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CHAPTER 6

Continuous Tableting Line Simulator for Tablet Weight, Dose and Material Tracking

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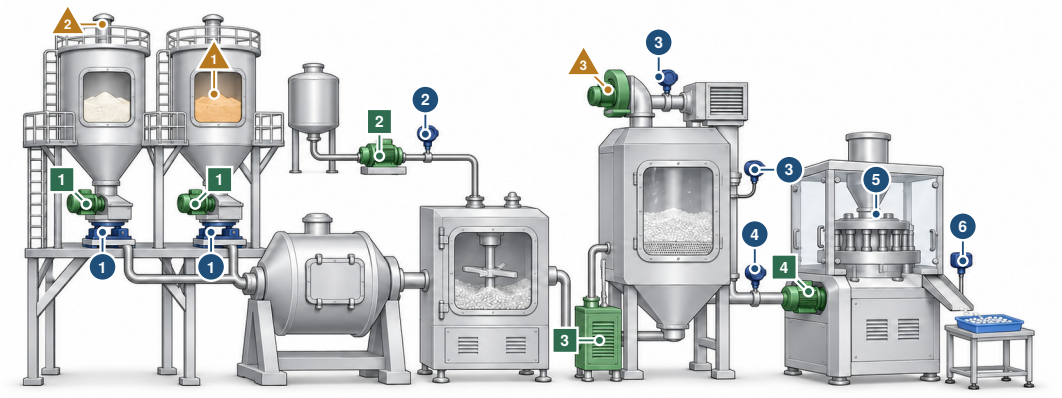
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CHAPTER 6

Continuous Tableting Line Simulator for Tablet Weight, Dose and Material Tracking



The controller moves 1 feeder screws, one per ingredient 2 binder water pump 3 heater of the drying air 4 press: fill depth, punch gap and speed

The controller reads 1 load cells under each feeder 2 binder water flow 3 drying-air temperature and humidity 4 moisture of each dryer cell as it empties 5 compression force, read as tablet weight 6 at-line weight and hardness tests

What disturbs it 1 a denser excipient lot 2 a feeder refill 3 humid intake air

Notice that the press checks the weight of every tablet, while the medicine content was set at the two feeders on the far left and reaches the press only after the dryer. Illustration, not to scale.

IN PLAIN TERMS **The Right Weight, the Wrong Dose**

The main idea. A tablet line mixes a medicine powder with a filler, makes the mix into small grains, dries them and presses them into tablets. The press judges each tablet's weight by how hard it squeezes, and corrects the weight within a second.

The challenge. How much medicine a tablet holds is set at the feeders, twelve minutes upstream, where the press cannot see it. A feeder being topped up briefly feeds too much, so the line follows each portion of powder to know which tablets to throw away.

Why it matters. A tablet can weigh exactly right and still hold the wrong amount of medicine.

THREE WAYS TO READ THIS CHAPTER

Explore	11 min	the first page, the history segment (Section 6.2), the fact on batch size (Section 6.3), the try-its on the feeder refill and the slow analyzer and the fact on the graded shift (Section 6.6) and the key points
Study	50 min	the whole chapter with its three pause points and the twelve exercises at its end
Practice	15 min	the first page, the results (Section 6.6), Technology in Practice (Section 6.7), Limitations (Section 6.8) and the open challenge

The control question A tablet press holds every tablet's weight from its compression force in about a second, while the feeders fix the composition twelve minutes upstream and run blind while they refill. Which instrument sees each part of a dose error, and what can feedforward, material tracking and a reject gate still guarantee when the dose is wrong?

Learning objectives

- Compute the recipe feeds, the dryer package and the tablets made during an analyzer delay from the line's design data.
- Explain why a tablet at its target weight can carry the wrong dose, and which instrument sees a weight error and which a composition error.
- Derive the feeder's rate gain over a refill and the part of it that the refill feedforward leaves.
- Compare a moisture cascade sampled once per dryer cell with a humidity feedforward on a dryer whose cells see an upset in progress.
- Judge when a reject gate driven by a delayed analyzer, or by a tracker on the measured inputs, protects every accepted tablet.

Prerequisites Sections 1.4.4 (residence-time distributions and material tracking), 1.4.5 (sampled results), 1.4.8 (soft sensors and late references) and 1.6.2 (the PI algorithm and controller action).

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

See also Volume 3, Chapter 2 for matching a loop structure to where a disturbance enters, Volume 3, Chapter 6 for a dose computed from a measured upstream variable ahead of a long delay, and Volume 3, Chapter 8 for a pharmaceutical formulation line with a ratio block, a release rule and a divert valve.

6.1 Introduction

The simulated tablet press weighs every tablet it makes. It measures the compression force of each one, as the instrumented tableting machine reported in 1954 was built to do [1], converts that force into a weight and holds the weight by moving the depth to which each die is filled. The dose is a different quantity. The content of active pharmaceutical ingredient (API) in a tablet is its weight times the API share of the powder that filled its die, and on a continuous line that share was set by loss-in-weight feeders several kilograms of powder upstream. Batch manufacture could leave the question to the batch, which is accepted or rejected as a whole [2]. A continuous line has to name the tablets a disturbance reached, and the residence-time distribution of each unit [3] is the tool for naming them [4, 5].

The line modeled here is a continuous wet-granulation train. Two loss-in-weight feeders meter the API and an excipient blend into a continuous blender, a twin-screw granulator wets the powder [6, 7], a segmented fluid-bed dryer takes the granules in six cells [8], a mill and a final blender add lubricant, and a rotary press with 24 stations makes 24 tablets a second. A near-infrared (NIR) analyzer reads the blend in the press feed frame, a measurement that has been demonstrated in line on continuous direct compression [9] and used to monitor a commercial continuous run of 28 h [10]. A feeder cannot weigh its own delivery while its hopper is being refilled, and refills are known to disturb the feed rate [11].

What sets this plant apart is where each part of the dose is decided and where it is seen. The weight is controlled at the press in about a second, blind to composition. The composition is fixed at the feeders and carried through 4.38 kg of material in process for a mean of 707 s, spread by three mixers and cut by the dryer into packages of 2160 tablets, so that a feeder error of half a minute arrives as one or two rich or lean packages. The last line of defense is a gate that can reject tablets but cannot correct them, fed by an analyzer whose readings arrive 10 s after their scans, or 240 tablets later. A feeder that delivers nothing cannot be corrected by any loop at all.

The misconception the simulator is designed to correct is that a tablet at its target weight carries its target dose, together with its corollary, that an analyzer at the press protects every tablet it reads. In the second case of the application the true mean tablet weight stays between 249.3 and 250.6 mg

while the package made during a feeder refill reaches the press at 104.77 % LC. The class of problem is general. Any process whose quality is set upstream, carried through a residence-time distribution and released unit by unit needs the same traceability, which a residence-time model of a whole granulation and tableting line has been shown to provide [5], and control of a direct compaction line has combined a dead-time compensator on the API concentration with discarding off-specification powder before the press [12]. However, the control studies of continuous tablet lines cited here are pilot-plant demonstrations built for research [12–14], and a course that meets the press as a transfer function with a dead time has no place for a dose error that the weight loop never measures.

This chapter works with a continuous tableting line simulator that records the true weight, dose and moisture of every tablet apart from what the load cells, the force transducer, the two analyzers and a tracker report, so that a refill, a bridge, a lot change or a slow analyzer can be followed from its cause to the tablets it reaches. Loss-in-weight feeding, tanks-in-series residence-time models, cascade and feedforward control, weight control from compression force and material tracking are all established methods. The simulator joins them in a 133-state line that conserves every component to round-off, turns the stream into dryer packages and individual tablets and runs a measurement-only tracker beside it, and the chapter gives every equation, parameter and default needed to rebuild it. Eight cases and a graded shift separate what each loop, analyzer and gate can and cannot guarantee. The simulator is intended for education in equipment control and runs one locked teaching recipe. Its quality proxies and acceptance limits are illustrative, they have not had quality-assurance review, and neither the application nor this chapter is regulatory or quality-assurance guidance.

Section 6.2 traces the domain from the instrumented press to continuous lines and their residence-time models. Section 6.3 models the line: the recipe, the feeders, the mixers and the granulator, the segmented dryer, the press and the instruments. Section 6.4 separates weight from dose and shows where each is decided and where each is seen, through the tablet spreads, the transport in dryer packages, a refill the load cells cannot weigh and a moisture loop that learns once per cell. Section 6.5 describes the control system as implemented, and Section 6.6 the measured cases and the graded shift. Section 6.7 sets the loops on plant hardware, Section 6.8 states the limitations and Section 6.9 draws the lessons together. The exercises are in Section 6.10.

6.2 Tablets, Granules and Continuous Lines

Instruments on the tablet press date at least to 1954, when the design and construction of an instrumented tableting machine was reported as the third part of a series on the physics of tablet compression [1]. Such a machine measures the forces on its punches, and the force is the only signal the simulated press has of each tablet. It reports how much powder a die received and nothing about what the powder is.

Granules were made in batches. A 2001 paper on trends in granule production noted that a batch offers advantages for quality assurance because it can be accepted or rejected as a whole, while its scale-up may cause problems, and it presented a quasi-continuous line that makes small and large batches on the same equipment [2]. Continuous twin-screw extrusion was then found to wet-granulate lactose robustly and proposed as a possible alternative to high-shear granulation [6], and continuous granulation in the pharmaceutical industry was reviewed in 2005 [7]. By 2016 the continuous manufacture of powder-based pharmaceutical products was the subject of a perspective of its own [15].

A continuous line gives up the batch as the unit of acceptance, and residence-time distributions took its place. The distribution of residence times in continuous flow systems was formalized in 1953 [3], and continuous powder mixing has been characterized by its residence-time distribution [4]. On a continuous dry-granulation tableting line, the distributions of the blender, the roller compactor and the tablet press were measured with NIR, joined into a model of the whole line and checked against the propagation of a step in the API, the traceability that the definition of a batch or lot and the control strategy both need [5]. The feeders can cause such composition steps themselves, since

the hopper refill of a loss-in-weight feeder causes feed-rate deviations [11]. The same traceability decides which material a divert valve sends away on the continuous drug-substance line of Chapter 7.

> ⧖ HISTORY **2002 to 2019: Medicines Begin to Leave the Batch**
>
> Medicines have long been made in batches, while most commodity chemicals, petrochemicals and foods are made continuously. In August 2002 the United States Food and Drug Administration launched an initiative to modernize its regulation of pharmaceutical manufacturing, and a series of guidances followed [16]. A 2015 review by the agency's staff noted that the regulatory definition of a batch rests on an amount of material, not on the mode of manufacture, so a continuous line can still make batches, and it called an understanding of how material flows through the line critical to tracing it [17]. The first end-to-end continuous pharmaceutical process with automated, model-based control ran at bench scale in 2011, and a 2019 summary counted six small-molecule drugs made in part by continuous manufacturing [18].

