints

5 Regulatory Layer (AVEVA™)

1. Automated valve manifold executes switching
2. Internal solvers automatically adjust other variables

TCI, ∑ TOC(t=1,…,n)

6 Performance Evaluation Engine (Python)

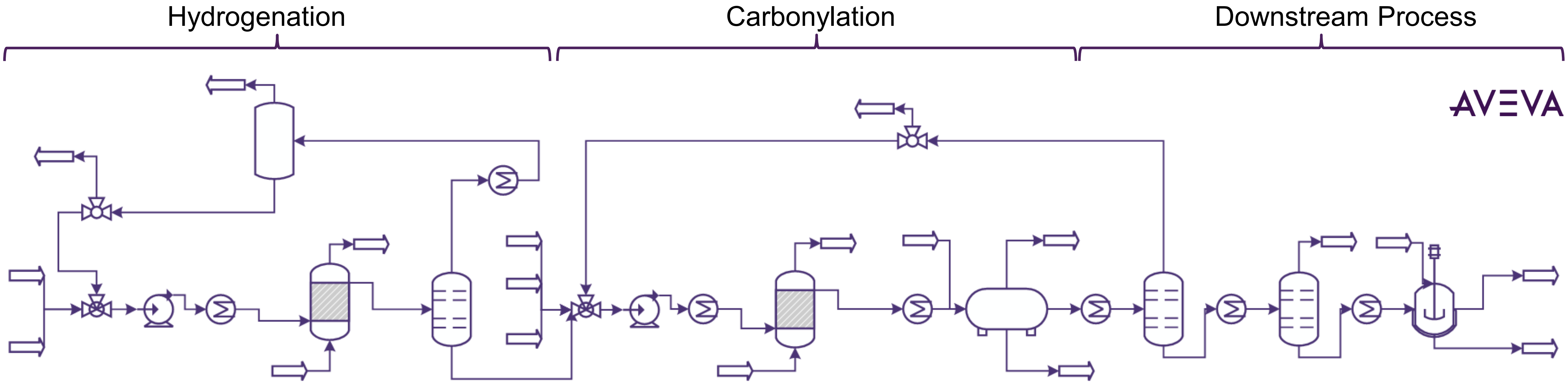
LCOP Uncertainty Analysis (Monte Carlo method)	**Economic Risk Analysis** (Ruin Probability)

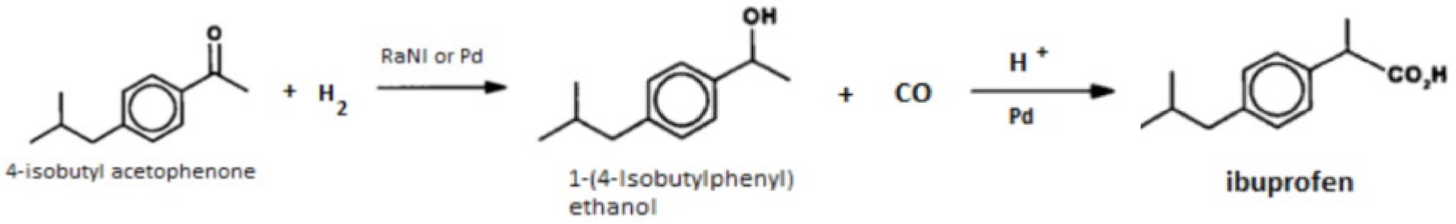
MiEI
Doctoral network for microprocess engineering for electrosynthesis

Asrav, T., Alvarado-Morales, M., Sin, G. (2026). Modular Design and Supervisory Control for Enhanced Economic Resilience in Continuous Pharmaceutical Manufacturing. *Accepted for publication in AICHE Journal*.

Case Study: Ibuprofen Continuous Manufacturing

➢ **Continuous Process Flowsheet**





Liquid-liquid eq:

Non-random Two Liquid (NRTL)

+UNIFAC Dortmund (Group Contribution Method)

Vapor-liquid eq:

Soave-Redlich-Kwong (SRK)

Asrav, T., Alvarado-Morales, M., Sin, G. (2026). Simulation-based Techno-economic Optimization of Continuous Ibuprofen Manufacturing under Uncertainty. *Chemical Engineering Research and Design 231, 637-644*.

Conventional Plant: Fixed-Capacity Reactor Design

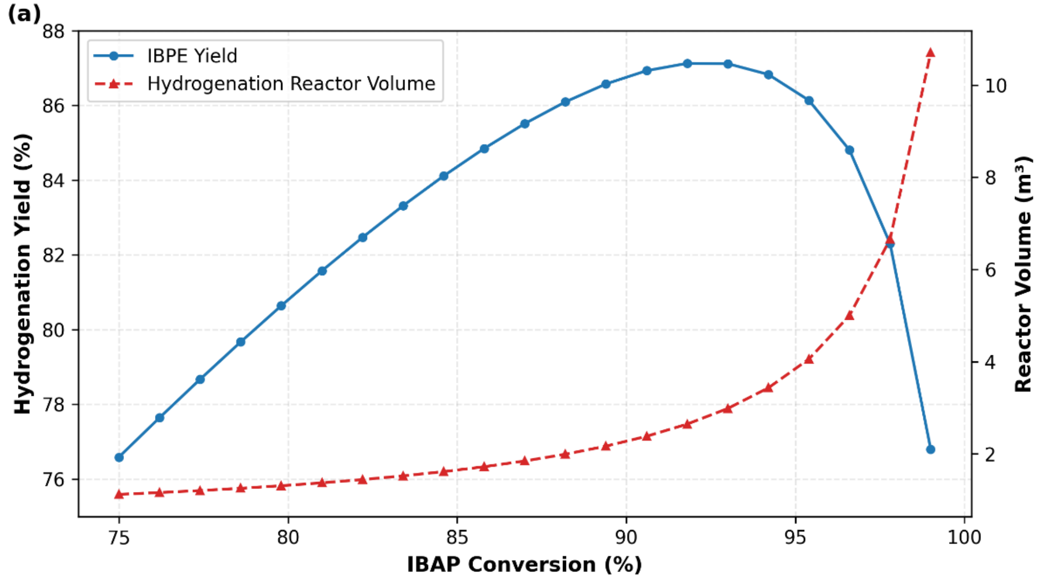
Nominal design point: 380 kg/h (7.5% of global demand in 2040 based on mean CAGR of 2.82%)

