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CHAPTER 7

Material Diversion by Residence-Time Tracking in a Simulated Continuous Flow Synthesis

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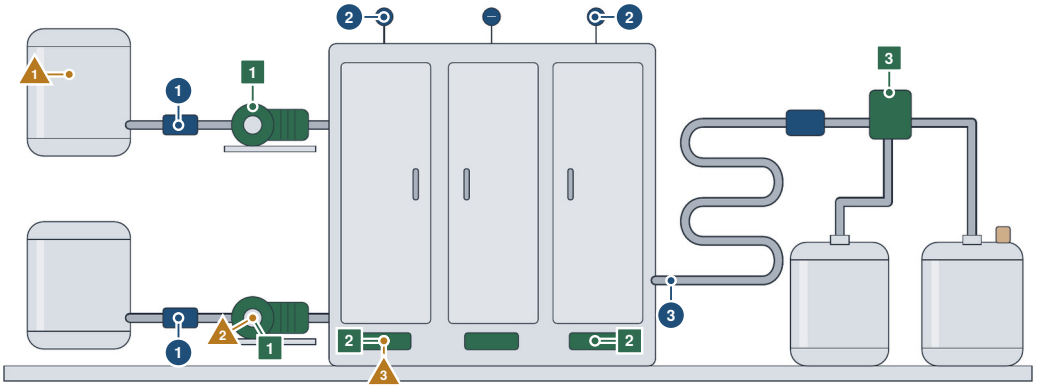
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CHAPTER 7

Material Diversion by Residence-Time Tracking in a Simulated Continuous Flow Synthesis



The controller moves 1 feed pumps for substrate A and reagent B 2 circulators that heat or cool the reactor zones 3 divert valve to the accepted or the divert tank

The controller reads 1 feed flow meters 2 zone thermometers 3 analyzer sample point at the coil inlet

What disturbs it 1 a feed A drum stronger than its label 2 an air lock in pump B 3 lost cooling in zone 1

The analyzer samples the product before the long coil, which holds each part until its verdict reaches the valve. Illustration, not to scale.

IN PLAIN TERMS **Following a Medicine Through a Pipe**

The main idea. A continuous line makes a medicine ingredient by pumping two liquids through a warm tube, where they react. A tester checks a sample every few minutes, and a valve then sends each part to a good tank or to waste.

The challenge. The tube spreads a short upset out, so bad product reaches the valve early and stays long. Each test result comes after its sample has moved on, so a long pipe holds the product until the result is in.

Why it matters. Only a line that knows where each liter is can throw out the bad part and keep the rest.

THREE WAYS TO READ THIS CHAPTER

Explore	11 min	the first page, the fact on run time (Section 7.1), the history segment (Section 7.2), the try-its on the air lock and the slow analyzer and the fact on method time (Section 7.6) and the key points
Study	65 min	the whole chapter with its three pause points and the twelve exercises at its end
Practice	20 min	the first page, the results (Section 7.6), Technology in Practice (Section 7.7), Limitations (Section 7.8) and the open challenge

The control question A continuous synthesis has no batch to hold back. When a dispersive reactor spreads an upset and the analyzer reports on material that has already moved on, which part of the stream must be diverted, and does a plug-flow delay or residence-time tracking find it?

Learning objectives

- Compute the mean residence times, spreads and coil quantiles of a line of well-mixed cells, and the plug-flow time from mixer to valve.
- Size a hold-up coil against an analyzer method and a throughput with $t_{det} = 2t_{run} + t_{tr}$, and predict how often a change escapes.
- Explain why a plug-flow delay releases off-specification material at both ends of a spread upset, and measure it on the same material in the app.
- Distinguish the upsets a soft sensor sees through its meters from those only the analyzer sees.
- Separate what a predictive controller gains from its plan and from its target when it is compared with a retuned quality trim.

Prerequisites Sections 1.4.4, 1.4.5, 1.4.8, 1.6.2 and 1.6.3. Chapter 4 for material followed on the measured flow.

The app https://apmonitor.com/apps/continuous-api/

See also Volume 8, Chapter 13 for a flow diversion valve under a supervisor that judges each parcel's history, Volume 8, Chapter 9 for results that arrive after later product has been made, and Volume 8, Chapter 2 for heat removal as the limit on how fast an exothermic reaction may be fed.

7.1 Introduction

A batch of drug substance that goes wrong can be held, tested and rejected as one lot. A continuous line has no such unit. Its product leaves every minute, so when a reagent pump loses its prime or a feed drum is stronger than its label, the question becomes which part of the stream the fault reached, and whether all of that part went to waste. An industry roundtable has named continuous processing a research priority and surveyed its members about the hurdles that slowed its implementation [1], and a review of regulatory readiness has stated that the U.S. Food and Drug Administration supports it on science- and risk-based grounds [2]. Continuous-flow reactors with small channels suit the hazardous and fast exothermic steps of active pharmaceutical ingredient (API) synthesis, because their fast heat transfer prevents the accumulation of heat and the formation of hot spots [3].

The simulator of this chapter is a continuous reaction step of that kind at the scale of a laboratory flow system. Substrate A and reagent B are pumped at 100 mL/min in total, meet in a 15 mL mixer and react through four jacketed zones of 0.40 L, each with its own circulator and temperature loop. A quench stream destroys the unreacted reagent, an at-line high-performance liquid chromatograph (HPLC) samples the quenched stream every 3 min, and a 1.5 L hold-up coil carries the material to a three-way valve that sends it to an accepted tank or to a divert tank. An over-reaction of the product with excess reagent and a thermal decomposition of the substrate compete with the desired reaction, so conversion and impurities pull against each other in temperature, ratio and residence time. As an educational equipment-control simulation, the application uses illustrative kinetics, invented for teaching and standing for no real synthesis, and illustrative quality limits. Neither has had quality-assurance review, and nothing in the application or in this chapter is regulatory or quality-assurance guidance.

✦ DID YOU KNOW? A Run Measured in Months

In the worked example of a continuous drug-substance line with two plug-flow reactors in the ICH Q13 guidance, a risk assessment supports a proposed run time of up to several months [4]. The graded campaign of this chapter runs six hours.

Three properties separate this plant from a reactor with a temperature loop and a dead time. The reactor and the coil are distributed, so a disturbance at the mixer reaches the valve spread out. A four-minute air lock in the reagent pump sends off-specification material to the valve from 24.07 to 35.85 min after it begins, starting 4.58 min before the plug-flow time of 28.65 min and ending 3.20 min after the plug-flow image of the air lock has passed. The analyzer is late by construction, because each result describes a sample drawn one method run and one transport earlier, 3.5 min with the default method, and by then the sampled material has moved on toward the valve. Some disturbances, such as a drum made up 10 % stronger than its label, are seen only in the product.

The simulator addresses the belief that a disturbance reaches the outlet one plug-flow time after it enters and lasts there as long as it lasted at the inlet. That belief is the fixed dead time of a transfer function, and it is also the simplest rule for diverting product. The class of problem is general. Residence-time distributions have been used to define batches and to trace raw materials through a continuous direct compaction line, with the methods stated to extend to wet and dry granulation, hot melt extrusion and capsule filling [5], and to size the waste at the candidate diversion points of a continuous dry granulation line for four feeder upsets [6]. A pasteurizer's flow diversion valve, a tablet press with a delayed composition measurement and a refinery blend with an at-line analyzer have the same shape, and Volume 8, Chapter 13 and Chapter 6 treat the first two. However, the transport delay of an introductory course is a constant, and a constant delay represents neither the spread that a mixed volume gives a disturbance nor a verdict that arrives after the material has moved on. Sections 1.4.4 and 1.4.5 set out both departures on the running example of Chapter 1.

A concern about a gap between process control theory and practice had been voiced by 1950 [7], and a survey of good practice in control teaching centers its discussion on laboratories, software and assessment [8]. A continuous line asks its engineers to answer for every liter it made, and the answer rests on residence time and analyzer timing more than on the gains of any single loop.

This chapter compares, on one simulated flow line and on the same material, a plug-flow delay and residence-time tracking as rules for deciding what a continuous synthesis must divert, and it describes the line in enough detail to be rebuilt. Every method used is established: tanks-in-series residence-time models, ratio control, conditional integration, model-based soft sensors, diversion valves and model predictive control (MPC), whose industrial use has been surveyed [9]. The line has 1205 states. The plant and a measurement-driven copy of it share one set of equations, a supervisor follows material in volume and scores the unselected rule on the same material, and a truth record is kept apart from the instruments. The application pairs the two rules on identical material through eight cases and a six-hour campaign, and a ninth case asks how much of what an optional MPC achieves over the shipped quality trim is the plan and how much is the target it is tuned to.

Section 7.2 reviews the domain. Section 7.3 sets down the model of the line, its chemistry, jackets, coil, pumps and valve, and Section 7.4 works out its residence times, its operating window and the rule that sizes the coil against the analyzer. Section 7.5 describes the instruments, the loops, the soft sensor, the diversion supervisor and the predictive controller. Section 7.6 reports what each case and the campaign measured, including the comparison of the predictive controller with the quality trim and the worst cases under each structure. Section 7.7 sets the line beside the instruments, valves and control platforms of real plants, Section 7.8 states the limitations and Section 7.9 draws the conclusions.

7.2 Residence Time and Continuous Drug Manufacturing

The vocabulary for how a continuous vessel spreads what enters it dates from 1953. The distribution of residence times of a continuous flow system, and its measurement with a tracer, was set out that year [10]. In the same year the dispersion of a solute in slow laminar flow through a tube was traced to the combined action of the velocity profile and radial molecular diffusion [11], so the spread of a real tube depends on its diameter, its flow and the diffusivity of what it carries. A chain of well-mixed cells is the simplest model with an adjustable spread, and it is the one used here.

Continuous processing had been used for decades in other industries while pharmaceutical manufacturing was slow to adopt it, primarily because of regulatory uncertainty [5]. The batch is the unit of release, and the record, the testing and the filing are organized around it. A review of continuous processing in the industry appeared in 2005 [12]. An end-to-end continuous pilot plant then made a finished drug product from chemical intermediates in one integrated system [13]. A plant-wide control strategy was then designed for a system inspired by that pilot plant, as the history segment after this paragraph tells. Two plant-wide MPC designs for an end-to-end pilot plant, one from subspace identification and one from linearized differential-algebraic equations, were later evaluated on a nonlinear simulator of it under uncertain reaction kinetics [14]. A refrigerator-sized reconfigurable system later made four APIs to U.S. Pharmacopeia standards by continuous-flow synthesis and formulation [15]. A review of the transition found continuous drug product already used in approved processes, with continuous API steps under current good manufacturing practice lagging behind it in regulatory filings [16].

> ⧖ HISTORY **2013: A Control Strategy for a Whole Continuous Plant**
>
> The end-to-end pilot plant made a pharmaceutical product in a fully continuous fashion, from the synthesis of its intermediates to the coating of the drug product. A 2013 study designed a plant-wide control strategy for a system inspired by it. Its authors argued that, instead of the fixed recipes of batch work, control of a continuous plant must actively hold it within a safe region of operation, so the key challenge is a strategy for the plant as a whole rather than for isolated units. They split the plant into a hierarchy of levels, chose the loops at each level from sensitivities computed with a plant-wide dynamic model, and in simulation kept the critical quality attributes of the final product close to specification under significant and persistent disturbances [17].

Traceability is what the batch had provided for free. With the residence-time distribution as the tool, methods were proposed for defining a batch, tracing raw materials and choosing the frequency of the sensors on a continuous line [5]. Residence-time models of the units of a dry granulation line were built from tracer tests and used to compute how much material each candidate diversion point would reject in four feeder upsets [6]. The measurements come from process analytical technology, whose sensors and whose monitoring and control methods have been reviewed together with the regulatory view of them [18]. On flow reactors, inline infrared and nuclear magnetic resonance spectroscopy have been combined with an online chromatograph on one modular platform [19], and a perspective on quality by control holds that active process control based on process knowledge and model-based techniques is indispensable in continuous manufacturing [20]. The ICH Q13 guideline, issued in the United States as guidance for industry in March 2023, describes scientific and regulatory considerations specific to the continuous manufacturing of drug substances and drug products [4]. It is cited here as context only.

7.3 A Line of Well-Mixed Cells

At its design point the line feeds 47.62 mL/min of substrate A and 52.38 mL/min of reagent B, both 1.00 mol/L and preheated to 55 °C, which is a molar ratio of 1.10. A quench of 20 % of the feed brings the coil flow to 120 mL/min, and the product reaches the valve at 98.66 % assay with 0.54 % impurities and 0.392 mol/L of P. The feeds, the mixer, the four zones with their jackets and circulators,

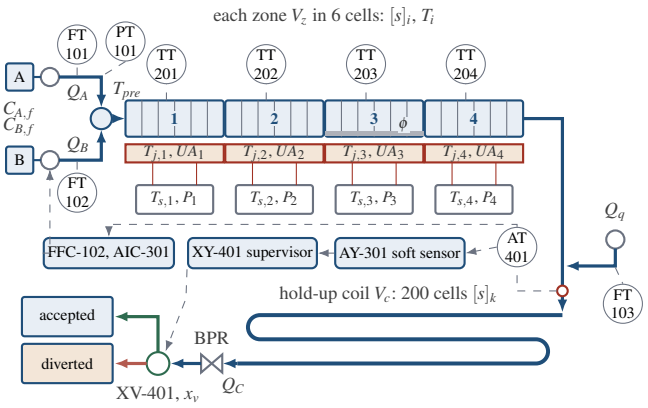


Figure 7.1 Continuous flow synthesis as modeled. Substrate A and reagent B of strengths $C_{A,f}$ and $C_{B,f}$ are pumped at Q_A and Q_B past FT-101 and FT-102 into the mixer at T_{pre}, with PT-101 on the pump discharge. Four zones of volume V_z, six cells each, exchange heat through jackets at $T_{j,z}$ (UA_z) with circulators at supply temperature $T_{s,z}$ and duty P_z, and TT-201 to TT-204 read the third cell of each zone. A deposit ϕ can grow in zone 3. The quench Q_q (FT-103) joins before the sample point of AT-401, and the coil flow Q_C passes the hold-up coil and the BPR to XV-401, which routes it to the accepted or the divert tank. The dashed lines are the signals of the soft sensor, the supervisor, the ratio station and the quality trim.