Measurement and control followed. An in-line NIR method on a continuous direct compression line with two loss-in-weight feeders predicted the API content with root mean square errors of prediction of 0.96 % for the powder at the mixer and 1.37 % for the tablets at the press [9]. At a commercial site, the NIR readings of the blend over a 28 h continuous run averaged 101.17 % LC with a standard deviation of 2.17 % over 12 633 spectra, while 500 of the tablets averaged 100.86 % LC with a standard deviation of 0.4 % [10]. A hybrid of model predictive and PID control with NIR feedback was implemented on the feeders and blender of a continuous direct compaction pilot plant [13], and model predictive control of the main and precompression forces through the compression height and the fill depth held the tablet weight and breaking force together on a pilot-plant press [14]. A control concept for a direct compaction line combined a Smith predictor for the API concentration with model predictive control of the press hopper level [12], and a moving-horizon estimator that reconciles the feeders' mass measurements has been proposed to estimate the composition of the powder they deliver [19]. The dryer between the granulator and the press is a fluidized bed, whose mechanistic models range from single porous granules to the whole bed [8].

6.3 Model of the Line

The simulated line makes a 250 mg tablet at 24 tablets a second, 21.60 kg/h of finished blend, from 20.96 kg/h of powder and 4.611 kg/h of granulation water. Figure 6.1 draws the units, the instruments and the variables of the equations, and Table 6.1 gives each variable its role.

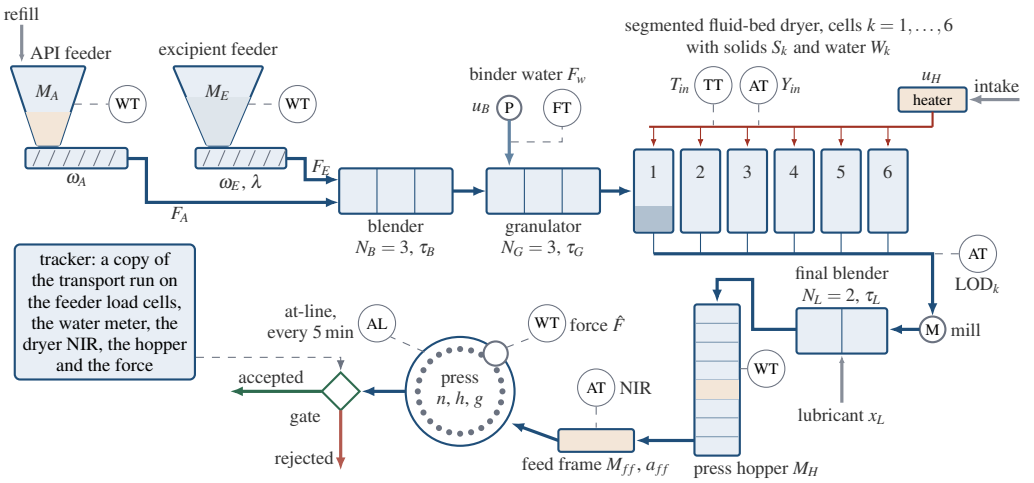


Figure 6.1 The continuous wet-granulation line as modeled. Load cells (WT) weigh the API and excipient feeder hoppers M_A and M_E to give their rates at screw speeds ω_A and ω_E, except during a refill, when the powder at the screw is compacted by D_A or D_E, and a new excipient lot changes its bulk density by λ. The blender and the twin-screw granulator are three tanks in series each, with binder water F_w from the pump u_B on a Coriolis meter (FT). Six dryer cells share one inlet air at T_{in} and humidity Y_{in}, measured by TT and a hygrometer (AT), from a heater u_H, and a dryer NIR (AT) reads each cell's moisture as it discharges. The mill and a two-tank final blender with lubricant feed the press hopper M_H, which passes its slices on first in, first out to the feed frame and its NIR analyzer. The press at turret speed n sets the fill depth h and the punch gap g, measures the force $\hat{F}$ of every tablet and sends ten tablets to the at-line tests (AL) every 5 min. The gate accepts or rejects each tablet on the force, the NIR and the tracker.

> ✦ **DID YOU KNOW? A Batch Set by Running Time**
>
> In the continuous direct compression line that the ICH Q13 guidance works through as an example, the run time at a predefined mass flow rate defines the batch, and market demand calls for batches of 360 to 1080 kilograms [20]. The simulated line makes 21.60 kg/h of finished blend.

Fourteen lumped states hold the two hoppers, screw speeds and refill compactions, the binder pump and the inlet air, together with six running totals, of the API, excipient, water and lubricant fed, of the water evaporated and of the heater's energy. The blender, the granulator, the six dryer cells, the final blender and the feed frame are fifteen vessels that each carry seven components, the API A, the excipient E, water W and lubricant L in kilograms, a granule-size property Z in µm kg, a bulk-density excess R that marks excipient from a new lot, and an inert tracer Q. With the cumulative outflow of the final blender and the pressed totals, the vector has 133 states, integrated together. The dryer schedule, the refills, the press hopper's slices and the tablets are handled as discrete events after every integration step.

6.3.1 Recipe

The recipe is locked. A tablet of $m_t = 250\,\text{mg}$ carries $x_A = 10.0\,\%$ API, which is 25.0 mg, the label claim (LC), at a moisture of $\text{LOD}^* = 2.0\,\%$ loss on drying and with $x_L = 1.0\,\%$ lubricant per kilogram of dried granule. The API share of the powder feed and the powder feed that keeps a press at turret speed n supplied follow, as shown in Equation (6.1).

$$r_A = x_A \frac{1 + x_L}{1 - \text{LOD}^*} = 0.10306, \quad F_s = \frac{N_s n}{60} m_t \frac{1 - \text{LOD}^*}{1 + x_L} \tag{6.1}$$

Table 6.1 Variables of the Line at the Reference Operating Point

Symbol	Role	Reference	Range
$\hat{F}_A$, $\hat{F}_E$	CVs, load-cell rates	2.160, 18.80 kg/h	ratio SP
$\widehat{L/S}$	CV, binder ratio	0.220 kg/kg	SP 0.10–0.35
T_{in}	CV, inlet air	60.1 °C	35–80
LOD_k	CV, cell at discharge	2.0 %	SP 1.2–2.8
$\hat{m}$	CV, weight from force	250 mg	SP 240–260
$\hat{H}$	CV, hardness proxy	100 N	SP 60–140
M_H	CV, press hopper	1.0 kg	SP 0.5–2
ω_A, ω_E	MVs, screw speeds	51.1, 62.0 %	0–100
u_B, u_H	MVs, pump, heater	53.4, 50.2 %	0–100
h	MV, fill depth	7.15 mm	4–12
g	MV, punch gap	3.08 mm	2.4–4.2
n	production rate	60 rpm	30–80
refill	DV, feeder event	at 25 %	or forced
b	DV, bridged share	0	0.85 or 1
λ	DV, excipient lot	0 %	±15
Y_{in}	DV, air humidity	6 g/kg	0–30
block	DV, binder nozzle	open	40 s event
θ_N	DV, NIR delay	10 s	2–120
b_N	DV, NIR bias	0 % LC	±5
M_A, M_E	states, hopper fill	78, 70 %	—
D_A, D_E	states, compaction	0	—
$m_{i,c}$	states, 15 vessels	7 components	—
slices, tablets	discrete states	30 g, 250 mg	—

where $N_s = 24$ is the number of stations. At 60 rpm the powder feed is 20.96 kg/h, of which the API is 2.160 kg/h and the excipient 18.80 kg/h, and the water at the recipe liquid-to-solid ratio $(L/S)^* = 0.22$ is 4.611 kg/h. The acceptance limits of a single tablet are illustrative teaching values, a weight within ±5 % of 250 mg, a dose of 95 to 105 % LC and a moisture of 1.0 to 3.0 % LOD.

6.3.2 Loss-in-Weight Feeders

Each feeder delivers its screw speed times a feed factor that follows the bulk density of the powder at the screw, as shown in Equation (6.2) for the API.

$$\begin{aligned} F_A &= \omega_A \, F_{A,max} \, \tilde{\rho}_A \, (1-b) \, \pi_A \, (1+\varepsilon_A) \\ \tilde{\rho}_A &= 1 + \beta_A \left(f_A - \tfrac{1}{2} \right) + D_A \\ \frac{\mathrm{d}D_A}{\mathrm{d}t} &= -\frac{D_A}{\tau_D} + \frac{\delta_A}{t_R} \, \sigma_R, \qquad \frac{\mathrm{d}M_A}{\mathrm{d}t} = -F_A + F_R \, \sigma_R \end{aligned} \tag{6.2}$$

Here $f_A = M_A / M_{A,cap}$ is the hopper fill, β_A the rise of the feed factor from an empty to a full hopper, D_A the extra compaction a refill gives the powder at the screw, σ_R one while a refill runs and zero otherwise, b the share of the screw blocked by a bridge, π_A a priming factor that rises to one over 8 s once the screw first turns at a start-up, and ε_A a feed-factor variation, first-order colored noise with a 20 s correlation time. A refill starts when the hopper falls below 25 % of its capacity and fills it to 80 % at the constant rate F_R over $t_R = 20$ s for the API and 30 s for the excipient. The screw follows its command through a first-order lag of 1 s. The excipient feeder obeys the same law with its own parameters, priming in 3.2 s and multiplied by $1 + \lambda$, where λ is the bulk-density change of a new excipient lot. A hopper that holds nothing delivers nothing. Loss-in-weight feeders that dose additives into a polymer extruder, with refills and a held weighed flow that is not a held product concentration, are the subject of Volume 12, Chapter 12.