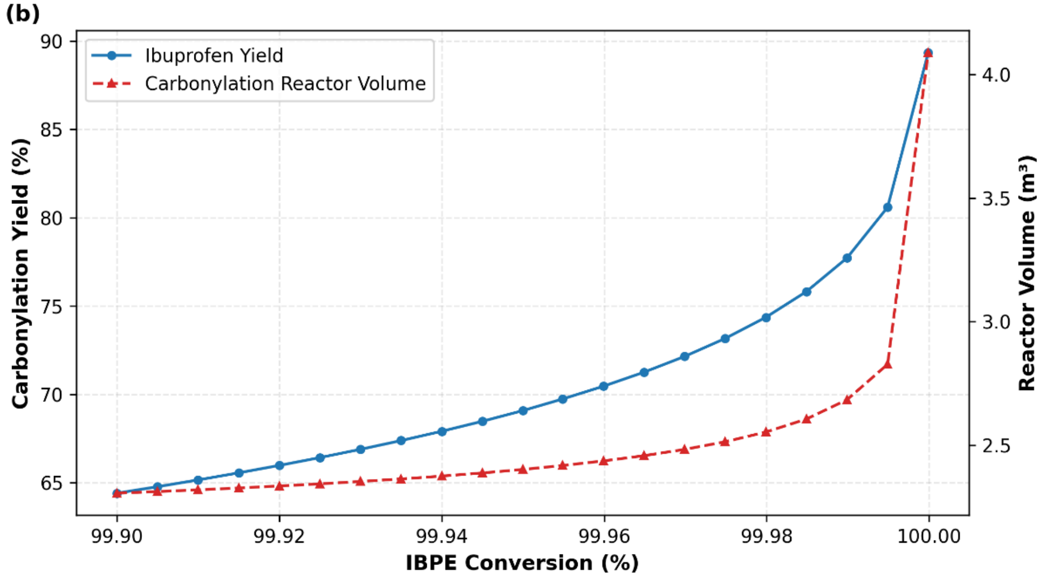
Hydrogenation

- Reactor volume: 3 m^3
- Conversion: 93%
- Yield: 87%

Carbonylation

- Reactor volume: 2.7 m^3
- Conversion: 99.99%
- Yield: 77%





Modular Plant: Reactor Module & Topology Design

- Standardized module: 2.5 m^3 plug flow reactor (PFR).

Hydrogenation (Parallel)

Yield / selectivity-driven

Insufficient residence time → conversion loss

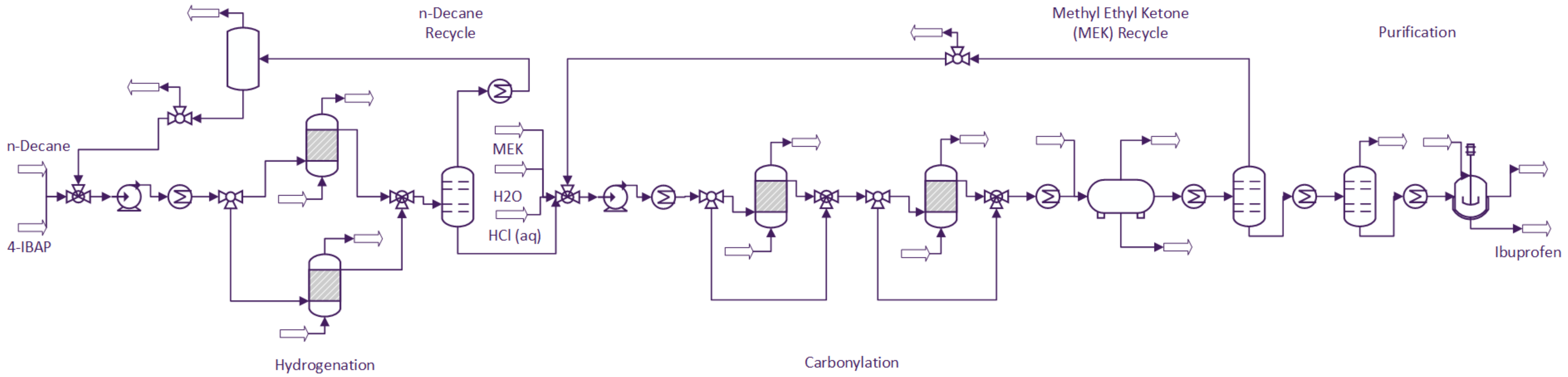
Excessive residence time → selectivity loss

Carbonylation (Series)