Table 7.1 What Each Line Variable Is, Its Design Value and Its Range

Variable	Role	Design value	Range
Q_{SP}	SP, total feed flow	100 mL/min	0–200
R_{SP}	SP, molar ratio B/A	1.10	0.9–1.5
$T_{z,SP}$	SP, zones 1–4	55, 60, 60, 60 °C	30–90
A_{SP}	SP, residual A (trim)	0.8 %	0.2–2.5
Q_m, R_m	CV, FT-101 + FT-102	100 mL/min, 1.10	—
$T_{z,m}$	CV, TT-201 to 204	55, 60, 60, 60 °C	—
α_m	CV, AT-401 residual A	0.80 %	—
u_A, u_B	MV, pump speeds	23.8, 26.2 %	0–100
$T^*_{s,z}$	MV, supplies	45.6, 62.3, 59.1, 60.1 °C	0–100
ΔR	MV, ratio trim	0	−0.10–0.30
x_v	MV of XV-401	accept	or divert
δ_A, $\dot{\delta}_A$	DV, strength, drift	0, 0 %/h	±15, ±20
$\delta_{A,as}$	DV, entered assay	0 %	±15
η_B	DV, pump B delivery	100 %	20–110
β_B	DV, FT-102 bias	0 %	±10
c_1	DV, zone 1 cooling	100 % of 200 W	10–100
t_{run}	DV, HPLC method run	3 min	1–15
r_ϕ	DV, deposit growth	0 %/h	0–100
$[s]_i$, T_i	states, 25 reaction cells	7 each	—
$[s]_k$	states, 200 coil cells	5 each	—
$T_{j,z}$, $T_{s,z}$	states	4 each	—
Q_A, Q_B, Q_q	states, pumps	47.6, 52.4, 20 mL/min	—

the quench, the sample point, the coil, the back-pressure regulator (BPR), the divert valve, the two tanks and each instrument appear in Figure 7.1.

Table 7.1 lists the variables by role. The state vector has 1205 elements: seven per reaction cell (A, B, P, I, D, an inert tracer X and the temperature) for the mixer and 24 zone cells, five per coil cell (A, P,

I, D and X) for 200 coil cells, four jacket and four supply temperatures, three pump deliveries, twelve tank contents and seven ledgers of feed, quench and energy. The discrete events are a four-minute air lock in pump B, a new assayed drum of feed A, a stop and a restart of the feeds, a trip reset, a cleaning of zone 3 and a tracer pulse of 10 mmol over 10 s at the mixer.

7.3.1 Chemistry and Rates

Three reactions are carried, as shown in Equation (7.1).

$$\begin{aligned} &\mathrm{A}+\mathrm{B}\rightarrow\mathrm{P}, \qquad \mathrm{P}+\mathrm{B}\rightarrow\mathrm{I}, \qquad \mathrm{A}\rightarrow\mathrm{D} \\ &r_1 = k_1[\mathrm{A}][\mathrm{B}], \qquad r_2 = k_2[\mathrm{P}][\mathrm{B}], \qquad r_3 = k_3[\mathrm{A}] \\ &k_j = k_{j,60}\exp\Big[-\frac{E_j}{R}\Big(\frac{1}{T+273.15}-\frac{1}{333.15}\Big)\Big] \end{aligned} \tag{7.1}$$

where P is the product, I the impurity made when the product meets excess reagent, D the impurity made when the substrate decomposes, T is in °C and $R = 8.314\,\mathrm{J/(mol\,K)}$. Negative concentrations are clipped to zero inside the rates. The activation energies rise from 60 through 95 to 160 kJ/mol, so a hotter reactor converts more of A and makes more of both impurities, the decomposition fastest of all. The heats of reaction are −120, −80 and −60 kJ/mol.

7.3.2 Reaction Cells, Jackets and Circulators

The mixer, cell 0 of volume V_{mix}, and the 24 zone cells of volume $V_z/6$ form one chain carried by the reactor flow $Q_R = Q_A + Q_B$, as shown in Equation (7.2).

$$\begin{aligned} \frac{\mathrm{d}[s]_i}{\mathrm{d}t} &= \frac{Q_R}{V_i}\big([s]_{i-1}-[s]_i\big)+\sum_{j=1}^{3}\nu_{sj}\,r_{j,i} \\ \rho c_p\frac{\mathrm{d}T_i}{\mathrm{d}t} &= \rho c_p\frac{Q_R}{V_i}(T_{i-1}-T_i)+\sum_{j=1}^{3}(-\Delta H_j)\,r_{j,i} \\ &\quad -\frac{UA_z}{6V_i}(T_i-T_{j,z}) \end{aligned} \tag{7.2}$$

where s is one of A, B, P, I, D and X, and ν_{sj} is its stoichiometric coefficient in reaction j. The inlet of the mixer is the mixed feed, $[\mathrm{A}]_{in} = Q_A C_A/Q_R$ and $[\mathrm{B}]_{in} = Q_B C_{B,f}/Q_R$ at T_{pre}, where the true strength $C_A = C_{A,f}(1+\delta_A/100)$ carries the unmeasured strength error δ_A in percent, the slider value plus a drift integrated at $\dot{\delta}_A$ and bounded at $\pm 15\,\%$. The jacket term acts on the six cells of zone z and not on the mixer. Each jacket is fed by a circulator that moves its bath toward the command $T^{*}_{s,z}$ of TIC-20z within power limits, as shown in Equation (7.3).

$$\begin{aligned} C_j\frac{\mathrm{d}T_{j,z}}{\mathrm{d}t} &= \sum_{i\in z}\frac{UA_z}{6}(T_i-T_{j,z})+F_j c_p\,(T_{s,z}-T_{j,z}) \\ C_b\frac{\mathrm{d}T_{s,z}}{\mathrm{d}t} &= F_j c_p\,(T_{j,z}-T_{s,z})+P_z \\ P_z &= \mathrm{clamp}\big(P_z^{req},\,-P_{c,z},\,P_h\big) \\ P_z^{req} &= \frac{C_b}{\tau_c}(T^{*}_{s,z}-T_{s,z})+F_j c_p\,(T_{s,z}-T_{j,z}) \end{aligned} \tag{7.3}$$

Here P_z^{req} is the duty that the circulator's internal controller requests. Away from its limits the supply therefore follows its command as a first-order lag of $\tau_c = 60\,\mathrm{s}$. In this chapter τ_c is the circulator's response time, not the closed-loop time constant of Section 1.3. The cooling capacity $P_{c,z}$ is 200 W for zone 1, scaled by the disturbance c_1, and 100 W for zones 2 to 4, and every circulator can heat by $P_h = 300\,\mathrm{W}$.

7.3.3 Quench, Coil and Quality

At the quench the unreacted reagent is destroyed and the other solutes are diluted into the coil flow $Q_C = Q_R + Q_q$. The coil is a second chain of 200 cells of volume $V_k = V_c/200$, as shown in Equation (7.4).

$$[s]_q = \frac{Q_R}{Q_C}[s]_{24}, \qquad \frac{\mathrm{d}[s]_k}{\mathrm{d}t} = \frac{Q_C}{V_k}\left([s]_{k-1} - [s]_k\right) \tag{7.4}$$

where s is A, P, I, D or X, $[s]_q$ feeds coil cell 0, and nothing reacts after the quench. The quality of a quenched composition follows Equation (7.5).

$$a = \frac{100[\mathrm{P}]}{S}, \quad \iota = \frac{100([\mathrm{I}]+[\mathrm{D}])}{S}, \quad \alpha = \frac{100[\mathrm{A}]}{S} \tag{7.5}$$

where $S = [\mathrm{A}]+[\mathrm{P}]+[\mathrm{I}]+[\mathrm{D}]$, a is the assay, ι the total impurities and α the residual A, all area percentages of the solutes as an in-process HPLC reports them, so dilution does not change them. The strength is [P] itself, which catches solvent at startup. Material is in specification when $a \geq a_{min}$, $\iota \leq i_{max}$ and $[\mathrm{P}] \geq s_{min}$, with illustrative limits of 97.5 %, 1.0 % and 0.33 mol/L. At the design point the sample point carries 98.66 % assay, 0.80 % residual A and 0.54 % impurities, 0.344 % of it I and 0.195 % D, at 99.20 % conversion of A.

7.3.4 Pumps, Pressure and the Zone 3 Deposit

The feed and quench pumps are first-order drives, and the pump discharge pressure is the BPR setting plus laminar drops that scale with the flows, as shown in Equation (7.6).

$$\begin{aligned}
\tau_p \frac{\mathrm{d}Q_A}{\mathrm{d}t} &= \frac{u_A}{100}Q_{A,max} - Q_A \\
\tau_p \frac{\mathrm{d}Q_B}{\mathrm{d}t} &= \eta_B \frac{u_B}{100}Q_{B,max} - Q_B \\
\tau_p \frac{\mathrm{d}Q_q}{\mathrm{d}t} &= \min(q\,Q_m, Q_{q,max}) - Q_q \\
P &= P_{BPR} + \Delta P_c \frac{Q_C}{Q_{C,0}} + \Delta P_z \frac{Q_R}{Q_{R,0}}\,(4 + 40\,\phi)
\end{aligned} \tag{7.6}$$

where u_A and u_B are pump speeds in percent, η_B is pump B's delivery factor (0.1 during the air lock, times the delivery disturbance), $q = 0.20$ is the quench ratio applied to the measured feed flow Q_m, $Q_{C,0} = 120\,\mathrm{mL/min}$, $Q_{R,0} = 100\,\mathrm{mL/min}$, and $\phi \in [0,1]$ is the deposit fraction in zone 3. The deposit grows as $\mathrm{d}\phi/\mathrm{d}t = r_\phi/(100 \times 3600)$ per second with r_ϕ in percent of its full extent per hour, it multiplies the hydraulic resistance of zone 3 by $1 + 40\phi$, 41 times its clean value at $\phi = 1$, and it reduces the jacket transfer of zone 3 to $UA_z(1 - 0.5\phi)$. At design the discharge is 4.30 bar. Above $P_{trip} = 10\,\mathrm{bar}$ a relay stops both feed pumps and the quench until an operator resets the trip and restarts the feeds.

7.3.5 Valve, Tanks and the Truth Record

The divert valve XV-401 splits the coil outflow in proportion to its position x_v, which moves toward 1 (accept) or 0 (divert) at $1/t_{XV}$ per second with $t_{XV} = 4\,\mathrm{s}$. The tanks integrate the volume and the moles of each solute that reach them. After every step the true composition of the last coil cell is judged against the limits, and $x_v Q_C \Delta t$ joins the off-specification volume released whenever that composition fails. A second valve position, driven by the unselected tracking rule, is scored against the same composition, and no controller reads either record. The A backbone ($[\mathrm{A}]+[\mathrm{P}]+[\mathrm{I}]+[\mathrm{D}]$) and the B content ($[\mathrm{B}]+[\mathrm{P}]+2[\mathrm{I}]$) are conserved by all three reactions, so their ledgers (fed, minus the change held in the line, the two tanks and the reagent the quench destroyed) close to within 1×10^{-14} of what was fed in every run made for this chapter, and so does the energy of the cells, jackets and baths.

Table 7.2 Parameters of the Line. Visible Parameters Appear as Sliders in the Model Panel, Hidden Ones Do Not

Symbol	Meaning	Value	Class
V_{mix}, V_z, V_c	mixer, zone, coil	15 mL, 0.40, 1.5 L	hidden
T_{pre}	feed preheat	55 °C	visible
$C_{A,f}$, $C_{B,f}$	feed label strengths	1.00 mol/L each	visible
q	quench per feed flow	20 %	visible
ρc_p	stream heat capacity	1.8 MJ/(m^3 K)	hidden
$Q_{A,max}$, $Q_{B,max}$	pumps at full speed	200 mL/min each	visible
$Q_{q,max}$, τ_p	quench pump, drive lag	100 mL/min, 2 s	hidden
t_{XV}	valve full stroke	4 s	visible
$k_{1,60}$	A + B → P at 60 °C	4 L/(mol min)	visible
$k_{2,60}$	P + B → I at 60 °C	0.0032 L/(mol min)	visible
$k_{3,60}$	A → D at 60 °C	0.0015 min^{-1}	visible
E_1, E_2, E_3	activation energies	60, 95, 160 kJ/mol	visible
ΔH_1	heat of R1	−120 kJ/mol	visible
ΔH_2, ΔH_3	heats of R2, R3	−80, −60 kJ/mol	hidden
UA_z	jacket, per zone	12 W/K	visible
$F_j c_p$	jacket fluid flow	123 W/K	hidden
C_j, C_b	jacket, bath capacities	1.5, 2.0 kJ/K	hidden
τ_c, P_h	circulator response, heating	60 s, 300 W	hidden
$P_{c,1}$, $P_{c,2..4}$	cooling capacities	200, 100 W	visible
P_{BPR}	BPR setting	3.0 bar	visible
ΔP_z, ΔP_c	zone, coil drops	0.20, 0.50 bar	hidden
P_{alarm}, P_{trip}	discharge limits	8, 10 bar	visible
t_{tr}	sample transport	30 s	visible
σ_α, σ_ι	analyzer noise, A and I + D	0.03, 0.015 %	hidden
σ_s	strength noise, of reading	0.5 %	hidden
τ_{TT}, τ_{FT}	thermometer, meter lags	5, 1 s	hidden
a_{min}, i_{max}	assay, impurity limits	97.5, 1.0 %	visible
s_{min}	strength limit	0.33 mol/L	visible

7.3.6 Initial State, Integration and Checks

Table 7.2 lists the parameters, where ΔP_z is the drop per clean zone at 100 mL/min and ΔP_c the coil drop at 120 mL/min. Every scenario except startup and the campaign begins on the steady line, solved cell by cell. Each cell's balances reduce to three reaction extents and an energy balance solved by Newton's method, and a secant search on each supply temperature puts the thermometer cell of its zone on the setpoint. The supplies then sit at 45.58, 62.27, 59.12 and 60.06 °C, and the jackets at 46.39, 62.03, 59.21 and 60.05 °C. Startup fills the line with solvent at the zone temperatures and no flow. The engine (Section 1.6.1) integrates all 1205 states by fourth-order Runge-Kutta with a 1 s step. Halving the step leaves the volume diverted in case 3 at 1.5277 L (within 2 parts in 10^8), because the valve is commanded only at control executions, which fall at the same instants, and moves its worst released assay by 0.009 points (97.778 against 97.769 %). The cell counts are the declared dispersion rather than a discretization, and 3, 6, 12, 24 and 48 cells per zone give design assays of 98.39, 98.66, 98.78, 98.84 and 98.87 %. A 10 s tracer pulse at the mixer reproduces the declared means and variances of the reactor and of the reactor and coil together within 0.05 % at 100 mL/min and 0.07 % at 150 mL/min.