6.3.3 Mixers, Granulation and Granule Size

The blender, the granulator and the final blender are N ideal stirred tanks in series, and every component passes through them by the same law, as shown in Equation (6.3).

$$\frac{\mathrm{d}m_{i,c}}{\mathrm{d}t} = k\,(m_{i-1,c} - m_{i,c}), \qquad k = \frac{N}{\tau} \tag{6.3}$$

where $m_{0,c}$ stands for the inflow divided by k. The blender has $N_B = 3$ and $\tau_B = 45\,\mathrm{s}$, the granulator $N_G = 3$ and $\tau_G = 12\,\mathrm{s}$, and the final blender $N_L = 2$ and $\tau_L = 20\,\mathrm{s}$, so each has the residence-time distribution of N tanks with mean τ and variance τ^2/N [3], the Erlang form of Equation (1.7). The blender receives F_A, F_E and a density excess λF_E, and the binder water $F_w = w_B F_{w,max}(1 - \text{block})$ joins at the granulator inlet, where the pump state w_B follows the command $u_B/100$ through a 2 s lag. The granule size forms at the granulator outlet from the local liquid-to-solid ratio, as shown in Equation (6.4).

$$\begin{aligned} d_{50} &= d_p + (d_{ref} - d_p)\,\min\Big[2.5,\,\Big(\frac{W/S}{(L/S)^*}\Big)^2\Big] \\ \varphi &= \max\big(0,\,1 - d_{50}/d_{ref}\big) \end{aligned} \tag{6.4}$$

where W/S is the water over the solids in the last granulator tank, $d_p = 50\,\mu\mathrm{m}$ the ungranulated powder, $d_{ref} = 300\,\mu\mathrm{m}$ the granule at the recipe ratio and φ the fines index used by the press. The granule size is carried as the flux $Z = (A + E)\,d_{50}$, the mill caps it at 450 µm, and the lubricant enters the final blender at x_L times the discharged granule.

6.3.4 The Segmented Dryer

The six dryer cells run a fixed cycle of 540 s. Cell k fills for $T_f = 90\,\mathrm{s}$ starting at $(k-1)T_f$ modulo the cycle, dries for $T_{dry} = 390\,\mathrm{s}$, discharges for $T_d = 45\,\mathrm{s}$ and stands empty for 15 s, so one cell is always filling and a package leaves every 90 s. A filling cell receives the whole granulator outflow, and each cell is a well-mixed bed of solids S_k and water W_k whose drying follows Equation (6.5).

$$\begin{aligned} \frac{\mathrm{d}W_k}{\mathrm{d}t} &= F_{w,k} - R_c\,\min\Big(1,\,\frac{X_k - X_{eq}}{X_c - X_{eq}}\Big) \\ R_c &= G\,\eta\,\big[Y_s(T_{wb}) - Y_{in}\big], \qquad X_k = W_k/S_k \\ X_{eq} &= X_{e0} + X_{e1}\,\mathrm{RH}(T_{in}, Y_{in}) \end{aligned} \tag{6.5}$$

where $F_{w,k}$ is the water entering while the cell fills, G the dry air per cell, η its contact efficiency, X_c the critical moisture on a dry basis and the rate is zero once $X_k \le X_{eq}$. Drying runs while a cell fills and dries, not while it discharges. The wet-bulb temperature solves $(T_{in} - T_{wb})(1.005 + 1.88\,Y_{in}) = (2501 - 2.36\,T_{wb})[Y_s(T_{wb}) - Y_{in}]$ in kJ/kg by bisection, with the saturation humidity $Y_s = 0.622\,p_s/(P - p_s)$ from a Magnus vapor pressure $p_s = 0.61094\exp[17.625T/(T + 243.04)]$ kPa at $P = 101.325\,\mathrm{kPa}$. A discharging cell empties at the rate $(4/T_d)m_{k,c}$ for every component, and the 1.8 % left after 45 s joins the final blender when the cell turns empty. The inlet air follows the heater through $\tau_h\,\mathrm{d}T_{in}/\mathrm{d}t = T_{amb} + u_H\,\Delta T_{max}/100 - T_{in}$. With the recipe feed and 6 g/kg air, a cell holds 0.524 kg of solids and 0.085 kg of water at the end of its fill, a dry-basis moisture of 0.161, passes below X_c 184.5 s after its fill began, and leaves at 2.0 % LOD with inlet air at 60.1 °C, a heater at 50.2 % and 7.24 kW of heat. The air then has a wet-bulb temperature of 25.4 °C and a constant-rate capacity R_c of 0.342 g/s per cell.

6.3.5 Press Hopper, Feed Frame and Press

The final blender's outflow enters the press hopper as slices of 30 g, which leave from the bottom in the order they arrived, so a dryer package keeps its boundaries until the feed frame mixes it. The feed frame is one well-mixed 90 g holdup refilled from the hopper with a 5 s time constant. The press

starts when the hopper first holds 0.50 kg, stops when it falls below 0.12 kg, restarts above 0.50 kg, and draws the rate $N_s n/60$ times the mean die fill of Equation (6.6).

$$\begin{aligned} \bar{m} &= \rho_f A_d\, h \left[1 - k_\eta (n/n_0 - 1)\right] \\ \rho_f &= \rho_0 \,(1 + k_{\rho w} \Delta\mathrm{LOD})(1 + k_\lambda\, \lambda_{ff}) \left[1 + k_{\rho d} \left(\frac{d_{50}}{d_{ref}} - 1\right)\right] \\ F &= F_{ref} \left(\frac{m}{\rho_t A_d\, g\, SF_{ref}}\right)^{k} (1 - k_w\, \Delta\mathrm{LOD}) \\ H &= H_{ref}\, (F/F_{ref})^{0.8} \left[1 - k_{dw} (n/n_0 - 1)\right] \end{aligned} \tag{6.6}$$

where A_d is the area of the 9 mm die, ΔLOD the feed-frame moisture less 2.0 %, $\lambda_{ff} = R/E$ the lot's density change weighted by the share of new-lot excipient in the feed frame, SF the solid fraction and H a teaching proxy for tablet hardness. With $k = 8$ a tablet 1 % heavier needs 8.29 % more force at the same gap, which is what lets the press weigh every tablet by its force. The reference fill depth is 7.145 mm and the reference gap 3.082 mm, where the force is $F_{ref} = 10$ kN and the hardness 100 N.

Each revolution makes individual tablets, 24 a second at 60 rpm. Tablet i draws two independent standard normal deviates cut off at ± 3, and its weight and dose follow Equation (6.7).

$$m_i = \bar{m}\,(1 + \sigma_m z_{m,i}), \qquad \mathrm{LC}_i = \frac{100\, m_i\, a_{ff}\,(1 + \sigma_a z_{a,i})}{x_A\, m_t} \tag{6.7}$$

where a_{ff} is the API mass fraction of the feed-frame blend and LC_i the dose in percent of label claim. The spreads are $\sigma_m = \sigma_a = 0.6\,\%$ for well-granulated material, widened to $\sigma_m(1 + 3\varphi)$ and $\sigma_a(1 + 8\varphi)$ by fines, which fill dies less evenly and segregate. Each tablet has the moisture of the feed frame. Its true weight, dose and moisture are recorded against the limits, whatever the gate decides.

6.3.6 Instruments

No loop reads a true state. The load cells give each feeder's weight-loss rate through a 4 s filter with 1 % colored noise of 2 s correlation, and give nothing while a refill runs and for 15 s after it. The Coriolis meter reads the water with a 1 s lag and 0.5 % noise, the inlet-air thermometer with a 5 s lag and 0.2 °C, and the hygrometer with a 30 s lag and 0.1 g/kg. The dryer NIR reads each cell's LOD as it starts to discharge, with 0.05 % noise and an optional bias. The feed-frame NIR scans every 2 s, reports the blend's dose with 0.3 % LC of noise and its LOD with 0.05 %, and delivers each reading $\theta_N = 10$ s after its scan with an optional bias b_N. The force transducer reads every tablet with 0.5 % noise, and the press infers the weight and a hardness proxy from it through calibrations made at the recipe moisture and speed, as shown in Equation (6.8). Both are soft sensors in the sense of Section 1.4.8.

$$\begin{aligned} \hat{m}_i &= c_W\, SF_{ref}\, \rho_t A_d\, g\, (\hat{F}_i/F_{ref})^{1/k} \\ \hat{H} &= c_H H_{ref}\, (\hat{F}/F_{ref})^{0.8} \end{aligned} \tag{6.8}$$

The weight calibration ignores the moisture term of Equation (6.6) and the hardness proxy ignores its dwell term. Every 300 s ten tablets are weighed with 0.2 mg of noise and tested for hardness with 3 %, and the results arrive 60 s later. Every deviate is drawn from the seeded generator of Section 1.6.1, so each scenario replays exactly.

6.3.7 Initialization and Numerical Checks

The parameters are collected in Table 6.2. Fixed in the code are the correlation times of the noise, the lags of the Coriolis meter, the thermometer and the hygrometer, the 2 s of rejection after a restart, the heat capacity of 1020 J/(kg K) used for the heater's energy, and the at-line sample of ten tablets. Every case except the start-up begins at the reference operating point, with the mixers at their steady composition, each dryer cell where its schedule puts it at $t = 0$ from one cycle integrated at the

Table 6.2 Line Parameters, Either Adjustable (A) in the Application's Model Dialog or Hidden (H) From It

Symbol	Meaning	Value	Class
$F_{A,max}$, $F_{E,max}$	feeder capacities	4.0, 30 kg/h	A
$M_{A,cap}$, $M_{E,cap}$	hopper capacities	2.0, 12 kg	A
—	refill below, to	25, 80 %	A
t_R	refill time, API, excipient	20, 30 s	A
t_S	weight settling after a refill	15 s	A
β_A, β_E	feed factor rise, full hopper	20, 5 %	A
δ_A, δ_E	compaction by a refill	8, 1 %	A, H
τ_D	compaction relaxation	90 s	A
ε_A, ε_E	feed-factor variation (1σ)	1.0, 0.8 %	A, H
—	screw lag, priming	1, 8 s	H
τ_B, τ_G, τ_L	mixer residence times	45, 12, 20 s	A
$F_{w,max}$	binder pump capacity	8.64 kg/h	A
d_p, d_{ref}	powder, granule size	50, 300 µm	A
—	mill screen, pump lag	450 µm, 2 s	H
T_f, T_{dry}, T_d	cell fill, dry, discharge	90, 390, 45 s	H
G, η	air per cell, contact efficiency	106.2 kg/h, 0.80	A
X_c	critical moisture, dry basis	0.10	A
X_{e0}, X_{e1}	equilibrium moisture	0.004, 0.12	H
T_{amb}	air intake	20 °C	H
ΔT_{max}, τ_h	heater rise, air lag	80 K, 20 s	A
$T_{in,max}$	air the API tolerates	80 °C	A
—	hopper capacity, start, stop	2.5, 0.50, 0.12 kg	A
—	hopper slice	30 g	H
M_{ff}	feed frame holdup	90 g	A
N_s, n_0, d	stations, speed, die	24, 60 rpm, 9 mm	H
ρ_t, ρ_0	true, fill density	1500, 550 kg/m^3	A
$k_{\rho w}$, $k_{\rho d}$, k_λ	fill density factors	0.01, 0.20, 0.75	H
SF_{ref}	solid fraction at F_{ref}	0.85	H
F_{ref}, k	reference force, exponent	10 kN, 8	A
k_w	force loss per % LOD	0.08	A
H_{ref}, k_{dw}, k_η	hardness, dwell, fill loss	100 N, 0.35, 0.10	A
σ_m, σ_a	tablet spreads	0.6, 0.6 %	A
—	growth with fines, σ_m, σ_a	3, 8	H
—	NIR period, noise	2 s, 0.3 % LC	A
—	LOD noise, both NIR	0.05 %	A
—	water, inlet-air noise	0.5 %, 0.2 °C	H
—	hygrometer noise	0.1 g/kg	H
—	load-cell filter, noise	4 s, 1 %	A
—	force noise	0.5 %	H
—	at-line interval, delay	300, 60 s	A

recipe feed, the hopper holding its 1.0 kg setpoint of recipe blend, and the feed factors, screws and pump at the values that deliver the recipe. The start-up case instead begins with every vessel, the hopper and the feed frame empty, the screws, the pump and the heater at rest, the air at T_{amb}, and the press waiting for 0.50 kg in its hopper. At the reference point the line holds 4.376 kg, 0.262 kg in the blender, 0.085 kg in the granulator, 2.819 kg in the dryer, 0.120 kg in the final blender, 1.000 kg in the hopper and 0.090 kg in the feed frame. The states advance by a classical fourth-order Runge-Kutta step of 0.5 s. With the noise off, halving the step moves the peak dose of the refill package in case 2 from 104.676 to 104.677 % LC and the last cell's LOD by less than 0.0001 %, and halving the hopper slice moves the peak by 0.0001 % LC. The component ledger, fed less held less pressed less evaporated, closes to within 5.3×10^{-14} kg in every case, where the application's own check allows

1 µg.