Conversion / operability-driven

Insufficient residence time → conversion loss

Excessive residence time → operability & quality concerns



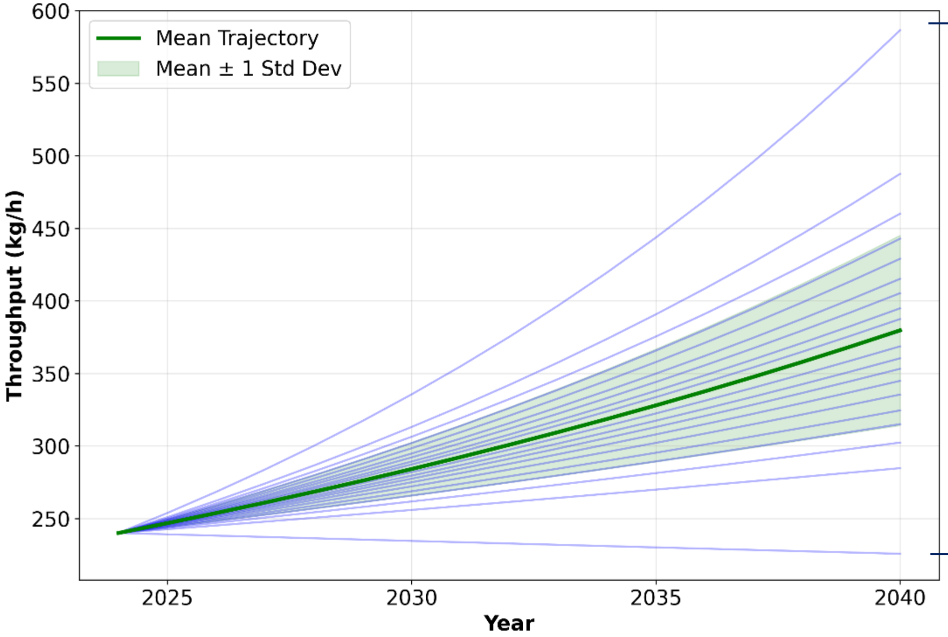
Sampling for Market Demand Uncertainty

- Production target is 7.5% of the global annual ibuprofen volume
- CAGR $\sim N(\mu, \sigma^2)$ with μ = 2.82% and $\sigma = 1.1\%$ from 2025 to 2040 →

Fixed-Rate Scenario

- CAGR remain constant over the project lifetime

$$D_t = D_{t-1}(1 + CAGR)$$



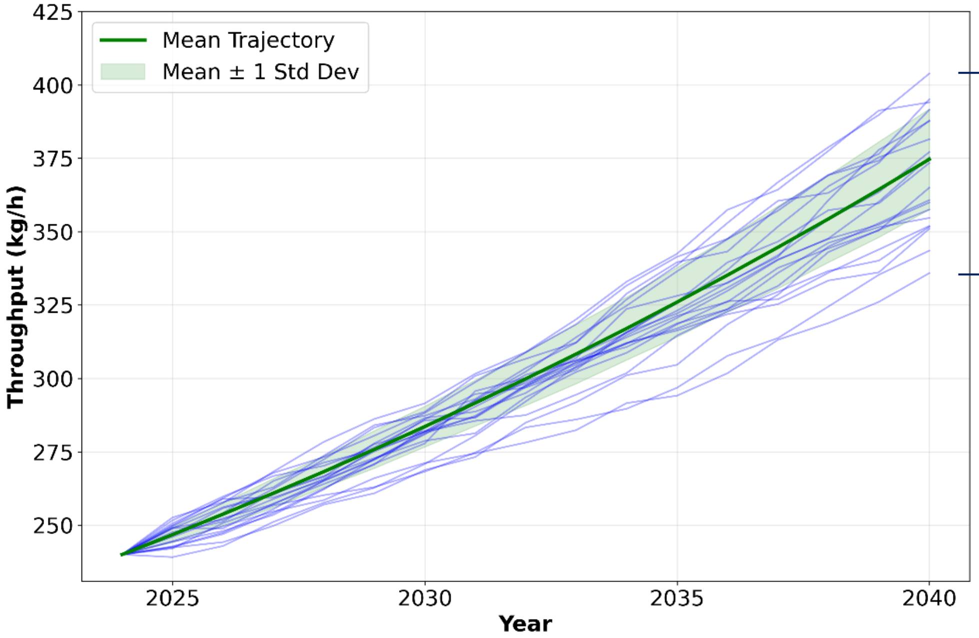
→ $LCOP_1$

→ $LCOP_{100}$

Time-Dependent Scenario

- CAGR vary annually

$$D_t = D_{t-1}(1 + CAGR_t)$$



→ $LCOP_1$

→ $LCOP_{100}$

Christensen, P., Gillingham, K., & Nordhaus, W. (2018). Uncertainty in forecasts of long-run economic growth. *Proceedings of the National Academy of Sciences of the United States of America.*

Sensitivity Analysis Defines Switching Thresholds

Doctoral network for microprocess engineering for electrosynthesis

- Active module count per processing step: $n_{j,t}$

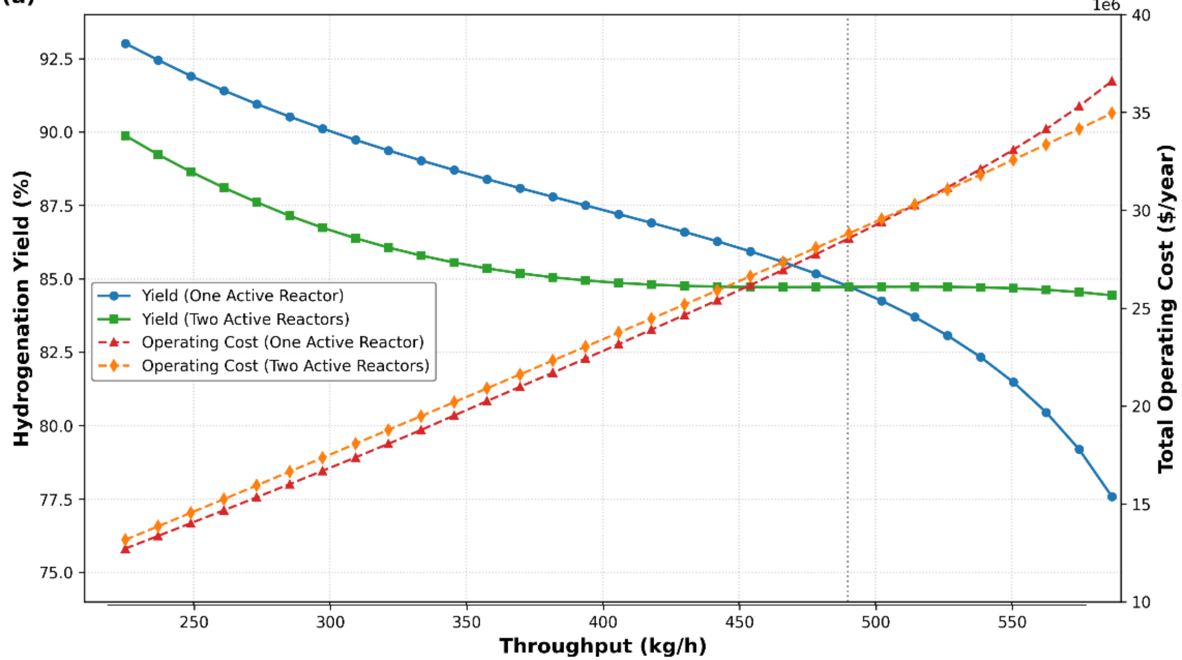
Hydrogenation (Parallel)

