Self-Optimizing Control of a Continuous-Flow Pharmaceutical Manufacturing Plant

David Pérez Piñeiro [1] Anastasia Nikolakopoulou [2]
Johannes Jäschke [1] Richard D. Braatz [2]

[1]Norwegian University of Science and Technology

[2]Massachusetts Institute of Technology

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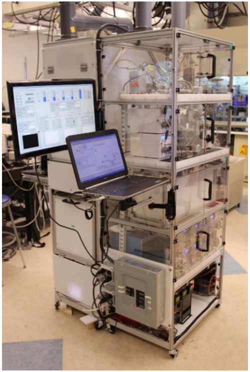
Outline

Outline

Pharmaceutical Manufacturing is Moving Towards Continuous Processing



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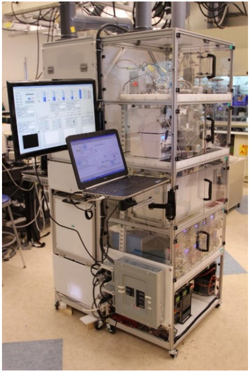

- Advantages of continuous manufacturing:
  - Lower drug production costs
  - Waste reduction
  - Fewer supply chain disruptions

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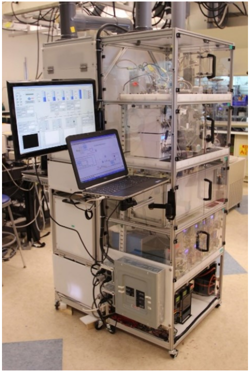

- Advantages of continuous manufacturing:
  - Lower drug production costs
  - Waste reduction
  - Fewer supply chain disruptions
- Advantages of on-demand, compact, modular systems:
  - Robust to sudden changes in demand
  - Pharmaceuticals for small populations

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Self-optimizing control

Definition

Self-optimizing control is when we can achieve an acceptable loss with constant setpoint values for the controlled variables (without the need to reoptimize when disturbances occur)[a].

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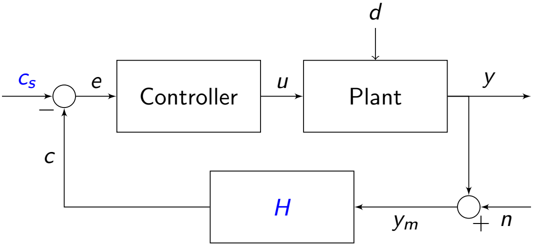
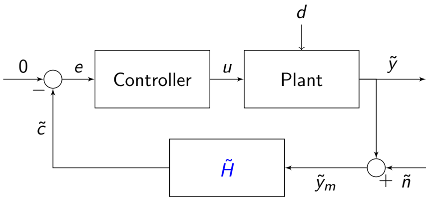
- Control architecture parameterized by H and c_s



- Equivalent control architecture parameterized by $\tilde{H}$

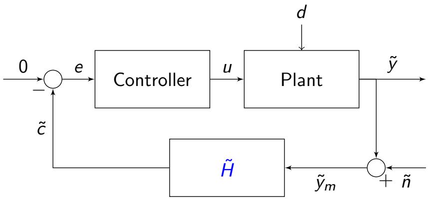


$$\tilde{H} = \begin{bmatrix} -c_s & H \end{bmatrix}$$

$$\tilde{y} = \begin{bmatrix} 1 \\ y \end{bmatrix}$$

Self-optimizing control

- Equivalent control architecture parameterized by $\tilde{H}$



$$\tilde{H} = \begin{bmatrix} -c_s & H \end{bmatrix}$$

$$\tilde{y} = \begin{bmatrix} 1 \\ y \end{bmatrix}$$

- Self-optimizing control problem: Find the optimal $\tilde{H}$

Problem formulation

Given a steady-state cost function J, disturbance d, sensor noise n, and combination matrix H, we define:

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- Loss:

$$L(n, d, H) = J(n, d, H) - J^*(d)$$

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- Average loss:

$$L_{av}(H) = \mathbb{E}[L(n, d, H)]$$

Problem formulation

Given a steady-state cost function J, disturbance d, sensor noise n, and combination matrix H, we define:

- Loss:

$$L(n, d, H) = J(n, d, H) - J^*(d)$$

- Average loss:

$$L_{av}(H) = \mathbb{E}[L(n, d, H)]$$

The combination matrix that minimizes the average loss is the solution to

$$\begin{aligned} \min_{H} \quad & L_{av}(H) & \\ \text{s.t.} \quad & y = f(u, d) & \text{Process model} \\ & H(y + n) = 0 & \text{Feedback control effects} \end{aligned}$$

$\Rightarrow$ Intractable

Approximate methods

Local methods

- Null-space method (Alstad and Skogestad, 2007)
- Extended Null-space method (Alstad et al., 2009)
- Minimum Loss method (Alstad et al., 2009)

Global methods

- Polynomial zero loss-method (Jäschke and Skogestad, 2012)
- Regression approach (Ye et al., 2013)
- Controlled variable adaptation (Ye et al., 2014)
- Global approximation of controlled variables (Ye et al., 2015)

Global Approximation of Controlled Variables

- Key simplification: Second order Taylor expansion of L around c

$$L = e_c^\top J_{cc} e_c, \qquad J_{cc} = (HG_y)^\top J_{uu} (HG_y)$$

Global Approximation of Controlled Variables

- Key simplification: Second order Taylor expansion of L around c

$$L = e_c^\top J_{cc} e_c, \qquad J_{cc} = (HG_y)^\top J_{uu}(HG_y)$$

- Separate the loss contribution due to disturbances and due to noise:

$$L_{av} = \mathbb{E}[L_d] + \mathbb{E}[L_n] \approx \frac{1}{N}\sum_{i=1}^{N}[L_d^{(i)} + L_n^{(i)}]$$

$$L_d^{(i)} = \frac{1}{2} y^{*(i)\top} H^\top J_{cc}^{(i)} H y^{*(i)}$$

$$L_n^{(i)} = \frac{1}{2}\text{trace}(W^2 H^\top J_{cc}^{(i)} H)$$

$$W^2 = \mathbb{E}(nn^\top)$$

Global Approximation of Controlled Variables

- Simplified optimization problem:

$$\min_{H} \; \frac{1}{N}\sum_{i=1}^{N}[L_d^{(i)} + L_n^{(i)}], \quad i = 1, \ldots, N \qquad \Rightarrow \text{Nonconvex}$$

$$\text{s.t.} \quad HG_y = J_{uu}^{1/2}$$

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- Additional assumption: Constant J_{cc}

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- Additional assumption: Constant J_{cc}
- Simplified convex optimization problem:

$$\min_{H} \ \tfrac{1}{2}\|\tilde{Y}H^\top\|_F^2 \qquad \tilde{Y} = \begin{bmatrix} \frac{1}{\sqrt{N}}Y \\ W \end{bmatrix}, \quad Y = \begin{bmatrix} (y_1^{\text{opt}})^\top \\ \vdots \\ (y_N^{\text{opt}})^\top \end{bmatrix}$$

$$\text{s.t.} \quad HG_y = J_{uu}^{1/2}$$

Global Approximation of Controlled Variables

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$$\min_{H} \ \frac{1}{N}\sum_{i=1}^{N}[L_d^{(i)} + L_n^{(i)}], \quad i = 1,\ldots,N \qquad \Rightarrow \text{Nonconvex}$$
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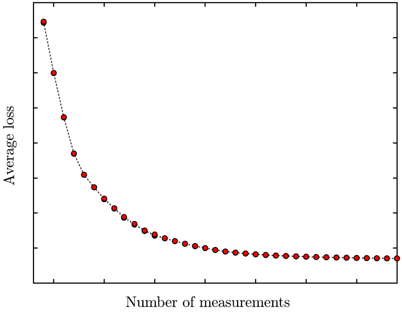
$$\text{s.t.} \quad HG_y = J_{uu}^{1/2}$$

- Analytical solution: $H^{\top} = (\tilde{Y}^{\top}\tilde{Y})^{-1}G_y$

Selecting Subsets of Measurements

- Pareto Frontier



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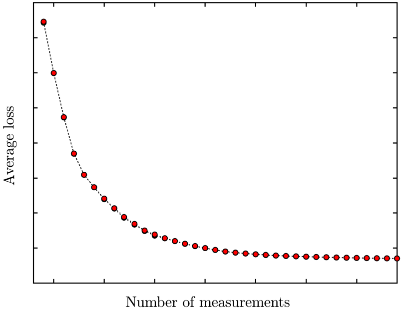