6.3.8 Assumptions

The mixers are ideal tanks in series whose residence time does not change with flow, and nothing segregates in them. Real continuous blenders hold more powder at higher rates, and a cohesive API can separate from its excipient, which would change both the delay and the spread that the tracker assumes.

Granulation is one number, a granule size set by the local liquid ratio, with no nucleation, growth or breakage kinetics. Fines act only through the fill density and the tablet spreads.

Each dryer cell is a lumped, well-mixed bed under one inlet air, with a constant-rate and falling-rate law and illustrative coefficients. The bed temperature, the air leaving each cell, attrition and elutriation are not modeled, where single-granule and bed models are available [8].

The press is lumped, with a power-law compaction curve and a hardness proxy, and the API and the excipient fill and compact alike, so the force carries no information about composition. Capping, lamination, punch wear, relaxation after ejection and differences between stations are not modeled, and the normal spreads cut at three standard deviations mean no tablet is an extreme outlier.

The instruments are lags with noise and additive bias. The feed-frame NIR reads the whole feed-frame blend with 0.3 % LC of noise, far less than the 2.17 % standard deviation reported for NIR on a commercial line [10], and it has no spectral model, sampling volume or calibration maintenance. The refill feedforward reads the hopper mass exactly.

The recipe, the acceptance limits, the hardness proxy and every correlation are illustrative. They were chosen to make the control problem visible and have not had quality-assurance review.

6.4 Where the Dose Is Decided and Where It Is Seen

The dose of Equation (6.7) is a product of two factors that are controlled, measured and disturbed in different places. This section quantifies the three consequences that shape the control problem.

6.4.1 Weight, Composition and the Instruments That See Them

To first order a dose error is the sum of a weight error and a composition error. The force sees the weight, amplified by $k = 8$, and nothing of the composition, because the API and the excipient compact alike in the model. The feed-frame NIR sees the composition of the blend and nothing of the weight or of the spread of individual tablets. The load cells see each feeder's rate, except during a refill. No instrument sees the dose of a tablet.

Pause. Try Exercise 6.1 before reading on.

The tablet spreads set the margin between the blend and the tablet limits. At the default spreads a tablet's dose differs from that of its blend by a standard deviation of 0.837 % and by at most +3.63 and −3.57 %, the truncated extremes, so a blend at a 250 mg mean weight between 98.52 % LC and 101.32 % LC cannot yield an out-of-limit tablet. A Monte Carlo of 4×10^7 tablets puts the share out of limits at 1.25×10^{-4} for a blend at 102 % LC, the default edge of the gate's guard band, 1.0×10^{-2} at 103 % LC and 0.127 at 104 % LC. Fines change the picture. With the 191 µm granules of case 5 the spreads grow to 1.25 and 2.34 %, the dose ratio's standard deviation to 2.62 %, and 5.65 % of tablets fall outside the limits from a blend exactly on target, which no analyzer that reads the blend can detect.

6.4.2 Transport and Packages

A tracer put into the blender at $t = 0$ first reaches a tablet at 637.5 s, is half pressed by 702.5 s and has a mean transit of 707.3 s. Most of that time is spent in the dryer, which holds the granules from the moment they enter a cell to the end of its drying, and in the hopper, whose 1.0 kg is 167 s of production. The dryer also changes the shape of a disturbance. Each cell averages the 90 s it receives into a package of 0.524 kg of solids, 0.540 kg of blend or 2160 tablets, and the hopper keeps the

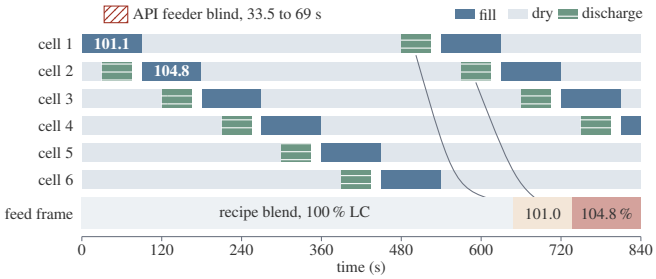


Figure 6.2 Dryer schedule and the refill of case 2. The API feeder is blind from 33.5 s to 69 s and the blender outlet peaks at 93.5 s, so the extra API lands in cell 1, filled from 0 to 90 s, and cell 2, filled from 90 to 180 s. Filling is drawn dark, drying light and discharge hatched. The packages leave at 101.05 % LC and 104.80 % LC when those cells discharge at 480 and 570 s, and reach the feed frame about 168 s later, after the hopper.

packages in order, as shown in Figure 6.2. A feeder error shorter than a fill therefore reaches the press as a step in composition lasting one or two packages rather than as a pulse. The press makes 240 tablets during the default 10 s analyzer delay and 960 during a 40 s one, and every one of them is pressed before the gate learns what the analyzer saw.

🕮 **Pause.** Try Exercise 6.2 before reading on.

6.4.3 A Refill the Load Cells Cannot Weigh

While the API feeder refills, its screw holds the speed the loop last asked for, and the delivered rate follows the density factor of Equation (6.2) alone. From a hopper at 25 %, and ignoring the powder fed during the refill, the ratio of the rate at the end of the refill to the rate before it is given by Equation (6.9).

$$\frac{F_A(t_R)}{F_A(0)} = \frac{1+\beta_A(0.80-\frac{1}{2})+D_A(t_R)}{1+\beta_A(0.25-\frac{1}{2})} \qquad D_A(t_R) = \frac{\delta_A \tau_D}{t_R}\left(1-\mathrm{e}^{-t_R/\tau_D}\right) \tag{6.9}$$

The compaction reaches $D_A = 0.0717$ and the ratio 1.191. With the noise off, the engine's rate runs 18.78 % above its setpoint at the end of the refill, and the feeder delivers 3.31 g more API than asked over the first 400 s, against the 54.0 g a cell receives at the recipe. The load cells see only 0.47 g of the excess, the part delivered after their signal returns at the loop's execution at 69 s. The package that receives most of the powder fed during the blind window leaves at 104.70 % LC and the one before it at 101.03 % LC, while the tracker, which during the refill can only assume that the setpoint was delivered, believes 101.23 % LC and 100.01 % LC. At the default seed the feed-factor variation adds to the error, since a frozen screw cannot follow it either, and the rate peaks 19.9 % high, the blind window from 33.5 to 69 s delivers 2.94 g of extra API, and the packages leave at 101.05 and 104.80 % LC against a belief of 100.10 and 101.09 % LC.

6.4.4 A Moisture Loop That Learns Once per Cell

The dryer NIR reports a cell only when it discharges, one reading every 90 s, and each reading summarizes 480 s of filling and drying, a sampled and held result of the kind treated in Section 1.4.5. At the reference point the discharge LOD falls 0.0935 % per kelvin of inlet air. Air at 16 g/kg needs 69.7 °C for the setpoint and air at 24 g/kg needs 75.2 °C, and with the air held at 60.1 °C the same humidities leave the cells at 3.08 and 3.89 %. A change reaches a cell already in the dryer only in part, as shown in Table 6.3. A humidity step at a cell's age of 270 s carries 0.689 of its full effect on that cell, and a correction of the air at the same age carries only 0.535. The humidity keeps more of

Table 6.3 Share of a Step's Full Effect on the Discharge LOD of One Cell, by the Cell's Age When the Step Occurs, at the Reference Point

Age (s)	0	90	180	270	360	420	480
Y_{in} from 6 to 16 g/kg	1.000	0.896	0.802	0.689	0.500	0.299	0
T_{in} up 1 K	1.000	0.850	0.698	0.535	0.345	0.190	0

Table 6.4 Loops, Defaults and Output Limits. All Are PI in the Velocity Form

Loop	PV to MV	K_c	τ_I	Output
FIC-A	$\hat{F}_A$ to ω_A	12.5 %/(kg/h)	5 s	0–100 %
FIC-E	$\hat{F}_E$ to ω_E	1.6 %/(kg/h)	5 s	0–100 %
FIC-B	$\hat{F}_w$ to u_B	5 %/(kg/h)	4 s	0–100 %
TIC	$\hat{T}_{in}$ to u_H	1.2 %/K	25 s	0–100 %
MIC	$\widehat{\mathrm{LOD}}_k$ to $T_{in,SP}$	8 K/%	200 s	35 °C–80
WIC	$\hat{m}$ to h	0.014 mm/mg	3 s	4–12 mm
HIC	$\hat{H}$ to g	0.0024 mm/N	3 s	2.4–4.2 mm
level	M_H to $F_{s,SP}$	2 (kg/h)/kg	P only	±15 %

its effect because it also raises the equilibrium moisture toward which the falling-rate period relaxes, with a time constant $S(X_c - X_{eq})/R_c$ of about 138 s, while a correction of the air acts mainly through the drying rate over the time that remains. The outer loop is therefore a sampled integrating controller on a plant whose response to each move is spread over the next five to six samples.

6.5 Control System as Implemented

The controllers execute every 1 s, at whole seconds of simulated time, one turret revolution at 60 rpm, on the instruments of Section 6.3. A step follows the order of Figure 1.9, with the discrete events and the tablets after the integration. The historian logs a row every 5 s, and the application runs from 1 to 120 times real time, 30 by default. The loops and their defaults are listed in Table 6.4.