$$n_{H,t} = \begin{cases} 1, & D_t < 490\ kg/h \\ 2, & D_t \geq 490\ kg/h \end{cases}$$

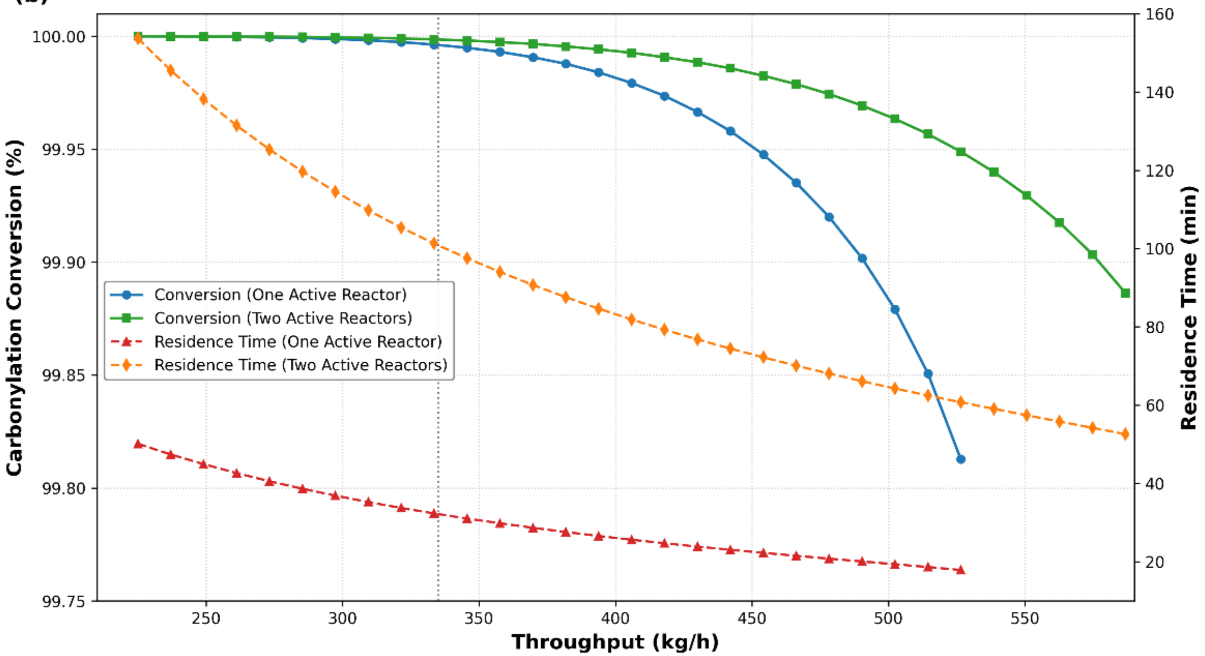
Carbonylation (Series)

$$n_{C,t} = \begin{cases} 1, & D_t < 335\ kg/h \\ 2, & D_t \geq 335\ kg/h \end{cases}$$

(a)



(b)



Hierarchical Supervisory Control

Doctoral network for microprocess engineering for electrosynthesis

Target throughput, D_t →

Supervisory Layer (Python)

Annual configuration decision

$$n_{j,t} = \arg\max_{n} J_j(n, D_t)$$

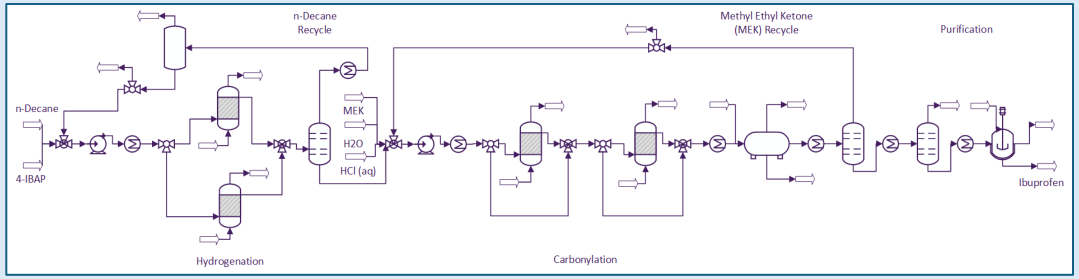
← Predefined switching thresholds (offline sensitivity analysis)

Discrete control action: $u_{j,t} = n_{j,t}$

AVEVA™ Process Simulation & Regulatory Layer

Discrete configuration control

On / off valves → Activate / bypass modules → $\tau_j(n, D_t) = \frac{V_{\text{active}}}{Q}$