7.3.7 Assumptions

The residence-time distribution is declared as tanks in series, 25 cells in the reactor and 200 in the coil. A real tube disperses by the mechanism of laminar dispersion [11], a coil adds secondary flow

Table 7.3 Steady Assay and Impurities (%) Against Throughput and the Zones 2–4 Setpoint, With Zone 1 at 55 °C and a Ratio of 1.10. An Asterisk Marks an Assay Below Its Limit

Feed	Zone 1 duty	55 °C	60 °C	65 °C
60 mL/min	59 W	99.01 / 0.61	99.09 / 0.76	98.97 / 0.98
100 mL/min	99 W	98.10 / 0.42	98.66 / 0.54	98.90 / 0.72
130 mL/min	128 W	97.14* / 0.35	98.05 / 0.46	98.57 / 0.64
160 mL/min	155 W	96.09* / 0.31	97.32* / 0.41	98.13 / 0.59

and a static mixer adds its own, so a real line has to be measured with a tracer. The conclusions depend on the declared spread, as the cell-count sensitivity above shows.

The chemistry is three reactions with invented constants in one liquid phase of constant ρc_p, with no volume change on reaction and no precipitation. The zone 3 deposit changes only the hydraulic resistance and the jacket transfer, so its own volume and mass are neglected.

The preheater is ideal, the mixer and the quench tee mix instantly, the quench destroys all unreacted B at once, and the coil is not modeled thermally. A real quench takes a finite time, during which the over-reaction continues.

Each jacket is well mixed, each circulator is a bath with a 60 s internal controller and fixed power limits, and there are no heat losses to the room.

The analyzer takes a point sample with Gaussian noise and has no calibration drift, failed injections or sample-line holdup, all of which a real at-line chromatograph adds.

The soft sensor uses the plant's declared kinetics. Its only errors come from what no instrument measures, from noise and lags, and from its corrections, while a real soft sensor also carries model error and would need a wider margin.

7.4 Dispersion and the Operating Window

The two chains of Equations (7.2) and (7.4) declare the dispersion of the line. A chain of N equal well-mixed cells of total volume V passes an impulse as the Erlang distribution of Equation (1.7) in Section 1.4.4, with mean $\tau = V/Q$ and variance $\sigma^2 = \tau^2/N$. The reactor is one 15 mL cell and 24 cells of 66.7 mL, so at 100 mL/min its mean residence is 16.15 min and its standard deviation $[(V_{mix}/Q_R)^2 + 24(V_z/6Q_R)^2]^{1/2} = 3.27$ min. The 200 coil cells of 7.5 mL give 12.5 min at 120 mL/min with a standard deviation of 0.88 min, close to plug flow. The 0.1 and 99.9 percent points of the coil's distribution fall at 0.7956 and 1.2328 coil volumes, 9.95 min and 15.41 min. The reactor spreads a disturbance, and the coil mostly delays it. The plug-flow time from the mixer to the valve is the sum of the two means, 28.65 min, and every coil window is a volume, so a throughput change moves the arrival of material in time without moving it in the coil.

🕮 **Pause.** Try Exercise 7.1 before reading on.

Total flow sets both the residence time and the heat the first zone must remove, as listed in Table 7.3. Complete conversion at 100 mL/min would release 95.2 W, an adiabatic rise of 31.7 K. The reaction starts in the mixer, which leaves at 62.1 °C and 22.3 % converted, so the hot spot is the first cell of zone 1 at 62.3 °C while TT-201, two cells downstream, reads its 55.0 °C setpoint. Zone 1's circulator removes 99 W of its 200 W. The zone leaves at 49.2 °C and 86.1 % converted, having formed 68 % of the decomposition product D, and zone 2's circulator then heats the stream by 29.1 W, while 68 % of the over-reaction product I forms in zones 2 to 4. The recipe is a map against throughput rather than one temperature. At 160 mL/min the design recipe gives 97.32 % assay with 2.26 % residual A, and zones 2 to 4 at 65 °C restore 98.13 % while impurities rise from 0.41 to 0.59 %. At 60 mL/min the longer residence lets the over-reaction grow to 0.76 % impurities. More reagent converts more of A and makes more I, since a ratio of 1.30 gives 99.17 % assay and 0.79 % impurities while 1.00 leaves 3.56 % residual A and 95.97 % assay. Zone 1 at 70 °C instead of 55 gives 1.105 % impurities, half of it D.

The coil has a second job. It holds material between the sample point and the valve while the analyzer decides, so its holding time has to cover the analyzer's worst case. A change that begins just after a sample is drawn is caught by the next sample, one method run t_{run} later, whose result is published one transport t_{tr} and one more run after that. Section 1.4.5 derives the same worst case on the running example. The condition for catching every such change is Equation (7.7).

$$t_{det} = 2\,t_{run} + t_{tr} \le \frac{V_c}{Q_C} \tag{7.7}$$

The comparison is with the coil's mean holding time because a change that has passed through the reactor is already smooth, and its crossing of a limit travels the nearly plug-flow coil at the mean. If the crossing falls at a uniformly distributed phase of the sampling cycle, the fraction of phases at which the change escapes is $(t_{det} - V_c/Q_C)/t_{run}$ whenever that is positive. With the default method $t_{det} = 6.5$ min against 12.5 min of coil. With a 10 min method it is 20.5 min, and Section 7.6.6 measures the cost. Taking the coil's leading edge, 9.95 min at 120 mL/min, in place of its mean gives a conservative form of the same rule.

7.5 Instruments, Loops, Soft Sensor and Supervisor

The controller runs on every second 1 s physics step, a control period $\Delta t_c = 2$ s, before the integration (at $t = 2$, 4, 6 s and so on after a priming execution at $t = 0$, as Section 1.6.1 describes), and the historian logs one row every 10 s, 2160 rows for a six-hour campaign. The application runs at 1 to 600 times real time, 60 by default.

7.5.1 Instruments

No loop reads a cell of the plant except through an instrument. The Coriolis meters FT-101, FT-102 and FT-103 are exact first-order lags of 1 s with multiplicative colored noise of 0.3 % and a 3 s correlation time, and FT-102 carries an optional bias β_B. The zone thermometers TT-201 to TT-204 read the third cell of each zone through a 5 s lag with 0.01 K of noise and a 4 s correlation time, the circulator supply thermometers read through a 3 s lag, and PT-101 reads through a 1 s lag with 0.01 bar of noise and a 2 s correlation time. The analyzer AT-401 takes a physical sample. At the start of each method run, from the first control step on, it draws the true quenched composition at the sample point, and it publishes the result one transport of 30 s plus one run later, with Gaussian noise of 0.03 % on residual A, 0.015 % on impurities and 0.5 % of reading on strength. The assay it reports is 100 minus those two percentages.

7.5.2 The PI Algorithm

Every loop runs the framework's single PI algorithm, written in velocity form, as given by Equation (7.8).

$$\begin{aligned} e_k &= a\,(\mathrm{SP}_k - \mathrm{PV}_k), \qquad P_k = K_c\,e_k \\ S_k &= S_{k-1} + (P_k - P_{k-1}), \qquad c_k = S_k + I_{k-1} \\ u_k &= \mathrm{clamp}(c_k, u_{min}, u_{max}) \\ I_k &= I_{k-1} + \left[\frac{K_c}{\tau_I}\,e_k + \frac{u_k - c_k}{\tau_I}\right]\Delta t_c \end{aligned} \tag{7.8}$$

with $a = \pm 1$ giving the direction of action. These are Equations (1.15) to (1.18) of Section 1.6.2 with no derivative term, no output bias ($c_k = v_k$) and the tracking time $T_t = \tau_I$, so the running sum S_k equals P_k, the limits act on the emitted output only and transfer from manual is bumpless. No output is rate limited. Under the ISA convention every loop but the quality trim is reverse acting.

7.5.3 Flow, Ratio and Zone Loops

FIC-101 and FIC-102 hold the two feed flows in mL/min on the pump speeds with $K_c = 0.3$ % per mL/min and $\tau_I = 10$ s, within 0 to 100 %. Each pump delivers 2 mL/min per percent of speed through

a 2 s drive and a 1 s meter, a loop gain of 0.6. The ratio station FFC-102 sets both setpoints from the total-flow reference Q_{ref} and the measured substrate flow, as shown in Equation (7.9).

$$r_v = \frac{(R_{SP} + \Delta R)\, C_{A,b}}{C_{B,f}}$$
$$Q_{A,SP} = \frac{Q_{ref}}{1 + r_v}, \qquad Q_{B,SP} = r_v\, Q_{A,m} \tag{7.9}$$

where $C_{A,b}$ is the drum label $C_{A,f}$ or the entered batch assay $C_{A,f}(1 + \delta_{A,as}/100)$. The measured ratio is $R_m = Q_{B,m} C_{B,f} / (Q_{A,m} C_{A,b})$, and neither basis sees a drum that drifts after it was assayed. TIC-201 to TIC-204 each circulator's supply command within 0 to 100 °C from the zone thermometer, with $K_c = 2\,^{\circ}\mathrm{C}$ per °C and $\tau_I = 120\,\mathrm{s}$. The circulator's power limit lies downstream of that range, where the back-calculation of Equation (7.8) cannot see it, so while a circulator reports a power limit in the direction its error asks for, the loop runs with $\tau_I = \infty$ for that scan, the integral stops and the proportional term still acts. The quench pump runs in open loop at 20 % of the measured feed flow.

7.5.4 Throughput Scheduler and Quality Trim

FY-100 moves Q_{ref} toward the lower of the setpoint and a ceiling Q_{cap} at the ramp limit $r = 10\,\mathrm{mL/min}$ per minute, and downward at $3r$ while a limit is cutting. Each circulator's cooling duty per unit of measured feed flow is learned through a 600 s filter while it cools with power in hand and the feed exceeds 30 mL/min. With the cooling limiter on, a circulator at full cooling whose zone runs more than 0.5 K above setpoint jumps the ceiling to the flow that 90 % of its capacity supports, and the ceiling then falls 1 mL/min per minute while the condition lasts. With the pressure limiter on, a discharge above 8 bar cuts the ceiling at the same rate. The ceiling climbs back 1 mL/min per minute once every circulator has 15 % of its cooling in hand and the discharge is 0.3 bar under the alarm, and it never falls below 10 mL/min. Both limiters are off in the reference configuration.

AIC-301 trims the ratio from the analyzer's residual A. It executes once per analyzer result, with Δt_c in Equation (7.8) set to the time since the previous result, because between results there is nothing new to act on. The laboratory loop of Section 1.4.5 acts once per result in the same way. A result from a sample with no product in it is skipped. It is direct acting ($a = -1$), since more residual A must raise the ratio, with a target of 0.8 %, $K_c = 0.04$ mol/mol per percent, $\tau_I = 20\,\mathrm{min}$ and the trim ΔR held within -0.10 to 0.30. It is off in the reference configuration, where ΔR is the operator's.

7.5.5 The Soft Sensor

AY-301 starts from its own steady line (from solvent in the two startup cases) and integrates a copy of the 1179 line states of Equations (7.2) to (7.4), in two 1 s Runge-Kutta steps per control period, driven only by the three flow meters, the measured supply temperatures, the batch-assay strength of feed A and the declared T_{pre}, UA_z, kinetics and volumes. Two corrections keep it honest, as shown in Equation (7.10).

$$\frac{\mathrm{d}\hat{T}_i}{\mathrm{d}t} \mathrel{+}= \frac{1}{90\,\mathrm{s}}\left(T_{z,m} - \hat{T}_{z,m}\right), \quad i \in z$$
$$b \leftarrow \mathrm{clamp}\left[b + g\,(y - \hat{y}(t_s) - b),\ \pm b_{max}\right] \tag{7.10}$$

where $\hat{T}_{z,m}$ is the model's thermometer cell passed through the same 5 s lag as TT-20z, y is an analyzer result, $\hat{y}(t_s)$ the model's prediction for that sample stored when it was drawn, $g = 0.5$, and the bias b on assay, impurities and strength is bounded at 3 %, 0.6 % and 0.06 mol/L. Comparing a result with the prediction stored when its sample was drawn is the alignment of Equation (1.14), and the update is the steady scalar filter of Equation (1.12) with $\lambda = g$. The bias is applied to every prediction at once, so it corrects a slow, persistent mismatch well and a short slug of unmeasured material not at all.