6.5.1 The PI Algorithm

The seven PI loops use the framework's velocity-form PID of Section 1.6.2 as it stands, while the level trim is the proportional law of Equation (6.10). In the symbols of Equations (1.15) to (1.18), each loop has its own action $a = \pm 1$ and output bias u_b, executes every 1 s and uses a tracking time T_t equal to τ_I. No loop here uses derivative action ($\tau_D = 0$), and the back-calculation runs only in loops that have integral action. The output limits of Table 6.4 and any rate limit bound only what reaches the actuator. The weight loop's output slews at most 0.5 mm/s and the hardness loop's at 0.05 mm/s. In manual mode, or whenever a loop does not drive its actuator, it tracks by setting $I_k = u_k - u_b - S_k$, so every return to automatic is bumpless. For a settled scenario, untouched manual stations are initialized from the solved screw speeds, binder pump, heater, fill depth and punch gap. Selecting Manual before Run therefore holds the solved lineup. Station values that the reader sets are restored before priming and survive Reset. The empty start-up keeps its deliberate starting commands.

The moisture loop and the hardness loop have $a = -1$, since a wet cell must raise the air and a soft tablet must close the gap. Their output moves in the same direction as their measurement, so they are direct acting in the convention of Section 1.6.2. The other five PI loops have $a = +1$ and are reverse acting.

6.5.2 Feeders, Ratio Master and Binder

The press speed is the production rate. It slews at 2 rpm/s toward its setpoint, and the ratio master sets the powder demand F_d of Equation (6.1) at the current speed plus a proportional trim on the press

hopper, as shown in Equation (6.10).

$$\begin{aligned} F_{s,SP} &= F_d + \mathrm{clamp}\left[K_H(M_{H,SP} - \bar{M}_H), \pm 0.15 F_d\right] \\ F_{A,SP} &= r_A F_{s,SP} \\ F_{E,SP} &= (1 - r_A) F_{s,SP} \quad \text{or} \quad (1 - r_A)\hat{F}_A / r_A \end{aligned} \tag{6.10}$$

where $\bar{M}_H$ is the hopper load through a 90 s filter and the second excipient setpoint is the measured-API option. The trim is slow on purpose, because the dryer lies between the feeders and the hopper. FIC-A and FIC-E move the screws on the load-cell rates. During a refill and its settling the feeder is volumetric, and its loop tracks the speed it last asked for, and for the first 20 s of a start-up it runs at the speed its calibration gives for the setpoint. With the refill feedforward on, the command is divided by the density factor that the feeder's identified profile predicts, as shown in Equation (6.11).

$$\begin{aligned} \omega_A &= \frac{u_A/100}{1 + 0.95\beta_A(f_A - \tfrac{1}{2}) + \hat{D}_A} \\ \frac{\mathrm{d}\hat{D}_A}{\mathrm{d}t} &= -\frac{\hat{D}_A}{\tau_D} + \frac{0.95\,\delta_A}{t_R}\,\sigma_R \end{aligned} \tag{6.11}$$

The identified profile is 5 % low on both terms, and the loop's upper limit is raised to 100 times the predicted density factor so that the screw can still reach full speed. FIC-B sets the water to $(L/S)_{SP}$ times the measured powder rate, using a feeder's setpoint while it is volumetric.

6.5.3 Moisture Cascade and Humidity Feedforward

TIC holds the measured inlet air on its setpoint every second. It is the inner loop of the cascade, and the humidity enters outside it, so TIC does nothing against a humid intake and MIC answers it only once it has reached a cell. Volume 3, Chapter 2 shows how the place where a disturbance enters bounds what a loop structure can reject. MIC acts only when a cell holding at least 70 % of a nominal fill starts to discharge, on the dryer NIR's reading, and the step it integrates over is the interval since its previous update, nominally 90 s, so the partly filled cells of a start-up do not mislead it. Its output is the inlet-air setpoint, limited to 35 to 80 °C, the highest air the API tolerates. With the humidity feedforward on, the bias of MIC is $b_k = T_{ff}(\hat{Y}_{in}) - T_{ff}(6\,\mathrm{g/kg})$, where $T_{ff}(Y)$ is the inlet temperature the drying model needs for the setpoint at humidity Y, tabulated from 0 to 30 g/kg in steps of 3 at the current production rate and interpolated. Between cells the bias moves the setpoint while the integral does not. With the air fixed, the operator's setpoint is used and MIC tracks. The spray dryer of Chapter 10 also adds a humidity feedforward, because its moisture result arrives late as well.

6.5.4 Weight and Hardness From Force

WIC moves the fill depth to hold the mean force-inferred weight of the tablets made in the last second at its setpoint. HIC moves the punch gap to hold the hardness proxy of Equation (6.8). Each at-line result is a late reference for a soft sensor, as the laboratory is in Section 1.4.8, and trims its calibration by 70 % of the relative difference between the tested and the inferred value, bounded between 0.95 and 1.05 for the weight and between 0.8 and 1.2 for the hardness. Neither loop sees the composition.

6.5.5 Tracker and Reject Gate

The tracker is a copy of the transport run on measurements alone, the tracking of material of Section 1.4.4. It carries the solids, the API, the water and a suspect mass through tanks in series with the plant's structure, fed by the load-cell rates, or by the setpoints while a feeder is volumetric, with the dryer's schedule, the discharge law, each cell's LOD from the dryer NIR, hopper slices scaled to the hopper load cells and a feed frame drawn at the press speed and inferred weight. It never reads a true composition. Powder made before both feeders have held within 3 % of their setpoints for

Table 6.5 Outcomes at the Default Seed. Made and Accepted Count Tablets Outside the Limits, Worst Is the Largest Dose Deviation Accepted

Case, window, configuration	Made	Rejected	Accepted	Worst
1, 1500 s, tracking on	256	3444	0	3.37 %
1, 1500 s, tracking off	256	1644	0	3.37 %
2, 1200 s, feedforward off	609	2712	0	4.90 %
2, 1200 s, feedforward on	0	0	0	3.51 %
3, 1500 s, recipe ratio	5437	7152	0	3.36 %
3, 1500 s, measured API	929	5256	0	3.22 %
3, 1500 s, tracking off	5437	6840	138	9.80 %
4, 1500 s, weight on	0	0	0	3.35 %
4, 1500 s, weight off	15 397	15 101	372	6.45 %
5, 1200 s, tracking on	116	5088	0	3.34 %
5, 1200 s, tracking off	116	0	116	8.75 %
6, 2400 s, cascade	0	0	0	3.86 %
6, 2400 s, air fixed	35 376	37 704	0	3.16 %
6, 2400 s, humidity FF	0	0	0	3.75 %
7, 1800 s, tracking off	4371	11 640	816	10.92 %
7, 1800 s, tracking on	4371	12 672	0	3.36 %
8, 2400 s, trim off or on	0	0	0	3.63 %

20 s, powder granulated while the measured liquid ratio is more than 10 % off, and cells read outside 1.1 to 2.9 % LOD are suspect. The gate rejects a tablet, in this order, during start-up, for 2 s after a restart, when its inferred weight is more than 5 % from the setpoint, when the tracker puts the feed frame outside the guard band $|\mathrm{LC} - 100| > b = 2.0\,\%\ LC$ or its suspect share above 2 %, and when the latest NIR reading is outside the band, or its LOD outside 1.1 to 2.9 %, and for $t_{hold} = 10$ s after. After a start-up the gate opens once the NIR has read inside the band for 20 s, the inferred weight has held within 2 % for 10 s and the tracker holds no suspect material in the feed frame.

6.5.6 Simulation, Control and Internal Models

Section 6.3 describes the simulation model. The controllers carry their own, simpler models, namely the identified feed-factor profile of Equation (6.11), the drying model inverted by the humidity feedforward, which is the plant's own law, the press calibrations of Equation (6.8), and the tracker, which shares the plant's residence-time structure exactly, so that its only errors come from its inputs. No model is identified inside the application.

6.6 Scenarios and Measured Results

The subsections follow the cases in selector order, and the tablets that each configuration made out of limits, rejected and let through are counted in Table 6.5. Each case has a completion rule of the kind described in Section 1.6.4, met when the reader makes the comparison runs it names in Auto and the simulation reaches the state it names. The challenge is judged on the case as given, so changing a model parameter or a disturbance voids the attempt. Unless a change is named, a case runs the reference configuration, with both feedforwards, tracking, the NIR and force gates and both at-line trims on. The values reported here were measured on the engine itself, run without the interface at each scenario's seed, with any named change made at $t = 0$ before the run starts. The application gives the same run when the change is carried through Reset instead. Figure 6.3 draws the worst accepted dose deviation of each configuration against the dose limit.

6.6.1 Start-Up

Case 1 starts every unit empty. The API screw primes over 8 s and the excipient screw in 3.2 s, so at 10 s the blender outlet carries only 55.4 % of the recipe's API share, and the first dryer cell takes all of that lean start. It leaves at 480 s holding only 0.215 kg, dried to 1.09 % LOD by air meant for a full cell. While the press hopper is empty the level trim asks for 2.0 kg/h, 9.5 % above the demand,

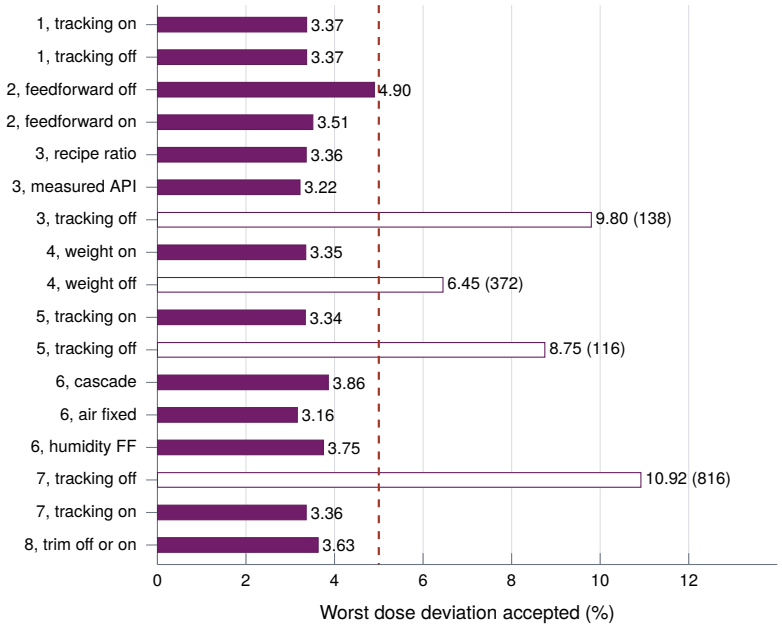


Figure 6.3 The cases by configuration, from Table 6.5: the largest dose deviation among accepted tablets, with the dashed line at the 5 % dose limit. Dark bars accept no tablet out of limits. White bars accept some, and the number accepted out of limits is given in parentheses. Notice that every white bar is a configuration without tracking or without weight control, and that the feeder refill of case 2 with its feedforward off stays inside the limit only because the analyzer's gate reacts in time.

so the next cells leave fuller and wetter, at 2.36, 2.21 and then 2.07 % LOD, as the moisture loop adjusts. The press starts at 605 s. With tracking on the gate opens at 748.5 s, after 3444 rejected tablets carrying 85.0 g of API, of which 256 were truly out of limits. With tracking off it opens at 673.5 s after 1644, and no tablet out of limits is accepted either way. The tracker's extra 75 s is caution about start-up material it cannot vouch for, and it costs 1800 tablets.