Continuous-variable regulation

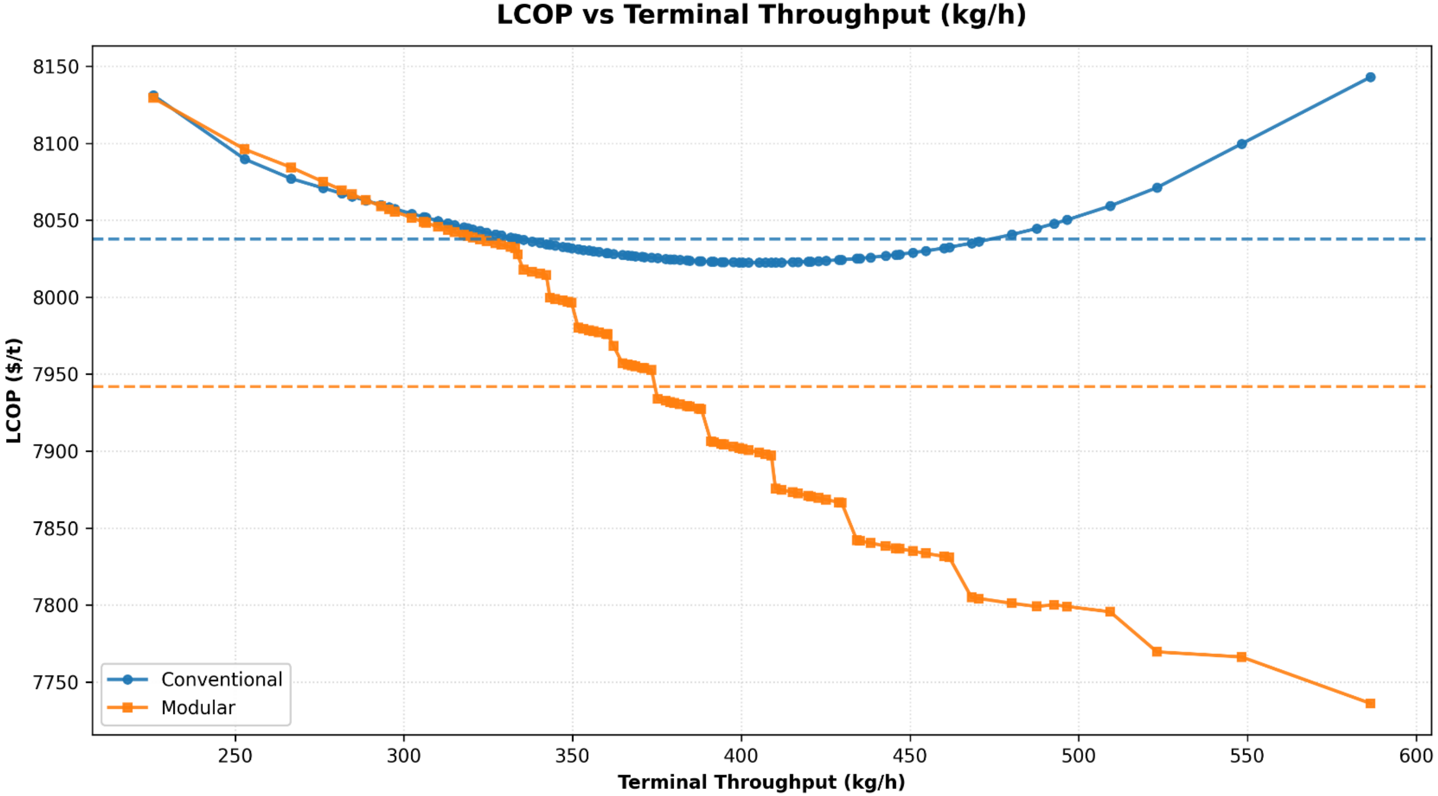
- Internal AVEVA™ solvers continuously adjust manipulated variables to maintain process setpoints.

Process Unit	Controlled Variable	Manipulated Variable
Distillation Column	Distillate–bottoms split ratios	Reflux and boil-up ratios
Flash Drum	Flash temp.	Flash thermal duty
Reactor	Isothermal temp.	Cooling jacket duty

Economic Response Curve Analysis (Fixed-Rate Scenario)