7.5.6 The Diversion Supervisor

XY-401 follows material in volume rather than in time, the delay kept in volume of Equation (1.6), as Chapter 4 advances its chip column on the measured flow. It counts the measured volume $W(t) = \int (Q_{A,m} + Q_{B,m} + Q_{q,m})\,\mathrm{d}t$ that has passed the sample point, and material sampled at $W = w$ reaches the valve while W lies in $[w + 0.7956\,V_c,\ w + 1.2328\,V_c]$, the declared quantiles of the coil. In the plug-flow mode an upset seen at the inlet, a measured ratio more than 5 % off its setpoint, a zone more than 3 K off its setpoint or a feed flow more than 10 % off its reference, opens a window from $t_0 + \tau$ to $t_1 + \tau$, with $\tau = V_R/Q_m + V_c/[(1+q)Q_m]$ evaluated at the start of the upset. A failing analyzer result diverts while $W - V_c$ lies between the failing sample and the next good one, and after startup or a restart the valve accepts one plug-flow time after the feeds start. In the residence-time (RTD) mode the valve diverts in three cases, as shown in Equation (7.11).

$$\begin{aligned} &[W - 1.2328\,V_c,\ W - 0.7956\,V_c] \cap [w_a, w_b] \neq \emptyset \\ &W - 1.2328\,V_c < w_{rel} \\ &\hat{q}_k \notin \mathrm{spec} - m, \quad k \geq 200 - n_G \end{aligned} \tag{7.11}$$

where $[w_a, w_b]$ is a window opened by a failing result that the soft sensor did not foresee, reaching back to the last good sample and closed at the first of the confirming run of good results, w_{rel} is the release boundary set at the first confirming sample after startup or a stop, and $\hat{q}_k$ is the predicted quality of coil cell k with its bias. The margin m keeps 25 % of each attribute's design headroom in hand, 0.29 % of assay, 0.115 % of impurities and 0.0154 mol/L of strength, and the guard covers $n_G = \lceil [Q_{C,m}(t_{XV} + \Delta t_c) + 30\,\mathrm{mL}]/V_k \rceil$ cells, 6 at 120 mL/min. The number of confirming results is 1 in the reference configuration. A case that starts on a running line carries the analyzer's last result, computed from its starting state, and if that result fails the valve starts on divert with an analyzer window open from before the start until good results return. The valve cannot change anything upstream of itself, so both modes run on every step and the unselected one is scored on the same material through the second valve position.

7.5.7 Plant, Control and Internal Models

The line of Section 7.3 is the simulation model. The application identifies no model of its own, and the control models that the loops face come from step tests on the line, each the difference between a stepped and an unstepped run in manual from the same state. A 1 °C step of zone 1's supply command moves its thermometer cell by 0.827 °C, 10 % of the way after 40 s and 63 % after 122 s, and zone 2 gives 0.785 °C and 124 s, of which the circulator's own response takes 60 s. The flow loops face 2 mL/min per percent through 3 s of lags. The controllers' internal models are the stoichiometry of the ratio station, the scheduler's learned duty per unit flow, the plug-flow delay τ, the declared coil quantiles and the soft sensor's copy of the line, which has the plant's structure and declared kinetics. The predictive controller of Section 7.5.8 runs that same copy forward and adds a forced response identified by setpoint steps.

7.5.8 A Predictive Quality Controller

Section 1.6.3 describes the MPC option in general. This one plans on the soft sensor's nonlinear model rather than on a small linear model. The Quality control option offers Loops, the default of the application and of cases 1 to 8 and the campaign, and MPC. Under MPC in automatic, a receding-horizon plan replaces AIC-301 and moves three inputs, $u = [\Delta R,\ \Delta T_2,\ \Delta T_3]$, the ratio trim of Equation (7.9) within AIC-301's range of -0.10 to 0.30 and offsets of ± 5 K on the setpoints of TIC-202 and TIC-203. The flow, ratio and zone loops, FY-100 with both limiters, AY-301 and XY-401 act beneath and beside it unchanged. AIC-301 tracks the applied trim, and its switch and tuning leave the panel while the residual A target A_{SP} stays, since the plan holds the same target.

A decision is taken every $T_s = 30$ s, 15 control periods, on a rounded clock and on the priming call, and a plan step is 100 mL of reactor flow rather than a time, because a dead volume through the

cells is the same at every rate. The horizon is $N = 30$ steps, 3 L or 30 min at 100 mL/min and 20 min at 150 mL/min, in ten move blocks, three of one step and two of two, followed by blocks of 3, 4, 5, 5 and 6 steps. The predicted outputs $\hat{y} = [\hat{a},\ \hat{\imath},\ \hat{s},\ \hat{\alpha}]$ at the sample point are given by Equation (7.12).

$$\hat{y}_k = \bar{y}_k + \beta + \sum_{m=1}^{3} g_m(R_{op}, Q_{op}) \left[\xi_{m,k} - u_m(t)\right] \tag{7.12}$$

Here $\bar{y}_k$ is the free response, the soft sensor's 25 reaction cells and four jackets at the declared parameters run forward by fourth-order Runge-Kutta at 4 s from the controller's own estimate, with the four zone loops at their present tuning and commands, the circulators at their declared sizes, the feeds split at the station's present ratio and the total flow following FY-100's own ramp toward its target, sampled every 100 mL. That ramp is the preview, which an advanced switch turns Off to plan on the measured flow held. The term $\xi_{m,k}$ is input m passed through a dead volume θ_m and two equal lags of τ_m steps, from which the input in force, $u_m(t)$, is subtracted, fitted to the averaged up and down setpoint steps of the line in automatic at 100 mL/min, a ratio of 1.10 and the design recipe, each the difference of a stepped and an unstepped run on one seed. The fits give $\theta = 11.50$, 5.75 and 3.25 steps and $\tau = 2.58$, 2.00 and 1.83 steps for ΔR, ΔT_2 and ΔT_3, with root-mean-square residuals of 2.1, 3.6 and 2.0 % of the steady change in assay. The ratio enters at the mixer, 1.615 L or 16.2 steps above the sample point, and the fitted chain passes half its response at 15.9 steps. The gains g_m are interpolated at each decision from a table of the declared steady line over 40 to 200 mL/min and ratios of 0.90 to 1.50, at the mean planned flow Q_{op} and at the true ratio the estimator infers, R_{op}, because the assay is far from linear in the ratio, rising at 9.9 points per unit for a step of 0.02 up at the design point and falling at 14.0 for one down. Stepped again by 0.02 and 1 K, the plant's steady gains agree with the table's within 0.7 % and its half-response points with the chain's within 0.9 step for the ratio and 1.6 steps for the zones. The model leaves out the deposit, a lost circulator until it reports its limit, any change to the kinetics and a cutback before it starts.

The estimator keeps the controller's own copy of AY-301's model, stepped every control period on the same meters, supply thermometers and thermometer correction, with feed A entering at the strength AY-301 believes times a factor σ, an unmeasured input that travels with the material. Each HPLC result is compared with that copy's prediction stored at the sampling time, in the form of Equation (7.13).

$$\begin{aligned} \sigma &\leftarrow \operatorname{clamp}\left[\sigma + g_\sigma (R_{bel}/R^{*} - \sigma),\ 0.80,\ 1.25\right] \\ \beta_j &\leftarrow \operatorname{clamp}\left[\beta_j + 0.3\,(y_j - \hat{y}_j(t_s) - \beta_j),\ \pm\beta_{j,max}\right] \end{aligned} \tag{7.13}$$

where R_{bel} is the ratio the meters and labels gave when that sample's material entered the mixer, one reactor volume before t_s, σ_e the factor in force then, and R^{*} the ratio at which the declared steady line gives its residual A at R_{bel}/σ_e plus the residual $\alpha - \hat{\alpha}(t_s)$. The gain is $g_\sigma = 0.5$, j is $\imath$ or s, the biases are bounded at 0.6 % and 60 mmol/L, and the offset β of Equation (7.12) is $-\beta_\imath$ on assay, $\beta_\imath$ on impurities, β_s on strength and zero on residual A. Repeated results on material already in flight therefore do not wind σ up. With three integrating disturbances for the three measured attributes the estimate is offset-free, the condition stated for disturbance models in MPC [21] and in Section 1.4.7, and $R_{op} = R_{bel}/\sigma$. A result that arrives between decisions moves σ on arrival and the next decision plans with it. The output bias b of AY-301 was tried first and rejected, because a bias learned on material made at one ratio was applied to material made at another.

The plan solves the quadratic program of Equation (7.14) on the shared `LinearMPC` solver.

$$\begin{aligned}\min\ & \sum_{k=1}^{N}\Big[Q_\alpha(\hat{\alpha}_k - A_{SP})^2 + u_k^{\mathsf{T}} R_u u_k\Big] + \sum_{j=1}^{10} \Delta u_j^{\mathsf{T}} S\,\Delta u_j \\ & + \sum_{k\in\mathscr{K}}\ \sum_{i\in\{a,\iota\}} \big(\ell_i \varepsilon_{i,k} + \ell_i \varepsilon_{i,k}^2\big) + \ell_s(\varepsilon_s + \varepsilon_s^2) \\ \text{s.t. } & \hat{a}_k \ge a_{min} + m_a + c_a - \varepsilon_{a,k} \\ & \hat{\iota}_k \le i_{max} - m_\iota - c_\iota + \varepsilon_{\iota,k} \\ & \hat{s}_k \ge s_{min} + m_s + c_s - \varepsilon_s, \qquad k \in \mathscr{K} \\ & u_{min} \le u_k \le u_{max}, \quad |\Delta u_j| \le \Delta u_{max}, \quad \varepsilon \ge 0\end{aligned} \tag{7.14}$$

The judged steps $\mathscr{K}$ start at step 3, the dead volume of ΔT_3, take every second step, and include only steps where the free response predicts product, a strength of at least 0.8 s_{min}, so solvent and a startup front are not priced. The margins m are the supervisor's own, so a slack is a predicted diversion and its linear price the predicted off-specification volume. The weights are $Q_\alpha = 10$ per %^{2}, $R_u = \mathrm{diag}(20,2,2)$ and $S = \mathrm{diag}(800,2,2)$ in (mol/mol)$^{-2}$ and K^{-2}, $\ell_a = 4000$ and $\ell_\iota = 10\,000$ per percent, $\ell_s = 100$ per mmol/L, cushions $c = 0.2\,\%$, 0.02 % and 2 mmol/L, and caps $\Delta u_{max} = 0.02$, 0.5 K and 0.5 K per block boundary. The bounds on the inputs and their moves are hard, the assay and impurity bands are soft with one slack per judged step, and the strength is soft with one slack over the horizon. A zone whose circulator reports full cooling is never asked to run colder, nor one at full heating hotter. The program has 59 variables, 30 moves and 29 slacks. The cap applies at every block boundary whatever the block's length, and it binds at a later boundary in 92 of the 239 plans of case 9. Counted instead as a ramp of 0.02 per step between block centers, no case or worst case moves by more than 0.05 L, so the uniform cap was kept.

The controller keeps a solve only when its status is optimal and it is of the right shape, finite in its move, plan, predictions, cost and slacks, starts with the move it reports and keeps every planned input in its box. Otherwise the historian is marked MPC FALLBACK with the reason, AIC-301, which has tracked the trim, takes the ratio without a step, the offsets ramp back at 1 K/min, and the next valid plan resumes. A fallback forced at 40 min in case 9 hands over with a trim step of 0.0000 and offsets moving at most 0.0044 K/s, and the return moves the trim by 0.0009 against its cap of 0.02. Below 30 mL/min or with the feeds stopped the controller holds. With one block and no bound the first move equals the hand least-squares move to 10^{-16}, and with every step its own block it equals the linear-quadratic regulator's $-Kx_0$ to 2×10^{-8}. Under MPC only, XY-401 also remembers each failing result the soft sensor had foreseen, and if a revised bias later predicts that sample in specification the result's own window diverts, marked ANALYZER VERDICT HELD (Section 7.6.11).

The controller reads a packet of AY-301's state and bias, the meters and thermometers, the circulators' reported duties, the loops' commands and tuning, the panel's setpoints and FY-100's ramp, the labels and entered assay and the quality limits with their margins, and the declared parameters once at import. Doctored copies that read the plant, a run parameter, a disturbance or the truth record by 35 routes are all caught by the application's checks, and replaying every decision of case 9 recorded on a plant with changed kinetics, jackets and volumes into a fresh controller gives 140 of 140 identical decisions. In Chrome, measured while other work loaded the machine, a decision takes 3.2 to 3.9 ms on average and 22.0 ms at worst, 0.011 to 0.013 % of a core at real time and 6.5 to 7.7 % at 600 times. A frame guard would drop simulated time rather than frames if a frame overran 25 ms, and it held none, the longest frame taking 23.5 ms.

7.6 Nine Cases and a Campaign

The cases are listed in Table 7.4, numbered as the app's scenario list numbers them (Section 1.6.4). Each starts from the reference configuration (RTD tracking, one confirming result, a 25 % margin,

Table 7.4 Cases and Campaign, With the Event That Defines Each

#	Scenario and event	Teaching point
1	Startup from solvent	the front arrives spread
2	Feed A +30 %/h, 10–30 min	what no meter sees
3	Pump B air lock at 20 min	a slug and its tails
4	160 mL/min, then zones at 65 °C	residence, heat, recipe
5	130 mL/min, zone 1 cooling to 30 %	an infeasible rate
6	10 min method, drum +10 %	analyzer against coil
7	Zone 3 deposit, 60 %/h	pressure as a rate limit
8	Stop at 15, restart at 50 min	held material reacts
9	150 mL/min at 10, drum +8 % at 60 min	quality trim against MPC
10	Six-hour campaign	graded challenge

Table 7.5 Measured Outcomes, Default Seed. RTD Tracking Selected and the Plug-Flow Delay Scored as Its Shadow Unless Stated

Case	Measured outcome
1, strength at valve	0.01 mol/L at 28.2, half 33.9, 95 % at 39.8 min
1, RTD	accepts 42.4 min, 4.45 L diverted, 0 released
1, no confirmation	accepts 38.0 min, worst released 97.85 %
2, trim on	first failing result 42.5 min, trim +0.099
2, RTD and plug	3.59 L diverted, 0 released, plug 139 mL
2, trim off	assay settles 96.12 %, 9.29 L diverted
3, off-spec at valve	44.07–55.85 min, as low as 86.62 %
3, RTD	diverts 43.50–56.23 min, 1.53 L, 0 released
3, plug	diverts 45.50–60.43 min, 177 mL released
4, 160 mL/min	steady 97.32 %, RTD 5.84 L, plug 114 mL
4, ramp 2 mL/min per min	RTD 3.63 L, plug 466 mL
5, no limiter	zone 1 72.73 °C, 1.125 %, 18.0 L diverted
5, cooling limiter	feed down to 54.2 mL/min, 0.790 %, 0 diverted
6, 10 min method	803 mL released, plug 1039 mL
7, pressure limiter	alarm 46.25 min, 8.31 bar peak, 53.4 mL/min at 2 h
7, no limiter	10 bar trip at 71.2 min
8, held hot	impurities to 1.128 %, 3.85 L diverted, 0 released
8, cooled in the stop	at most 0.694 %, 1.86 L diverted

the label basis, the trim and both limiters off) apart from the stated changes, and case 9 starts with the trim on and Quality control on MPC. Each number below is a measurement on the engine, run headless at the default seed with the stated change made before the run starts, which gives the same run as making it and pressing Reset, and times are minutes of simulated time. Where RTD tracking is selected the plug-flow delay is the shadow, and selecting it instead releases exactly what the shadow scored, 177.0 mL in case 3. Table 7.5 gathers the outcomes.