6.6.2 A Refill: the Right Weight With the Wrong Dose

Case 2 starts with the API hopper at 26 % and the refill feedforward off. The refill runs from 33.5 to 53.5 s, the feeder loop has its weight signal back at its execution at 69 s, and the blender outlet peaks at 108.4 % of the recipe's API share at 93.5 s. The consequence arrives twelve minutes later, as shown in Figure 6.4. The first package raises the feed frame to about 101.0 % LC from 647.5 s, the second package crosses 102 % LC at 731.5 s and the feed frame peaks at 104.77 % LC at 814.5 s. Throughout, the true mean weight stays between 249.31 and 250.57 mg. In all, 609 tablets are pressed outside the dose limits, and the NIR gate rejects 2712 tablets by 1200 s, 2103 of them within every limit. No over-dosed tablet is accepted, but only just. The first reading above the guard band, from the scan at 730 s, arrives at 740 s, and the first over-dosed tablet is pressed in the next second. The tracker's prediction rises to only 101.06 % LC. With the feedforward on the rate runs at most 2.77 % high while the feeder is volumetric, the feed frame peaks at 100.39 % LC, and no tablet is made out of limits or rejected. Weight checks alone would have passed every tablet of this run.

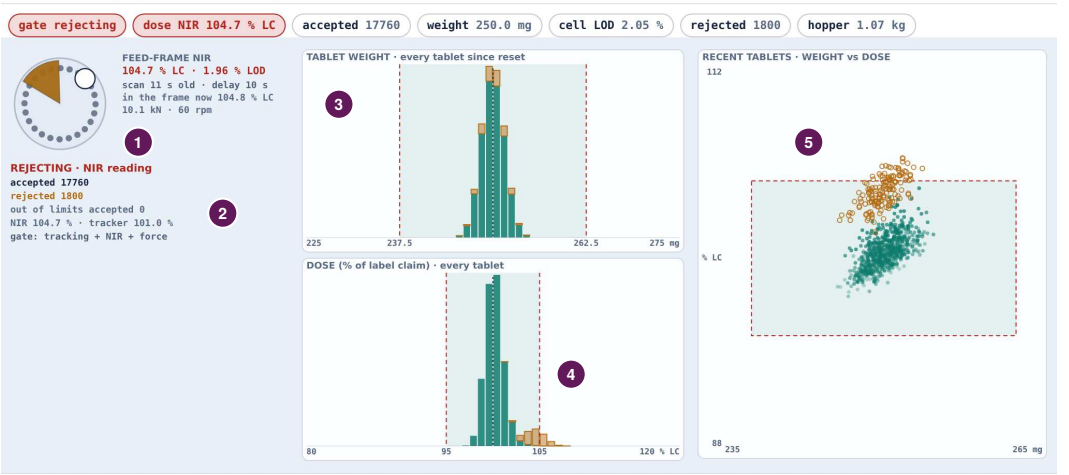


Figure 6.4 The application in case 2, feeder refill, with the refill feedforward off, paused at 815 s, cropped to the plant panel of the Tablets view. The header with the clock, the control panel, the trends and the Learn panel are cut. (1) The feed-frame dial: the package made during the refill fills the feed frame at 104.8 % LC, and the NIR reports 104.7 % LC from a scan 11 s old. (2) The gate's status: rejecting on the NIR while the tracker predicts only 101.0 % LC, with 17 760 accepted, 1800 rejected and none accepted out of limits. (3) The weight histogram of every tablet since reset, centered on 250 mg inside the ±5 % lines, while the status row above it gives the force-inferred weight as 250.0 mg. (4) The dose histogram, with a tail of rejected tablets reaching past 105 % LC. (5) The scatter of recent tablets (every twelfth since 365.5 s, by the application's setting, which the panel does not print), rising in a column of tablets near 250 mg out of its specification box, every one of them a rejected tablet drawn hollow.

> **TRY IT IN THE APP** **2 · Feeder Refill**
>
> Load the case and press Run. When the package made during the refill reaches the press, about 13 minutes in, open the Tablets view. Watch the weight histogram stay centered on 250 mg while the dose histogram grows a tail past 105 % LC. The feed frame peaks at 104.77 % LC at 814.5 s, and 609 tablets are pressed outside the dose limits.

6.6.3 A Feeder That Delivers Nothing

Case 3 stops the API completely for 90 s at 120 s, 54 g of API that never enters the line. FIC-A drives its screw to the limit within 10 s and holds it there for 83 s, and when the arch collapses the rate overshoots to 4.22 kg/h, twice its setpoint, before the loop winds back. No loop can restore the missing API, and the application does not pretend to. With the excipient on the recipe ratio, the package made during the stop falls to 32.4 % LC in the feed frame and 5437 tablets are made out of limits. The tracker, which saw the stop on the load cells, predicts 31.7 % LC, and the gate rejects 7152 tablets and accepts none out of limits. With the excipient following the measured API the composition stays between 95.2 and 102.9 % LC, only 929 tablets are made out of limits, and the cost moves to output, since the line makes less blend and the press hopper falls to 0.439 kg. With tracking off the NIR gate alone lets 138 out-of-limit tablets through before its readings arrive, the worst 9.80 % below label claim.

6.6.4 A Denser Lot: the Right Blend With the Wrong Weight

Case 4 fills the excipient feeder from a lot 8 % denser at 60 s. The excipient rate overshoots by 7.80 % for a few seconds before FIC-E corrects it, and the denser granules reach the feed frame near 745 s and raise the fill density from 550 to 583.0 kg/m^3, the 6.0 % that $k_\lambda \lambda$ predicts. With weight control on, the fill depth falls from a mean of 7.14 to 6.74 mm, and the weight holds at 250 mg apart from a peak of 252.2 mg at 741 s as the front arrives. With it off the tablets reach 265.1 mg, and their dose rises with them while the blend in the feed frame stays between 99.30 and 100.12 % LC. The force gate rejects 15 101 tablets as overweight, and 372 out of limits pass it, 145 on weight, whose force still put them inside ±5 %, and 260 on dose, 33 of them on both counts. The NIR, which reads the blend, sees nothing wrong. This case is the mirror of case 2, and each dose error is invisible to the instrument that watches the other factor.

6.6.5 A Binder Interruption

Case 5 blocks the granulation nozzle for 40 s at 120 s. The pump runs at its limit for 35 s, and when the nozzle clears the liquid ratio overshoots to 0.412 kg/kg at 160 s. The cell that took the dry powder leaves at 570 s with a granule size of 190 µm and 1.40 % LOD, and the next, which took the overshoot, at 318 µm and 2.26 %. The NIR reads between 98.35 and 101.08 % LC throughout, because the blend's mean is right, while 116 tablets are made outside the dose limits, as the fines spread of Section 6.4 predicts. The tracker flagged everything granulated while the ratio was more than 10 % off and rejects 5088 tablets, the affected package and its edges, accepting none out of limits. With tracking off all 116 are accepted, the worst 8.75 % from label claim.

6.6.6 Humid Air and a Cascade Sampled per Cell

Case 6 turns the drying air from 6 to 16 g/kg at 300 s with the humidity feedforward off. The cells already drying finish in humid air whatever the loop does next. With the cascade alone the worst cell leaves at 2.59 % at 480 s, the air setpoint climbs to 70.5 °C, and every cell from 930 s on is within 0.1 % of the setpoint, ten and a half minutes after the change. With the air fixed at 60 °C the cells climb to 3.10 %, 19 of them leave above the 3.0 % limit and 35 376 tablets are made too wet. Told by the dryer NIR which cells were out, the tracker rejects 35 928 tablets and the NIR 1776 more, none out of limits is accepted, and only 34.5 % of the output is kept. With the humidity feedforward the air moves as soon as the hygrometer does, the worst cell leaves at 2.24 %, and every cell from 570 s on is within 0.1 %. The feedforward spends 5.85 kWh of heat over the 40 min against 5.72 kWh for the cascade alone and 4.81 kWh with the air fixed.

🕮 **Pause.** Try Exercise 6.3 before reading on.

6.6.7 A Slow and Drifting Analyzer

Case 7 slows the feed-frame NIR to 40 s at 60 s, bridges the API to 15 % of its rate for 45 s at 120 s, and drifts the analyzer 3 % LC high at 1500 s, with tracking off. The lean package takes the feed frame below 98 % LC at 730.5 s and bottoms at 86.4 % LC at 899.5 s, and 816 tablets out of limits are accepted, the worst 10.92 % below label claim, every one pressed after its powder was scanned and before the scan was reported. With the normal 10 s delay the same bridge lets 103 through, and with tracking on none, because the tracker saw the bridge on the load cells twelve minutes before its package arrived. The drift is the opposite failure. Every reading after it lies outside the guard band, and in the last five minutes the gate rejects 6240 of the 7200 tablets made, all of them within every limit.

Table 6.6 Challenge Configurations Over 3600 s. Worst Is the Largest Dose Deviation Accepted

Configuration	Accepted	Rejected	Out	Worst
as shipped	71 952	14 448	194	9.39 %
all three on	82 992	3408	0	3.72 %
no refill feedforward	75 408	10 992	6	6.09 %
no humidity feedforward	77 280	9120	0	4.01 %
no tracking	83 304	3096	122	8.62 %

TRY IT IN THE APP 7 · NIR Delay and Bias

Press Run with Reject by material tracking Off, and read the Accepted out of limits tile once the lean package has passed, at about 17 minutes: 816 tablets, the worst 10.92 % below label claim. Reset, set Reject by material tracking to On and run again. None is accepted, because the tracker saw the bridge on the load cells.