- Two solution strategies:
  - Tailor-made branch and bound methods (Cao and Kariwala, 2008)
  - MIQP formulation (Yelchuru and Skogestad, 2012)

MIQP Formulation

- Vectorization

$$\begin{aligned} \min_{H} \quad & \frac{1}{2}\|\tilde{Y}H^\top\|_F^2 \\ \text{s.t.} \quad & HG_y = J_{uu}^{1/2} \end{aligned}$$

$$H = \begin{bmatrix} h_{11} & \dots & h_{1n_y} \\ \vdots & \ddots & \vdots \\ h_{n_u1} & \dots & h_{n_un_y} \end{bmatrix}$$

MIQP Formulation

- Vectorization

$$\min_{H} \quad \frac{1}{2}\|\tilde{Y}H^\top\|_F^2$$
$$\text{s.t.} \quad HG_y = J_{uu}^{1/2}$$

$$\Downarrow$$

$$\min_{h_\delta} \quad h_\delta^\top Y_\delta h_\delta$$
$$\text{s.t.} \quad {G_\delta^y}^\top h_\delta = j_\delta$$

$$H = \begin{bmatrix} h_{11} & \dots & h_{1n_y} \\ \vdots & \ddots & \vdots \\ h_{n_u 1} & \dots & h_{n_u n_y} \end{bmatrix}$$

$$\Downarrow$$

$$h_\delta = \left[h_{11} \dots h_{1n_y}, \dots, h_{n_u 1} \dots h_{n_u n_y}\right]^\top$$

G_δ^y, j_δ, and Y_δ are obtained similarly

MIQP Formulation

- MIQP formulation for selecting a subset of s measurements

$$\begin{aligned} \min_{h_\delta, \sigma} \quad & h_\delta^\top Y_\delta h_\delta \\ \text{s.t.} \quad & {G_\delta^y}^\top h_\delta = j_\delta \end{aligned}$$

MIQP Formulation

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$$\begin{aligned} \min_{h_\delta,\sigma} \quad & h_\delta^\top Y_\delta h_\delta \\ \text{s.t.} \quad & {G_\delta^y}^\top h_\delta = j_\delta \\ & P\sigma = s \end{aligned}$$

MIQP Formulation

- MIQP formulation for selecting a subset of s measurements

$$
\begin{aligned}
\min_{h_\delta,\sigma} \quad & h_\delta^\top Y_\delta h_\delta \\
\text{s.t.} \quad & {G_\delta^y}^\top h_\delta = j_\delta \\
& P\sigma = s \\
& \sigma_1 = 1
\end{aligned}
$$

MIQP Formulation

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\text{s.t.} \quad & G_\delta^{y\top} h_\delta = j_\delta \\
& P\sigma = s \\
& \sigma_1 = 1 \\
& -M\sigma_j \leq h_{ij} \leq M\sigma_j \quad \forall j \in \{1, \dots, n_y\} \\
& \qquad\qquad\qquad\qquad\quad \forall i \in \{1, \dots, n_u\}
\end{aligned}
$$

MIQP Formulation

- MIQP formulation for selecting a subset of s measurements

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\begin{aligned}
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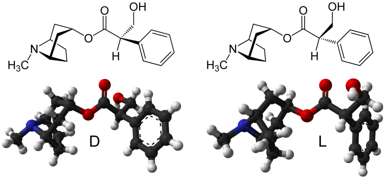
& P\sigma = s \\
& \sigma_1 = 1 \\
& -M\sigma_j \le h_{ij} \le M\sigma_j \quad \forall j \in \{1, \dots, n_y\} \\
& \qquad\qquad\qquad\qquad\quad \forall i \in \{1, \dots, n_u\} \\
& h_\delta \in \mathbb{R} \\
& \sigma \in \{0, 1\}
\end{aligned}
$$