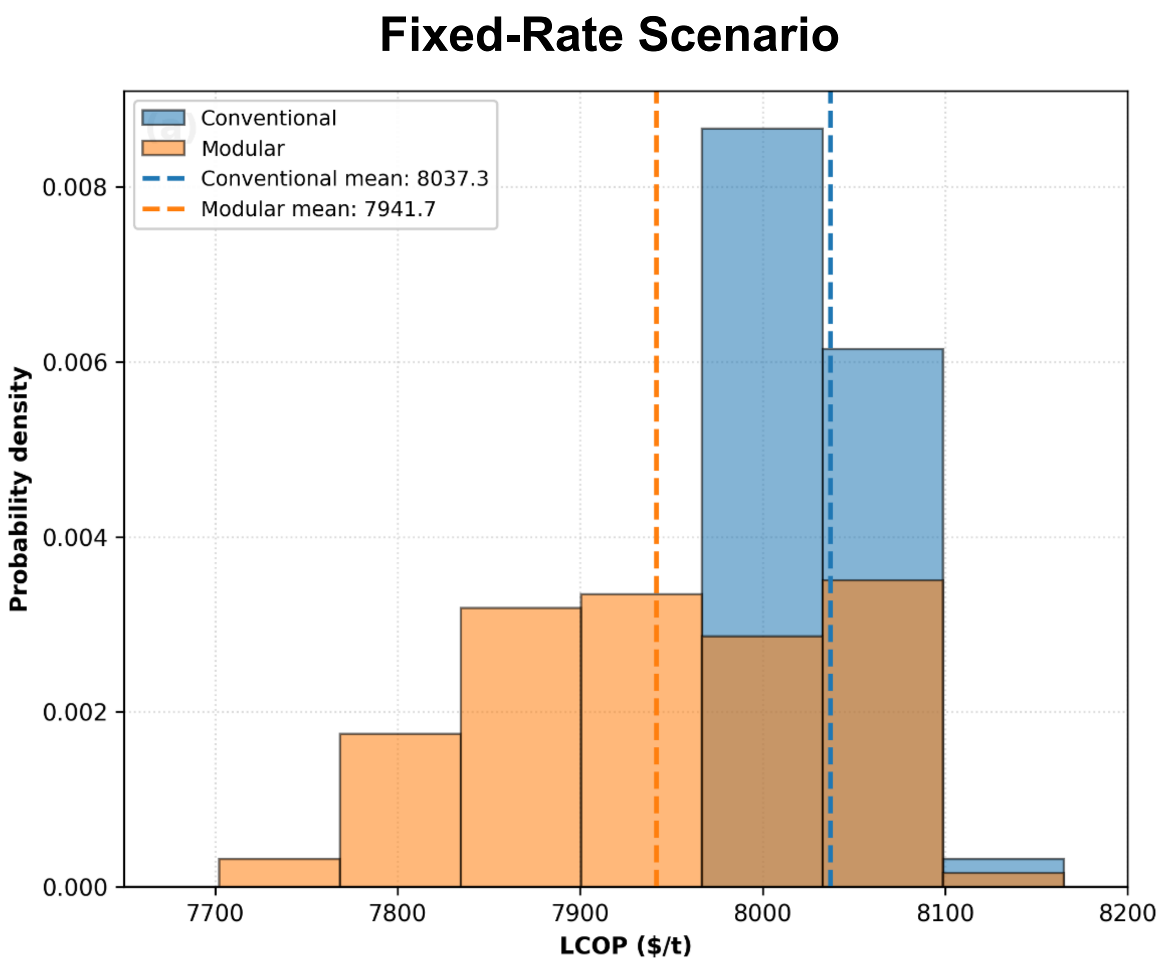
Doctoral network for microprocess engineering for electrosynthesis

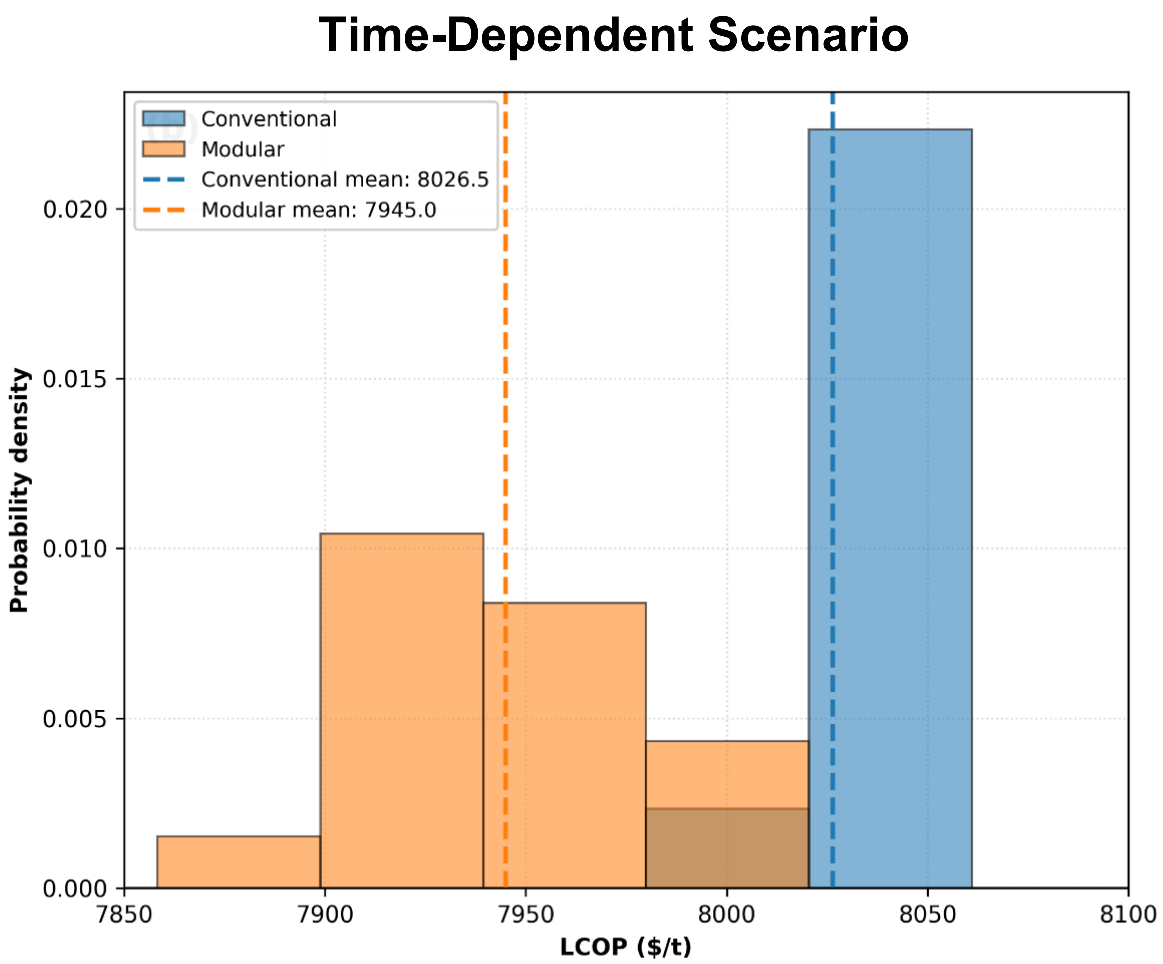
- **Economic performance metric:** levelized cost of production (LCOP) in $/t
- **Conventional:** LCOP is minimized near the design point and increases as throughput deviates from it
- **Modular:** supervisory switching adjusts active capacity, creating a stepped LCOP response as throughput increases