6.6.8 A Faster Press

Case 8 raises the press from 60 to 72 rpm at 120 s with the at-line hardness trim off. The feeders are told at once, but the extra powder takes about twelve minutes to arrive, and the press hopper, which swung between 0.90 and 1.10 kg before the change, falls to 0.254 kg at 757 s, while the fuller cells made at the higher rate leave at up to 2.74 % LOD. The dies fill 2 % less at speed, the true mean weight dips to 247.3 mg at 125.5 s, and WIC deepens the fill from 7.15 to 7.30 mm. HIC holds its proxy at 100 N while each tablet is compressed more briefly, and the true hardness settles near 93 N, the factor 0.930 of the dwell term, and reads 92.5 N at 40 min. With the at-line trim on, the ten-tablet tests correct the proxy by bounded steps, and the true hardness is 100.8 N at 40 min with the calibration at 0.918.

6.6.9 The Graded Shift

The challenge runs 3600 s. The API feeder refills at 167.5 s and again at 2014.5 s, the drying air turns to 24 g/kg at 600 s, which needs 75.2 °C inside the 80 °C limit, and the API bridges to 15 % of its rate for 30 s at 1800 s. The shift starts with the refill feedforward, the humidity feedforward and tracking off, and it is met with at least 80 000 tablets accepted and none accepted outside the weight, dose or moisture limits. Table 6.6 sets the configurations side by side. As shipped the gate accepts 71 952 tablets, 8048 short of the target, and 194 of them are out of the dose limits, 4 from the first refill, 189 from the bridge and 1 from the second refill. With all three settings on it accepts 82 992, 2992 above the target, and rejects 3408, and the worst accepted tablet is 2.26 % off in weight, 3.72 % in dose and 2.36 % in LOD at the wettest. Each setting is needed, and the three failures differ in kind. Without the refill feedforward 6 over-dosed tablets pass the NIR, without the humidity feedforward the cells reach 2.94 %, the tracker rejects them as a precaution and only 77 280 are accepted, and without tracking the bridge's package reaches the press before the NIR can react and 122 out-of-limit tablets are accepted.

DID YOU KNOW? Protection That Also Raises Output

From the simulator: in the graded shift as shipped, the gate accepts 71 952 tablets, 194 of them out of limits. With the refill feedforward, the humidity feedforward and tracking all on, it accepts 82 992 and none out of limits (Table 6.6). The settings that protect the dose also keep more tablets.

6.7 Technology in Practice

What Measures It

Three instruments divide a dose between them. The force transducer of the press reports how much powder each die received, the load cells report what each feeder delivers except while it refills, and a near-infrared analyzer in the feed frame reports what the blend contains. The 2023 guidance on continuous manufacturing finds process analytical technology well suited to continuous lines and names in-line near-infrared spectroscopy of blend uniformity or water content among its examples, because it lets disturbances be detected in real time [20]. In the chapter both analyzers are lags with noise and an additive bias, the load cells a filtered rate and the force a reading with 0.5 % of noise, as Section 6.3 sets out.

TECHNOLOGY Sensor: A Near-Infrared Analyzer on the Blend

Molecules absorb light at frequencies at which their atoms vibrate and rotate, in bands unique to each kind of molecule, which lets spectroscopy measure composition [21]. A near-infrared analyzer turns spectra of the flowing powder into an API content through a multivariate model calibrated against a reference method. On one continuous tableting line an analyzer at the blender took spectra from 860 to 1690 nm at 100 a second, averaged to one result a second, and its blend model had a cross-validation error of 0.47 percent by weight [5]. Powders limit how deep the light reaches, so the probe's place and sample size matter [17]. A model that drifts shows on a trend as a step between the analyzer and the true blend, as in case 7. The chapter's analyzer scans every 2 s with 0.3 % LC of noise and reports 10 s late.

What Moves It

The final elements are the two feeder screws, the binder pump, the heater of the drying air, the fill depth and punch gap of the press, and a reject gate after it. The feeders matter most for the dose, because no amount of blending corrects a blend whose ingredients enter at the wrong ratio [16]. In the chapter each screw follows its command through a 1 s lag and the pump through 2 s, and the fill depth slews at most 0.5 mm/s. Figure 6.5 draws the loops of Section 6.5 on these devices.

TECHNOLOGY Final Element: The Loss-in-Weight Feeder and Its Failures

A loss-in-weight feeder meters powder by screw speed under a gravimetric controller that reads its own load cells, and feeders are the most likely source of a content error on a continuous line. Some fluctuation of the feed rate is unavoidable. A hopper refill is the most common cause of a large deviation, because the feeder runs volumetrically while it refills and cannot correct for the change of density. Powder that accumulates in the downspout can break off and raise the content at once. A miscalibrated load cell makes the feeder dispense the wrong rate unseen by its own controller, and shows on a trend as a screw speed that departs from its history while the measured rate stays in range [16]. The chapter's load cells report nothing during a refill and for 15 s after it.

Where the Controller Runs

A distributed control system, used in industries that include pharmaceutical processing, oversees localized controllers that hold their variables at setpoints, with loop cycle times from milliseconds to minutes [22]. A review by the regulator's staff describes a supervisory layer that reconciles measurements of parameters, raw materials, in-process materials and product with a model of the process dynamics to support real-time release [17]. In the application every loop executes once a

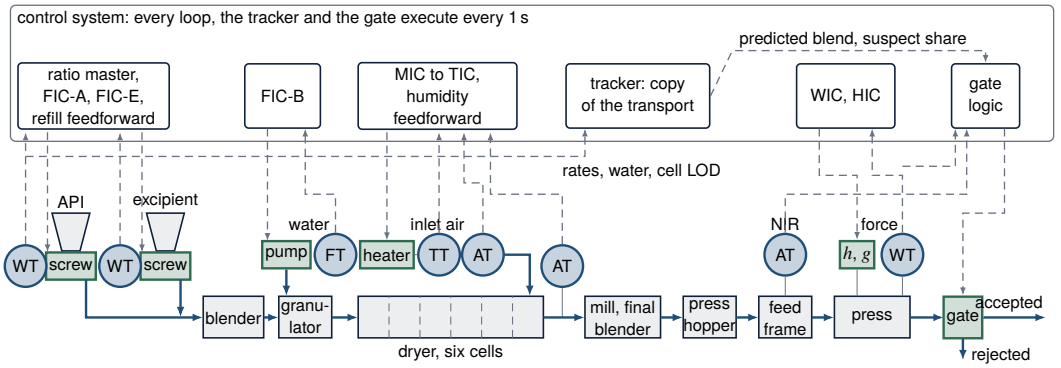


Figure 6.5 The loops of the tablet line on plant hardware. Load cells (WT) of the two feeders drive FIC-A and FIC-E, which move the screws under the ratio master. The water meter (FT) drives FIC-B on the binder pump, the dryer's moisture analyzer (AT at the cell discharge) drives MIC, which sets TIC on the air heater, and the force transducer (WT) drives WIC and HIC on the fill depth h and punch gap g. The tracker copies the transport on the measured rates, water and cell moisture, and the gate logic combines it with the feed-frame analyzer (NIR) and the force. Notice that the analyzer and the gate stand at the press, while the composition they judge was set at the screws on the far left.

second, one turret revolution at 60 rpm. The velocity-form PI loops of Table 6.4 are the base layer, and the tracker and the gate run above them as a copy of the transport driven by measured inputs.

What Is Modernizing It

Three developments bear on this line. The first is the process model inside the control strategy. The 2023 guidance allows process models in commercial control, including the diversion strategy, and defines a soft sensor as a model used in place of a physical measurement to estimate a variable or attribute from measured data [20]. The tracker of this chapter is such a model. The second is real-time release. Continuous manufacturing lends itself to judging the quality of a product from process data, and the volume of data supports multivariate statistical process control, which tracks fewer charts and can detect a changed relation between parameters and quality [17]. The third is advanced control. The same review names model predictive control among the areas in which research should continue [17].

> **IN PRACTICE** **Feeder and Analyzer Limits Tied to the Transport**
>
> The ICH Q13 guidance, published by the United States regulator in March 2023, works through a continuous direct compression line as an example. Its residence-time distributions were measured by replacing the API with a tracer of very similar flow properties. The feeders run gravimetrically except while they refill, and the duration and mass of a refill were studied to limit its effect. The analyzer sits in the press feed frame. The diversion strategy links the feeder and analyzer limits to the distribution from the feeders to the analyzer and to that from the probe to the diversion point, and each predefined segment of a batch carries a unique code [20]. The tracker and the gate of this chapter play those parts.

6.8 Limitations

The mixers are ideal tanks in series with fixed residence times and no segregation, so the tracker's structure is exact and its only errors come from its inputs. A real tracking model is fitted to measured residence-time distributions and carries their uncertainty [5]. The tracker is also an open-loop estimator driven by measured inputs. A moving-horizon estimator that reconciles the feeders' mass measurements [19], of the kind set out in Section 1.4.7, would sharpen exactly the estimate that a refill spoils.

OPEN CHALLENGE Where One Batch Ends

Back-mixing smooths the feeders' fluctuations, and a line in plug flow could not filter them, so a robust continuous line must mix along its length. The same back-mixing blurs the boundary between batches, so a recall of one batch may have to include its neighbors on both sides [16]. A 2015 review calls back-mixing a possible physical limitation to material traceability [17]. The tracker of this chapter knows the plant's mixing exactly, which a real one cannot. Progress would be a diversion rule that carries the uncertainty of measured distributions into the decision.

Granulation is a size proxy, drying is a lumped law with illustrative coefficients, and the press is a power-law compaction with a hardness proxy. The feed-frame NIR is a noisy, delayed reading of the whole feed frame, much quieter than NIR on a commercial line [10].

The recipe and its limits are illustrative. The simulator was built to teach equipment control, its quality proxies and limits have not had quality-assurance review, and nothing in it is regulatory or quality-assurance guidance.

6.9 Conclusion

A continuous tableting line controls the tablet weight at the press and fixes the composition at the feeders twelve minutes upstream, and the simulator described here records what each tablet truly contains apart from what every instrument reports. The force reports the weight magnified eightfold and the composition not at all, and in case 2 a feeder refill keeps the true mean weight within 0.7 mg of 250 mg while its package reaches the press at 104.77 % LC, and the NIR gate catches the first over-dosed tablet with less than a second to spare. The refill feedforward holds the feed frame to 100.39 % LC. The dryer turns the stream into packages of 2160 tablets and its moisture loop learns once per cell, so humid air leaves cells at 2.59 % LOD with the cascade alone and 2.24 % with the humidity feedforward. A 40 s analyzer delay lets 816 under-dosed tablets through a gate that the tracker closes, and a 90 s stop of the API feeder can only be rejected, 7152 tablets with none out of limits accepted. In the graded shift the three settings take the accepted out-of-limit tablets from 194 to none with 82 992 accepted. The model assumes ideal mixers, lumped drying and compaction and a quiet analyzer. A fuller model would add segregation and flow-dependent residence times, a fitted tracker with its uncertainty, a sampling model for the NIR and a state estimator on the feeders. The application puts in a browser a line on which a tablet at the right weight can be seen to carry the wrong dose.