Outline

Atropine

Source: **McGuff Medical Products**



Source: **Wikipedia**

Atropine

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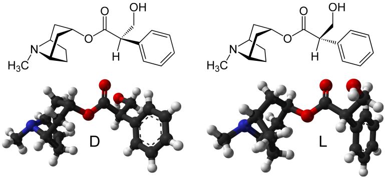

Source: **Wikipedia**

- Active pharmaceutical ingredient

Atropine

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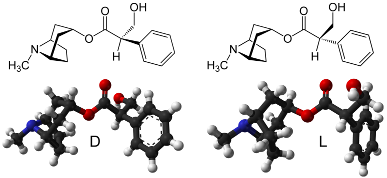

Source: **Wikipedia**

- Active pharmaceutical ingredient
- Identified as an essential medicine by the World Health Organization

Atropine

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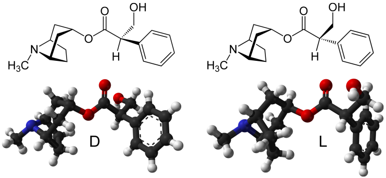
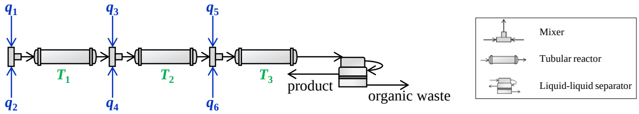


Source: **Wikipedia**

- Active pharmaceutical ingredient
- Identified as an essential medicine by the World Health Organization
- Uses:
  - Nerve agent and pesticide poisonings
  - Slow heart rate conditions
  - Reduce saliva production during surgery

Process Description

- Process flowsheet[1,2]



[1] Bédard, A.-C., Longstreet, A. R., Britton, J., Wang, Y., Moriguchi, H., Hicklin, R. W., Green, W. H., & Jamison, T. F. (2017). Minimizing e-factor in the continuous-flow synthesis of diazepam and atropine. *Bioorganic & medicinal chemistry, 25*(23), 6233–6241.

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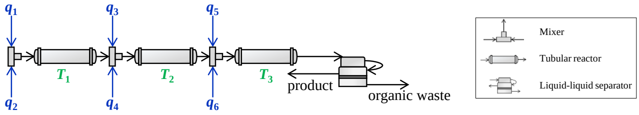
Process Description

- Process flowsheet[1,2]



- Reaction set

$$C_1 + C_3 \to C_4$$
$$C_4 + C_7 \to C_8 + C_{11} + C_{12}$$
$$C_5 + C_{11} \to C_9$$
$$C_5 + C_{11} \to C_8 + C_{10}$$

Chemical species	Chemical formula	Notation
Tropine	$C_8H_{15}NO$	C_1
Dimethylformamide	C_3H_7NO	C_2
Phenylacetylchloride	C_8H_7ClO	C_3
Intermediate	$C_{16}H_{21}O_2NHCl$	C_4
Formaldehyde	CH_2O	C_5
Methanol	CH_3OH	C_6
Sodium hydroxide	$NaOH$	C_7
Water	H_2O	C_8
Atropine	$C_{17}H_{23}NO_3$	C_9
Apoatropine	$C_{17}H_{21}NO_2$	C_{10}
Tropine ester	$C_{16}H_{21}O_2N$	C_{11}
Sodium chloride	NaCl	C_{12}
Buffer	NH_4Cl	C_{13}
Toluene	C_7H_8	C_{14}

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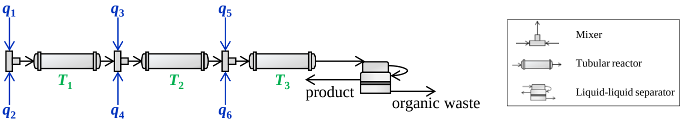
Measurement Candidates



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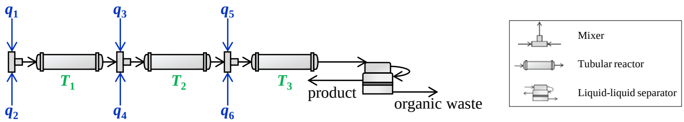
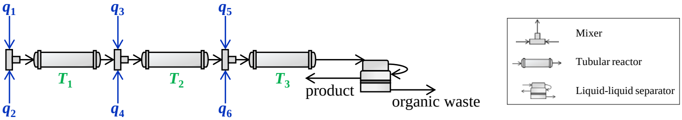