Uncertainty Analysis Results

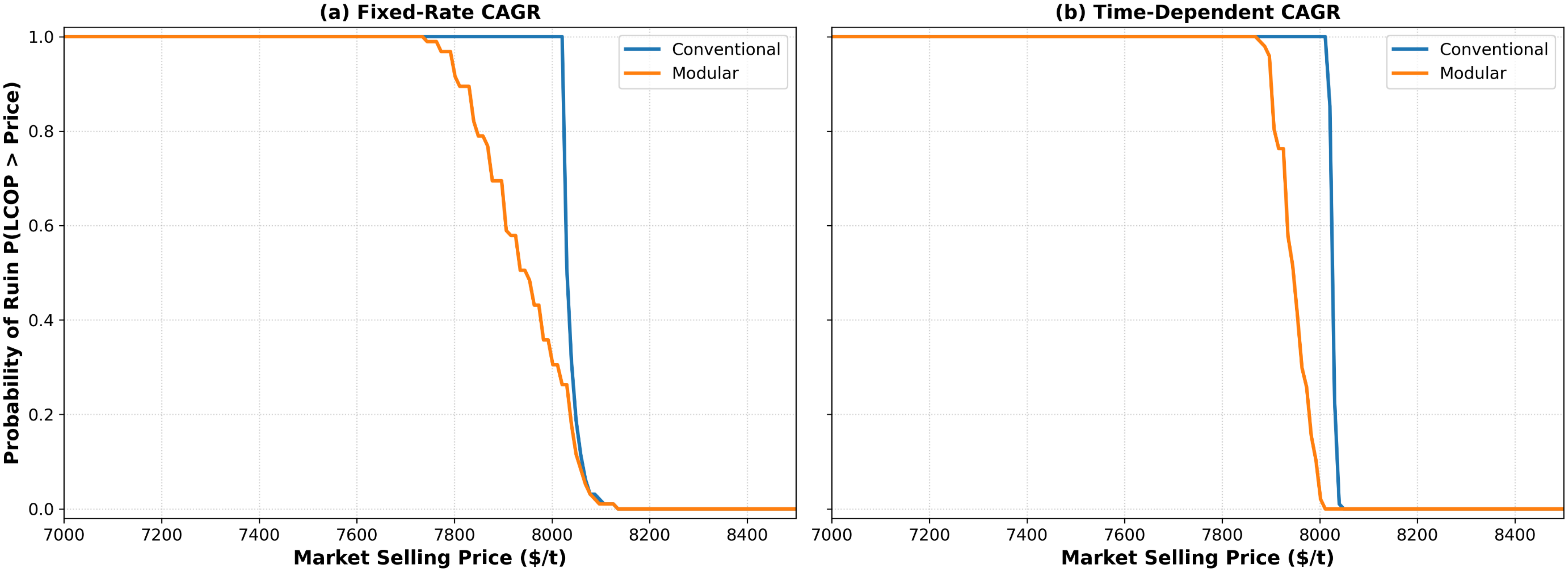
➢ Modular operation reduces mean LCOP under both demand uncertainty scenarios





Economic Risk Analysis Results

- We define economic ruin as the condition where LCOP exceeds the market selling price
- Modular operation reduces the probability of economic ruin across the critical selling-price range (informed by historical ibuprofen market-price analysis)



CONCLUSIONS

Supervisory control unlocks the **dynamic volume flexibility** provided by modular reactor design.

Operational performance is maintained by adapting active reactor volume to preserve favorable residence times and process conditions.

Adaptive modular operation enhances economic resilience, reducing mean LCOP and mitigating the probability of economic ruin under uncertain market demand.

Outlook: The framework is extensible to other continuous manufacturing processes.

THANK YOU FOR YOUR ATTENTION!

Contact information:

tusas@kt.dtu.dk

Reaction Kinetics

Hydrogenation

$$\frac{dC_{IBAP}}{dt} = -r_1 - 2r_3 = -\frac{C_{cat} a k_1 C_{IBAP} P_{H_2}}{\left(1 + K_{IBAP}C_{IBAP} + \sqrt{K_H P_{H_2}} + K_{H_2O}C_{H_2O}\right)^2} - 2r_3$$

$$\frac{dC_{Olig}}{dt} = r_3 = \frac{C_{cat} a k_3 C_{IBAP}^2}{\left(1 + K_{IBAP}C_{IBAP} + \sqrt{K_H P_{H_2}} + K_{H_2O}C_{H_2O}\right)^2}$$

$$\frac{dC_{IBEB}}{dt} = r_2 = \frac{C_{cat} a k_2 C_{IBPE} P_{H_2}}{\left(1 + K_{IBAP}C_{IBAP} + \sqrt{K_H P_{H_2}} + K_{H_2O}C_{H_2O}\right)^2}$$

$$\frac{dC_{IBPE}}{dt} = r_1 - r_2 \qquad \frac{dH_2O}{dt} = r_2$$

$$k_{i(T)} = k_{i(T_0)} exp\left(-\frac{E_A}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \qquad a = exp\left(-\alpha\frac{C_{olig}}{C_{cat}}\right)$$