7.6.1 Startup and the First Product

Case 1 starts from a line full of solvent and ramps the feed from zero to 100 mL/min in 10.0 min. The reactor's cells spread the product front, so the strength at the valve passes 0.01 mol/L at 28.2 min, half the design strength at 33.9 min and 95 % of it at 39.8 min, around the 28.65 min plug-flow time of full flow. The first good analyzer result is published at 30.5 min from a sample drawn at 27.0 min, and at that moment the material at the valve has 13.9 % of the design strength and 89.10 % assay. Good material reaches the valve from 37.4 min. The RTD supervisor releases material sampled from the first good sample on, once the coil's spread has carried all earlier material past the valve, and it accepts at 42.4 min after diverting 4.45 L, 0.61 L of it in specification, releasing nothing. With no confirming result the valve opens at 38.0 min, diverts 3.92 L and releases nothing, and the worst unit it accepts is 97.85 % assay, 0.35 points inside the limit.

7.6.2 A Drum That Strengthens Unseen

Case 2 strengthens feed A by 30 % per hour from 10 to 30 min, 10 % in all, with the trim on. The ratio station and the soft sensor both believe the label, so the first warning is a failing result published at 42.5 min, 32.5 min after the drift began. The soft sensor did not foresee it, and the supervisor diverts from 42.5 to 72.4 min, 3.59 L of which 1.39 L was in specification, while off-specification material reaches the valve from 50.4 to 68.7 min. The surprise moves the bias of every prediction at once, including those for material made early in the drift and still in specification, which is the price of a correction that cannot tell when a change began. AIC-301 raises the ratio by 0.099. Without the trim the assay settles at 96.12 % and 9.29 L are diverted in two hours. The plug-flow delay, which opens its window at the failing sample rather than at the last good one, releases 139 mL on the same material.

🕮 **Pause.** Try Exercise 7.2 before reading on.

7.6.3 A Four-Minute Air Lock

Case 3 takes pump B to a tenth of its stroke from 20 to 24 min. FT-102 sees the fall at once, FIC-102 holds pump B at full speed for 182 s, the measured ratio falls as low as 0.19 and the measured feed to 56.9 mL/min, and when the air clears the saturated pump overshoots to a ratio of 3.08 and a feed of 194.0 mL/min. Off-specification material passes the sample point from 31.9 to 43.1 min and reaches the valve from 44.07 to 55.85 min, as shown in Figure 7.2, 11.78 min for a four-minute cause, and the assay at the valve bottoms at 86.62 %. Four results fail, published at 36.5, 39.5, 42.5 and 45.5 min. The soft sensor saw the flows, and its predictions for those four samples, stored when each was drawn, lie within 0.08 points of their true assay, so none is a surprise. Its prediction at the valve stays within 0.11 points of the truth over 30 to 66 min. The RTD supervisor diverts on the prediction from 43.50 to 56.23 min, 1.53 L of which only 0.11 L was in specification, and releases nothing. The screenshot of Figure 7.3 was taken inside that diversion.

> **TRY IT IN THE APP 3 · Ratio Error**
>
> Load the case and press Run. At 20 min pump B turns red and a hatched slug enters zone 1. Follow it through the four zones, where it widens, and watch the violet prediction bar on the coil. XY-401 diverts from 43.50 to 56.23 min, 1.53 L in all, and releases nothing, while the plug-flow delay scored on the same material releases 177 mL.

The plug-flow delay does worse on the same material. Its analyzer window opens at the failing sample drawn at 33.0 min, which reaches the valve in plug flow at 45.50 min, 1.43 min after off-specification material began to arrive, so it releases 177 mL from the front of the slug, the worst at 94.98 %. The upset was raised at 20.03 min, when the measured feed had already fallen to 84.1 mL/min, so its delay is 34.05 min instead of 28.65 min, and its upset window runs from 54.08 to 60.42 min, opening 10.0 min after the front of the slug reached the valve and closing 4.57 min after its tail had passed. By 1 h it has diverted 1.74 L, 0.50 L of it in specification. A plug-flow delay is wrong at both ends of a spread disturbance, and here it is also timed from a flow that the disturbance itself had changed.

7.6.4 Throughput and the Recipe

Case 4 asks for 160 mL/min at 10 min, ramped at 10 mL/min per minute. The residence falls from 16.15 to 10.09 min in the reactor and from 12.5 to 7.81 min in the coil, and zone 1's circulator has to remove 155 W of its 200 W. The soft sensor sees the shorter residence coming, and the supervisor diverts from 26.7 to 57.1 min, 5.84 L, releasing nothing, while off-specification material reaches the valve from 28.3 to 55.3 min, as low as 96.99 %. The flow followed its reference, so the plug-flow delay had no upset to time and released 114 mL. At 45 min zones 2 to 4 go to 65 °C and the steady assay recovers to 98.13 %, with impurities up from 0.41 to 0.59 % and the hot spot moving to the

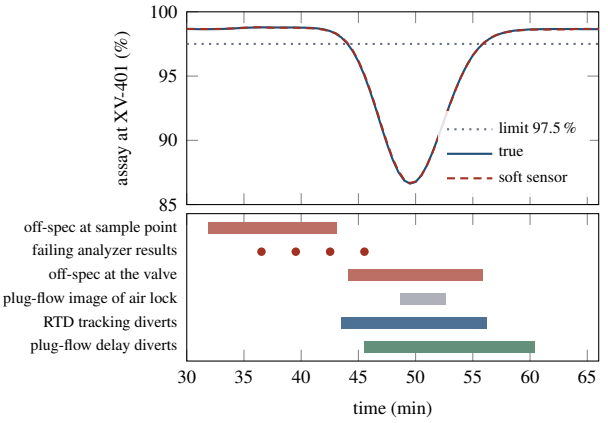


Figure 7.2 Case 3, the four-minute air lock at 20 min. Upper panel: the true assay at XV-401 (solid) and the soft sensor's prediction for the same material (dashed), which never differ by more than 0.11 points, with the 97.5 % limit dotted. Lower panel: when off-specification material passes the sample point and the valve, when the four failing results are published, where plug flow would have placed the air lock, and when each tracking rule diverts.

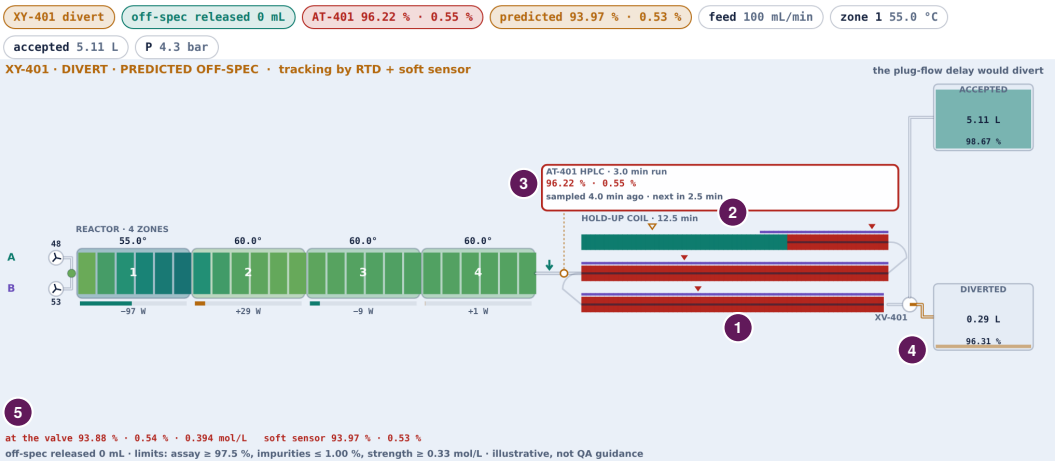


Figure 7.3 The application in case 3, ratio error, at $t = 46.00$ min, 26 min after the air lock began, in the Line view with RTD tracking selected, cropped to the plant panel (the clock is cut). The header reads XY-401 · DIVERT · PREDICTED OFF-SPEC, and the plug-flow delay, scored on the same material, would divert too. (1) The air-locked material fills 155 of the 200 cells of the hold-up coil in red, from the upper pass to the valve, and the soft sensor's violet bar runs over 161 cells, beginning six cells further upstream because of its margin (counts the panel draws but does not print). (2) Filled red triangles mark where the material behind the failing samples of 36.0, 39.0 and 42.0 min now is, and a hollow triangle near the coil inlet marks the sample of 45.0 min still being analyzed. (3) The analyzer box shows the latest failing result, 96.22 % assay and 0.55 % impurities, sampled 4.0 min earlier with the next due in 2.5 min. (4) XV-401 and the tanks, which hold 5.11 L accepted at 98.67 % and 0.29 L diverted. (5) The line under the scene gives 93.88 % assay at the valve against 93.97 % predicted. The zones read their setpoints with duties of −97, +29, −9 and +1 W.

Table 7.6 Drum Arrivals That Escape, at 12 Arrival Times One Minute Apart From 20 to 31 min. t_{det} and V_c/Q_C in Minutes

Method	Feed	t_{det}	V_c/Q_C	Predicted	Measured
5 min	100 mL/min	10.5	12.50	0	0 of 12
6 min	100 mL/min	12.5	12.50	0	0 of 12
6.5 min	100 mL/min	13.5	12.50	0.15	2 of 12, 29–87 mL
7 min	100 mL/min	14.5	12.50	0.29	3 of 12, 85–205 mL
10 min	100 mL/min	20.5	12.50	0.80	10 of 12, 83–923 mL
10 min	70 mL/min	20.5	17.86	0.26	3 of 12, 31–202 mL
10 min	60 mL/min	20.5	20.83	0	0 of 12

end of zone 2 at 70.5 °C. Conversion bought with temperature is paid for in impurity. A ramp of 2 mL/min per minute spreads the change, and the supervisor then diverts 3.63 L while the plug-flow delay releases 466 mL.

7.6.5 Lost Cooling and an Infeasible Rate

Case 5 runs at 130 mL/min, where zone 1 needs 128 W of cooling, and at 10 min its circulator falls to 30 %, 60 W. Zone 1 climbs to 72.73 °C, the decomposition grows fastest, and impurities at the valve reach 1.125 %, off specification from 70.47 min after the fault. Its supply climbs from 42.48 to 64.25 °C by 64.6 min while TIC-201, integral held, lowers the command on its proportional term alone to 7.5 °C by 100 min. The soft sensor sees that supply and tracks the zone thermometer within 0.073 K, so it predicts the rise, and the supervisor diverts everything from 64.6 min, 15.8 min before the first off-specification material arrives, because its margin flags impurities above 0.885 %. In three hours 18.0 L are diverted and 10.1 L accepted. With the cooling limiter on, FY-100 jumps the ceiling at 11.3 min to the 54.8 mL/min that 90 % of the remaining cooling supports, the feed falls as low as 54.2 mL/min, zone 1 never passes 55.94 °C, impurities stay at or below 0.790 %, and nothing is diverted, while 13.5 L are accepted. At 60 mL/min zone 1 needs 59 W. A lower rate is the only way to make material in specification with 60 W, and it accepts 13.5 L against the 10.1 L of the line that ran hot.

7.6.6 The Analyzer's Clock Against the Coil

Case 6 slows the method to 10 min, and at 25 min a drum 10 % stronger than its label goes into service unassayed. The soft sensor cannot help, because nothing measured changed. Off-specification material reaches the valve from 53.9 min, but the first failing result is published at 60.5 min from a sample drawn at 50.0 min, so 803 mL as low as 96.23 % are accepted, and the plug-flow delay would accept 1039 mL. With a 3, 5 or 7 min method the same drum is caught. At 60 mL/min the 10 min method catches it too, with the failing result published at 80.5 min and off-specification material reaching the valve at 83.2 min.

> **TRY IT IN THE APP** **6 · Slower Analyzer**
>
> Press Run and watch the analyzer box, where each result of the 10 min method arrives one run and one transport after its sample. The drum goes in at 25 min, and the first failing result is published at 60.5 min, after 803 mL as low as 96.23 % assay has been accepted. Reset, set Analyzer method run time to 3 min before Run, and the drum is caught.

Whether a drum escapes depends on where its arrival falls in the sampling cycle, and the rule of Equation (7.7) predicts how often, as listed in Table 7.6. With the 10 min method at 100 mL/min the drum escapes at 10 of 12 arrival times against a predicted fraction of 0.80, and the shipped arrival at 25 min is one of them. The 7 min method, safe for the shipped arrival, lets 3 of 12 through, 85 to 205 mL, and 70 mL/min lets 3 of 12 through with the 10 min method. No arrival escapes where t_{det}

is at or below the coil's mean holding time, and the boundary falls where the rule puts it, since a 6 min method ($t_{det} = 12.5$ min) lets none through while 6.5 min lets 2 of 12 through. Hold-up volume, analyzer cycle and throughput are therefore one design decision, and a single run at the shipped arrival time can make an unsafe design look safe.