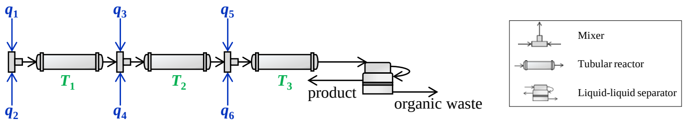
- Concentrations of chemical species at the outlet of the reactors, in the liquid-liquid separator, and in the feed streams

Measurement Candidates



- Concentrations of chemical species at the outlet of the reactors, in the liquid-liquid separator, and in the feed streams
- Temperatures in the reactors

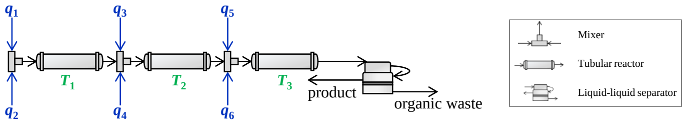
Measurement Candidates



- Concentrations of chemical species at the outlet of the reactors, in the liquid-liquid separator, and in the feed streams
- Temperatures in the reactors
- Volumetric flowrates in the feed streams

Measurement Candidates

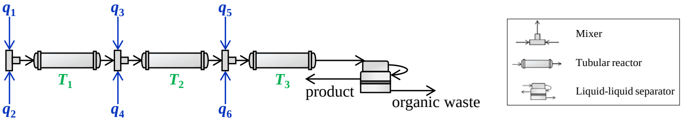
A total of 42 potential measurements



- Concentrations of chemical species at the outlet of the reactors, in the liquid-liquid separator, and in the feed streams
- Temperatures in the reactors
- Volumetric flowrates in the feed streams

Index	Measurement
1-2	Concentration of C_i at the outlet of TR1, $i = \{1, 3\}$
3-10	Concentration of C_i at the outlet of TR2, $i = \{1, 3, 5, 7, 9, 10, 11, 12\}$
11-18	Concentration of C_i at the outlet of TR3, $i = \{1, 3, 5, 7, 9, 10, 11, 12\}$
19-22	Concentration of C_i in LL (aqueous phase), $i = \{1, 7, 9, 12\}$
23-26	Concentration of C_i in LL (organic phase), $i = \{3, 5, 10, 11\}$
27-30	Concentration of C_i in the feed streams q_{1-4}, $i = \{1, 3, 5, 7\}$
31-33	Volume flowrates of TR1, TR2, and TR3
34-35	Volume flowrates of aqueous and organic phases in LL
36-39	Volume flowrates of feed streams q_{1-4}
40-42	Temperatures of TR1, TR2, and TR3

Manipulated Variables



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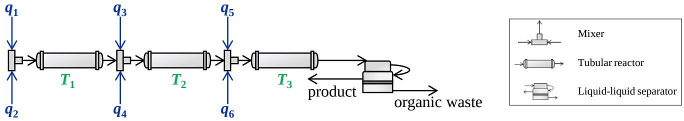

- The manipulated variables are the volume flowrates of the feed streams containing reactants: $u = (q_1, q_2, q_3, q_4)$

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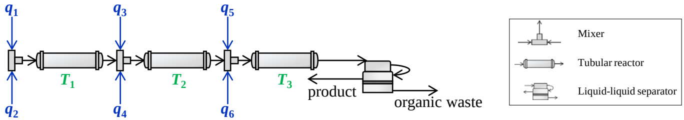

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- Feed streams containing solvents are assumed constant: $q_5 = 0.2$ mL/min and $q_6 = 0.5$ mL/min

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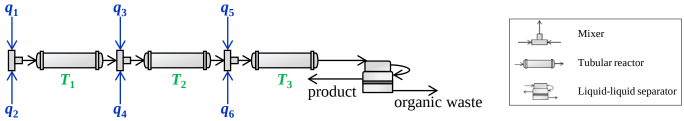

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- Feed streams containing solvents are assumed constant: $q_5 = 0.2$ mL/min and $q_6 = 0.5$ mL/min
- Constraints: $0 \leq q_i \leq 4$ mL/min for $i = \{1, 2, 3, 4\}$