Carbonylation

$$\frac{dC_{IBPE}}{dt} = -r_1 = -k_1 C_{IBPE} C_{H+}$$

$$\frac{dC_{IBS}}{dt} = r_1 - r_2 + r_{-2} = -k_1 C_{IBPE} C_{H+} - k_2 C_{IBS} C_{H+} C_{Cl-} + k_2 C_{IBPCl}$$

$$\frac{dC_{IBPCl}}{dt} = r_2 - r_{-2} - r_3 = k_2 C_{IBS} C_{H+} C_{Cl-} - k_2 C_{IBPCl} - \frac{k_3 C_{IBPCl} C_{H_2O} C_{CO} {C_{cat}}^{0.43}}{1 + K + C_{IBPCl}}$$

$$\frac{dC_{IBU}}{dt} = r_3 * 0.97 = \frac{k_3 C_{IBPCl} C_{H_2O} C_{CO} {C_{cat}}^{0.43}}{1 + K + C_{IBPCl}} * 0.97$$

$$\frac{dC_{3-IPPA}}{dt} = r_3 * 0.03 = \frac{k_3 C_{IBPCl} C_{H_2O} C_{CO} {C_{cat}}^{0.43}}{1 + K + C_{IBPCl}} * 0.03$$

$$k_i = k_{0,i} exp\left(-\frac{E_A}{RT}\right) \qquad C_{CO} = P_{CO} H_e$$

Thakar, N., Berger, R. J., Kapteijn, F., Moulijn, J. (2007) Modelling kinetics and deactivation for the selective hydrogenation of an aromatic ketone over Pd/SiO2. *Chem. Eng. Sci. 62(18-20) 5322−5329.*
Seayad , A.M., Seayad, J., Mills, P.L., Chaudhari, R.V. (2003) Kinetic Modeling of Carbonylation of 1-(4-Isobutylphenyl)ethanol Using a Homogeneous PdCl2(PPh3)2/TsOH/LiCl Catalyst System. *Ind. Eng. Chem. Res. 42, 2496-2506*

Economic Analysis

Economic Metric

Levelized cost of production (LCOP) gives us the average cost of producing one unit of product over the entire operational lifetime of a manufacturing plant.

$$LCOP = \frac{Total\ Capital\ Investment + \sum_{t=1}^{n} \frac{Total\ Operating\ Cost_t}{(1+r)^t}}{\sum_{t=1}^{n} \frac{Total\ Product_t}{(1+r)^t}}$$

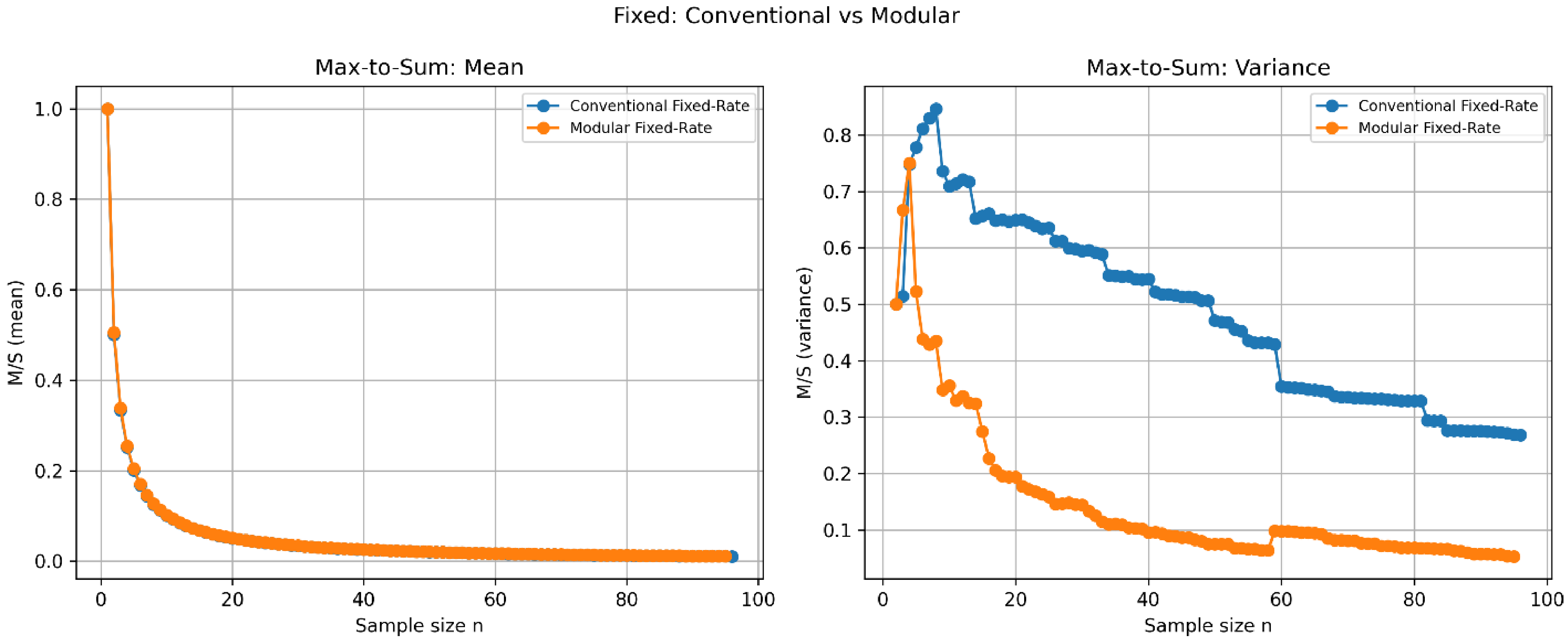
$r: discount\ rate \rightarrow 0.10$
$n: project\ lifetime \rightarrow 15\ years$

➢ We use costing correlations integrated in AVEVA to estimate the purchased equipment costs

➢ Aveva uses Lang Factor Method to estimate the total capital investment (TCI)

- $TCI = TCI_{lang} \sum_{i=1}^{n} C_{p,i}$

Statistical Convergence



Statistical Convergence