> **DID YOU KNOW? Half a Minute of Method Time**
>
> From the simulator: at 100 mL/min, drum arrivals one minute apart all get caught with a 6 min analyzer method, while a 6.5 min method lets 2 of 12 through, 29 to 87 mL each (Table 7.6). The detection time has just passed the coil's mean holding time of 12.50 min.

7.6.7 A Deposit and a Pressure Limit

Case 7 grows a deposit in zone 3 at 60 % of its full extent per hour, full at 100 min, with the pressure limiter on. The discharge rises from 4.30 bar to the 8 bar alarm at 46.25 min. PT-101, whose reading carries noise, first reads above the alarm at 46.0 min, and FY-100 then cuts the feed to hold the discharge there, 8.31 bar at most, reaching 53.4 mL/min at two hours. The reactor residence lengthens to 30.2 min, the over-reaction grows, and impurities at the valve rise from 0.54 to 0.707 %, still in specification, with nothing diverted. Without the limiter the discharge reaches 10 bar at 71.2 min and the relay stops the feed pumps and the quench, leaving the line full of hot material. A pressure limit is a capacity limit in disguise.

7.6.8 Material Held Through a Stop

Case 8 stops the feeds at 15 min and restarts them at 50 min. With no reaction heat to remove, zone 1's circulator warms its supply from 45.58 to 55.0 °C during the hold, so it has to swing back when the feeds return, and the hottest cell reaches 63.81 °C at 56.8 min. The reactor contents keep over-reacting with the excess reagent, and they reach the valve from 68.7 to 82.0 min with impurities up to 1.128 %, while the coil's contents, quenched before the stop, stay good. The supervisor diverts from the stop until 87.4 min, waiting from the restart for a confirming result, 3.85 L in all, and releases nothing. With the zones held at 25 °C during the stop, impurities stay at or below 0.694 % and 1.86 L are diverted, all of it in specification.

7.6.9 The Campaign

The challenge runs six hours from a cold start. Feed A batch 2, 6 % strong, arrives at 1.5 h and batch 3, 4 % weak, at 4 h, both assayed, an air lock strikes at 3 h, and batch 3 drifts unmeasured at 12 % per hour from 4.5 to 5 h. The target is no off-specification material released, at least 16.5 mol of P accepted, at most 8 L diverted and both ledgers closed within 1×10^{-6}. The configurations are listed in Table 7.7. As shipped, with the plug-flow delay, no confirmation, the label basis and no trim at 100 mL/min, 4831 mL of off-specification material is released. The suggested configuration releases nothing, accepts 17.23 mol and diverts 6.09 L, of which 0.45 L was in specification, so it passes with 0.73 mol above the target and 1.91 L below the limit, in one run whether it is revealed before Run or carried through Reset. The campaign is judged on the case as given, and a changed model parameter or disturbance voids the attempt. Each element has its own job. The plug-flow delay releases 305 mL even with every other element in place, the trim is what keeps the unmeasured drift from filling the divert tank (14.38 L without it), and 120 mL/min is needed for the product, since 100 mL/min accepts only 14.21 mol. With the trim on, the batch-assay basis adds little, 17.23 against 17.18 mol, since on the label basis the trim itself raises the ratio after batch 2, from 0.042 at 1.75 h to 0.090 at 2 h. Figure 7.4 draws the configurations as a chart.

7.6.10 A Predictive Controller Against the Quality Trim

Case 9 asks for 150 mL/min at 10 min, which shortens the reactor residence from 16.2 to 10.8 min, and puts an unassayed drum of feed A, 8 % strong, into service at 60 min. With Quality control on

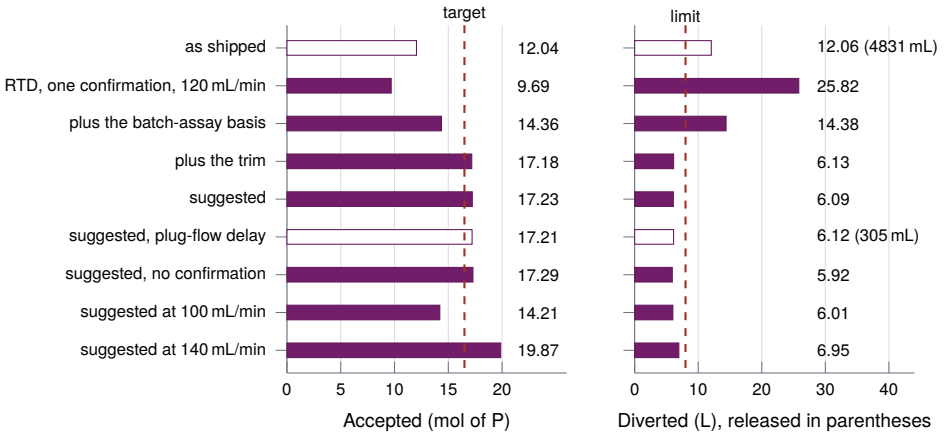


Figure 7.4 The six-hour campaign of Table 7.7 as a chart: product accepted against the 16.5 mol target (left) and volume diverted against the 8 L limit (right) for each configuration. Dark bars release nothing off specification; white bars release the volume in parentheses. Notice that only the plug-flow delay releases anything once the other elements are in place, and that without the trim the unmeasured drift fills the divert tank.

Table 7.7 Campaign Configurations Over Six Hours. Target: Nothing Released, at Least 16.5 mol Accepted, at Most 8 L Diverted

Configuration	Released	Accepted	Diverted
as shipped	4831 mL	12.04 mol	12.06 L
RTD, one confirmation, 120 mL/min	0	9.69 mol	25.82 L
plus the batch-assay basis	0	14.36 mol	14.38 L
plus the trim	0	17.18 mol	6.13 L
suggested[a]	0	17.23 mol	6.09 L
suggested, plug-flow delay	305 mL	17.21 mol	6.12 L
suggested, no confirmation	0	17.29 mol	5.92 L
suggested at 100 mL/min	0	14.21 mol	6.01 L
suggested at 140 mL/min	0	19.87 mol	6.95 L

[a] RTD, one confirmation, batch-assay basis, trim on, 120 mL/min

Loops and AIC-301 on, the trim is still at 0.008 at 20 min, because it learns of the faster material only from analyzer results, and XY-401 diverts from 28.1 to 94.3 min, 4.85 L of which 2.04 L was in specification, as shown in Figure 7.5. Under the MPC the trim reaches 0.112 by 15 min while FY-100 is still ramping, nothing is diverted, and 8.06 mol of P is accepted at 1.178 mol of B per mole against 6.20 mol and 1.513. With the preview Off the trim reaches 0.097 by 15 min, since the meters report the faster flow as it comes and the free response follows it, and again nothing is diverted. The drum is a draw. Both structures first see it in an analyzer result under 98.2 % assay, at 72.5 min under Loops and 75.5 min under the MPC, whose estimator settles at $\sigma = 1.081$, and under the MPC the true assay at the sample point dips to 97.69 %, inside the limit but under the supervisor's margin, until the added reagent has passed the reactor.

Three rows of Table 7.8 carry the comparison: the loops as shipped, AIC-301 retuned once against every knob it has by the rule the MPC was tuned by, and the strongest classical form, which gives the retuned trim every signal the MPC receives. That rule, fixed before any grid and applied on case 9 alone, asks for nothing released, no trip and no more time at a cooling limit than the loops, then the least volume diverted, then within 0.05 L the least reagent and then the least trim travel. Its tie-break was switched from the displayed two-decimal value to the ledger's exact value before any result was

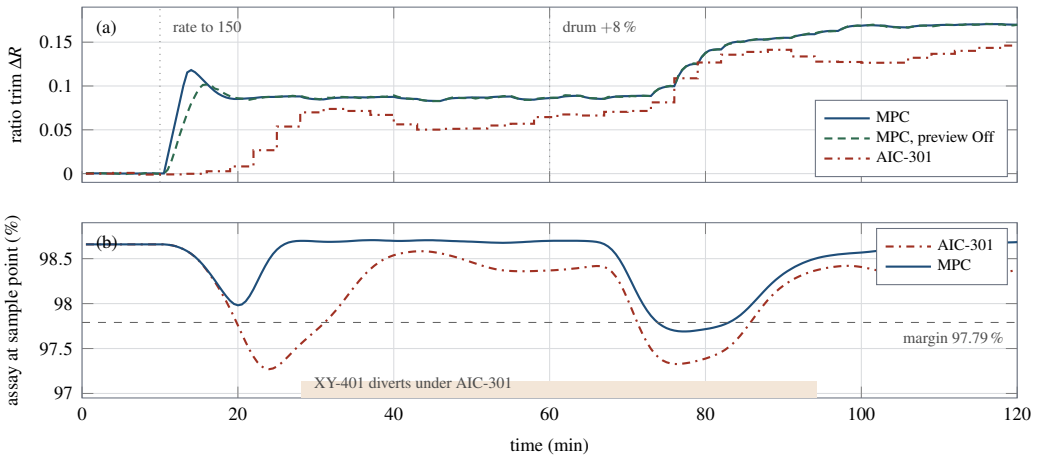


Figure 7.5 Case 9 over two hours, the rate raised to 150 mL/min at 10 min and an unassayed drum 8 % strong at 60 min. (a) The ratio trim as the MPC sets it with its preview (solid) and without it (dashed), and as AIC-301 sets it with Quality control on Loops (dash-dotted). (b) The true assay at the sample point under AIC-301 (dash-dotted) and under the MPC (solid), with the supervisor's margin (dashed) and the shaded interval in which XY-401 diverts under AIC-301, 4.85 L in all. Nothing is diverted under the MPC.

Table 7.8 Volume Diverted (L) and Off-Specification Product Released (mL, in Parentheses Where Any), Two Hours, Six for Case 10 With Its Suggested Settings. Reagent in mol B per mol P Accepted on Case 9

Structure, residual A target	9	B/P	4	2	6	10
Loops as shipped	4.85	1.513	5.84	3.59	7.13 (803)	6.09
AIC-301 on, 0.8 %	4.85	1.513	2.54	3.59	3.60 (809)	6.09
AIC-301 retuned, 0.4 %[a]	0.00	1.181	0.27	1.79	1.79 (33)	5.90
AIC-301 retuned, 0.8 %[b]	1.74	1.280	2.21	3.23	3.60 (815)	6.12
finer retune, 0.4 %[c]	0.00	1.171	1.02	2.51	2.99 (225)	5.91
classical, 0.4 %[d]	0.00	1.224	0.00	0.72	1.79 (25)	6.08
classical, 0.8 %[d]	0.00	1.201	0.58	2.87	2.86 (815)	6.14
MPC, 0.8 %	0.00	1.178	0.00	3.95	4.80 (801)	5.81
MPC, preview Off	0.00	1.177	0.00	3.95	4.80 (801)	5.89
MPC, no zone offsets	0.00	1.178	0.00	3.95	4.80 (801)	5.82
MPC, output bias	0.00	1.192	0.00	7.78	6.11 (807)	5.82
MPC, 0.4 %	0.00	1.222	0.00	0.00	0.00	5.75

[a]Retuned once by the MPC's rule over gain, integral time and target: $K_c = 0.08$, $\tau_I = 40$ min. [b]Target held: 0.08, 20 min. [c]A finer grid of the same rule: 0.06, 40 min. [d]Row *a* or *b* plus a ratio feedforward on FY-100's ramp from the declared steady table and the ratio corrected by a copy of the MPC's σ.

read, and 288 of the 324 MPC settings divert nothing on case 9, so the top settings are equivalent. The product threshold of the bands was moved from the strength limit to 0.8 of it after a worst case, a drift of −20 % per hour, diverted 3.62 L that was all in specification, a design error that leaves case 9 unchanged. The same seed, duration, instruments and noise apply to every row, and the MPC is never retuned per case. Against the shipped loops the gain is mostly the target that tuning chooses. AIC-301 retuned by that rule moves its target from 0.8 to 0.4 % and then diverts nothing on case 9 and 0.27 L on case 4. At an equal target the MPC wins or ties every row. At 0.8 % it diverts nothing on the two ramps, where the retuned trim diverts 1.74 and 2.21 L and the classical form 0.00 and 0.58 L, with the least reagent of those rows, 1.178 against 1.201. At 0.4 % it diverts nothing on all four cases, where the classical form still diverts 0.72 L on the drift and 1.79 L with 25 mL released on the slow analyzer. On the campaign it diverts 5.81 and 5.75 L against 6.14 and 6.08 L. The preview is worth at most 0.08 L, on the campaign, and the zone offsets nothing measurable, every row lying within

0.01 L without them, while they raise the hot spot by 4 K (68.7 against 64.7 °C on the campaign). On reagent alone the MPC does not beat the trim either, since a finer grid of the same rule finds AIC-301 at 0.06 and 40 min diverting nothing on case 9 at 1.171, though that setting loses cases 4, 2 and 6. The output-bias estimator that was rejected diverts 7.78 L on the drift.

🕮 **Pause.** Try Exercise 7.3 before reading on.

The MPC loses two rows at the shipped target. On case 2 it diverts 3.95 L against the loops' 3.59 L and the classical form's 0.72 L, because σ assumes a constant strength and lags a ramping drift. Moving σ fully on each result gives 3.59 L and a quarter of the way 4.67 L, and most of the gap to the classical row is its target, the MPC at 0.4 % diverting nothing. On case 6 every structure at 0.8 % releases about 800 mL, because a 10 min method is too slow for the coil whatever moves the ratio, and the MPC releases 801 mL against the retuned trim's 33 mL. The MPC made 240 decisions in two hours and 713 in the campaign with no fallback.