KEY POINTS

- A tablet at its target weight need not carry its target dose: the force sees how much powder fills a die, not what the powder is.
- The composition is fixed at the feeders and carried for a mean of 707 s, cut by the dryer into packages of 2160 tablets.
- A feeder refill keeps the true mean weight within 0.7 mg of 250 mg while its package reaches the press at 104.77 % LC.
- A 40 s analyzer delay lets 816 under-dosed tablets through a gate that the tracker closes, because the tracker sees the bridge on the load cells.

Where else this applies. Chapter 7 diverts material by the same residence-time tracking, Volume 12, Chapter 12 meets the refill of a loss-in-weight feeder on a polymer extruder, and Chapter 10 adds a humidity feedforward to a moisture result that arrives late.

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6.10 Exercises

6.1 Concept check · 2 min

In case 4 an excipient lot 8 % denser reaches the press with Weight control Off. The tablets reach 265.1 mg while the blend in the feed frame stays between 99.30 and 100.12 % LC. Which instrument on the line can see that these tablets carry too much API?

(a) The feed-frame NIR, because the dose is the API share of the blend it scans
(b) The force transducer, because a heavier tablet needs more force at the same gap
(c) The tracker, because it follows the new lot from the excipient load cells
(d) The excipient load cells, because the denser lot raises the feeder's rate

6.2 Concept check · 1 min

A feeder error that lasts 30 s reaches the feed frame about twelve minutes later as a step in composition lasting one or two dryer packages, not as a short pulse. What gives it that shape?

(a) The blender's three tanks in series spread every error over about twelve minutes
(b) The feed-frame NIR averages its scans over the 10 s of its delay
(c) Each dryer cell mixes its 90 s into one package, which the hopper keeps in order
(d) The press hopper is a well-mixed 1.0 kg tank that blends neighboring packages

6.3 Concept check · 2 min

In case 6 the drying air turns from 6 to 16 g/kg at 300 s. The worst cell leaves at 2.59 % LOD with the moisture cascade alone and at 2.24 % with the humidity feedforward. Why does the feedforward do better?

(a) It raises the gain of the moisture loop, so each cell's reading moves the air further
(b) It replaces the dryer NIR with the hygrometer, which reports each cell's moisture sooner
(c) It holds the inlet air at 80 °C, the highest the API tolerates, until the cells are dry
(d) It moves the air at the hygrometer's reading, so cells already drying are partly corrected

6.4 Theory and calculation · 6 min

Use Equation (6.1) with $N_s = 24$, $m_t = 250\,\text{mg}$, $x_A = 10.0\,\%$, $x_L = 1.0\,\%$ and $\text{LOD}^* = 2.0\,\%$.

(a) Compute the API share r_A of the powder feed, the powder feed F_s at 60 and at 72 rpm, and the API rate at each speed. *Checkpoint:* $r_A = 0.10306$. F_s = 20.96 and 25.15 kg/h, API 2.160 and 2.592 kg/h.

(b) A dryer cell takes the granulator's outflow for 90 s at 60 rpm. Compute its solids, the finished blend they become with lubricant and moisture, and the number of tablets that blend makes. *Checkpoint:* 0.524 kg of solids, 0.540 kg of blend, 2160 tablets.

(c) How many tablets does the press make during a 10 s and a 40 s analyzer delay at 60 rpm, and during the 40 s delay at 72 rpm? *Checkpoint:* 240, 960 and 1152 tablets.

6.5 Theory and calculation · 8 min

A tablet's dose relative to its blend is $(1+\sigma_m z_m)(1+\sigma_a z_a)$ at a 250 mg mean weight, Equation (6.7), with independent standard normal deviates cut off at ± 3 and $\sigma_m = \sigma_a = 0.6\,\%$.

(a) The variance of a standard normal cut off at ± 3 is $1 - 6\varphi(3)/[2\Phi(3) - 1]$, with $\varphi(3) = 0.004432$ and $\Phi(3) = 0.99865$. Compute the standard deviation of the dose ratio. *Checkpoint:* 0.837 %.

(b) Compute the largest and the smallest dose ratio, and the range of blend dose inside which no tablet can fall outside 95 to 105 % LC. *Checkpoint:* +3.63 and −3.57 %. Blend from 98.52 to 101.32 % LC.

(c) The binder interruption of case 5 gives granules of 191 µm. With $\varphi = 1 - d_{50}/d_{ref}$ and the widening by fines of Section 6.3, compute σ_m and σ_a, and say why the feed-frame NIR cannot protect these tablets. *Checkpoint:* $\varphi = 0.363$, $\sigma_m = 1.25\,\%$, $\sigma_a = 2.34\,\%$.

6.6 Theory and calculation · 7 min

Use Equations (6.2), (6.9) and (6.11) for the API feeder, with $\beta_A = 20\,\%$, $\delta_A = 8\,\%$, $\tau_D = 90\,\text{s}$ and $t_R = 20\,\text{s}$. A refill starts at 25 % fill and ends at 80 %. Ignore the powder fed during the refill.

(a) With the screw speed frozen through the refill, compute $D_A(t_R)$ and the ratio of the rate at the end of the refill to the rate before it. *Checkpoint:* $D_A = 0.0717$, ratio 1.191.

(b) With the refill feedforward on, the command is divided by the identified profile of Equation (6.11), which is 5 % low on both terms, and the loop had settled on its setpoint before the refill with the feedforward in place. Find the ratio of the delivered rate at the end of the refill to the setpoint. *Checkpoint:* 1.0085, 0.85 % high.

(c) The chapter reports that, with the feedforward on, the rate runs at most 2.77 % high while the feeder is volumetric. Name two causes of the difference that part (b) leaves out. *Checkpoint:* The feed-factor variation, which a held screw cannot follow, and the 1 s lag of the screw behind a falling command.

6.7 App challenge · 8 min

Load scenario 2, Feeder refill, with the default seed and the settings as loaded (Refill feedforward Off). Run at a speed of 30 until the clock passes 1200 s, about 40 s of wall-clock time, pause and export the CSV file.

(a) In the row at 1200 s, read `metric_rejected`, `metric_false_rejects`, `metric_escapes` and `metric_oos_made`. *Checkpoint:* 2712, 2103, 0 and 609.

(b) Find the highest `api_ff_pct` up to 1200 s and the lowest and highest `m_true_mg`. What do the two ranges say about what the force-based weight loop protects? *Checkpoint:* 104.76 % LC at 810 s, within 0.05. Weight from 249.64 to 250.55 mg, within 0.05 mg.

(c) Set Refill feedforward On, press Reset and run to 1200 s again. Read `metric_rejected` and the highest `api_ff_pct`. *Checkpoint:* 0 rejected, 100.39 % LC within 0.05.

6.8 App challenge · 8 min

Load scenario 6, Dryer humidity change, with the default seed and the settings as loaded: Inlet air setpoint from Cascade and Humidity feedforward Off. Run at a speed of 60 to 2400 s, about 40 s of wall-clock time, and export the CSV file. Press reload, set Inlet air setpoint from to Fixed, run to 2400 s and export again. Press reload, set Humidity feedforward On, run to 2400 s and export a third time.

(a) For each run, find the highest `lod_meas_pct`, the dryer NIR's reading of each cell at discharge, and `metric_heater_kWh` at 2400 s. *Checkpoint:* Cascade 2.56 % and 5.72 kWh. Fixed 3.16 % and 4.81 kWh. Feedforward 2.19 % and 5.85 kWh. Within 0.01.

(b) For the fixed-air run, read `metric_rejected`, `metric_rej_track`, `metric_rej_nir`, `metric_accepted` and `metric_made` at 2400 s, and compute the share of the output kept. *Checkpoint:* 37 704 rejected, 35 928 on tracking and 1776 on the NIR, 19 896 of 57 600 kept, 34.5 %.

(c) The chapter reports that, with the cascade alone, the worst cell leaves at 2.59 % LOD at 480 s. Explain why the highest reading in your first file is lower. *Checkpoint:* The dryer NIR reads each cell with 0.05 % of noise.

6.9 App challenge · 7 min

Load the ninth scenario, Challenge, one shift, three upsets, with the default seed and the settings as loaded. Run at a speed of 120 to 3600 s, about 30 s of wall-clock time, and export the CSV file. In the row at 3600 s, read `metric_accepted`, `metric_rejected`, `metric_escapes` and `metric_worst_api_pct`.

(a) Report the four values and say whether the shift meets its target. *Checkpoint:* 71 952, 14 448, 194 and 9.39 %, within 0.01. Not met.

(b) Set Refill feedforward, Humidity feedforward and Reject by material tracking On, press Reset, run to 3600 s and read the same columns. *Checkpoint:* 82 992, 3408, 0 and 3.72 %.

(c) Set Reject by material tracking Off, press Reset and run again. Read the same columns, and say which upset sends out-of-limit tablets through the gate and why the NIR cannot stop them. *Checkpoint:* 83 304, 3096, 122 and 8.62 %. The bridge at 1800 s.

6.10 Application area · 3 min

The model's feed-frame NIR reads the blend with 0.3 % LC of noise. The chapter cites a commercial line whose blend readings had a standard deviation of 2.17 % over a 28 h run, while 500 of its tablets had 0.4 %.

(a) If the NIR's noise were 2.17 % LC at one standard deviation, what share of readings of a blend exactly on target would fall outside the default guard band of ±2.0 % LC? *Checkpoint:* About 36 %.

(b) What would that do to the gate, and name two ways a plant can use such an analyzer for release. *Checkpoint:* The gate, which holds for 10 s after each out-of-band reading, would reject most of the output.

6.11 Application area · 4 min

In case 1 the line starts empty. With tracking on the gate opens at 748.5 s after 3444 rejected tablets carrying 85.0 g of API. With tracking off it opens at 673.5 s after 1644, and no tablet out of limits is accepted either way.

(a) What do the tracker's extra 75 s cost in tablets and in finished blend, and how does the API in the 3444 rejects compare with 3444 tablets at label claim? *Checkpoint:* 1800 tablets, 0.45 kg of blend. 85.0 g against 86.1 g at label claim.

(b) Give one reason a validated process may still keep the tracker's rule, and one cost of start-up that the simulation leaves out.

6.12 Review the agent · 5 min

An AI assistant is asked how to save the tablets that case 3 rejects, where the API stops for 90 s. It replies: "Add a makeup term to FIC-A. Integrate the API that the load cells show missing, 54 g, and feed it back at twice the setpoint for the 90 s after the arch collapses. The run then averages exactly 100 % LC, the tracker has nothing to reject, and the 7152 rejected tablets are saved." Find the flaw, and say how you would check it.