Uncertainty

- Disturbances $d \sim \mathcal{N}(\mu, \sigma^2)$
  - Separation coefficient of atropine D_{C_9}
  - Pre-exponential factors k_i
  - Activation energies E_{Ai}
  - Molarity of components C_1 and C_7 in the feed streams
  - Reactor temperatures T_i

Disturbance	Unit	μ	σ
M_{C_1}	mol/L	2	0.01μ
M_{C_7}	mol/L	4	0.01μ
T_1	K	373.15	1
T_2	K	373.15	1
T_3	K	323.15	1
k_1	$\mathrm{mol/(mL \cdot min)}$	34206	0.05μ
k_2	$\mathrm{mol/(mL \cdot min)}$	10000	0.05μ
k_3	$\mathrm{mol/(mL \cdot min)}$	24	0.05μ
k_4	$\mathrm{mol/(mL \cdot min)}$	43599	0.05μ
E_{A1}	J/mol	1000	0.05μ
E_{A2}	J/mol	100	0.05μ
E_{A3}	J/mol	1819	0.05μ
E_{A4}	J/mol	26207	0.05μ
$\log(D_{C_9})$	-	-2	0.5

Uncertainty

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  - Separation coefficient of atropine D_{C_9}
  - Pre-exponential factors k_i
  - Activation energies E_{Ai}
  - Molarity of components C_1 and C_7 in the feed streams
  - Reactor temperatures T_i
- Sensor noise $n \sim \mathcal{N}(0, \sigma^2)$
  - Volume flowrates: $\sigma = 0.025 q_{nom}$
  - Concentrations: $\sigma = 0.025 C_{nom}$
  - Temperatures: $\sigma = 1\,\mathrm{K}$

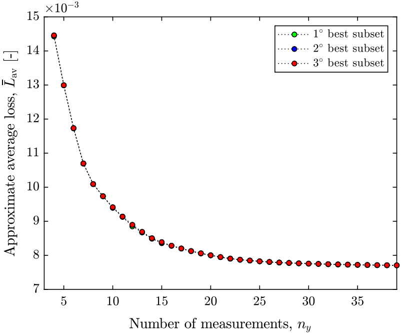
Disturbance	Unit	μ	σ
M_{C_1}	mol/L	2	0.01μ
M_{C_7}	mol/L	4	0.01μ
T_1	K	373.15	1
T_2	K	373.15	1
T_3	K	323.15	1
k_1	$\mathrm{mol/(mL \cdot min)}$	34206	0.05μ
k_2	$\mathrm{mol/(mL \cdot min)}$	10000	0.05μ
k_3	$\mathrm{mol/(mL \cdot min)}$	24	0.05μ
k_4	$\mathrm{mol/(mL \cdot min)}$	43599	0.05μ
E_{A1}	J/mol	1000	0.05μ
E_{A2}	J/mol	100	0.05μ
E_{A3}	J/mol	1819	0.05μ
E_{A4}	J/mol	26207	0.05μ
$\log(D_{C_9})$	-	-2	0.5

Objective Function

- Minimize the E-factor, which is the mass of waste per mass of product

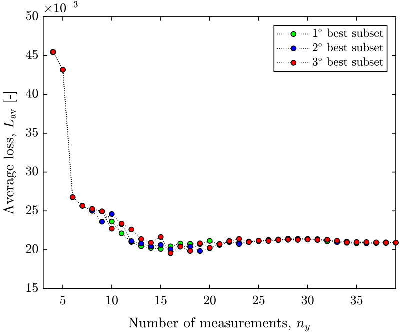
$$J = \text{E-factor} = \frac{\text{mass of waste}}{\text{mass of atropine}}$$

Screening Self-Optimizing Variables



n_y	Measurement subset	$\bar{L}_{\mathrm{av}}$ ($\times 10^{-3}$)
4	[13, 19, 20, 26]	14.427
	[3, 13, 20, 26]	14.456
	[11, 13, 20, 26]	14.457
5	[13, 17, 19, 20, 36]	12.990
	[11, 13, 17, 20, 36]	12.992
	[3, 13, 17, 20, 36]	12.994
6	[7, 13, 19, 20, 21, 26]	11.725
	[7, 11, 13, 20, 21, 26]	11.733
	[3, 7, 13, 20, 21, 26]	11.734
7	[7, 13, 19, 20, 21, 24, 26]	10.690
	[7, 11, 13, 20, 21, 24, 26]	10.696
	[3, 7, 13, 20, 21, 24, 26]	10.698
⋮	⋮	⋮
42	all measurements	7.7056