7.6.11 Worst Cases Under Every Structure

Table 7.9 runs every case and 18 extremes under the loops as shipped, with AIC-301 on, and under the MPC, against every limit the line has, the specification on the true composition accepted, the supervisor's margins, the circulators' power, the 8 bar alarm and the 10 bar trip. Every ledger closes within 1×10^{-6}. The MPC trips the pumps only where every structure does, with the pressure limiter off, releases off-specification product only where the loops also release it, and never spends more than 1.0 min longer than the loops at a cooling limit (6.7 against 5.7 min with three air locks). What it raises is the hot spot, by 4.0 K at startup and by up to 5.3 K with a weak drum, with no limit involved, and on the campaign the zone offsets account for it, the MPC without them peaking at 64.7 °C against 68.7 °C. Its losses beside cases 2 and 6 are the air lock of case 3, 1.68 against 1.53 L, three air locks in a row, 4.10 L against 2.50 L, a drift of 20 % per hour, 5.75 against 4.67 L, and 0.38 L with the cooling limiter where the loops divert nothing.

A review of the application made two behavior fixes, both outside every shipped and suggested run, whose original columns stay bit-identical. First, under the MPC an unassayed drum 15 % strong at 25 min in case 3 released 109 mL and FT-102 reading 10 % high 135 mL, where the shipped loops released none. A failing result that the soft sensor had foreseen opens no window, by the rule of Equation (7.11). The MPC then moves the ratio on the analyzer's evidence, results on the new material shrink AY-301's single bias from -2.95 to -1.14, and material made before the move, still in the coil at 96.2 to 97.3 %, is predicted in specification and released. Neither the band stride, the product threshold, the cushion nor the cap changes either release, and removing the residual A target removes both. The verdict rule of Section 7.5.8 releases nothing in either run, at a price of 3.96 to 4.67 L and 3.37 to 3.79 L diverted, and moves no other case or extreme under any structure. Making every foreseen failing result keep its window was measured too and rejected, because it adds 0.56 L to the campaign. Second, a running case whose last result is off-specification, as on a plant the reader changed before Run, had accepted the coil until the next result, 427 mL with $k_{1,60}$ halved in case 3 under the loops and the MPC alike and 385 mL in case 9 with zone 1 at 10 % and the limiter on. Under the start rule of Section 7.5 both release nothing, diverting 14.29 L under the loops (13.86 before) and 9.66 L under the MPC (8.88) with $k_{1,60}$ halved and 5.36 L (4.98) with the lost cooling, and case 5 at 180 mL/min with the limiter, which starts off specification, falls from 5 mL released to none under every structure.

Two defects of the shipped soft sensor and scheduler were fixed at the same time. AY-301 had been built from the run's parameters, so a reader's change to the plant reached it at once, and with $k_{1,60}$ halved it predicted the true 95.934 % at reset before any result, where the declared model gives 98.659 %. It now runs on the declared values, the model mismatch a real soft sensor faces. FY-100's jump at a cooling limit read the cooling-loss disturbance and now reads the duty the circulator reports, which at full cooling is the same number. No shipped, suggested or quoted number moved with either fix.

Table 7.9 Every Case and Extreme Under Each Structure: Volume Diverted (L) With Off-Specification Product Released (mL) in Parentheses, the Worst Unit Accepted Under the MPC (Assay %, Impurities %, Strength mol/L), and the Hot Spot (°C), Minutes at a Cooling Limit and Peak Discharge (bar) Under the Loops and the MPC. Two Hours, Six for Case 10, Unless Stated, After the Fixes of Section 7.6.11

Case and change	Loops	AIC-301 on	MPC	MPC worst accepted	Hot spot	Cooling limit	Discharge
1 startup	4.45	4.45	4.45	98.48/0.597/0.389	63.9/67.9	0.0/0.1	4.30/4.30
2 drift	3.59	3.59	3.95	97.91/0.546/0.391	63.1/63.1	0.0/0.0	4.30/4.30
3 air lock	1.53	1.54	1.68	97.80/0.627/0.382	64.3/64.0	2.2/3.1	5.52/5.50
4 throughput	5.84	2.54	0.00	97.99/0.624/0.373	70.5/70.5	0.8/0.7	5.09/5.09
5 cooling	8.63	8.79	7.86	98.05/0.885/0.382	73.3/73.2	110.0/110.0	4.69/4.70
6 slow analyzer	7.13 (803)	3.60 (809)	4.80 (801)	96.27/0.539/0.391	63.3/63.3	0.0/0.0	4.30/4.30
7 deposit	0.00	0.00	0.00	98.65/0.630/0.391	62.9/62.9	0.0/0.0	8.31/8.31
8 stop held hot	3.85	3.85	3.49	98.08/0.860/0.390	63.8/63.8	0.6/1.0	4.30/4.30
9 rate and drum	4.85	4.85	0.00	97.69/0.539/0.376	63.8/63.8	0.0/0.0	4.96/4.96
10 as shipped	12.06 (4831)	6.13 (55)	6.21 (43)	97.03/0.639/0.372	65.1/67.9	2.4/3.4	5.52/5.49
10 suggested	6.09	6.09	5.81	97.79/0.629/0.377	65.0/68.7	3.2/4.1	5.67/5.64
5, limiter on	0.00	0.00	0.38	97.77/0.739/0.384	63.1/63.1	10.3/10.9	4.69/4.70
5, 180 mL/min, limiter	5.11	6.38	4.31	97.78/0.863/0.369	64.6/69.1	14.1/14.9	5.34/5.35
5, zone 1 at 10 %, limiter	0.55	0.47	0.55	98.05/0.886/0.384	63.1/63.1	103.8/77.4	4.69/4.70
7, pressure limiter off	0.00	0.00	0.00	98.63/0.540/0.391	62.3/62.3	0.7/0.7	10.00[f]/10.00[f]
7, deposit 100 %/h	0.00	0.00	0.00	98.65/0.664/0.391	62.9/62.9	0.0/0.0	9.34/9.34
3, drum +15 % at 25 min	8.93	3.24 (291)	4.67	98.23/0.553/0.391	63.7/63.7	0.0/0.0	4.30/4.30
3, drum −15 % at 25 min	7.85	5.40	2.52	98.65/0.712/0.342	62.3/67.6	0.0/0.1	4.30/4.30
3, FT-102 +10 %	8.23	3.78	3.79	97.89/0.551/0.388	62.5/62.5	0.0/0.0	4.30/4.30
3, FT-102 −10 %	0.00	0.00	0.00	98.59/0.659/0.375	62.3/62.3	0.0/0.0	4.37/4.37
3, pump B at 60 %	0.00	0.00	0.00	98.46/0.542/0.391	62.5/62.5	0.0/0.0	4.30/4.30
2, +20 %/h for 3 h	4.67	4.67	5.75	97.89/0.552/0.391	63.4/63.4	0.0/0.0	4.30/4.30
2, −20 %/h for 3 h	2.88	2.88	0.00	98.65/0.639/0.347	62.3/62.3	0.0/0.0	4.30/4.30
6, 15 min method	7.13 (805)	5.40 (817)	7.13 (803)	96.25/0.539/0.391	63.3/63.3	0.0/0.0	4.30/4.31
4, 200 mL/min for 3 h	37.25	3.74	0.00	98.01/0.539/0.360	64.9/66.8	4.4/3.7	5.61/5.61
4, 160 then 60 mL/min	0.00	0.00	0.00	98.27/0.704/0.381	63.2/64.4	0.0/0.3	4.91/4.90
8, cooled in the stop	1.86	1.86	1.86	98.27/0.701/0.391	62.6/62.6	22.1/22.1	4.30/4.30
3, air locks at 20, 25, 30 min	2.50	3.78	4.10	97.78/0.624/0.382	65.1/64.7	5.7/6.7	5.52/5.50
9, 10 min stop at 62 min	7.47	7.47	6.83	98.00/0.910/0.376	64.3/64.3	2.3/2.7	4.96/4.96

[f] the 10 bar relay trips the feed pumps and the quench.

7.7 Technology in Practice

What Measures It

The line reads its feeds on three flow meters, its zones on four thermometers, its pump discharge on one pressure transmitter and its product on an at-line chromatograph. In the chapter the meters are 1 s lags with colored noise, the thermometers 5 s lags, and the analyzer a point sample reported one run and one transport late, as Section 7.5 sets out.

> **TECHNOLOGY Sensor: An At-Line Liquid Chromatograph**
>
> A chromatograph separates the species of a sample by their time-delayed travel down a packed column, and a detector at the outlet reads each species as it leaves. One instrument can measure the product leaving a reactor, the unreacted reactants and the unwanted products in the same stream. Cycle times of minutes are not uncommon even for on-line chromatographs, and some dead time is inevitable, since the method separates species in time. A leaking sample valve alters the baseline or corrupts the analysis [22]. The ICH Q13 guidance names online HPLC for monitoring the conversion of a chemical reaction and lists periodic system-suitability checks of the analyzer among the controls of a long run [4]. AT-401 draws a perfect sample at the start of each 3 min run, with noise and no drift.

The ICH Q13 guidance finds process analytical technology well suited to continuous manufacturing, because it lets disturbances be detected in real time [4]. In its integrated example the residence-time distribution of the drug-substance segment sets the time frame for monitoring quality,

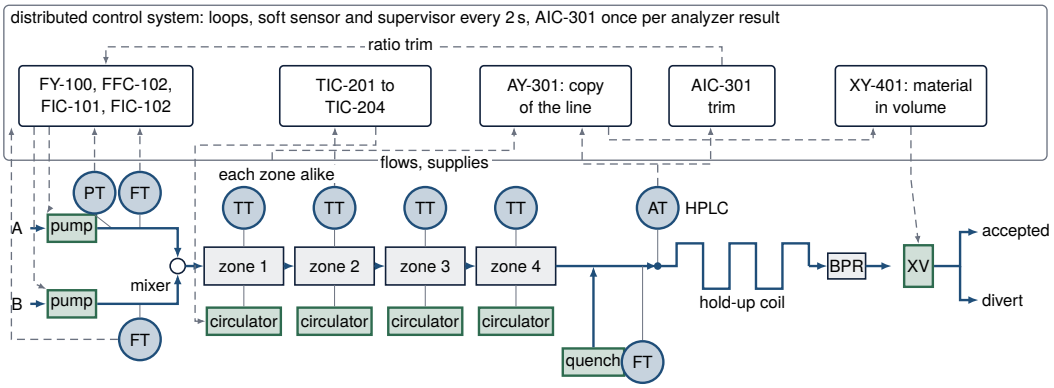


Figure 7.6 The loops of the flow line on plant hardware. Flow meters (FT) on the two feeds drive FIC-101 and FIC-102 on the pumps under the ratio station FFC-102 and the scheduler FY-100, and PT-101 on the pump discharge feeds the pressure limiter. Each zone thermometer (TT) drives its TIC on the circulator's supply. The at-line chromatograph (AT-401, HPLC) at the sample point feeds the quality trim AIC-301, which moves the ratio, and the soft sensor AY-301, which copies the line on the measured flows and supplies. XY-401 follows material in volume through the hold-up coil and the back-pressure regulator (BPR) and sets the divert valve XV. Notice that the analyzer sits upstream of the coil, which must hold the material until its verdict arrives.

which has to allow for the sampling frequency, the test method, the time the measurement takes and the instrument's capability [4]. That is the balance of Equation (7.7).

What Moves It

The final elements are the two feed pumps and the quench pump, the four circulators and the divert valve. In the 2013 plant-wide study the pumps were calibrated volumetric pumps, used both as actuators and as flow indicators [17]. The chapter meters each feed separately, and FT-102 sees the air lock of case 3 at once. The guidance's drug-substance example adds pressure sensors at the discharge of the feed pumps to watch for fouling, and backup pumps at key locations [4], the part PT-101 and the pressure limiter play against the zone 3 deposit of case 7. Figure 7.6 draws the loops of Section 7.5 on these devices.

> **TECHNOLOGY** **Final Element: The Three-Way Divert Valve**
>
> A three-way valve has three ports and sends the flow into one path or the other, like a single-pole double-throw switch. In a solenoid-operated valve a coil pulls an armature against a return spring, so the valve takes its normal position whenever the coil is de-energized, and the solenoid must be much stronger than the spring for the valve to act fast. Process pressure that works against the spring can keep a de-energized valve from reaching its normal position [22]. Diverting takes material out of the stream, so in the guidance's integrated example it changes the mass flow and may need a compensating strategy downstream that considers the residence-time distribution [4]. XV-401 strokes between accept and divert in 4 s, and the supervisor's guard covers that stroke.

Where the Controller Runs

A distributed control system, used in industries that include pharmaceutical processing, holds a supervisory level of control over localized controllers, and its loops run with cycle times from milliseconds to minutes [23]. In the application the flow, ratio and zone loops form the base layer and execute every 2 s. The scheduler FY-100, the soft sensor AY-301 and the supervisor XY-401 run above them on the same period, while the quality trim AIC-301 executes once per analyzer result,

every 3 min with the default method. The supervisor is the layer that holds this chapter's lesson: it follows material in volume and decides at the valve.

What Is Modernizing It

Two developments bear on this line. The first is the process model inside the control strategy. The guidance allows process models in commercial production, including the diversion strategy, and to predict quality attributes in real time. It asks that their developers understand the model's assumptions, naming plug flow against mixed flow, and that the model be maintained and its performance monitored during commercial manufacture [4]. The soft sensor and the two tracking rules of this chapter are such models, and the choice between plug flow and mixing is what the cases measure. The second is active quality control. The 2013 study noted that controlling product properties actively, through feedback and process analytical tools, may be a more efficient way to develop pharmaceutical processes than exhaustively documenting a design space [17]. The predictive controller of Section 7.5.8 is one such controller, and Section 7.6.10 measures what it gains over the trim.

> **IN PRACTICE** **Diversion in a Guidance Example**
>
> The ICH Q13 guidance works through a continuous drug-substance line with two plug-flow reactors. The first reaction's stoichiometry is held by the concentrations and flow rates of the feeds, and the second by feedback of an addition rate on an analyzer's reading of the residual intermediate. The residence-time distribution was modeled for every unit and surge point and confirmed by tracer studies on parts of the commercial equipment. Diversion is triggered by comparing process parameters and analyzer results with predefined criteria, its timing and duration are informed by the distribution, and at start-up material is diverted for a time based on it [4]. AIC-301, the declared cell chains and XY-401 play those parts in this chapter.

7.8 Limitations

The kinetics are invented, the quality limits are illustrative, and neither has had quality-assurance review. A real specification names each impurity and justifies each limit, and a real release decision rests on a quality system, lot genealogy and electronic batch records that this application does not model.

The residence-time distribution is declared rather than computed, so the spread of a real coil, which depends on its flow regime, has to be measured before a tracking rule can be trusted [11].

The soft sensor shares the plant's declared kinetics, so its case 3 predictions are better than a real model's and its 25 % margin is thin.

The analyzer takes a point sample every run, so a change narrower than the sampling interval at the sample point could pass unseen, although every disturbance here enters upstream of a reactor whose 3.27 min standard deviation widens it. During a stop the analyzer keeps sampling the stagnant outlet cell, which a real sample line without flow would not deliver.

> **OPEN CHALLENGE** **A Sample That Speaks for the Stream**
>
> A review by the regulator's staff calls the sampling interface of a continuous line challenging. Industrial experience finds poor measurement performance more often in the sampling system than in the analyzer itself, and on-line and in-line measurements may reduce sampling errors without removing them. The review asks that the process dynamics, such as the residence-time distribution, set the sampling frequency, so that a pulse of variability from a disturbance is resolved [2]. The analyzer of this chapter draws a perfect point sample with no line holdup and no failed injection. Progress would be a sampling system whose delays and failures are measured and carried into the rule that sizes the coil.

The predictive controller's model is the soft sensor's at the declared parameters, with a forced response fitted once at 100 mL/min and the design recipe and scaled by the declared steady line. It knows no deposit, no lost cooling until a circulator reports it, no change to the kinetics and no

cutback before it starts, and its strength factor assumes a constant feed strength, so a ramping drift is learned late (3.95 L against 3.59 L on case 2). The single analyzer bias that AY-301 applies to every batch in the line is kept as the declared design. Under the MPC the supervisor holds a foreseen failing result's verdict, while the shipped structures keep the rule of Equation (7.11), under which AIC-301 releases 291 mL after an unassayed drum 15 % strong. Holding the verdict under every structure would remove that release and change case 6 with AIC-301 on from 3.60 to 4.19 L diverted, a teaching choice left open.

7.9 Conclusion

A continuous synthesis has no batch to hold back, and this chapter has treated that as a problem of following material. Its reactor spreads a four-minute air lock into 11.78 min of off-specification material at the valve, starting 4.58 min before the 28.65 min plug-flow time, and residence-time tracking with a soft sensor diverts all of it in 1.53 L while a plug-flow delay, late at the front and timed from a flow the air lock had changed, releases 177 mL. A drum that no instrument sees is caught only by the analyzer, and the coil must hold longer than twice the method run plus the transport. At 100 mL/min a 10 min method lets the drum through at 10 of 12 arrival times, while a coil holding 20.83 min at 60 mL/min lets none through. Lost cooling at 130 mL/min leaves a choice between 18.0 L diverted and a rate cut to 54.2 mL/min with nothing diverted. The campaign moves from 4831 mL released to none, with 17.23 mol accepted. A predictive controller on the soft sensor's own model diverts nothing through the rate change of case 9, where the shipped trim diverts 4.85 L, but the trim retuned to the target its rule prefers diverts nothing either, and only at an equal target does the plan win every row. The model has invented kinetics, illustrative limits, a declared distribution and a soft sensor that shares the plant's declared kinetics. A fuller study would add a measured coil distribution, individual impurity limits, soft-sensor model error, a finite quench and a quality review of each diversion. The simulated line is a browser plant for practice in following material, rather than signals, to the point where it is routed.

KEY POINTS

- A continuous line has no batch to hold back, so it has to follow its material to the valve and divert the part an upset reached.
- The reactor spreads a four-minute air lock into 11.78 min of off-specification material at the valve, and residence-time tracking diverts all of it while a plug-flow delay releases 177 mL.
- A drum that no instrument sees is caught only by the analyzer, and the coil must hold longer than twice the method run plus the transport.
- Against the shipped loops, the gain of the MPC is mostly the target its tuning chose, and only at an equal target does the plan win every row.

Where else this applies. Volume 8, Chapter 13 judges each parcel's history at a diversion valve, Chapter 6 tracks a tablet line with a late analyzer, and Chapter 4 advances material on the measured flow.

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7.10 Exercises

7.1 Concept check · 2 min

In case 3 pump B delivers a tenth of its stroke from 20 to 24 min. Off-specification material reaches the divert valve from 24.07 to 35.85 min after the air lock began, starting 4.58 min before the 28.65 min plug-flow time. Why does it arrive early?

(a) The air lock cut the feed flow, which shortened the residence time of the material behind it

(b) The reactor's 25 well-mixed cells spread the slug, so part of it leaves well before the mean residence time

(c) The analyzer reports 3.5 min after each sample, so the supervisor marks the slug ahead of time

(d) The 200 cells of the hold-up coil give the slug a wider spread than the reactor gives it

7.2 Concept check · 2 min

In case 6 a drum of feed A made up 10 % stronger than its label goes into service unassayed at 25 min. The soft sensor AY-301 predicted the case 3 air lock to within 0.11 points, yet here it cannot help. Why?

(a) It runs on the declared kinetics, so it cannot predict a change in a rate constant

(b) Its bias is bounded at 3 % of assay, which is smaller than the drum's effect

(c) No meter, thermometer or entered assay changes, so its model receives no input that carries the drum

(d) The supervisor stops using its predictions once the method is longer than the coil's holding time

7.3 Concept check · 2 min

In case 9 the MPC diverts nothing, where the shipped loops with AIC-301 on divert 4.85 L. AIC-301 retuned once by the rule the MPC was tuned by moves its residual A target from 0.8 to 0.4 % and also diverts nothing on case 9. What does this comparison show?

(a) Most of the MPC's gain comes from its preview of FY-100's throughput ramp

(b) Most of the MPC's gain comes from its offsets on the zone 2 and zone 3 setpoints

(c) The MPC plans on a more accurate model than the soft sensor that AY-301 runs

(d) Against the shipped loops the gain is mostly the target the tuning chose, and only at an equal target does the plan win

7.4 Theory and calculation · 6 min

The reactor is a 15 mL mixer and four zones of 0.40 L, each six equal cells. The hold-up coil is 1.5 L in 200 cells, and the quench adds 20 % of the feed.

(a) At a feed of 100 mL/min, compute the mean residence time and the standard deviation of the reactor and of the coil, and the plug-flow time from the mixer to the valve. *Checkpoint:* Reactor 16.15 min and 3.27 min, coil 12.5 min and 0.88 min, plug flow 28.65 min.

(b) Repeat the residence times at 160 mL/min, the rate of case 4. *Checkpoint:* Reactor 10.09 min, coil 7.81 min, plug flow 17.91 min.

(c) In case 3 the plug-flow delay times its upset window from the measured feed at the start of the upset, 84.1 mL/min. Compute the delay $\tau = V_R/Q_m + V_c/[(1+q)Q_m]$ and the window it opens for an upset from 20 to 24 min. *Checkpoint:* About 34.1 min, so the window runs from about 54.1 to 58.1 min.

7.5 Theory and calculation · 7 min

Use Equation (7.7) with the 30 s sample transport and the escape fraction $(t_{det} - V_c/Q_C)/t_{run}$ of Section 7.4.

(a) At a feed of 100 mL/min, compute t_{det} and the predicted escape fraction for the default 3 min method and for the 7 and 10 min methods. *Checkpoint:* 6.5, 14.5 and 20.5 min against 12.5 min of coil, so 0, 0.29 and 0.80.

(b) Find the longest method that the coil covers at 100 mL/min by the mean rule, and by the conservative rule that uses the coil's leading edge, 0.7956 coil volumes. *Checkpoint:* 6.0 min and about 4.7 min.

(c) Find the highest feed at which the 10 min method is covered by the mean rule, and the predicted escape fraction at 70 mL/min. *Checkpoint:* About 61 mL/min, and 0.26 at 70 mL/min.

7.6 Theory and calculation · 6 min

Reaction 1 releases 120 kJ/mol. At the design point feed A enters at 47.62 mL/min and 1.00 mol/L in a reactor flow of 100 mL/min, and the stream carries $\rho c_p = 1.8\,\mathrm{MJ/(m^3\,K)}$.

(a) Compute the concentration of A at the mixer inlet, the heat that complete conversion would release, and the adiabatic temperature rise. *Checkpoint:* 0.476 mol/L, 95.2 W and 31.7 K.

(b) In case 5 the line runs at 130 mL/min, where zone 1 needs 128 W of cooling, when zone 1's circulator falls to 60 W. Taking the duty as proportional to the feed, find the feed at which 90 % of the remaining cooling suffices. *Checkpoint:* About 54.8 mL/min, the ceiling FY-100 jumps to at 11.3 min.

(c) Find the feed that would use the full 60 W, and compare it with Table 7.3. *Checkpoint:* About 61 mL/min, and the table gives 59 W at 60 mL/min.

7.7 App challenge · 8 min

Load scenario 3, Ratio error, with the default seed. Run at a speed of 300 and press Pause when the clock is between 62 and 90 min (the tiles do not change in that interval). Read the Off-spec released, Diverted and Shadow tiles of the scorecard.

(a) Report what RTD tracking released and diverted, and what the plug-flow shadow would have released and diverted on the same material. *Checkpoint:* 0 mL released, 1.53 L diverted (0.11 L in specification). Shadow 177 mL and 1.79 L, each within one unit of the last digit.

(b) Press Reset, set Material tracking to Plug-flow delay, and run to the same window. Report the Off-spec released, Worst released and Diverted tiles. *Checkpoint:* 177 mL, worst assay 94.98 %, 1.79 L diverted (0.55 L in specification), each within one unit of the last digit.

(c) The plug-flow image of the air lock reaches the valve from 48.65 to 52.65 min. Use Figure 7.2 to explain where the 177 mL came from, and why the plug-flow delay still diverted more than RTD tracking. *Checkpoint:* The front of the slug, before 45.50 min.

7.8 App challenge · 7 min

Load scenario 6, Slower analyzer, with the default seed. It runs the 10 min HPLC method, and an unassayed drum 10 % strong goes into service at 25 min. Run at a speed of 600 to any time after 1.5 h and read the Off-spec released, Worst released and Shadow tiles.

(a) Report the off-specification volume released, its worst assay, and what the plug-flow shadow would have released. *Checkpoint:* 803 mL at 96.23 %, shadow 1039 mL, each within 5 mL and 0.02 points.

(b) Press Reset, set Analyzer method run time to 7 min before pressing Run, and run again to any time after 1.5 h. Report the off-specification volume released. *Checkpoint:* 0 mL.

(c) Exercise 7.5 predicts that the 7 min method lets a change through at 0.29 of the arrival phases. Explain why the run of part (b) does not contradict it, and what a design check must use instead of one run. *Checkpoint:* Table 7.6: 3 of 12 arrivals escape with the 7 min method.

7.9 App challenge · 9 min

Load scenario 9, Rate and drum: quality trim against MPC, with the default seed. Quality control is on MPC, the residual A target at 0.8 %. Run at a speed of 300 and press Pause when the clock is between 1.9 and 2.1 h. Read the Diverted and Reagent B per mol P tiles. Make each change below after pressing Reset and before pressing Run, and repeat.

(a) Report both tiles under the MPC as loaded, and with Quality control set to Loops (the quality trim stays on). *Checkpoint:* MPC 0.00 L and 1.18 mol. Loops 4.85 L (2.04 L in specification) and 1.51 mol, within 0.03 mol.

(b) Under Loops, set Trim gain to 0.08, Trim integral time to 40 min and Residual A target to 0.4 %, the retuned trim of Table 7.8. Report both tiles. *Checkpoint:* 0.00 L and 1.18 mol.

(c) Set Quality control back to MPC, keeping the 0.4 % target. Report both tiles, and say what the four runs show about the plan and the target. *Checkpoint:* 0.00 L and 1.22 mol.

7.10 Application area · 4 min

A plant engineer proposes to replace the 1.5 L hold-up coil with a 1.0 L coil of the same construction to cut the hold-up, keeping the 3 min HPLC method.

(a) Check the proposal at a feed of 100 mL/min and at 160 mL/min, by the mean rule and by the conservative leading-edge rule. *Checkpoint:* At 100 mL/min the coil holds 8.33 min with its leading edge at 6.63 min, against $t_{det} = 6.5$ min. At 160 mL/min it holds 5.21 min, short of it.

(b) The supervisor's windows use the coil's 0.1 and 99.9 % points. What must be done before those points can be trusted on a real coil, and why? *Checkpoint:* A tracer test on the installed coil.

7.11 Application area · 3 min

In case 7 a deposit grows in zone 3. With the pressure limiter on, FY-100 holds the discharge near the 8 bar alarm by cutting the feed to 53.4 mL/min at two hours. Without it the 10 bar relay trips at 71.2 min.

(a) Compute the reactor residence time at 53.4 mL/min and the share of the design rate left, and say why the impurities rise from 0.54 to 0.707 %. *Checkpoint:* About 30.2 min and 53 %.

(b) What does a trip leave in the line, and what does case 8 suggest an operator should do with it? *Checkpoint:* Hot material that keeps reacting. Cooling the zones during a stop cuts the diversion from 3.85 to 1.86 L in case 8.

7.12 Review the agent · 5 min

An AI assistant is asked how to divert the material of a pump B air lock from 20 to 24 min at 100 mL/min. It replies: "The plug-flow time from the mixer to the valve is 28.65 min, so divert from 48.65 to 52.65 min, plus 1 min on each side for safety, from 47.65 to 53.65 min. A fixed delay is better than the app's plug-flow mode, which times the delay from a flow the air lock had already cut." Find the flaw, and say how you would check it.