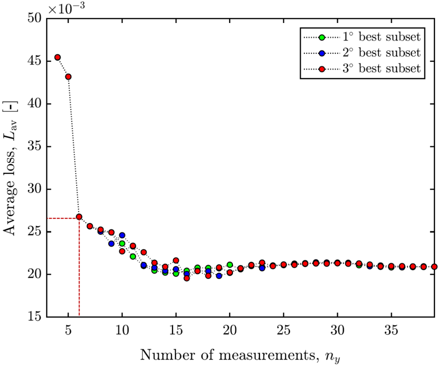
Steady-State Validation Using the Nonlinear Model



n_y	Measurement subset	L_{av} ($\times 10^{-3}$)
4	[13, 19, 20, 26]	45.428
5	[13, 17, 19, 20, 36]	43.177
6	[7, 13, 19, 20, 21, 26]	26.753
7	[7, 13, 19, 20, 21, 24, 26]	25.654
8	[7, 13, 17, 19, 20, 21, 24, 36]	25.033
9	[7, 12, 13, 17, 20, 21, 23, 24, 36]	23.614
10	[7, 12, 13, 17, 20, 21, 22, 23, 24, 36]	22.717
⋮	⋮	⋮
42	all measurements	20.889

Example: Control Architecture with 6 Measurements

$$H = \begin{bmatrix} -1.65 & -1.39 & 0.29 & -69.9 & 2.88 & 1.10 & 2.15 \\ -2.15 & -1.57 & 0.79 & -38.9 & 15.5 & 1.32 & 1.87 \\ -1.90 & -1.21 & 1.55 & -8.44 & 10.6 & 0.98 & 0.80 \\ -3.18 & -2.25 & 1.65 & -12.9 & 15.0 & 1.84 & 2.45 \end{bmatrix}$$



n_y	Measurement subset	L_{av} ($\times 10^{-3}$)
4	[13, 19, 20, 26]	45.428
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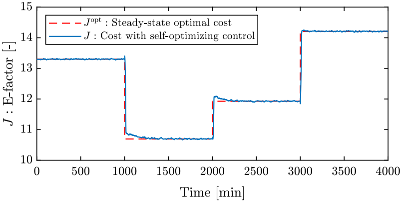
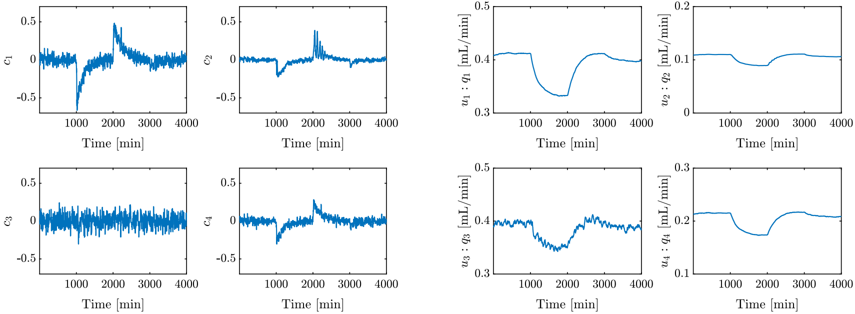
10	[7, 12, 13, 17, 20, 21, 22, 23, 24, 36]	22.717
⋮	⋮	⋮
42	all measurements	20.889

Dynamic Simulation





Outline

Conclusions

- Self-optimizing control is a simple policy for near-optimal control of steady-state systems under uncertainty

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- Self-optimizing control is a simple policy for near-optimal control of steady-state systems under uncertainty
- Problem reformulation for selecting subsets of measurements
- Applied to a continuous pharmaceutical manufacturing plant under
  - Parametric model uncertainty
  - Process disturbances
  - Sensor noise

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